

2024 ESC Guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS)

Developed by the task force for the management of atrial fibrillation of the European Society of Cardiology (ESC), with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC.

Endorsed by the European Stroke Organisation (ESO)

Authors/Task Force Members: Isabelle C. Van Gelder  ^{*}†, (Chairperson) (Netherlands), Michiel Rienstra  [±], (Task Force Co-ordinator) (Netherlands), Karina V. Bunting  [±], (Task Force Co-ordinator) (United Kingdom), Ruben Casado-Arroyo  (Belgium), Valeria Caso  ¹ (Italy), Harry J.G.M. Crijns  (Netherlands), Tom J.R. De Potter  (Belgium), Jeremy Dwight (United Kingdom), Luigina Guasti  (Italy), Thorsten Hanke  ² (Germany), Tiny Jaarsma  (Sweden), Maddalena Lettino  (Italy), Maja-Lisa Løchen  (Norway), R. Thomas Lumbers  (United Kingdom), Bart Maesen  ² (Netherlands), Inge Mølgaard (Denmark), Giuseppe M.C. Rosano (United Kingdom), Prashanthan Sanders  (Australia), Renate B. Schnabel  (Germany), Piotr Suwalski  ² (Poland), Emma Svennberg  (Sweden), Juan Tamargo  (Spain), Otilia Tica  (Romania), Vassil Traykov  (Bulgaria), Stylianos Tzeis (Greece), Dipak Kotecha  ^{*}†, (Chairperson) (United Kingdom), and ESC Scientific Document Group

* Corresponding authors: Isabelle C. Van Gelder, Department of Cardiology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands. Tel: +31 50 361 1327. Email: i.c.van.gelder@umcg.nl; and Dipak Kotecha, Institute of Cardiovascular Sciences, University of Birmingham, United Kingdom & NIHR Birmingham Biomedical Research Centre, University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom. Tel: +44 121 371 8124. Email: d.kotecha@bham.ac.uk

† The two Chairpersons contributed equally to the document and are joint corresponding authors.

± The two Task Force Co-ordinators contributed equally to the document.

Author/Task Force Member affiliations are listed in author information.

¹ Representing European Stroke Organisation (ESO).

² Representing European Association for Cardio-Thoracic Surgery (EACTS).

ESC Clinical Practice Guidelines (CPG) Committee: listed in the Appendix.

ESC subspecialty communities having participated in the development of this document:

Associations: Association of Cardiovascular Nursing & Allied Professions (ACNAP), Association for Acute CardioVascular Care (ACVC), European Association of Cardiovascular Imaging (EACVI), European Association of Preventive Cardiology (EAPC), European Association of Percutaneous Cardiovascular Interventions (EAPCI), European Heart Rhythm Association (EHRA), Heart Failure Association (HFA).

Councils: Council for Cardiology Practice, Council of Cardio-Oncology, Council on Cardiovascular Genomics, Council on Stroke.

Working Groups: Cardiac Cellular Electrophysiology, Cardiovascular Pharmacotherapy, E-Cardiology, Thrombosis.

Patient Forum

© The European Society of Cardiology 2024. All rights reserved. For permissions, please email: journals.permissions@oup.com.

Document Reviewers: Nikolaos Dagres, (CPG Review Co-ordinator) (Germany), Bianca Rocca, (CPG Review Co-ordinator) (Italy), Syed Ahsan (United Kingdom)², Pietro Ameri (Italy), Elena Arbelo (Spain), Axel Bauer (Austria), Michael A. Borger (Germany), Sergio Buccheri (Sweden), Barbara Casadei (United Kingdom), Ovidiu Chioncel (Romania), Dobromir Dobrev (Germany), Laurent Fauchier (France), Bruna Gigante (Sweden), Michael Glikson (Israel), Ziad Hijazi (Sweden), Gerhard Hindricks (Germany), Daniela Husser (Germany), Borja Ibanez (Spain), Stefan James (Sweden), Stefan Kaab (Germany), Paulus Kirchhof (Germany), Lars Køber (Denmark), Konstantinos C. Koskinas (Switzerland), Thomas Kumler (Denmark), Gregory Y.H. Lip (United Kingdom), John Mandrola (United States of America), Nikolaus Marx (Germany), John William Mcevoy (Ireland), Borislava Mihaylova (United Kingdom), Richard Mindham (United Kingdom), Denisa Muraru (Italy), Lis Neubeck (United Kingdom), Jens Cosedis Nielsen (Denmark), Jonas Oldgren (Sweden), Maurizio Paciaroni (Italy)¹, Agnes A. Pasquet (Belgium), Eva Prescott (Denmark), Filip Rega² (Belgium), Francisco Javier Rossello (Spain), Marcin Rucinski (Poland), Sacha P. Salzberg² (Switzerland), Sam Schulman (Canada), Philipp Sommer (Germany), Jesper Hastrup Svendsen (Denmark), Jurrien M. ten Berg (Netherlands), Hugo Ten Cate (Netherlands), Ilonca Vaartjes (Netherlands), Christiaan Jm. Vrints (Belgium), Adam Witkowski (Poland), and Katja Zeppenfeld (Netherlands)

SD All experts involved in the development of these guidelines have submitted declarations of interest which are reported in a supplementary document to the guidelines. See the *European Heart Journal* online or www.escardio.org/guidelines for supplementary documents as well as evidence tables.

Disclaimer. The ESC Guidelines represent the views of the ESC and were produced after careful consideration of the scientific and medical knowledge and the evidence available at the time of their publication. The ESC is not responsible in the event of any contradiction, discrepancy and/or ambiguity between the ESC Guidelines and any other official recommendations or guidelines issued by the relevant public health authorities, in particular in relation to good use of healthcare or therapeutic strategies. Health professionals are encouraged to take the ESC Guidelines fully into account when exercising their clinical judgment, as well as in the determination and the implementation of preventive, diagnostic or therapeutic medical strategies; however, the ESC Guidelines do not override, in any way whatsoever, the individual responsibility of health professionals to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient and, where appropriate and/or necessary, the patient's caregiver. Nor do the ESC Guidelines exempt health professionals from taking into full and careful consideration the relevant official updated recommendations or guidelines issued by the competent public health authorities, in order to manage each patient's case in light of the scientifically accepted data pursuant to their respective ethical and professional obligations. It is also the health professional's responsibility to verify the applicable rules and regulations relating to drugs and medical devices at the time of prescription. The ESC warns readers that the technical language may be misinterpreted and declines any responsibility in this respect.

Permissions. The content of these European Society of Cardiology (ESC) Guidelines has been published for personal and educational use only. No commercial use is authorized. No part of the ESC Guidelines may be translated or reproduced in any form without written permission from the ESC. Permissions can be obtained upon submission of a written request to Oxford University Press, the publisher of the *European Heart Journal* and the party authorized to handle such permissions on behalf of the ESC (journals.permissions@oup.com).

Keywords

Guidelines • Atrial fibrillation • AF-CARE • Comorbidity • Risk factors • Anticoagulation • Rate control • Rhythm control • Cardioversion • Antiarrhythmic drugs • Catheter ablation • AF surgery • Evaluation • Stroke • Thromboembolism

Table of contents

1. Preamble	6	7.2.6. Anticoagulation in patients undergoing catheter ablation ..	46
2. Introduction	8	7.2.7. Endoscopic and hybrid AF ablation	47
2.1. What is new	9	7.2.8. AF ablation during cardiac surgery	48
3. Definitions and clinical impact	13	7.2.9. Atrial tachycardia after pulmonary vein isolation	48
3.1. Definition and classification of AF	13	8. [E] Evaluation and dynamic reassessment	48
3.2. Diagnostic criteria for AF	14	8.1. Implementation of dynamic care	49
3.3. Symptoms attributable to AF	15	8.2. Improving treatment adherence	49
3.4. Diagnostic evaluation of new AF	15	8.3. Cardiac imaging	49
3.5. Adverse events associated with AF	16	8.4. Patient-reported outcome measures	50
3.6. Atrial flutter	17	9. The AF-CARE pathway in specific clinical settings	51
4. Patient pathways and management of AF	17	9.1. AF-CARE in unstable patients	51
4.1. Patient-centred, multidisciplinary AF management	17	9.2. AF-CARE in acute and chronic coronary syndromes	51
4.1.1. The patient at the heart of care	17	9.3. AF-CARE in vascular disease	53
4.1.2. Education and shared decision-making	18	9.4. AF-CARE in acute stroke or intracranial haemorrhage	53
4.1.3. Education of healthcare professionals	19	9.4.1. Management of acute ischaemic stroke	53
4.1.4. Inclusive management of AF	19	9.4.2. Introduction or re-introduction of anticoagulation after ischaemic stroke	54
4.2. Principles of AF-CARE	19	9.4.3. Introduction or re-introduction of anticoagulation after haemorrhagic stroke	54
5. [C] Comorbidity and risk factor management	25	9.5. AF-CARE for trigger-induced AF	54
5.1. Hypertension	26	9.6. AF-CARE in post-operative patients	55
5.2. Heart failure	26	9.7. AF-CARE in embolic stroke of unknown source	55
5.3. Type 2 diabetes mellitus	27	9.8. AF-CARE during pregnancy	56
5.4. Obesity	27	9.9. AF-CARE in congenital heart disease	57
5.5. Obstructive sleep apnoea	27	9.10. AF-CARE in endocrine disorders	57
5.6. Physical inactivity	27	9.11. AF-CARE in inherited cardiomyopathies and primary arrhythmia syndromes	57
5.7. Alcohol excess	28	9.12. AF-CARE in cancer	58
6. [A] Avoid stroke and thromboembolism	28	9.13. AF-CARE in older, multimorbid, or frail patients	58
6.1. Initiating oral anticoagulation	28	9.14. AF-CARE in atrial flutter	58
6.1.1. Decision support for anticoagulation in AF	28	10. Screening and prevention of AF	58
6.2. Oral anticoagulants	30	10.1. Epidemiology of AF	58
6.2.1. Direct oral anticoagulants	31	10.2. Screening tools for AF	59
6.2.2. Vitamin K antagonists	32	10.3. Screening strategies for AF	60
6.2.3. Clinical vs. device-detected subclinical AF	32	10.3.1. Single timepoint screening 'snapshot'	61
6.3. Antiplatelet drugs and combinations with anticoagulants	33	10.3.2. Prolonged screening	61
6.4. Residual ischaemic stroke risk despite anticoagulation	33	10.4. Factors associated with incident AF	62
6.5. Percutaneous left atrial appendage occlusion	33	10.5. Primary prevention of AF	62
6.6. Surgical left atrial appendage occlusion	34	10.5.1. Hypertension	63
6.7. Bleeding risk	35	10.5.2. Heart failure	63
6.7.1. Assessment of bleeding risk	35	10.5.3. Type 2 diabetes mellitus	63
6.7.2. Management of bleeding on anticoagulant therapy	35	10.5.4. Obesity	63
7. [R] Reduce symptoms by rate and rhythm control	38	10.5.5. Sleep apnoea syndrome	63
7.1. Management of heart rate in patients with AF	38	10.5.6. Physical activity	63
7.1.1. Indications and target heart rate	39	10.5.7. Alcohol intake	64
7.1.2. Heart rate control in the acute setting	39	11. Key messages	64
7.1.3. Long-term heart rate control	39	12. Gaps in evidence	64
7.1.4. Atrioventricular node ablation and pacemaker implantation	40	13. 'What to do' and 'What not to do' messages from the guidelines	66
7.2. Rhythm control strategies in patients with AF	40	14. Evidence tables	69
7.2.1. General principles and anticoagulation	40	15. Data availability statement	69
7.2.2. Electrical cardioversion	43	16. Author information	69
7.2.3. Pharmacological cardioversion	43	17. Appendix	70
7.2.4. Antiarrhythmic drugs	44	18. References	71
7.2.5. Catheter ablation	45		

Tables of Recommendations

Recommendation Table 1 — Recommendations for the diagnosis of AF (see also Evidence Table 1)	15
Recommendation Table 2 — Recommendations for symptom evaluation in patients with AF (see also Evidence Table 2)	15
Recommendation Table 3 — Recommendations for diagnostic evaluation in patients with new AF (see also Evidence Table 3)	15
Recommendation Table 4 — Recommendations for patient-centred care and education (see also Evidence Table 4)	19
Recommendation Table 5 — Recommendations for comorbidity and risk factor management in AF (see also Evidence Table 5)	26
Recommendation Table 6 — Recommendations to assess and manage thromboembolic risk in AF (see also Evidence Table 6)	29
Recommendation Table 7 — Recommendations for oral anticoagulation in AF (see also Evidence Table 7)	31
Recommendation Table 8 — Recommendations for combining antiplatelet drugs with anticoagulants for stroke prevention (see also Evidence Table 8)	33
Recommendation Table 9 — Recommendations for thromboembolism despite anticoagulation (see also Evidence Table 9)	33
Recommendation Table 10 — Recommendations for percutaneous left atrial appendage occlusion (see also Evidence Table 10)	34
Recommendation Table 11 — Recommendations for surgical left atrial appendage occlusion (see also Evidence Table 11)	35
Recommendation Table 12 — Recommendations for assessment of bleeding risk (see also Evidence Table 12)	35
Recommendation Table 13 — Recommendations for management of bleeding in anticoagulated patients (see also Evidence Table 13) ...	38
Recommendation Table 14 — Recommendations for heart rate control in patients with AF (see also Evidence Table 14)	38
Recommendation Table 15 — Recommendations for general concepts in rhythm control (see also Evidence Table 15)	42
Recommendation Table 16 — Recommendations for electrical cardioversion of AF (see also Evidence Table 16)	43
Recommendation Table 17 — Recommendations for pharmacological cardioversion of AF (see also Evidence Table 17)	43
Recommendation Table 18 — Recommendations for antiarrhythmic drugs for long-term maintenance of sinus rhythm (see also Evidence Table 18)	45
Recommendation Table 19 — Recommendations for catheter ablation of AF (see also Evidence Table 19)	46
Recommendation Table 20 — Recommendations for anticoagulation in patients undergoing catheter ablation (see also Evidence Table 20)	47
Recommendation Table 21 — Recommendations for endoscopic and hybrid AF ablation (see also Evidence Table 21)	47
Recommendation Table 22 — Recommendations for AF ablation during cardiac surgery (see also Evidence Table 22)	48
Recommendation Table 23 — Recommendations to improve patient experience (see also Evidence Table 23)	51
Recommendation Table 24 — Recommendations for patients with acute coronary syndromes or undergoing percutaneous intervention (see also Evidence Table 24)	53
Recommendation Table 25 — Recommendations for trigger-induced AF (see also Evidence Table 25)	55

Recommendation Table 26 — Recommendations for management of post-operative AF (see also Evidence Table 26)	55
Recommendation Table 27 — Recommendations for patients with embolic stroke of unknown source (see also Evidence Table 27)	56
Recommendation Table 28 — Recommendations for patients with AF during pregnancy (see also Evidence Table 28)	56
Recommendation Table 29 — Recommendations for patients with AF and congenital heart disease (see also Evidence Table 29)	57
Recommendation Table 30 — Recommendations for prevention of thromboembolism in atrial flutter (see also Evidence Table 30)	58
Recommendation Table 31 — Recommendations for screening for AF (see also Evidence Table 31)	61
Recommendation Table 32 — Recommendations for primary prevention of AF (see also Evidence Table 32)	63

List of tables

Table 1 Classes of recommendations	7
Table 2 Levels of evidence	7
Table 3 New recommendations	9
Table 4 Revised recommendations	12
Table 5 Definitions and classifications for the temporal pattern of AF	14
Table 6 Other clinical concepts relevant to AF	14
Table 7 The modified European Heart Rhythm Association (mEHRA) symptom classification	16
Table 8 Diagnostic work-up for patients with AF	17
Table 9 Achieving patient-centred AF management	18
Table 10 Updated definitions for the CHA ₂ DS ₂ -VA score	29
Table 11 Recommended doses for direct oral anticoagulant therapy	32
Table 12 Drugs for rate control in AF	39
Table 13 Antiarrhythmic drugs for sinus rhythm restoration	44
Table 14 Non-cardiac conditions associated with trigger-induced AF	54
Table 15 Tools for AF screening	60
Table 16 Factors associated with incident AF	62
Table 17 'What to do' and 'what not to do'	66

List of figures

Figure 1 Impacts and outcomes associated with clinical AF. AF, atrial fibrillation	16
Figure 2 Multidisciplinary approach to AF management	18
Figure 3 Central illustration. Patient pathway for AF-CARE (see Figures 4, 5, 6, and 7 for the [R] pathways for first-diagnosed, paroxysmal, persistent and permanent AF)	20
Figure 4 [R] Pathway for patients with first-diagnosed AF	21
Figure 5 [R] Pathway for patients with paroxysmal AF	22
Figure 6 [R] Pathway for patients with persistent AF	23
Figure 7 [R] Pathway for patients with permanent AF	24
Figure 8 Management of key comorbidities to reduce AF recurrence	25
Figure 9 Common drug interactions with oral anticoagulants	30
Figure 10 Modifying the risk of bleeding associated with OAC	36
Figure 11 Management of oral anticoagulant-related bleeding in patients with AF	37
Figure 12 Approaches for cardioversion in patients with AF	41
Figure 13 Relevance of echocardiography in the AF-CARE pathway	50
Figure 14 Antithrombotic therapy in patients with AF and acute or chronic coronary syndromes	52

Figure 15 Non-invasive diagnostic methods for AF screening 59

Figure 16 Approaches to screening for AF 61

Abbreviations and acronyms

AAD	Antiarrhythmic drugs	CABANA	Catheter Ablation versus Anti-arrhythmic Drug Therapy for Atrial Fibrillation (trial)
ACE	Angiotensin-converting enzyme	CAD	Coronary artery disease
ACEi	Angiotensin-converting enzyme inhibitor	CASTLE-AF	Catheter Ablation versus Standard Conventional Treatment in Patients With Left Ventricle (LV) Dysfunction and AF (trial)
ACS	Acute coronary syndromes	CASTLE-HTx	Catheter Ablation for Atrial Fibrillation in Patients With End-Stage Heart Failure and Eligibility for Heart Transplantation (trial)
ACTIVE W	Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (trial)	CCS	Chronic coronary syndrome
AF	Atrial fibrillation	CHADS ₂	Congestive heart failure, hypertension, age >75 years, diabetes; previous stroke (2 points)
AF-CARE	Atrial fibrillation—[C] Comorbidity and risk factor management, [A] Avoid stroke and thromboembolism, [R] Reduce symptoms by rate and rhythm control, [E] Evaluation and dynamic reassessment	CHA ₂ DS ₂ -VA	Congestive heart failure, hypertension, age ≥75 years (2 points), diabetes mellitus, prior stroke/transient ischaemic attack/arterial thromboembolism (2 points), vascular disease, age 65–74 years (score)
AFEQT	Atrial Fibrillation Effect on QualiTy-of-Life (questionnaire)	CHA ₂ DS ₂ -VASc	Congestive heart failure, hypertension, age ≥75 years (2 points), diabetes mellitus, prior stroke or TIA or thromboembolism (2 points), vascular disease, age 65–74 years, sex category
AFFIRM	Atrial Fibrillation Follow-up Investigation of Rhythm Management (trial)	CKD	Chronic kidney disease
AFL	Atrial flutter	CMR	Cardiac magnetic resonance
AFQLQ	Atrial Fibrillation Quality of Life Questionnaire	COMPASS	Cardiovascular Outcomes for People Using Anticoagulation Strategies (trial)
AF-QoL	Atrial Fibrillation Quality of Life (questionnaire)	CPAP	Continuous positive airway pressure
AFSS	Atrial Fibrillation Severity Scale	CrCl	Creatinine clearance
AI	Artificial intelligence	CRT	Cardiac resynchronization therapy
APACHE-AF	Apixaban After Anticoagulation-associated Intracerebral Haemorrhage in Patients With Atrial Fibrillation (trial)	CT	Computed tomography
APAF-CRT	Ablate and Pace for Atrial Fibrillation—cardiac resynchronization therapy	CTA	Computed tomography angiography
ARB	Angiotensin receptor blocker	CTI	Cavo-tricuspid isthmus
ARTESiA	Apixaban for the Reduction of Thromboembolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation (trial)	DAPT	Dual antiplatelet therapy
AT	Atrial tachycardia	DOAC	Direct oral anticoagulant
ATHENA	A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg twice daily for the Prevention of Cardiovascular Hospitalization or Death from Any Cause in Patients with Atrial Fibrillation/Atrial Flutter (trial)	EAST-AFNET 4	Early treatment of Atrial fibrillation for Stroke prevention Trial
AUGUSTUS	An open-label, 2 × 2 factorial, randomized controlled, clinical trial to evaluate the safety of apixaban vs. vitamin k antagonist and aspirin vs. aspirin placebo in patients with atrial fibrillation and acute coronary syndrome or percutaneous coronary intervention	ECG	Electrocardiogram
AVERROES	Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (trial)	ECV	Electrical cardioversion
AVN	Atrioventricular node	EHRA	European Heart Rhythm Association
b.p.m.	Beats per minute	ELAN	Early versus Late initiation of direct oral Anticoagulants in post-ischaemic stroke patients with atrial fibrillationN (trial)
BMI	Body mass index	ESUS	Embolic stroke of undetermined source
BNP	B-type natriuretic peptide	FFP	Fresh frozen plasma
BP	Blood pressure	GI	Gastrointestinal
C ₂ HES	Coronary artery disease or chronic obstructive pulmonary disease (1 point each); hypertension (1 point); elderly (age ≥75 years, 2 points); systolic heart failure (2 points); thyroid disease (hyperthyroidism, 1 point)	GWAS	Genome-wide association studies
		HAS-BLED	Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 years), Drugs/alcohol concomitantly (score)
		HAVOC	Hypertension, age, valvular heart disease, peripheral vascular disease, obesity, congestive heart failure, and coronary artery disease
		HbA1c	Haemoglobin A1c (glycated or glycosylated haemoglobin)
		HCM	Hypertrophic cardiomyopathy
		HF	Heart failure
		HFmrEF	Heart failure with mildly reduced ejection fraction
		HFpEF	Heart failure with preserved ejection fraction
		HFrfEF	Heart failure with reduced ejection fraction
		HR	Hazard ratio
		i.v.	Intravenous

ICH	Intracranial haemorrhage	SAVE	Sleep Apnea cardioVascular Endpoints (trial)
ICHOM	International Consortium for Health Outcomes Measurement	SBP	Systolic blood pressure
IMT	Intima-media thickness	SGLT2	Sodium-glucose cotransporter-2
INR	International normalized ratio (of prothrombin time)	SIC-AF	Successful Intravenous Cardioversion for Atrial Fibrillation
LA	Left atrium	SORT-AF	Supervised Obesity Reduction Trial for AF Ablation Patients (trial)
LAA	Left atrial appendage	SoSTART	Start or STop Anticoagulants Randomised Trial
LAAO	Left atrial appendage occlusion	SR	Sinus rhythm
LAAOS III	Left Atrial Appendage Occlusion Study	STEEER-AF	Stroke prevention and rhythm control Therapy: Evaluation of an Educational programme of the European Society of Cardiology in a cluster-Randomised trial in patients with Atrial Fibrillation (trial)
LEGACY	Long-Term Effect of Goal directed weight management on Atrial Fibrillation Cohort: a 5 Year follow-up study	STEMI	ST-segment elevation myocardial infarction
LMWH	Low molecular weight heparin	STROKESTOP	Systematic ECG Screening for Atrial Fibrillation Among 75 Year Old Subjects in the Region of Stockholm and Halland, Sweden (trial)
LOOP	Atrial Fibrillation Detected by Continuous ECG Monitoring (trial)	TE	Thromboembolism
LV	Left ventricle	TIA	Transient ischaemic attack
LVEF	Left ventricular ejection fraction	TIMING	Timing of Oral Anticoagulant Therapy in Acute Ischemic Stroke With Atrial Fibrillation (trial)
LVH	Left ventricular hypertrophy	TOE	Transoesophageal echocardiography
mEHRA	Modified European Heart Rhythm Association score	TSH	Thyroid-stimulating hormone
MI	Myocardial infarction	TTE	Transthoracic echocardiogram
MRI	Magnetic resonance imaging	TTR	Time in therapeutic range
NOAH	Non-vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes (trial)	UFH	Unfractionated heparin
NSAID	Non-steroidal anti-inflammatory drug	VKA	Vitamin K antagonist
NT-proBNP	N-terminal pro-B-type natriuretic peptide		
NYHA	New York Heart Association		
OAC	Oral anticoagulant(s)		
OR	Odds ratio		
OSA	Obstructive sleep apnoea		
PAD	Peripheral arterial disease		
PCC	Prothrombin complex concentrate		
PCI	Percutaneous intervention		
PFO	Patent foramen ovale		
POAF	Post-operative atrial fibrillation		
PPG	Photoplethysmography		
PROM	Patient-reported outcome measure		
PVD	Peripheral vascular disease		
PVI	Pulmonary vein isolation		
QLAF	Quality of Life in Atrial Fibrillation (questionnaire)		
QRS	Q wave, R wave, and S wave, the 'QRS complex' represents ventricular depolarization		
RACE 7	Rate Control versus Electrical Cardioversion		
ACWAS	Trial 7—Acute Cardioversion versus Wait and See (trial)		
RACE I	RAte Control versus Electrical cardioversion study		
RACE II	Rate Control Efficacy in Permanent Atrial Fibrillation (trial)		
RACE 3	Routine versus Aggressive upstream rhythm Control for prevention of Early AF in heart failure (trial)		
RACE 4	IntegRATED Chronic Care Program at Specialized AF Clinic Versus Usual CarE in Patients with Atrial Fibrillation (trial)		
RATE-AF	RAte control Therapy Evaluation in permanent Atrial Fibrillation (trial)		
RCT	Randomized controlled trial		
RR	Relative risk		

1. Preamble

Guidelines evaluate and summarize available evidence with the aim of assisting health professionals in proposing the best diagnostic or therapeutic approach for an individual patient with a given condition. Guidelines are intended for use by health professionals and the European Society of Cardiology (ESC) makes its Guidelines freely available.

ESC Guidelines do not override the individual responsibility of health professionals to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient or the patient's caregiver where appropriate and/or necessary. It is also the health professional's responsibility to verify the rules and regulations applicable in each country to drugs and devices at the time of prescription and to respect the ethical rules of their profession.

ESC Guidelines represent the official position of the ESC on a given topic and are regularly updated when warranted by new evidence. ESC Policies and Procedures for formulating and issuing ESC Guidelines can be found on the ESC website (<https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Guidelines-development/Writing-ESC-Guidelines>). This guideline updates and replaces the previous version from 2020.

The Members of this task force were selected by the ESC to include professionals involved with the medical care of patients with this pathology as well as patient representatives and methodologists. The selection procedure included an open call for authors and aimed to include members from across the whole of the ESC region and from relevant ESC Subspecialty Communities. Consideration was given to diversity

and inclusion, notably with respect to gender and country of origin. The task force performed a critical review and evaluation of the published literature on diagnostic and therapeutic approaches including assessment of the risk–benefit ratio. The strength of every recommendation and the level of evidence supporting them were weighed and scored according to predefined scales as outlined in [Tables 1 and 2](#) below. Patient-reported outcome measures (PROMs) and

patient-reported experience measures were also evaluated as the basis for recommendations and/or discussion in these guidelines. The task force followed ESC voting procedures and all approved recommendations were subject to a vote and achieved at least 75% agreement among voting members. Members of the task force with declared interests on specific topics were asked to abstain from voting on related recommendations.

Table 1 Classes of recommendations

Classes of recommendations	Definition		Wording to use
	Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended or is indicated
	Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
	Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.	Should be considered
	Class IIb	Usefulness/efficacy is less well established by evidence/opinion.	May be considered
	Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

©ESC 2024

Table 2 Levels of evidence

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

©ESC 2024

The experts of the writing and reviewing panels provided declaration of interest forms for all relationships that might be perceived as real or potential sources of conflicts of interest. Their declarations of interest were reviewed according to the ESC declaration of interest rules which can be found on the ESC website (<http://www.escardio.org/guidelines>) and have been compiled in a report published in a supplementary document with the guidelines. Funding for the development of ESC Guidelines is derived entirely from the ESC with no involvement of the healthcare industry.

The ESC Clinical Practice Guidelines (CPG) Committee supervises and co-ordinates the preparation of new guidelines and is responsible for the approval process. In addition to review by the CPG Committee, ESC Guidelines undergo multiple rounds of double-blind peer review by external experts, including members from across the whole of the ESC region, all National Cardiac Societies of the ESC and from relevant ESC Subspecialty Communities. After appropriate revisions, the guidelines are signed off by all the experts in the task force. The finalized document is signed off by the CPG Committee for publication in the *European Heart Journal*.

ESC Guidelines are based on analyses of published evidence, chiefly on clinical trials and meta-analyses of trials, but potentially including other types of studies. Evidence tables summarizing key information from relevant studies are generated early in the guideline development process to facilitate the formulation of recommendations, to enhance comprehension of recommendations after publication, and reinforce transparency in the guidelines development process. The tables are published in their own section of ESC Guidelines and reference specific recommendation tables.

Off-label use of medication may be presented in this guideline if a sufficient level of evidence shows that it can be considered medically appropriate for a given condition. However, the final decisions concerning an individual patient must be made by the responsible health professional giving special consideration to:

- The specific situation of the patient. Unless otherwise provided for by national regulations, off-label use of medication should be limited to situations where it is in the patient's interest with regard to the quality, safety, and efficacy of care, and only after the patient has been informed and has provided consent.
- Country-specific health regulations, indications by governmental drug regulatory agencies, and the ethical rules to which health professionals are subject, where applicable.

2. Introduction

Atrial fibrillation (AF) is one of the most commonly encountered heart conditions, with a broad impact on all health services across primary and secondary care. The prevalence of AF is expected to double in the next few decades as a consequence of the ageing population, an increasing burden of comorbidities, improved awareness, and new technologies for detection.

The effects of AF are variable across individual patients; however, morbidity from AF remains highly concerning. Patients with AF can suffer from a variety of symptoms and poor quality of life. Stroke and heart failure as consequences of AF are now well appreciated by healthcare professionals, but AF is also linked to a range of other thromboembolic outcomes. These include subclinical cerebral damage (potentially leading to vascular dementia), and thromboembolism to every other organ, all of which contribute to the higher risk of mortality associated with AF.

The typical drivers of AF onset and progression are a range of comorbidities and associated risk factors. To achieve optimal care for patients with AF, it is now widely accepted that these comorbidities and risk factors must be managed early and in a dynamic way. Failure to do so contributes to recurrent cycles of AF, treatment failure, poor patient outcomes, and a waste of healthcare resources. In this iteration of the European Society of Cardiology (ESC) practice guidelines on AF, the task force has consolidated and evolved past approaches to develop the AF-CARE framework (Atrial Fibrillation—[C] Comorbidity and risk factor management, [A] Avoid stroke and thromboembolism, [R] Reduce symptoms by rate and rhythm control, [E] Evaluation and dynamic reassessment). Comorbidities and risk factors is placed as the initial and central component of patient management. This should be considered first as it applies to all patients with AF, regardless of their thromboembolic risk factors or any symptoms that might warrant intervention. This is followed by considering how best to [A] avoid stroke and thromboembolism, and then the options available to reduce symptoms, and in some cases improve prognosis, through [R] rate and rhythm control. [E] Evaluation and reassessment should be individualized for every patient, with a dynamic approach that accounts for how AF and its associated conditions change over time.

Patient empowerment is critical in any long-term medical problem to achieve better outcomes, encourage adherence, and to seek timely guidance on changes in clinical status. A patient-centred, shared decision-making approach will facilitate the choice of management that suits each individual patient, particularly in AF where some therapies and interventions improve clinical outcomes, and others are focused on addressing symptoms and quality of life. Education and awareness are essential, not only for patients but also healthcare professionals in order to constrain the impact of AF on patients and healthcare services.

With this in mind, the task force have created a range of patient pathways that cover the major aspects of AF-CARE. At present, these remain based on the time-orientated classification of AF (first-diagnosed, paroxysmal, persistent, and permanent), but ongoing research may allow for pathology-based classifications and a future of personalized medicine. Clinical practice guidelines can only cover common scenarios with an evidence base, and so there remains a need for healthcare professionals to care for patients within a local multidisciplinary team. While guideline-adherent care has repeatedly been shown to improve patient outcomes, the actual implementation of guidelines is often poor in many healthcare settings. This has been demonstrated in the ESC's first randomized controlled trial (RCT), STEER-AF (Stroke prevention and rhythm control Therapy: Evaluation of an Educational programme of the European Society of Cardiology in a cluster-Randomised trial in patients with Atrial Fibrillation), which has sought to improve guideline adherence in parallel to guideline production. The task force developing the 2024 AF Guidelines have made implementation a key goal by focusing on the underpinning evidence and using a consistent writing style for each recommendation (the intervention proposed, the population it should be applied to, and the potential value to the patient, followed by any exceptions). [Tables 3](#) and [4](#) below outline new recommendations and those with important revisions. These initiatives have been designed to make the 2024 ESC Guidelines for the management of AF easier to read, follow, and implement, with the aim of improving the lives of patients with AF. A patient version of these guidelines is also available at <http://www.escardio.org/Guidelines/guidelines-for-patients>.

2.1. What is new

Table 3 New recommendations

	Class ^a	Level ^b
Diagnostic evaluation of new AF—Section 3.4		
A transthoracic echocardiogram is recommended in patients with an AF diagnosis where this will guide treatment decisions.	I	C
Principles of AF-CARE—Section 4.2		
Education directed to patients, family members, caregivers, and healthcare professionals is recommended to optimize shared decision-making, facilitating open discussion of both the benefit and risk associated with each treatment option.	I	C
Access to patient-centred management according to the AF-CARE principles is recommended in all patients with AF, regardless of gender, ethnicity, and socioeconomic status, to ensure equality in healthcare provision and improve outcomes.	I	C
Patient-centred AF management with a multidisciplinary approach should be considered in all patients with AF to optimize management and improve outcomes.	IIa	B
[C] Comorbidity and risk factor management—Section 5		
Diuretics are recommended in patients with AF, HF, and congestion to alleviate symptoms and facilitate better AF management.	I	C
Appropriate medical therapy for HF is recommended in AF patients with HF and impaired LVEF to reduce symptoms and/or HF hospitalization and prevent AF recurrence.	I	B
Sodium-glucose cotransporter-2 inhibitors are recommended for patients with HF and AF regardless of left ventricular ejection fraction to reduce the risk of HF hospitalization and cardiovascular death.	I	A
Effective glycaemic control is recommended as part of comprehensive risk factor management in individuals with diabetes mellitus and AF, to reduce burden, recurrence, and progression of AF.	I	C
Bariatric surgery may be considered in conjunction with lifestyle changes and medical management in individuals with AF and body mass index ≥ 40 kg/m ² ^c where a rhythm control strategy is planned, to reduce recurrence and progression of AF.	IIb	C
Management of obstructive sleep apnoea may be considered as part of a comprehensive management of risk factors in individuals with AF to reduce recurrence and progression.	IIb	B
When screening for obstructive sleep apnoea in individuals with AF, using only symptom-based questionnaires is not recommended.	III	B
Initiating oral anticoagulation—Section 6.1		
Oral anticoagulation is recommended in patients with clinical AF at elevated thromboembolic risk to prevent ischaemic stroke and thromboembolism.	I	A
A CHA ₂ DS ₂ -VA score of 2 or more is recommended as an indicator of elevated thromboembolic risk for decisions on initiating oral anticoagulation.	I	C
A CHA ₂ DS ₂ -VA score of 1 should be considered an indicator of elevated thromboembolic risk for decisions on initiating oral anticoagulation.	IIa	C
Oral anticoagulation is recommended in all patients with AF and hypertrophic cardiomyopathy or cardiac amyloidosis, regardless of CHA ₂ DS ₂ -VA score, to prevent ischaemic stroke and thromboembolism.	I	B
Individualized reassessment of thromboembolic risk is recommended at periodic intervals in patients with AF to ensure anticoagulation is started in appropriate patients.	I	B
Direct oral anticoagulant therapy may be considered in patients with asymptomatic device-detected subclinical AF and elevated thromboembolic risk to prevent ischaemic stroke and thromboembolism, excluding patients at high risk of bleeding.	IIb	B
Oral anticoagulants—Section 6.2		
A reduced dose of DOAC therapy is not recommended, unless patients meet DOAC-specific criteria, to prevent underdosing and avoidable thromboembolic events.	III	B
Maintaining VKA treatment rather than switching to a DOAC may be considered in patients aged ≥ 75 years on clinically stable therapeutic VKA with polypharmacy to prevent excess bleeding risk.	IIb	B
Antiplatelet drugs and combinations with anticoagulants—Section 6.3		
Adding antiplatelet treatment to oral anticoagulation is not recommended in AF patients for the goal of preventing ischaemic stroke or thromboembolism.	III	B

Continued

Residual ischaemic stroke risk despite anticoagulation—Section 6.4		
A thorough diagnostic work-up should be considered in patients taking an oral anticoagulant and presenting with ischaemic stroke or thromboembolism to prevent recurrent events, including assessment of non-cardioembolic causes, vascular risk factors, dosage, and adherence.	IIa	B
Adding antiplatelet treatment to anticoagulation is not recommended in patients with AF to prevent recurrent embolic stroke.	III	B
Switching from one DOAC to another, or from a DOAC to a VKA, without a clear indication is not recommended in patients with AF to prevent recurrent embolic stroke.	III	B
Surgical left atrial appendage occlusion—Section 6.6		
Surgical closure of the left atrial appendage should be considered as an adjunct to oral anticoagulation in patients with AF undergoing endoscopic or hybrid AF ablation to prevent ischaemic stroke and thromboembolism.	IIa	C
Stand-alone endoscopic surgical closure of the left atrial appendage may be considered in patients with AF and contraindications for long-term anticoagulant treatment to prevent ischaemic stroke and thromboembolism.	IIb	C
Management of bleeding on anticoagulant therapy—Section 6.7.2		
Specific antidotes should be considered in AF patients on a DOAC who develop a life-threatening bleed, or bleed into a critical site, to reverse the antithrombotic effect.	IIa	B
Management of heart rate in patients with AF—Section 7.1		
Rate control therapy is recommended in patients with AF, as initial therapy in the acute setting, an adjunct to rhythm control therapies, or as a sole treatment strategy to control heart rate and reduce symptoms.	I	B
Beta-blockers, diltiazem, verapamil, or digoxin are recommended as first-choice drugs in patients with AF and LVEF >40% to control heart rate and reduce symptoms.	I	B
Atrioventricular node ablation combined with cardiac resynchronization therapy should be considered in severely symptomatic patients with permanent AF and at least one hospitalization for HF to reduce symptoms, physical limitations, recurrent HF hospitalization, and mortality.	IIa	B
General principles and anticoagulation—Section 7.2.1		
Direct oral anticoagulants are recommended in preference to VKAs in eligible patients with AF undergoing cardioversion for thromboembolic risk reduction.	I	A
Cardioversion of AF (either electrical or pharmacological) should be considered in symptomatic patients with persistent AF as part of a rhythm control approach.	IIa	B
A wait-and-see approach for spontaneous conversion to sinus rhythm within 48 h of AF onset should be considered in patients without haemodynamic compromise as an alternative to immediate cardioversion.	IIa	B
Implementation of a rhythm control strategy should be considered within 12 months of diagnosis in selected patients with AF at risk of thromboembolic events to reduce the risk of cardiovascular death or hospitalization.	IIa	B
Early cardioversion is not recommended without appropriate anticoagulation or transoesophageal echocardiography if AF duration is longer than 24 h, or there is scope to wait for spontaneous cardioversion.	III	C
Electrical cardioversion—Section 7.2.2		
Electrical cardioversion as a diagnostic tool should be considered in patients with persistent AF where there is uncertainty about the value of sinus rhythm restoration on symptoms, or to assess improvement in left ventricular function.	IIa	C
Antiarrhythmic drugs—Section 7.2.4		
Antiarrhythmic drug therapy is not recommended in patients with advanced conduction disturbances unless antibradycardia pacing is provided.	III	C
Catheter ablation—Section 7.2.5		
Sinus node disease/tachycardia–bradycardia syndrome		
Atrial fibrillation catheter ablation should be considered in patients with AF-related bradycardia or sinus pauses on AF termination to improve symptoms and avoid pacemaker implantation.	IIa	C
Recurrence after catheter ablation		
Repeat AF catheter ablation should be considered in patients with AF recurrence after initial catheter ablation, provided the patient's symptoms were improved after the initial PVI or after failed initial PVI, to reduce symptoms, recurrence, and progression of AF.	IIa	B
Anticoagulation in patients undergoing catheter ablation—Section 7.2.6		
Uninterrupted oral anticoagulation is recommended in patients undergoing AF catheter ablation to prevent peri-procedural ischaemic stroke and thromboembolism.	I	A

Continued

Endoscopic and hybrid AF ablation—Section 7.2.7		
Continuation of oral anticoagulation is recommended in patients with AF at elevated thromboembolic risk after concomitant, endoscopic, or hybrid AF ablation, independent of rhythm outcome or LAA exclusion, to prevent ischaemic stroke and thromboembolism.	I	C
Endoscopic and hybrid ablation procedures should be considered in patients with symptomatic persistent AF refractory to AAD therapy to prevent symptoms, recurrence, and progression of AF, within a shared decision-making rhythm control team of electrophysiologists and surgeons.	IIa	A
AF ablation during cardiac surgery—Section 7.2.8		
Intraprocedural imaging for detection of left atrial thrombus in patients undergoing surgical ablation is recommended to guide surgical strategy, independent of oral anticoagulant use, to prevent peri-procedural ischaemic stroke and thromboembolism.	I	C
Concomitant surgical ablation should be considered in patients undergoing non-mitral valve cardiac surgery and AF suitable for a rhythm control strategy to prevent symptoms and recurrence of AF, with shared decision-making supported by an experienced team of electrophysiologists and arrhythmia surgeons.	IIa	B
Patient-reported outcome measures—Section 8.4		
Evaluating quality of care and identifying opportunities for improved treatment of AF should be considered by practitioners and institutions to improve patient experiences.	IIa	B
Acute and chronic coronary syndromes in patients with AF—Section 9.2		
Recommendations for AF patients with chronic coronary or vascular disease		
Antiplatelet therapy beyond 12 months is not recommended in stable patients with chronic coronary or vascular disease treated with oral anticoagulation, due to lack of efficacy and to avoid major bleeding.	III	B
Trigger-induced AF—Section 9.5		
Long-term oral anticoagulation should be considered in suitable patients with trigger-induced AF at elevated thromboembolic risk to prevent ischaemic stroke and systemic thromboembolism.	IIa	C
Post-operative AF—Section 9.6		
Peri-operative amiodarone therapy is recommended where drug therapy is desired to prevent post-operative AF after cardiac surgery.	I	A
Concomitant posterior peri-cardiotomy should be considered in patients undergoing cardiac surgery to prevent post-operative AF.	IIa	B
Patients with embolic stroke of unknown source (ESUS)—Section 9.7		
Initiation of oral anticoagulation in ESUS patients without documented AF is not recommended due to lack of efficacy in preventing ischaemic stroke and thromboembolism.	III	A
Atrial flutter—Section 9.14		
Oral anticoagulation is recommended in patients with atrial flutter at elevated thromboembolic risk to prevent ischaemic stroke and thromboembolism.	I	B
Screening strategies for AF—Section 10.3		
Review of an ECG (12-lead, single, or multiple leads) by a physician is recommended to provide a definite diagnosis of AF and commence appropriate management.	I	B
Population-based screening for AF using a prolonged non-invasive ECG-based approach should be considered in individuals aged ≥ 75 years, or ≥ 65 years with additional CHA ₂ DS ₂ -VA risk factors to ensure earlier detection of AF.	IIa	B
Primary prevention of AF—Section 10.5		
Maintaining optimal blood pressure is recommended in the general population to prevent AF, with ACE inhibitors or ARBs as first-line therapy.	I	B
Appropriate medical HF therapy is recommended in individuals with HFrEF to prevent AF.	I	B
Maintaining normal weight (BMI 20–25 kg/m ²) is recommended for the general population to prevent AF.	I	B
Maintaining an active lifestyle is recommended to prevent AF, with the equivalent of 150–300 min per week of moderate intensity or 75–150 min per week of vigorous intensity aerobic physical activity.	I	B
Avoidance of binge drinking and alcohol excess is recommended in the general population to prevent AF.	I	B
Metformin or SGLT2 inhibitors should be considered for individuals needing pharmacological management of diabetes mellitus to prevent AF.	IIa	B
Weight reduction should be considered in obese individuals to prevent AF.	IIa	B

AAD, antiarrhythmic drugs; ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; AF-CARE, atrial fibrillation—[C] Comorbidity and risk factor management, [A] Avoid stroke and thromboembolism, [R] Reduce symptoms by rate and rhythm control, [E] Evaluation and dynamic reassessment; ARB, angiotensin receptor blocker; BMI, body mass index; CHA₂DS₂-VA, congestive heart failure, hypertension, age ≥ 75 years (2 points), diabetes mellitus, prior stroke/transient ischaemic attack/arterial thromboembolism (2 points), vascular disease, age 65–74 years; DOAC, direct oral anticoagulant; ECG, electrocardiogram; ESUS, embolic stroke of undetermined source; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LAA, left atrial appendage; LVEF, left ventricular ejection fraction; PVI, pulmonary vein isolation; SGLT2, sodium-glucose cotransporter-2; VKA, vitamin K antagonist.

^aClass of recommendation.

^bLevel of evidence.

^cOr body mass index ≥ 35 kg/m² with obesity-related complications.

Table 4 Revised recommendations

Recommendations in 2020 version	Class ^a	Level ^b	Recommendations in 2024 version	Class ^a	Level ^b
Section 3.2—Diagnostic criteria for AF					
ECG documentation is required to establish the diagnosis of AF. A standard 12-lead ECG recording or a single-lead ECG tracing of ≥ 30 s showing heart rhythm with no discernible repeating P waves and irregular RR intervals (when atrioventricular conduction is not impaired) is diagnostic of clinical AF.	I	B	Confirmation by an electrocardiogram (12-lead, multiple, or single leads) is recommended to establish the diagnosis of clinical AF and commence risk stratification and treatment.	I	A
In patients with AF, it is recommended to: - Evaluate AF-related symptoms (including fatigue, tiredness, exertional shortness of breath, palpitations, and chest pain) and quantify the patient symptom status using the modified EHRA symptom scale before and after initiation of treatment. - Evaluate AF-related symptoms before and after cardioversion of persistent AF to aid rhythm control treatment decisions.	I	C	Evaluating the impact of AF-related symptoms is recommended before and after major changes in treatment to inform shared decision-making and guide treatment choices.	I	B
Section 5—[C] Comorbidity and risk factor management					
Attention to good BP control is recommended in AF patients with hypertension to reduce AF recurrences and risk of stroke and bleeding.	I	B	Blood pressure lowering treatment is recommended in patients with AF and hypertension to reduce recurrence and progression of AF and prevent adverse cardiovascular events.	I	B
In obese patients with AF, weight loss together with management of other risk factors should be considered to reduce AF incidence, AF progression, AF recurrences, and symptoms.	IIa	B	Weight loss is recommended as part of comprehensive risk factor management in overweight and obese individuals with AF to reduce symptoms and AF burden, with a target of 10% or more reduction in body weight.	I	B
Physical activity should be considered to help prevent AF incidence or recurrence, with the exception of excessive endurance exercise, which may promote AF.	IIa	C	A tailored exercise programme is recommended in individuals with paroxysmal or persistent AF to improve cardiorespiratory fitness and reduce AF recurrence.	I	B
Advice and management to avoid alcohol excess should be considered for AF prevention and in AF patients considered for OAC therapy.	IIa	B	Reducing alcohol consumption to ≤ 3 standard drinks (≤ 30 grams of alcohol) per week is recommended as part of comprehensive risk factor management to reduce AF recurrence.	I	B
Section 6.6—Surgical left atrial appendage occlusion					
Surgical occlusion or exclusion of the LAA may be considered for stroke prevention in patients with AF undergoing cardiac surgery.	IIb	C	Surgical closure of the left atrial appendage is recommended as an adjunct to oral anticoagulation in patients with AF undergoing cardiac surgery to prevent ischaemic stroke and thromboembolism.	I	B
Section 6.7—Bleeding risk					
For a formal risk-score-based assessment of bleeding risk, the HAS-BLED score should be considered to help address modifiable bleeding risk factors, and to identify patients at high risk of bleeding (HAS-BLED score ≥ 3) for early and more frequent clinical review and follow-up.	IIa	B	Assessment and management of modifiable bleeding risk factors is recommended in all patients eligible for oral anticoagulation, as part of shared decision-making to ensure safety and prevent bleeding.	I	B

Continued

Section 7.2—Rhythm control strategies in patients with AF					
AF catheter ablation for PVI should/may be considered as first-line rhythm control therapy to improve symptoms in selected patients with symptomatic: • Paroxysmal AF episodes.	Ila	B	Catheter ablation is recommended as a first-line option within a shared decision-making rhythm control strategy in patients with paroxysmal AF, to reduce symptoms, recurrence, and progression of AF.	I	A
Thoracoscopic procedures—including hybrid surgical ablation—should be considered in patients who have symptomatic paroxysmal or persistent AF refractory to AAD therapy and have failed percutaneous AF ablation, or with evident risk factors for catheter ablation failure, to maintain long-term sinus rhythm. The decision must be supported by an experienced team of electrophysiologists and surgeons.	Ila	B	Endoscopic and hybrid ablation procedures may be considered in patients with symptomatic paroxysmal AF refractory to AAD therapy and failed percutaneous catheter ablation strategy to prevent symptoms, recurrence, and progression of AF, within a shared decision-making rhythm control team of electrophysiologists and surgeons.	IIb	B
Thoracoscopic procedures—including hybrid surgical ablation—may be considered in patients with persistent AF with risk factors for recurrence, who remain symptomatic during AF despite at least one failed AAD and who prefer further rhythm control therapy.	IIb	C	Endoscopic and hybrid ablation procedures should be considered in patients with symptomatic persistent AF refractory to AAD therapy to prevent symptoms, recurrence, and progression of AF, within a shared decision-making rhythm control team of electrophysiologists and surgeons.	Ila	A
Concomitant AF ablation should be considered in patients undergoing cardiac surgery, balancing the benefits of freedom from atrial arrhythmias and the risk factors for recurrence (left atrial dilatation, years in AF, age, renal dysfunction, and other cardiovascular risk factors).	Ila	A	Concomitant surgical ablation is recommended in patients undergoing mitral valve surgery and AF suitable for a rhythm control strategy to prevent symptoms and recurrence of AF, with shared decision-making supported by an experienced team of electrophysiologists and arrhythmia surgeons.	I	A
Section 9.6—Post-operative AF					
Long-term OAC therapy to prevent thromboembolic events may be considered in patients at risk for stroke with post-operative AF after cardiac surgery, considering the anticipated net clinical benefit of OAC therapy and informed patient preferences.	IIb	B	Long-term oral anticoagulation should be considered in patients with post-operative AF after cardiac and non-cardiac surgery at elevated thromboembolic risk, to prevent ischaemic stroke and thromboembolism.	Ila	B

AAD, antiarrhythmic drugs; AF, atrial fibrillation; BP, blood pressure; ECG, electrocardiogram; EHRA, European Heart Rhythm Association; HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 years), Drugs/alcohol concomitantly; LAA, left atrial appendage; OAC, oral anticoagulant; PVI, pulmonary vein isolation; RR, relative risk.

^aClass of recommendation.

^bLevel of evidence.

3. Definitions and clinical impact

3.1. Definition and classification of AF

Atrial fibrillation is one of the most common heart rhythm disorders. A supraventricular arrhythmia with uncoordinated atrial activation, AF results in a loss of effective atrial contraction (see [Supplementary data online](#) for pathophysiology). AF is reflected on the surface electrocardiogram (ECG) by the absence of discernible and regular P waves, and irregular activation of the ventricles. This results in no specific pattern to RR intervals, in the absence of an atrio-ventricular block. The definition of AF by temporal pattern is presented in [Table 5](#). It should be noted that these categories reflect observed episodes of AF and do not suggest the underlying pathophysiological process. Some patients may progress consecutively through these categories, while others may need periodic reclassification due to their individual clinical status. Over time, some patients

with AF develop atrial and ventricular damage, which can make attempts at rhythm control futile. For this reason, or when patients and physicians make a joint decision for rate control, AF is classified as permanent (the most common ‘type’ of AF in historical registries).¹ Despite many limitations, this task force have retained this temporal approach because most trials in patients with AF have used these definitions. Classifying AF by underlying drivers could inform management, but the evidence in support of the clinical use of such classification is currently lacking.

Several other classifications have been applied to patients with AF, many of which have limited evidence to support them. The definition of AF is a developing field and ongoing research may allow for pathology-based strategies that could facilitate personalized management in the future. [Table 6](#) presents some commonly used concepts in current clinical practice. Due to the lack of supporting evidence (particularly for the time periods stated), this task force have edited and updated these definitions by consensus.

Table 5 Definitions and classifications for the temporal pattern of AF

Temporal classification	Definition
First-diagnosed AF	AF that has not been diagnosed before, regardless of symptom status, temporal pattern, or duration.
Paroxysmal AF	AF which terminates spontaneously within 7 days or with the assistance of an intervention. Evidence suggests that most self-terminating paroxysms last <48 h. ²
Persistent AF	AF episodes which are not self-terminating. Many intervention trials have used 7 days as a cut-off for defining persistent AF. ^{3,4} Long-standing persistent AF is arbitrarily defined as continuous AF of at least 12 months' duration but where rhythm control is still a treatment option in selected patients, distinguishing it from permanent AF.
Permanent AF	AF for which no further attempts at restoration of sinus rhythm are planned, after a shared decision between the patient and physician.

AF, atrial fibrillation.

Table 6 Other clinical concepts relevant to AF

Clinical concept	Definition
Clinical AF	Symptomatic or asymptomatic AF that is clearly documented by an ECG (12-lead ECG or other ECG devices). The minimum duration to establish the diagnosis of clinical AF for ambulatory ECG is not clear and depends on the clinical context. Periods of 30 s or more may indicate clinical concern, and trigger further monitoring or risk stratification for thromboembolism.
Device-detected subclinical AF	Device-detected subclinical AF refers to asymptomatic episodes of AF detected on continuous monitoring devices. These devices include implanted cardiac electronic devices, for which most atrial high-rate episodes ^a may be AF, as well as consumer-based wearable monitors. Confirmation is needed by a competent professional reviewing intracardiac electrograms or an ECG-recorded rhythm. ^{5,6} Device-detected subclinical AF is a predictor of future clinical AF. ⁷

Continued

AF burden	The overall time spent in AF during a clearly specified and reported period of monitoring, expressed as a percentage of time.
Recent-onset AF	There is accumulating data on the value of the term recent-onset AF in decision-making for acute pharmacological or electrical cardioversion of AF. The cut-off time interval to define this entity has not yet been established. ^{8–10}
Trigger-induced AF	New AF episode in close proximity to a precipitating and potentially reversible factor. ^{11–14}
Early AF	The time since diagnosis that qualifies for early AF is dissociated from any underlying atrial cardiomyopathy and is not well defined, broadly ranging from 3 to 24 months. ^{15–17} The definition of early AF also does not necessarily determine early timing of intervention.
Self-terminating AF	Paroxysmal AF which terminates spontaneously. ² This definition may be of value for decisions on acute rhythm control taken jointly by the patient and healthcare provider.
Non-self-terminating AF	Atrial fibrillation which does not terminate spontaneously and, if needed, termination can be achieved only with an intervention.
Atrial cardiomyopathy	A combination of structural, electrical, or functional changes in the atria that leads to clinical impact (e.g. progression/recurrence of AF, limited effectiveness of AF therapy, and/or development of heart failure). ^{18,19} Atrial cardiomyopathy includes inflammatory and prothrombotic remodelling of the atria, neurohormonal activation (thereby affecting the ventricles), and fibrosis of myocardial tissue. ²⁰

AF, atrial fibrillation; b.p.m., beats per minute; ECG, electrocardiogram.
^aAtrial high-rate episodes are defined as episodes generally lasting more than 5 min with an atrial lead rate ≥170 b.p.m.,^{7,21–24} detected by implanted cardiac devices that allow for automated continuous monitoring and storage of atrial rhythm. Atrial high-rate episodes need to be visually inspected because some may be electrical artefacts or false positives.

3.2. Diagnostic criteria for AF

In many patients, the diagnosis of AF is straightforward, e.g. typical symptoms associated with characteristic features on a standard 12-lead ECG that indicate the need for AF management. Diagnosis becomes more challenging in the context of asymptomatic episodes or AF detected on longer-term monitoring devices, particularly those that do

not provide an ECG (see [Section 10](#)). To guard against inappropriate diagnosis of AF, this task force continues to recommend that ECG documentation is required to initiate risk stratification and AF management. In current practice, ECG confirmation can include multiple options: not only where AF persists across a standard 12-lead ECG, but also single- and multiple-lead devices that provide an ECG (see [Supplementary data online, Additional Evidence Table S1](#)). This does not include non-ECG wearables and other devices that typically use photoplethysmography. Note that many pivotal AF trials required two or more ECGs documenting AF, or an established AF diagnosis before randomization.^{25–29} The time period of AF required for diagnosis on monitoring devices is not clear cut. A standard 12-lead ECG measures 10 s, while 30 s or more on single-lead or multiple-lead ECG devices has generally been the consensus opinion, albeit with limited evidence.

Recommendation Table 1 — Recommendations for the diagnosis of AF (see also Evidence Table 1)

Recommendations	Class ^a	Level ^b
Confirmation by an electrocardiogram (12-lead, multiple, or single leads) is recommended to establish the diagnosis of clinical AF and commence risk stratification and treatment. ^{25–29}	I	A

AF, atrial fibrillation.
^aClass of recommendation.
^bLevel of evidence.

3.3. Symptoms attributable to AF

Symptoms related to episodes of AF are variable and broad, and not just typical palpitations ([Figure 1](#)). Asymptomatic episodes of AF can occur,³⁰ although 90% of patients with AF describe symptoms with variable severity.³¹ Even in symptomatic patients, some episodes of AF may remain asymptomatic.^{32,33} The presence or absence of symptoms is not related to incident stroke, systemic embolism, or mortality.³⁴ However, symptoms do impact on patient quality of life.^{35,36} Cardiac-specific AF symptoms such as palpitations are less common than non-specific symptoms such as fatigue, but they significantly impair quality of life.^{36,37} Although women are often underrepresented in clinical trials of AF,^{38–40} the available literature suggests that women with AF appear to be more symptomatic and have poorer quality of life.^{41,42} Patients with AF report a higher burden of anxiety and severity of depression (odds ratio [OR], 1.08; 95% confidence interval [CI], 1.02–1.15; *P* = .009) as compared with the general population,^{43,44} with higher prevalence of these symptoms in women with AF.⁴⁵

Assessment of AF-related symptoms should be recorded initially, after a change in treatment, or before and after intervention. The modified European Heart Rhythm Association score (mEHRA) symptom classification ([Table 7](#)) is similar to the New York Heart Association (NYHA) functional class for heart failure. It correlates with quality of life scores in clinical trials, is associated with clinical progress and events, and may be a valuable starting point in routine practice to assess the burden and impact of symptoms together with the patient.^{46–48} Note that symptoms may also relate to associated comorbidities and not just the AF component. The

patient-related effects of symptoms from AF over time can alternatively be evaluated using patient-reported outcome measures (see [Section 8.4](#)).

Recommendation Table 2 — Recommendations for symptom evaluation in patients with AF (see also Evidence Table 2)

Recommendations	Class ^a	Level ^b
Evaluating the impact of AF-related symptoms is recommended before and after major changes in treatment to inform shared decision-making and guide treatment choices. ^{17,36,46–55}	I	B

AF, atrial fibrillation.
^aClass of recommendation.
^bLevel of evidence.

3.4. Diagnostic evaluation of new AF

All patients with AF should be offered a comprehensive diagnostic assessment and review of medical history to identify risk factors and/or comorbidities needing active treatment. [Table 8](#) displays the essential diagnostic work-up for a patient with AF.

A 12-lead ECG is warranted in all AF patients to confirm rhythm, determine ventricular rate, and look for signs of structural heart disease, conduction defects, or ischaemia.⁵⁶ Blood tests should be carried out (kidney function, serum electrolytes, liver function, full blood count, glucose/glycated haemoglobin [HbA1c], and thyroid tests) to detect any concomitant conditions that may exacerbate AF or increase the risk of bleeding and/or thromboembolism.^{57,58}

Other investigations will depend on individualized assessment and the planned treatment strategy.^{59–65} A transthoracic echocardiogram (TTE) should be carried out in the initial work-up, where this will guide management decisions, or in patients where there is a change in cardiovascular signs or symptoms. The task force recognizes that accessibility to TTE might be limited or delayed in the primary care setting, but this should not delay initiation of oral anticoagulation (OAC) or other components of AF-CARE where indicated.⁶⁶ Further details on TTE and re-assessment (e.g. if elevated heart rate limits diagnostic imaging, or where there is a change in clinical status) are presented in [Section 8.3](#). Additional imaging using different modalities may be required to assist with comorbidity and AF-related management (see [Supplementary data online, Figure S1](#)).

Recommendation Table 3 — Recommendations for diagnostic evaluation in patients with new AF (see also Evidence Table 3)

Recommendations	Class ^a	Level ^b
A transthoracic echocardiogram is recommended in patients with an AF diagnosis where this will guide treatment decisions. ^{59,65,67}	I	C

AF, atrial fibrillation.
^aClass of recommendation.
^bLevel of evidence.

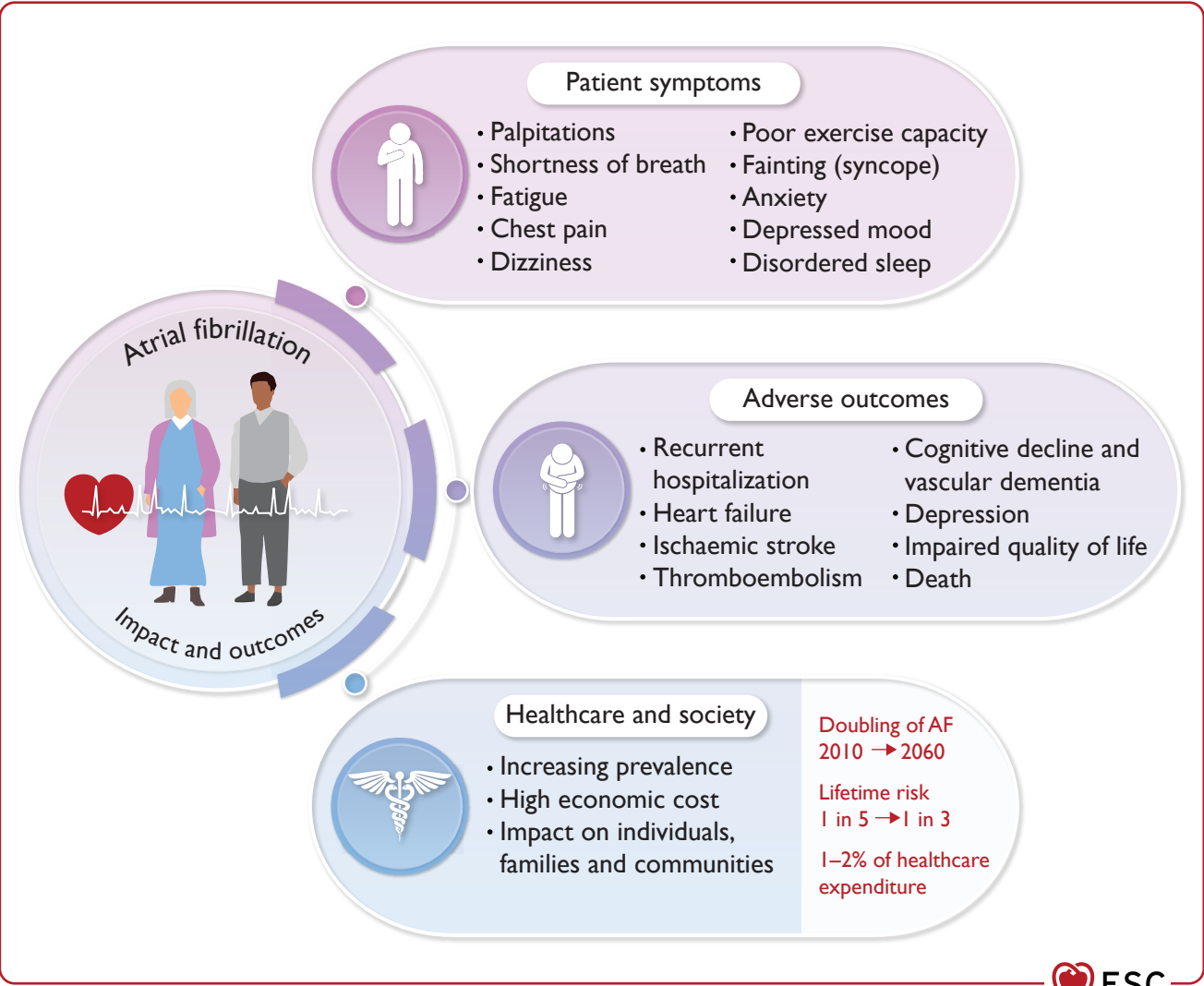


Figure 1 Impacts and outcomes associated with clinical AF. AF, atrial fibrillation.

Table 7 The modified European Heart Rhythm Association (mEHRA) symptom classification

Score	Symptoms	Description
1	None	AF does not cause any symptoms
2a	Mild	Normal daily activity not affected by symptoms related to AF
2b	Moderate	Normal daily activity not affected by symptoms related to AF, but patient troubled by symptoms
3	Severe	Normal daily activity affected by symptoms related to AF
4	Disabling	Normal daily activity discontinued

AF, atrial fibrillation.

3.5. Adverse events associated with AF

Atrial fibrillation is associated with a range of serious adverse events (Figure 1) (see [Supplementary data online, Additional Evidence Table S2](#)). Patients with AF also have high rates of hospitalization and complications from coexisting medical conditions. The most common non-fatal outcome in those with AF is heart failure, occurring in around half of patients over time. Patients with AF have a four- to five-fold increase in the relative risk (RR) of heart failure compared with those without AF, as demonstrated in two meta-analyses (RR, 4.62; 95% CI, 3.13–6.83 and RR, 4.99; 95% CI, 3.0–8.22).^{68,69} The next most common adverse impacts from AF are ischaemic stroke (RR, 2.3; 95% CI, 1.84–2.94), ischaemic heart disease (RR, 1.61; 95% CI, 1.38–1.87), and other thromboembolic events.^{69–71} The latter typically include arterial thromboembolic events (preferred to the term systemic), although venous thromboembolism is also associated

Table 8 Diagnostic work-up for patients with AF

All patients	Selected patients
• Medical history to determine AF pattern, relevant family history, and comorbidities, and to assess risk factors for thromboembolism and bleeding	• Ambulatory ECG monitoring for assessing AF burden and ventricular rate control • Exercise ECG to evaluate rate control or effects of class IC antiarrhythmic drugs
• 12-lead ECG	• Further blood tests for investigation of cardiovascular disease and refinement of stroke/bleeding risk (e.g. NT-proBNP, troponin)
• Assess symptoms and functional impairment	• Transoesophageal echocardiography for left atrial thrombus and valvular disease assessment
• Collect generic or AF-specific patient-reported outcome measures	• Coronary CT, angiography, or ischaemia imaging for suspected CAD
• Blood tests (full blood count, kidney function, serum electrolytes, liver function, glucose/HbA1c, and thyroid function)	• CMR for evaluation of atrial and ventricular cardiomyopathies, and to plan interventional procedures
• Transthoracic echocardiography where this will guide AF-CARE management decisions	• Brain imaging and cognitive function assessment for cerebrovascular disease and dementia risk

AF, atrial fibrillation; AF-CARE, atrial fibrillation—[C] Comorbidity and risk factor management, [A] Avoid stroke and thromboembolism, [R] Reduce symptoms by rate and rhythm control, [E] Evaluation and dynamic reassessment; CAD, coronary artery disease; CMR, cardiac magnetic resonance; CT, computed tomography; CTA, computed tomography angiography; ECG, electrocardiogram; HbA1c, glycated haemoglobin; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

with AF.^{72,73} Patients with AF also have an increased risk of cognitive impairment (adjusted hazard ratio [HR], 1.39; 95% CI, 1.25–1.53)⁷⁴ and dementia (OR, 1.6; 95% CI, 1.3–2.0).^{75–77} It should be noted that most of the observational studies on adverse events have a mix of patients taking and not taking OAC. When carefully controlling for the confounding effects of stroke, comorbidities, and OAC, AF exposure was still significantly associated with vascular dementia (HR, 1.68; 95% CI, 1.33–2.12; *P* < .001), but not Alzheimer’s disease (HR, 0.85; 95% CI, 0.70–1.03; *P* = .09).⁷⁸

Hospital admission rates due to AF vary widely depending on the population studied, and may be skewed by selection bias. In a Dutch RCT including first-diagnosed AF patients (mean age 64 years), cardiovascular hospitalization rates were 7.0% to 9.4% per year.⁷⁹ An Australian study identified 473 501 hospitalizations for AF during 15 years of follow-up (300 million person-years), with a relative increase in AF hospitalizations of 203% over the study period, in contrast to an increase for all hospitalizations of 71%. The age-specific incidence of hospital admission increased particularly in the older age groups.⁸⁰

Atrial fibrillation is also associated with increased mortality. In 2017, AF contributed to over 250 000 deaths globally, with an age-standardized mortality rate of 4.0 per 100 000 people (95% uncertainty interval 3.9–4.2).⁸¹ The most frequent cause of death in patients with AF is heart failure related,⁷⁰ with complex relationships to cardiovascular and non-cardiovascular disease.⁸² There is up to a two-fold increased risk of all-cause mortality (RR, 1.95; 95% CI, 1.50–2.54),⁶⁸ and cardiovascular mortality (RR, 2.03; 95% CI, 1.79–2.30)⁶⁹ in AF compared with sinus rhythm. Even in the absence of major thromboembolic risk factors, the incidence of death is 15.5 per 1000 person-years in those with AF exposure, compared with 9.4 per 1000 person-years without (adjusted HR, 1.44; 95% CI, 1.38–1.50; *P* < .001).⁷⁸ Patients with OAC-related bleeding have higher mortality, including both minor and major bleeding (as defined by the International Society on Thrombosis and Haemostasis scale).⁸³ Despite OAC, patients with AF remain at high residual risk of death, highlighting the importance of attention to concomitant disease.⁸⁴

3.6. Atrial flutter

Atrial flutter (AFL) is the among the most common atrial tachyarrhythmias, with an overall incidence rate of 88 per 100 000 person-years, rising to 317 per 100 000 person-years in people over 50 years of age.⁸⁵ Risk factors for AFL and AF are similar, and more than half of all patients with AFL will develop AF.⁸⁵ Observational studies suggest that thromboembolic risk is elevated in AFL.⁸⁶ In direct comparison of AFL with AF, some studies suggest a similar risk of stroke and others a lower risk in AFL,^{87–90} possibly due to different comorbidity burdens and the impact of confounders such as AFL/AF ablation and anticoagulation (more frequently stopped in AFL).⁹¹

4. Patient pathways and management of AF

4.1. Patient-centred, multidisciplinary AF management

4.1.1. The patient at the heart of care

A patient-centred and integrated approach to AF management means working with a model of care that respects the patient’s experience, values, needs, and preferences for planning, co-ordination, and delivery of care. A central component of this model is the therapeutic relationship between the patient and the multidisciplinary team of healthcare professionals (Figure 2). In patient-centred AF management, patients are seen not as passive recipients of health services, but as active participants who work as partners alongside healthcare professionals. Patient-centred AF management requires integration of all aspects of AF management. This includes symptom control, lifestyle recommendations, psychosocial support, and management of comorbidities, alongside optimal medical treatment consisting of pharmacotherapy, cardioversion, and interventional or surgical ablation (Table 9). Services should be designed to ensure that all patients have access to an organized model of AF management, including tertiary care specialist services when indicated (see Supplementary data online, Table S1, Evidence Table 4 and Additional Evidence Table S3). It is equally important to maintain pathways for patients to promptly re-engage with specialist services when their condition alters.

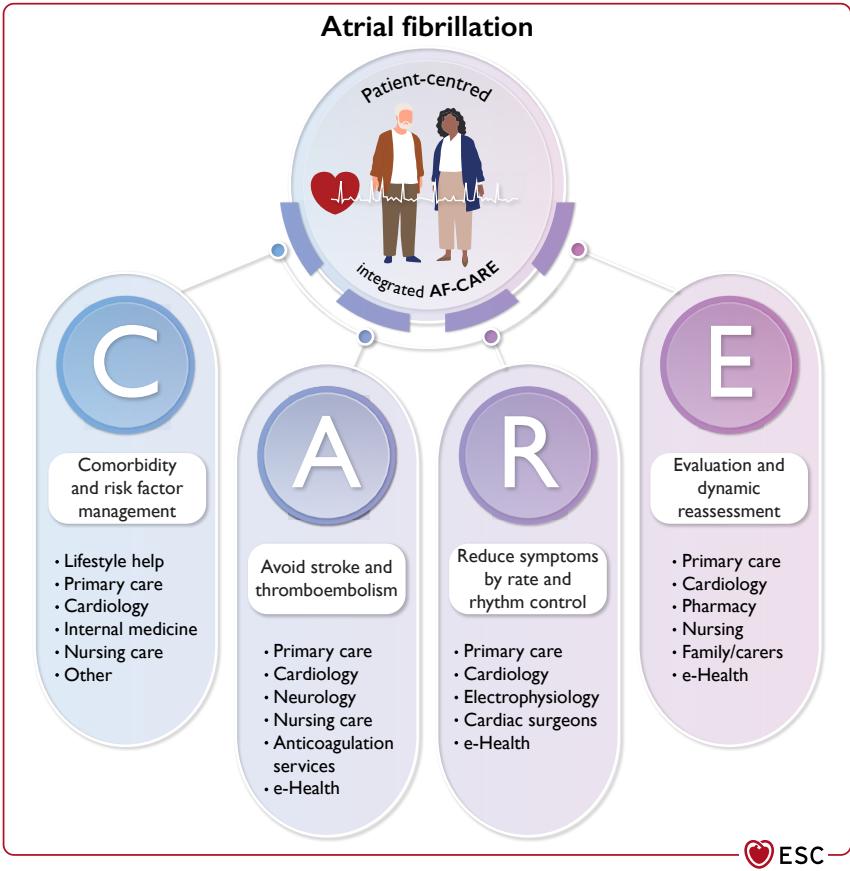


Figure 2 Multidisciplinary approach to AF management. Principal caregivers are involved in the community and hospital settings to provide optimal, patient-centred care for patients living with AF. AF-CARE, atrial fibrillation—[C] Comorbidity and risk factor management, [A] Avoid stroke and thromboembolism, [R] Reduce symptoms by rate and rhythm control, [E] Evaluation and dynamic reassessment.

Table 9 Achieving patient-centred AF management

Components of patient-centred AF management:
• Optimal treatment according to the AF-CARE pathway, which includes:
• [C] Comorbidity and risk factor management
• [A] Avoid stroke and thromboembolism
• [R] Reduce symptoms by rate and rhythm control
• [E] Evaluation and dynamic reassessment
• Lifestyle recommendations
• Psychosocial support
• Education and awareness for patients, family members, and caregivers
• Seamless co-ordination between primary care and specialized AF care
How to implement patient-centred AF management:
• Shared decision-making
• Multidisciplinary team approach
• Patient education and empowerment, with emphasis on self-care
• Structured educational programmes for healthcare professionals
• Technology support (e-Health, m-Health, telemedicine) ^a

AF, atrial fibrillation; AF-CARE, atrial fibrillation—[C] Comorbidity and risk factor management, [A] Avoid stroke and thromboembolism, [R] Reduce symptoms by rate and rhythm control, [E] Evaluation and dynamic reassessment.
^ae-Health refers to healthcare services provided using electronic methods; m-Health, refers to healthcare services supported by mobile devices; and telemedicine refers to remote diagnosis or treatment supported by telecommunications technology.

4.1.2. Education and shared decision-making

Clear advice about the rationale for treatments, the possibility of treatment modification, and shared decision-making can help patients live with AF (see [Supplementary data online, Table S2](#)).⁹² An open and effective relationship between the patient and the healthcare professional is critical, with shared decision-making found to improve outcomes for OAC and arrhythmia management.^{93,94} In using a shared approach, both the clinician and patient are involved in the decision-making process (to the extent that the patient prefers). Information is shared in both directions. Furthermore, both the clinician and the patient express their preferences and discuss the options. Of the potential treatment decisions, no treatment is also a possibility.⁹⁵ There are several toolkits available to facilitate this, although most are focused on anticoagulation decisions. For example, the Shared Decision-Making Toolkit (<http://afibguide.com>, <http://afibguide.com/clinician>) and the Successful Intravenous Cardioversion for Atrial Fibrillation (SIC-AF) score have been shown to reduce decisional conflict compared with usual care in patients with AF.^{93,94} Patient-support organizations can also make an important contribution to providing understandable and actionable knowledge about AF and its treatments (e.g. local support groups and international charities, such as <http://afa-international.org>). As AF is a chronic or recurrent disease in most patients, education is central to empower patients, their families, and caregivers.

4.1.3. Education of healthcare professionals

Gaps in knowledge and skills across all domains of AF care are consistently described among cardiologists, neurologists, internal medicine specialists, emergency physicians, general practitioners, nurses, and allied health practitioners.^{96–98} Healthcare professionals involved in multidisciplinary AF management should have a knowledge of all available options for diagnosis and treatment.^{99–101} In the STEER-AF trial,⁹⁹ real-world adherence to clinical practice guidelines for AF across six ESC countries was poor. These findings highlight the critical need for appropriate training and education of healthcare professionals.¹⁰²

Specifically targeted education for healthcare professionals can increase knowledge and lead to more appropriate use of OAC for prevention of thromboembolism.¹⁰³ However, educational interventions for healthcare providers are often not enough to sustainably impact behaviour.¹⁰⁴ Other tools may be needed, such as active feedback,¹⁰³ clinical decision support tools,¹⁰⁵ expert consultation,¹⁰⁶ or e-Health learning.¹⁰⁷

4.1.4. Inclusive management of AF

Evidence is growing on differences in AF incidence, prevalence, risk factors, comorbidities, and outcomes according to gender.¹⁰⁸ Women diagnosed with AF are generally older, have more hypertension and heart failure with preserved ejection fraction (HFpEF), and have less diagnosed coronary artery disease (CAD).¹⁰⁹ Registry studies have reported differences in outcomes, with higher morbidity and mortality in women, although these may be confounded by age and comorbidity burden.^{110–112} Women with AF may be more symptomatic, and report a lower quality of life.^{41,113} It is unclear whether this is related to delayed medical assessment in women, or whether there are genuine sex differences. Despite a higher symptom load, women are less likely to undergo AF ablation than men, even though antiarrhythmic drug therapy seems to be associated with more proarrhythmic events in women.¹⁰⁹ These observations call for more research on gender differences in order to prevent disparities and inequality in care. Other diversity aspects such as age, race, ethnicity, and transgender issues, as well as social determinants (including socioeconomic status, disability, education level, health literacy, and rural/urban location) are important contributors to inequality that should be actively considered to improve patient outcomes.¹¹⁴

4.2. Principles of AF-CARE

The 2024 ESC Guidelines for the management of AF have compiled and evolved past approaches to create principles of management to aid implementation of these guidelines, and hence improve patient care and outcomes. There is growing evidence that clinical support tools^{115–118} can aid best-practice management, with the caveat that any tool is a guide only, and that all patients require personalized attention. The AF-CARE approach covers many established principles in the management of AF, but does so in a systematic, time-orientated format with four essential treatment pillars (Figure 3; central illustration). Joint management with each patient forms the starting point of the AF-CARE approach. Notably, it takes account of the growing evidence base that therapies for AF are most effective when associated health conditions are addressed. A careful search for these comorbidities and risk factors [C] is critical and should be applied in all patients with a diagnosis of AF. Avoidance of stroke and thromboembolism [A] in patients with risk

factors is considered next, focused on appropriate use of anticoagulant therapy. Reducing AF-related symptoms and morbidity by effective use of heart rate and rhythm control [R] is then applied, which in selected patients may also reduce hospitalization or improve prognosis. The potential benefit of rhythm control, accompanied by consideration of all risks involved, should be considered in all patients at each contact point with healthcare professionals. As AF, and its related comorbidities, changes over time, different levels of evaluation [E] and re-evaluation are required in each patient, and these approaches should be dynamic. Due to the wide variability in response to therapy, and the changing pathophysiology of AF as age and comorbidities advance, reassessment should be built into the standard care pathway to prevent adverse outcomes for patients and improve population health.

AF-CARE builds upon prior ESC Guidelines, e.g. the five-step outcome-focused integrated approach in the 2016 ESC Guidelines for the management of AF,¹¹⁹ and the AF Better Care (ABC) pathway in the 2020 ESC Guidelines for the diagnosis and management of AF.¹²⁰ The reorganization into AF-CARE was based on the parallel developments in new approaches and technologies (in particular for rhythm control), with new evidence consistently suggesting that all aspects of AF management are more effective when comorbidities and risk factors have been considered. This includes management relating to symptom benefit, improving prognosis, prevention of thromboembolism, and the response to rate and rhythm control strategies. AF-CARE makes explicit the need for individualized evaluation and follow-up in every patient, with an active approach that accounts for how patients, their AF, and associated comorbidities change over time. The AF-CARE principles have been applied to different patient pathways for ease of implementation into routine clinical care. This includes the management of first-diagnosed AF (Figure 4), paroxysmal AF (Figure 5), persistent AF (Figure 6), and permanent AF (Figure 7).

Recommendation Table 4 — Recommendations for patient-centred care and education (see also Evidence Table 4)

Recommendation	Class ^a	Level ^b
Education directed to patients, family members, caregivers, and healthcare professionals is recommended to optimize shared decision-making, facilitating open discussion of both the benefit and risk associated with each treatment option. ^{94,103}	I	C
Access to patient-centred management according to the AF-CARE principles is recommended in all patients with AF, regardless of gender, ethnicity, and socioeconomic status, to ensure equality in healthcare provision and improve outcomes.	I	C
Patient-centred AF management with a multidisciplinary approach should be considered in all patients with AF to optimize management and improve outcomes. ^{79,121–124}	Ila	B

AF, atrial fibrillation; AF-CARE, Atrial fibrillation—[C] Comorbidity and risk factor management, [A] Avoid stroke and thromboembolism, [R] Reduce symptoms by rate and rhythm control, [E] Evaluation and dynamic reassessment.

^aClass of recommendation.

^bLevel of evidence.

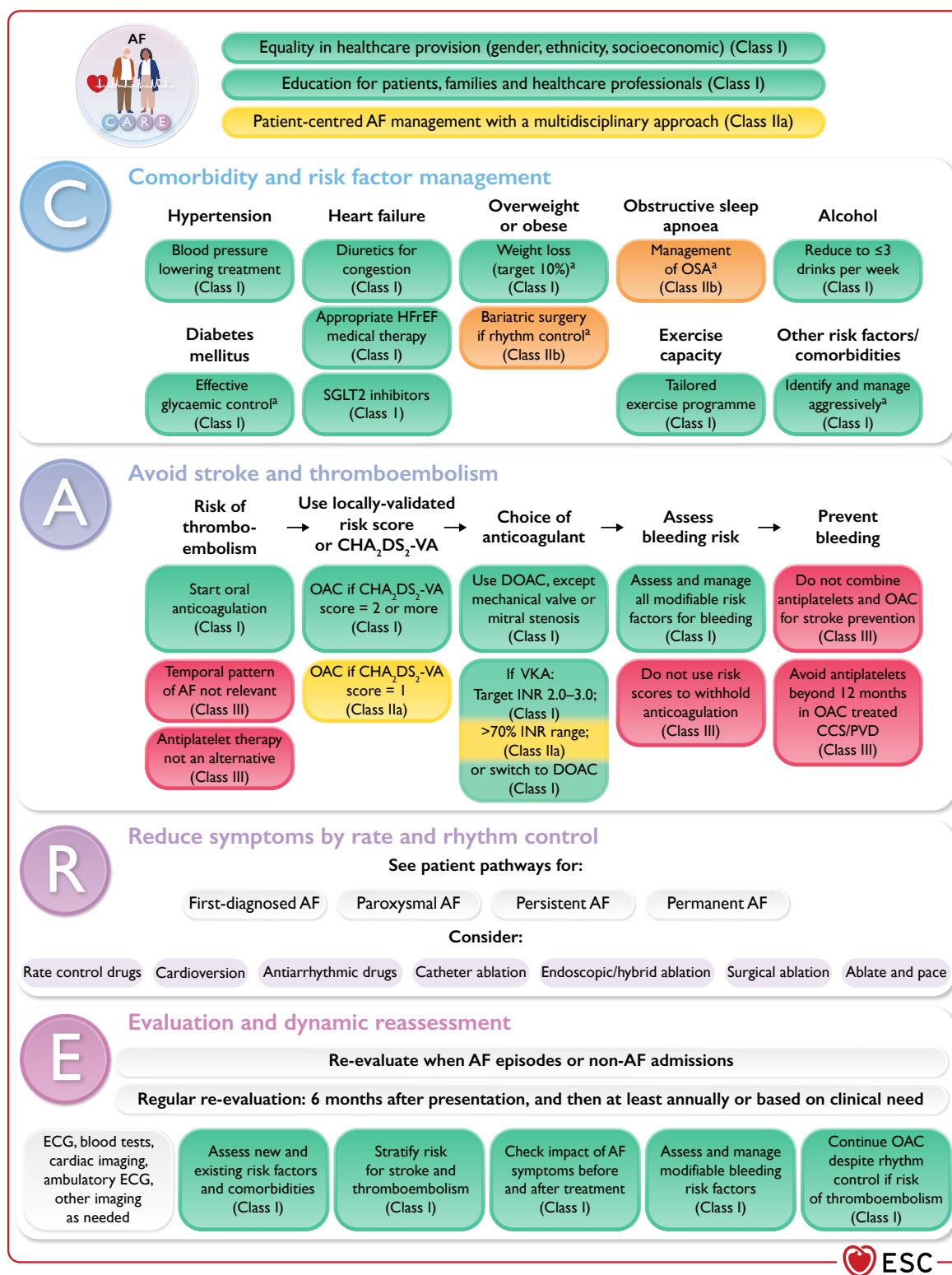


Figure 3 Central illustration. Patient pathway for AF-CARE (see [Figures 4, 5, 6, and 7](#) for the [R] pathways for first-diagnosed, paroxysmal, persistent and permanent AF). AF, atrial fibrillation; AF-CARE, atrial fibrillation—[C] Comorbidity and risk factor management, [A] Avoid stroke and thromboembolism, [R] Reduce symptoms by rate and rhythm control, [E] Evaluation and dynamic reassessment; CCS, chronic coronary syndrome; CHA₂DS₂-VA, congestive heart failure, hypertension, age ≥75 years (2 points), diabetes mellitus, prior stroke/transient ischaemic attack/arterial thromboembolism (2 points), vascular disease, age 65–74 years; DOAC, direct oral anticoagulant; ECG, electrocardiogram; HFrEF, heart failure with reduced ejection fraction; INR, international normalized ratio of prothrombin time; OAC, oral anticoagulant; OSA, obstructive sleep apnoea; PVD, peripheral vascular disease; SGLT2, sodium-glucose cotransporter-2; VKA, vitamin K antagonist. ^aAs part of a comprehensive management of cardiometabolic risk factors.

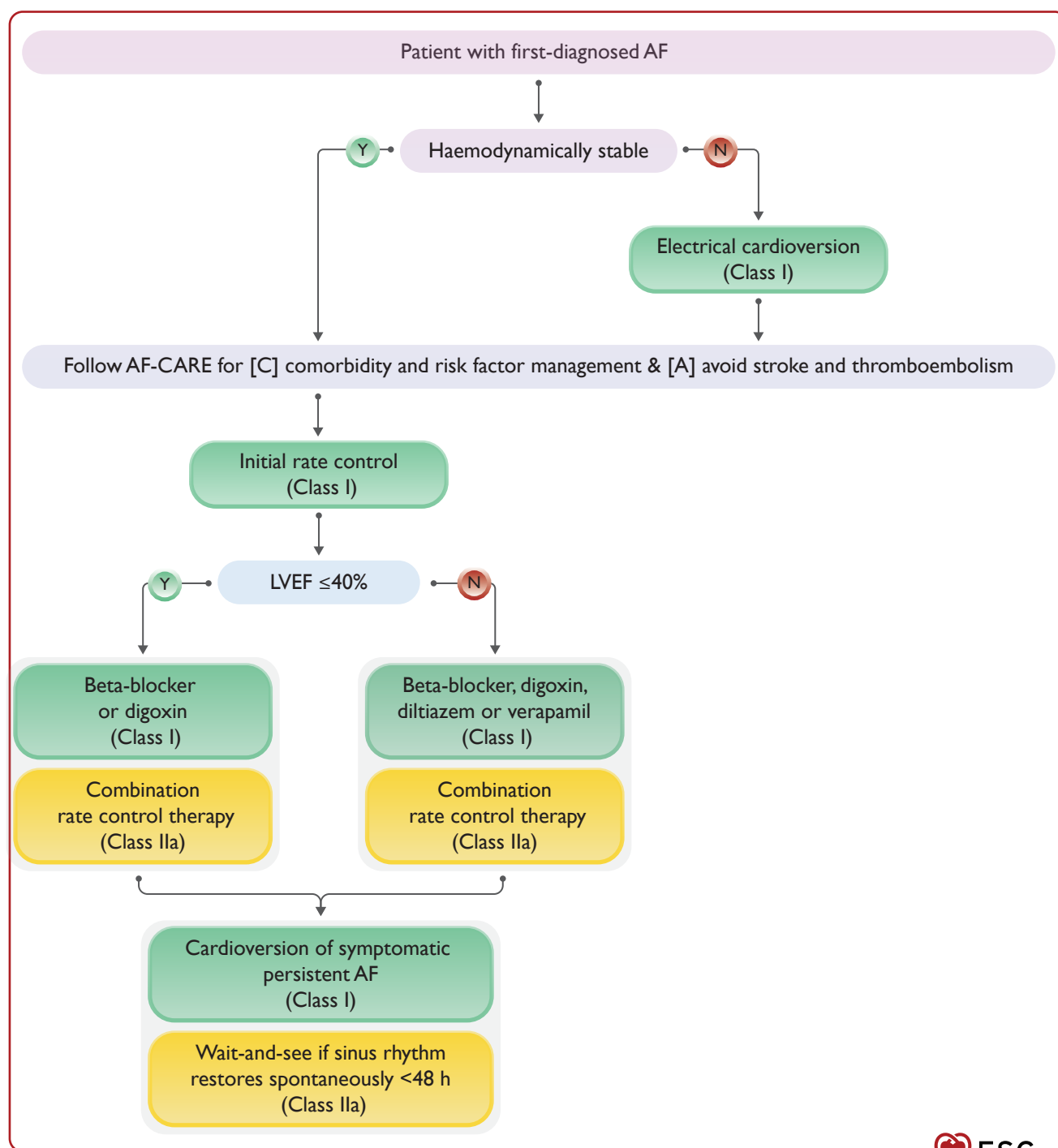


Figure 4 [R] Pathway for patients with first-diagnosed AF. AF, atrial fibrillation; AF-CARE, Atrial fibrillation—[C] Comorbidity and risk factor management, [A] Avoid stroke and thromboembolism, [R] Reduce symptoms by rate and rhythm control, [E] Evaluation and dynamic reassessment; LVEF, left ventricular ejection fraction. After following the pathway for first-diagnosed AF, patients with recurrent AF should enter the AF-CARE [R] pathway for paroxysmal, persistent, or permanent AF, depending on the type of their AF.

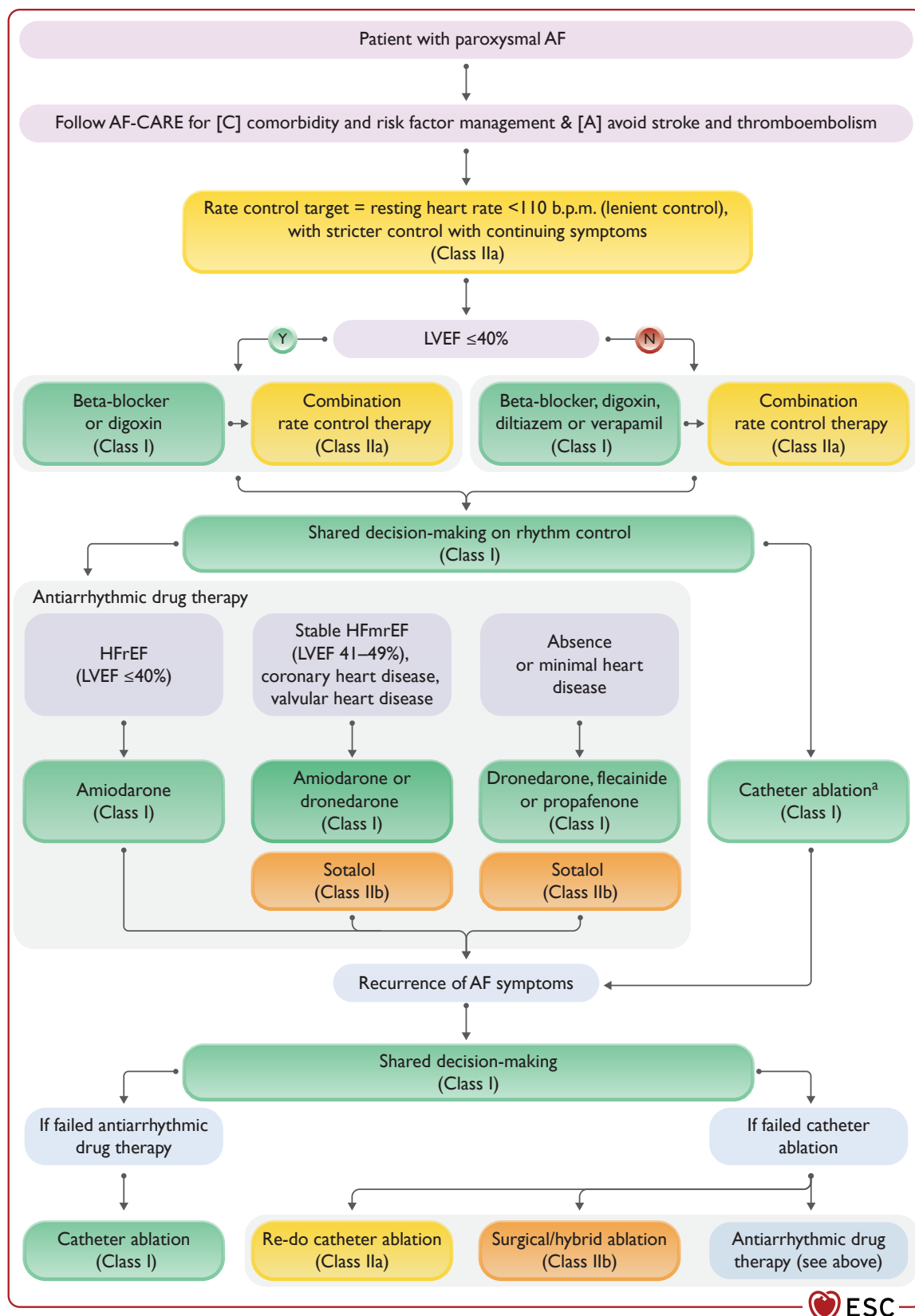


Figure 5 [R] Pathway for patients with paroxysmal AF. AF, atrial fibrillation; AF-CARE, atrial fibrillation—[C] Comorbidity and risk factor management, [A] Avoid stroke and thromboembolism, [R] Reduce symptoms by rate and rhythm control, [E] Evaluation and dynamic reassessment; b.p.m., beats per minute; HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF, Heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction. ^aIn patients with HFrEF: Class I if high probability of tachycardia-induced cardiomyopathy; and Class IIa in selected patients to improve prognosis.

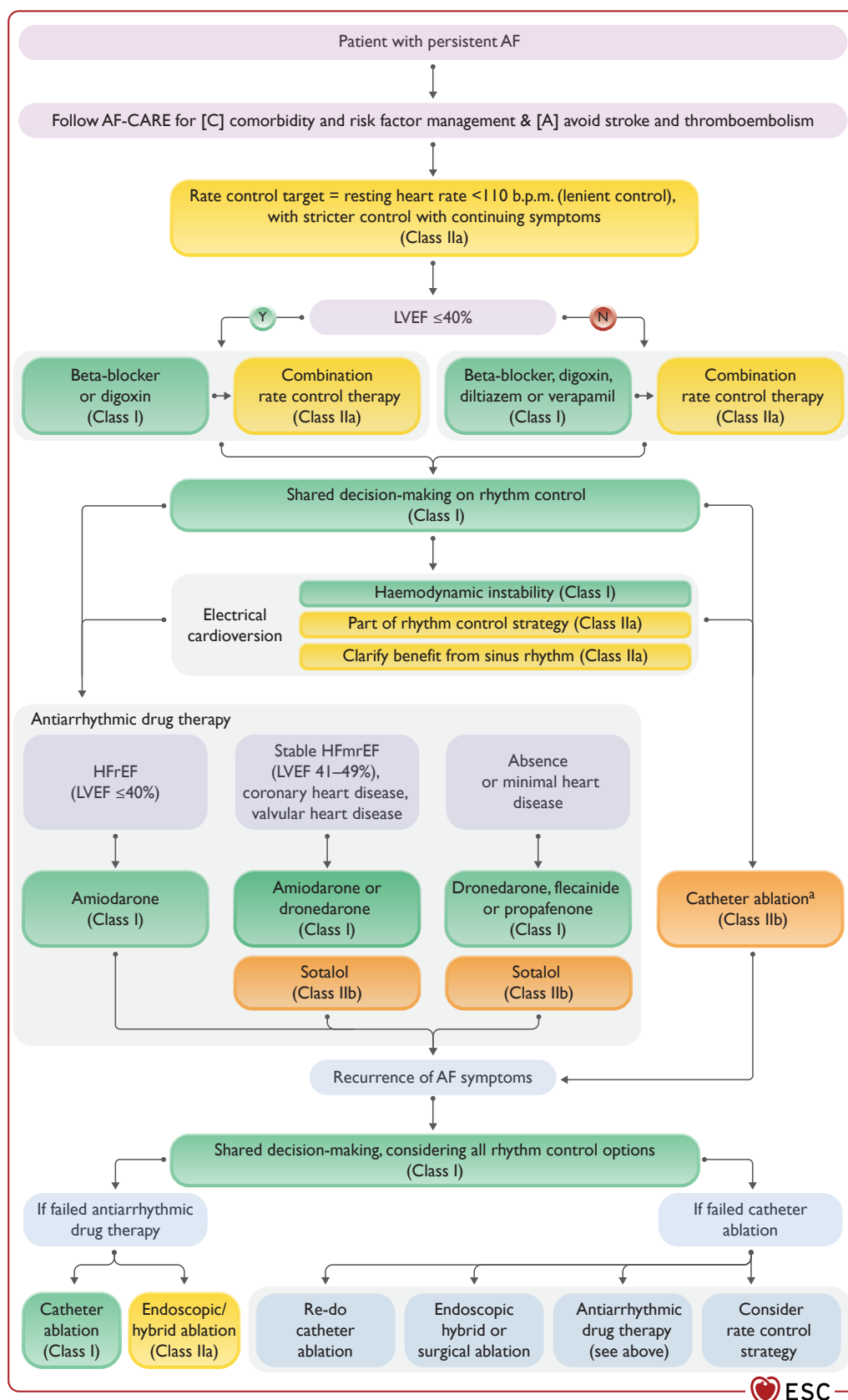


Figure 6 [R] Pathway for patients with persistent AF. AF, atrial fibrillation; AF-CARE, Atrial fibrillation—[C] Comorbidity and risk factor management, [A] Avoid stroke and thromboembolism, [R] Reduce symptoms by rate and rhythm control, [E] Evaluation and dynamic reassessment; b.p.m., beats per minute; HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction. ^aIn patients with HFrEF: Class I if high probability of tachycardia-induced cardiomyopathy; and Class IIa in selected patients to improve prognosis.

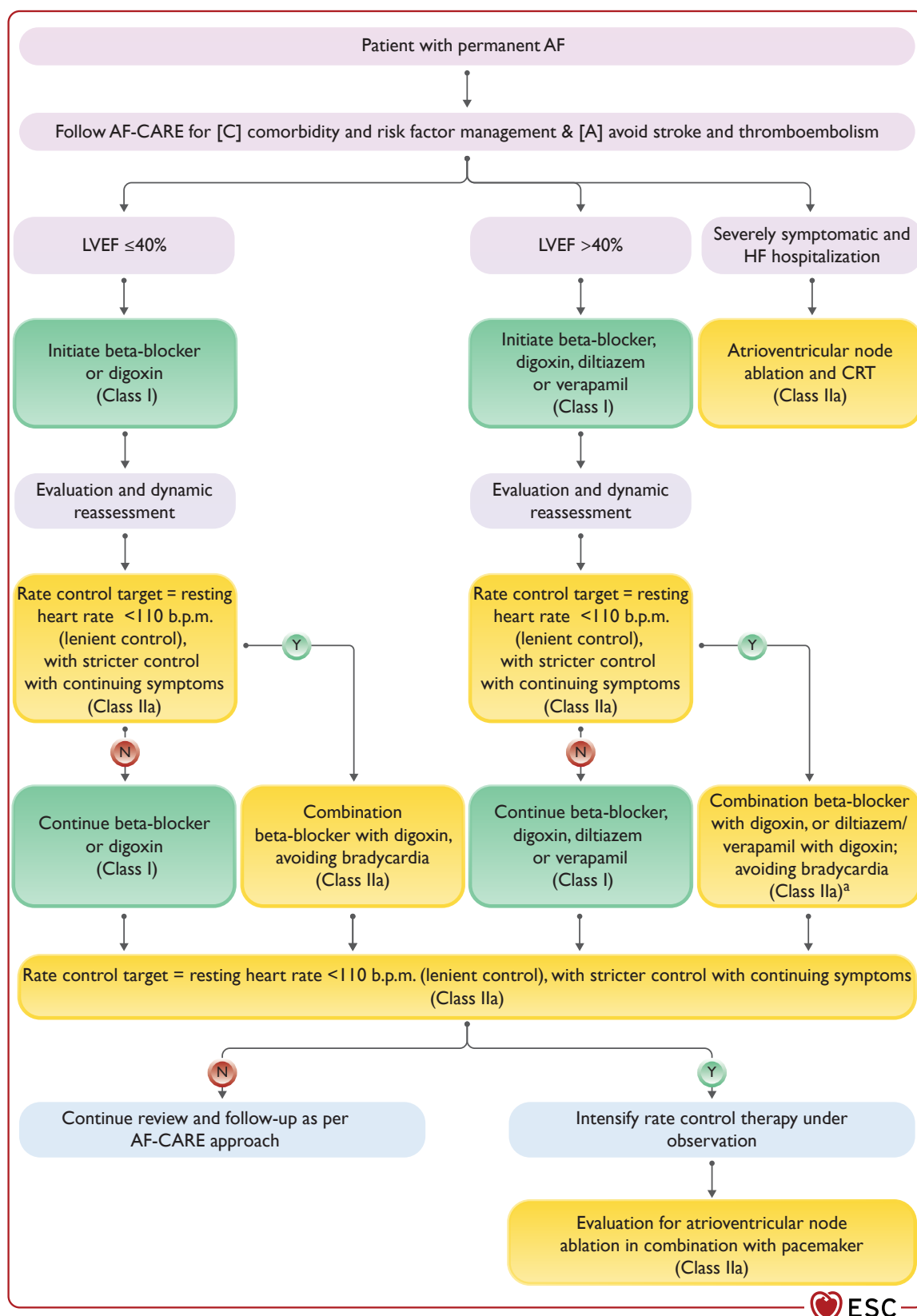


Figure 7 [R] Pathway for patients with permanent AF. AF, atrial fibrillation; AF-CARE, Atrial fibrillation—[C] Comorbidity and risk factor management, [A] Avoid stroke and thromboembolism, [R] Reduce symptoms by rate and rhythm control, [E] Evaluation and dynamic reassessment; b.p.m., beats per minute; CRT, cardiac resynchronization therapy; HF, heart failure; LVEF, left ventricular ejection fraction. Permanent AF is a shared decision made between the patient and physician that no further attempts at restoration of sinus rhythm are planned. ^aNote that the combination of beta-blockers with diltiazem or verapamil should only be used under specialist advice, and monitored with an ambulatory ECG to check for bradycardia.

5. [C] Comorbidity and risk factor management

A broad array of comorbidities are associated with the recurrence and progression of AF. Managing comorbidities is also central to the success of other aspects of care for patients with AF, with evidence available for hypertension, heart failure, diabetes mellitus, obesity, and sleep apnoea, along with lifestyle changes that improve physical

activity and reduce alcohol intake (see [Supplementary data online, Additional Evidence Table S4](#)). Identification and treatment of these comorbidities and clusters of risk factors form an important part of effective AF-CARE ([Figure 8](#)), with the evidence outlined in the rest of this section highlighting where management can improve patient outcomes or prevent AF recurrence. Many of these factors (and more) are also associated with incident AF (see [Section 10](#)).

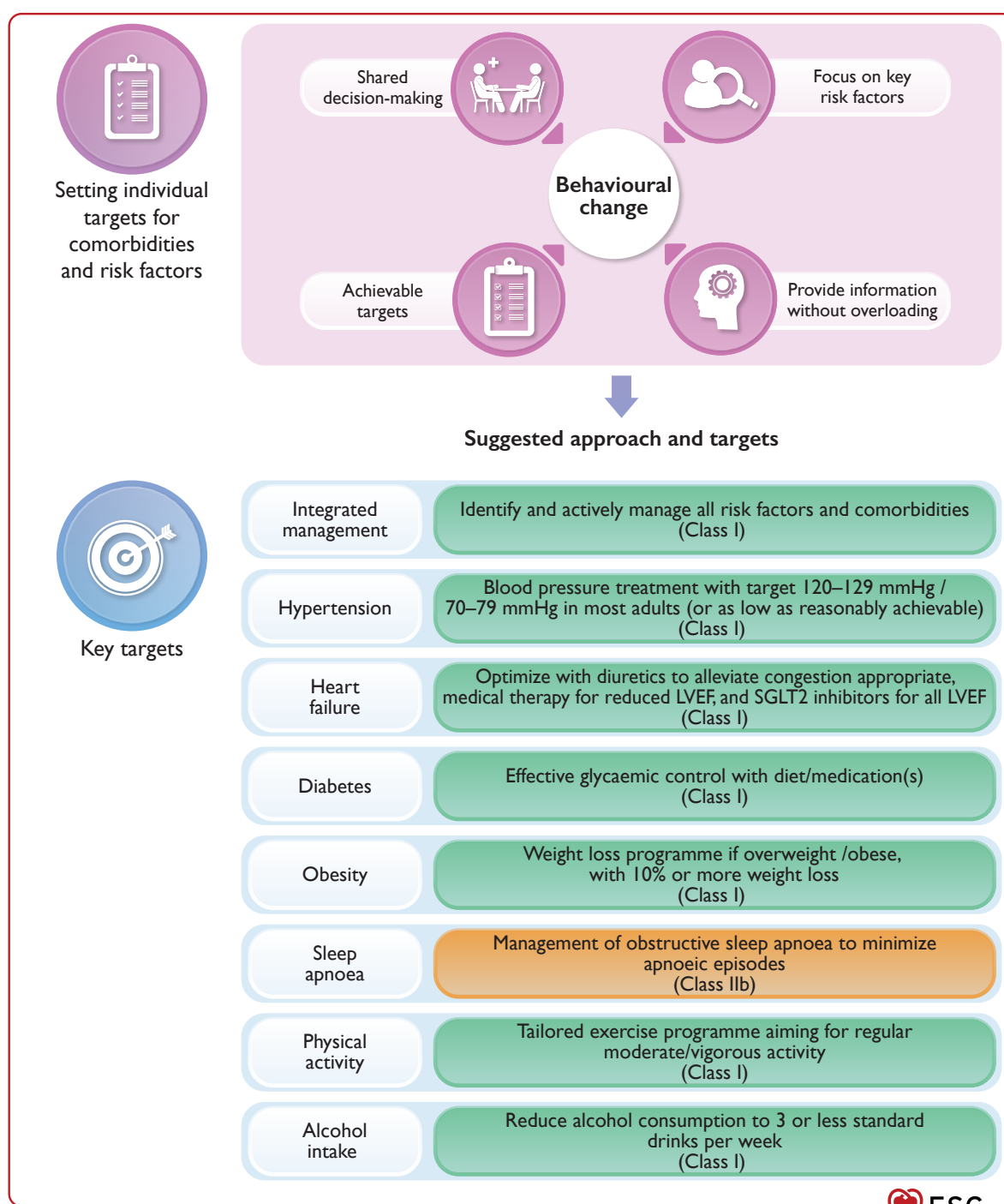


Figure 8 Management of key comorbidities to reduce AF recurrence. LVEF, left ventricular ejection fraction; SGLT2, sodium-glucose cotransporter-2.

Recommendation Table 5 — Recommendations for comorbidity and risk factor management in AF (see also Evidence Table 5)

Recommendation	Class ^a	Level ^b
Identification and management of risk factors and comorbidities is recommended as an integral part of AF care. ^{39,125–127}	I	B
Blood pressure lowering treatment is recommended in patients with AF and hypertension to reduce recurrence and progression of AF and prevent adverse cardiovascular events. ^{126–130}	I	B
Diuretics are recommended in patients with AF, HF, and congestion to alleviate symptoms and facilitate better AF management.	I	C
Appropriate medical therapy for HF is recommended in AF patients with HF and impaired LVEF to reduce symptoms and/or HF hospitalization and prevent AF recurrence. ^{131–137}	I	B
Sodium-glucose cotransporter-2 inhibitors are recommended for patients with HF and AF regardless of left ventricular ejection fraction to reduce the risk of HF hospitalization and cardiovascular death. ^{136,138–140}	I	A
Effective glycaemic control is recommended as part of comprehensive risk factor management in individuals with diabetes mellitus and AF, to reduce burden, recurrence, and progression of AF.	I	C
Weight loss is recommended as part of comprehensive risk factor management in overweight and obese individuals with AF to reduce symptoms and AF burden, with a target of 10% or more reduction in body weight. ^{125–128}	I	B
A tailored exercise programme is recommended in individuals with paroxysmal or persistent AF to improve cardiorespiratory fitness and reduce AF recurrence. ^{141–146}	I	B
Reducing alcohol consumption to ≤3 standard drinks (≤30 grams of alcohol) per week is recommended as part of comprehensive risk factor management to reduce AF recurrence. ^{126,127,147}	I	B
Bariatric surgery may be considered in conjunction with lifestyle changes and medical management in individuals with AF and body mass index ≥40 kg/m ² ^c where a rhythm control strategy is planned, to reduce recurrence and progression of AF.	IIb	C
Management of obstructive sleep apnoea may be considered as part of a comprehensive management of risk factors in individuals with AF to reduce recurrence and progression. ^{126–128,148–154}	IIb	B
When screening for obstructive sleep apnoea in individuals with AF, using only symptom-based questionnaires is not recommended. ^{155–157}	III	B

AF, atrial fibrillation; HF, heart failure; LVEF, left ventricular ejection fraction.

^aClass of recommendation.

^bLevel of evidence.

^cOr body mass index ≥35 kg/m² with obesity-related complications.

5.1. Hypertension

Hypertension in patients with AF is associated with an increased risk of stroke, heart failure, major bleeding, and cardiovascular mortality.^{158–161}

The target for treated systolic blood pressure (BP) in most adults is 120–129 mmHg. Where BP-lowering treatment is poorly tolerated, clinically significant frailty exists or the patient's age is 85 years or older, a more lenient target of <140 mmHg is acceptable or 'as low as reasonably achievable'. On-treatment diastolic BP should ideally be 70–79 mmHg.¹⁶² In an individual participant data meta-analysis of 22 randomized trials reporting baseline AF, a 5 mmHg reduction in systolic BP reduced the risk of major cardiovascular events by 9% (HR, 0.91; 95% CI, 0.83–1.00), with identical effect in patients with AF or sinus rhythm.¹²⁹

In individuals with AF, hypertension often coexists with other modifiable and non-modifiable risk factors that all contribute to recurrence of AF, readmission to hospital, and ongoing symptoms after rhythm control.^{163–171} Optimal control of blood pressure should be considered an essential component of treating AF and undertaken within a strategy of comprehensive risk factor management.^{126–128} Although the majority of research has focused on clinical outcomes, limited comparative data on hypertension medication suggests that use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) may be superior for prevention of recurrent AF.^{172–175}

5.2. Heart failure

Heart failure is a key determinant of prognosis in patients with AF, as well as an important factor associated with recurrence and progression of AF.^{176,177} During 30 years of follow-up in the Framingham cohort, 57% of those with new heart failure had concomitant AF, and 37% of those with new AF had heart failure.¹⁷⁸ Numerous cardiovascular and non-cardiovascular conditions impact the development of both AF and heart failure, leading to the common pathway of atrial cardiomyopathy.¹⁸ In patients with acute heart failure attending the emergency department, AF is one of the most prevalent triggering factors of the episode.¹⁷⁹ The development of heart failure in patients with AF is associated with a two-fold increase in stroke and thromboembolism,¹⁸⁰ even after anticoagulation,¹⁸¹ and 25% higher all-cause mortality.¹⁷⁸ Prognosis may be affected by left ventricular ejection fraction (LVEF), with the rate of death highest with the combination of AF and heart failure with reduced ejection fraction (HFrEF) (LVEF ≤ 40%), as compared with AF and HFpEF (LVEF ≥ 50%). However, rates of stroke and incident heart failure hospitalization are similar regardless of LVEF.¹⁸² Due to how common concomitant AF and heart failure are in clinical practice, strategies to improve outcomes in these patients are detailed within each component of the AF-CARE pathway. However, it is also critical that heart failure itself is managed appropriately in patients with AF to prevent avoidable adverse events.

Optimization of heart failure management should follow current ESC Guidelines: 2023 Focused Update¹⁸³ of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure.¹³⁷ Achieving euvoalaemia with diuretics is an important first step that not only manages the heart failure component, but can also facilitate better control of heart rate in AF. For HFrEF, it should be highlighted that many older guideline-recommended therapies lack specific evidence for benefit in patients with coexisting AF. No trial data are available in this context for ACE inhibitors, there are conflicting data on ARBs,^{132,184} and an individual patient-level analysis of RCTs found no

difference between beta-blockers and placebo for all-cause mortality in HFrEF with AF.¹³³ However, these drugs have clear proof of safety and there may be other indications for these therapies beyond prognosis, including comorbidity management and symptom improvement. These and other therapies may also have dual functions, for example, beta-blockers or digoxin for rate control of AF, in addition to improving heart failure metrics and reducing hospitalization.^{48,185,186} More recent additions to HFrEF management, such as eplerenone, sacubitril-valsartan, and sodium-glucose cotransporter-2 (SGLT2) inhibitors, had substantial numbers of patients with AF enrolled in RCTs, with no evidence that AF status affected their ability to reduce cardiovascular mortality/heart failure hospitalization.^{134–136} Cardiac resynchronization therapy (CRT) in the context of HFrEF and AF is discussed in detail in the 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy, with an important focus on ensuring effective biventricular pacing (with a low threshold for considering atrioventricular node ablation).¹⁸⁷ Patients who have heart failure with mildly reduced ejection fraction (HFmrEF) (LVEF 41%–49%) and AF should generally be treated according to guidance for HFrEF,¹³⁷ albeit with limited evidence to date in AF.^{188–190} For treatment of HFpEF and AF,¹⁹¹ pre-specified subgroup data on AF from multiple large trials show that the SGLT2 inhibitors dapagliflozin, empagliflozin, and sotagliflozin are effective in improving prognosis.^{138–140}

Appropriate management of heart failure has the potential to reduce recurrence of AF, e.g. by reducing adverse atrial and ventricular myocardial remodelling, but there are limited data for specific therapies. In the Routine versus Aggressive upstream rhythm Control for prevention of Early AF in heart failure (RACE 3) trial, combined management of mild-to-moderate heart failure with ACE inhibitors/ARBs, mineralocorticoid receptor antagonists, statins, and cardiac rehabilitation increased the maintenance of sinus rhythm on ambulatory monitoring at 12 months.³⁹ This benefit was not preserved at the 5 year follow-up, although this may have been confounded by the lack of ongoing intervention beyond the initial 12 months.¹⁹²

5.3. Type 2 diabetes mellitus

Diabetes mellitus is present in around 25% of patients with AF.^{193–195} Patients with both diabetes and AF have a worse prognosis,¹⁹⁶ with increased healthcare utilization and excess mortality and cardiovascular events. The prevalence and incidence of AF and type 2 diabetes are widely increasing, thus making the association of these two conditions a public health challenge.^{195,197} Moreover, diabetes is a major factor influencing thromboembolic risk.^{198,199} Following catheter ablation of AF, diabetes and higher HbA1c are associated with increased length of stay and a greater recurrence of AF.^{200–203}

In cohort studies, the management of diabetes mellitus as part of comprehensive risk factor management has been associated with reduced AF symptoms, burden, reversal of the type of AF (from persistent to paroxysmal or no AF), and improved maintenance of sinus rhythm.^{126–128} However, robust evidence is limited, and individual glucose-lowering medications have had variable effects on AF.^{204–206} There are emerging data of the use of SGLT2 and glucagon-like peptide-1 antagonists in patients with diabetes and AF that may impact on treatment choice in the near future. Importantly, diabetes frequently coexists with multiple risk factors in patients with AF, and a comprehensive approach to management is required. Further details are

provided in the 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes.²⁰⁷

5.4. Obesity

Obesity frequently coexists with other risk factors that have been independently associated with the development of AF.^{208,209} Obesity (body mass index [BMI] ≥ 30 kg/m²) and being overweight (BMI >25 kg/m²) are associated with a greater risk of recurrent atrial arrhythmias after AF ablation (13% increase for every 5 kg/m² higher BMI).^{210–212} In the setting of comprehensive risk factor management, weight loss of $\geq 10\%$ in overweight and obese individuals with AF has been associated with reduced AF symptoms and AF burden in an RCT (aiming for BMI <27 kg/m²).¹²⁵ Cohort studies have also shown a graded response to maintenance of sinus rhythm,¹²⁶ improved ablation outcomes,¹²⁸ and reversal of the type of AF¹²⁷ commensurate with the degree of weight loss and risk factor management. However, in the Supervised Obesity Reduction Trial for AF Ablation Patients (SORT-AF) randomized trial in AF ablation patients, a sole weight loss intervention that achieved 4% loss in weight over 12 months did not impact ablation outcomes.²¹³ This is consistent with the findings in LEGACY (Long-Term Effect of Goal directed weight management on Atrial Fibrillation Cohort: a 5 Year follow-up study) that showed that weight loss of $\leq 3\%$ had no impact on AF recurrence.¹²⁶ Observational studies have raised the possibility of a point of no return in terms of the benefit of weight loss,²¹⁴ but also the possibility that bariatric surgery can improve symptoms and reduce AF recurrence.^{215–217}

5.5. Obstructive sleep apnoea

Obstructive sleep apnoea (OSA) is a highly prevalent condition, particularly in patients with AF.^{157,218} Optimal screening tools in the AF population are still under evaluation, although it may be reasonable to screen for OSA in patients where a rhythm control strategy is being pursued. Polysomnography or home sleep apnoea testing are suggested in preference to screening questionnaires.^{155–157,219} Questionnaires assessing daytime sleepiness are poor predictors of moderate-to-severe OSA.¹⁵⁵ Which parameter should be used to focus on risk of AF in patients with OSA, and to guide OSA treatment in patients with AF, is still unclear.^{220,221}

Observational studies have suggested that individuals with OSA not treated with continuous positive airway pressure (CPAP) respond poorly to treatments for AF, with an increased risk of recurrence after cardioversion or ablation.²²² Conversely, OSA patients treated with CPAP seem to mitigate their propensity toward developing AF.^{148–153,222–224} A small randomized trial of CPAP vs. no therapy demonstrated reversal of atrial remodelling in individuals with moderate OSA.¹⁵⁴ However, other small RCTs have failed to show a benefit of CPAP therapy on ablation outcomes²²⁵ or post-cardioversion.²²⁶ Data on the cardiovascular mortality benefit of CPAP therapy in OSA are inconclusive.^{227–230}

5.6. Physical inactivity

Reduced cardiorespiratory fitness frequently coexists with other modifiable risk factors and has been associated with a greater recurrence of AF after catheter ablation.¹⁴¹ Better cardiorespiratory fitness has a demonstrated inverse relationship to AF burden in both middle-aged and elderly people.¹⁴¹ Small RCTs, meta-analyses, and observational

cohorts have shown that regular aerobic exercise may also improve AF-related symptoms, quality of life, and exercise capacity.^{142,143} Better cardiorespiratory fitness and a gain in cardiorespiratory fitness over time are associated with a greater reduction in AF burden and improved maintenance of sinus rhythm.^{141–145}

5.7. Alcohol excess

Alcohol consumption can increase the risk of adverse events in patients with AF, such as thromboembolism, death, or AF-related hospitalization.^{231,232} Alcohol is associated with an increased risk of ischaemic stroke in patients with newly diagnosed AF, and alcohol abstinence after AF diagnosis can reduce the risk of ischaemic stroke.²³³ In patients receiving OAC, alcohol excess is associated with a greater risk of bleeding,²³⁴ mediated by poor adherence, alcohol–drug interactions, liver disease, and variceal bleeding.

Alcohol consumption is associated with a dose-dependent increase in the recurrence of AF after catheter ablation.^{147,235} In an RCT among regular non-binge drinkers with AF, the goal of abstinence led to a significant reduction in AF recurrence and burden; alcohol intake was reduced from 16.8 to 2.1 standard drinks per week (≤ 30 grams or 3 standard drinks of alcohol) in the intervention arm, with 61% attaining abstinence.¹⁴⁷ In observational data of patients undergoing catheter ablation, reduction of consumption to ≤ 7 standard drinks (≤ 70 grams of alcohol) per week was associated with improved maintenance of sinus rhythm.^{128,235}

6. [A] Avoid stroke and thromboembolism

6.1. Initiating oral anticoagulation

Atrial fibrillation is a major risk factor for thromboembolism, irrespective of whether it is paroxysmal, persistent, or permanent.^{236,237} Left untreated, and dependent on other patient-specific factors, the risk of ischaemic stroke in AF is increased five-fold, and one in every five strokes is associated with AF.²³⁸ The default approach should therefore be to provide OAC to all eligible patients, except those at low risk of incident stroke or thromboembolism. The effectiveness of OAC to prevent ischaemic stroke in patients with AF is well established.^{239,240} Antiplatelet drugs alone (aspirin, or aspirin in combination with clopidogrel) are not recommended for stroke prevention in AF.^{241,242}

6.1.1. Decision support for anticoagulation in AF

Tools have been developed to enable easier implementation of OAC in patients with clinical AF. The majority of OAC clinical trials have used variations of the CHADS₂ score to indicate those at risk (with points for chronic heart failure, hypertension, age, diabetes, and 2 points for prior stroke/transient ischaemic attack [TIA]). Although most available stroke risk scores are simple and practical, the predictive value of scores is generally modest (see Supplementary data online, Table S3).^{243–245} Classification and discrimination of adverse events is relatively poor for all scores and hence the benefit of using them to select patients for OAC is unclear. There is also considerable variation in the definition of risk factors across countries,²⁴⁶ and a lack of evidence from clinical trials on the ability of stroke risk scoring to enhance clinical practice.²⁴³ This guideline continues to provide a

Class IA recommendation for the use of OAC in patients at risk of thromboembolism. However, in the absence of strong evidence for how to apply risk scores in real-world patients, this has been separated from the use of any particular risk score. This is also in line with regulatory approvals for direct oral anticoagulants (DOACs), which do not stipulate risk scores or numerical thresholds.^{25–28,245}

Substantive changes have occurred in the decades since these risk scores were developed in regards to population-level risk factor profiles, therapies, and targets.¹⁹⁸ Historical scores do not take into account parameters that have been associated with thromboembolism in contemporary cohorts, such as cancer, chronic kidney disease (CKD), ethnicity, and a range of circulating biomarkers (including troponin and B-type natriuretic peptide [BNP]). As an example, for CKD there is a correlation between decreasing glomerular filtration rate and proteinuria with stroke risk,^{247–250} and cohort data suggest a two-fold increased risk of ischaemic stroke and mortality in AF patients with CKD vs. without.²⁵¹ Other factors, such as atrial enlargement, hyperlipidaemia, smoking, and obesity, have been identified in specific cohort studies as additional risk factors for ischaemic stroke in AF.^{70,252,253} Biomarkers, such as troponin, natriuretic peptides, growth differentiation factor-15, cystatin C, and interleukin-6, can also indicate residual stroke risk among anticoagulated AF patients.^{254,255} Biomarker-guided stroke prevention is currently being evaluated in an ongoing RCT (NCT03753490). Until further validation within RCTs is available, this task force continues to support using simple clinical classification for implementation of OAC. Clinicians should use tools that have been validated in their local population and take an individualized approach to thromboembolic risk stratification that considers the full range of each patient's specific risk factors. The absolute risk level at which to start OAC in individual patients cannot be estimated from population-level studies. It will vary depending on how those factors interact with other medical issues, and the degree of risk acceptable or tolerated by that person. In general, most of the available risk scores have a threshold of 0.6%–1.0% per annum of thromboembolic events for clinical AF to warrant OAC prescription.

Across Europe, the most popular risk score is CHA₂DS₂–VASc, giving points for congestive heart failure, hypertension, age ≥ 75 years (2 points), diabetes mellitus, prior stroke/TIA/thromboembolism (2 points), vascular disease, age 65–74 years and female sex. However, implementation has varied in terms of gender. Female sex is an age-dependent stroke risk modifier rather than a risk factor per se.^{112,256,257} The inclusion of gender complicates clinical practice both for healthcare professionals and patients.²⁵⁸ It also omits individuals who identify as non-binary, transgender, or are undergoing sex hormone therapy. Previous guidelines from the ESC (and globally) have not actually used CHA₂DS₂–VASc; instead providing different score levels for women and men with AF to qualify for OAC. Hence, CHA₂DS₂–VA (excluding gender) has effectively been in place (Table 10).⁷⁸ This task force proposes, in the absence of other locally validated alternatives, that clinicians and patients should use the CHA₂DS₂–VA score to assist in decisions on OAC therapy (i.e. without a criterion for birth sex or gender). Pending further trials in lower risk patients (NCT04700826,²⁵⁹ NCT02387229²⁶⁰), OAC are recommended in those with a CHA₂DS₂–VA score of 2 or more and should be considered in those with a CHA₂DS₂–VA score of 1, following a patient-centred and shared care approach. Healthcare professionals should take care to assess for other thromboembolic risk factors that may also indicate the need for OAC prescription.

Recommendation Table 6 — Recommendations to assess and manage thromboembolic risk in AF (see also Evidence Table 6)

Recommendations	Class ^a	Level ^b
Oral anticoagulation is recommended in patients with clinical AF at elevated thromboembolic risk to prevent ischaemic stroke and thromboembolism. ^{239,240}	I	A
A CHA ₂ DS ₂ -VA score of 2 or more is recommended as an indicator of elevated thromboembolic risk for decisions on initiating oral anticoagulation.	I	C
Oral anticoagulation is recommended in all patients with AF and hypertrophic cardiomyopathy or cardiac amyloidosis, regardless of CHA ₂ DS ₂ -VA score, to prevent ischaemic stroke and thromboembolism. ^{270–276}	I	B
Individualized reassessment of thromboembolic risk is recommended at periodic intervals in patients with AF to ensure anticoagulation is started in appropriate patients. ^{277–280}	I	B

Continued

A CHA ₂ DS ₂ -VA score of 1 should be considered an indicator of elevated thromboembolic risk for decisions on initiating oral anticoagulation.	IIa	C
Direct oral anticoagulant therapy may be considered in patients with asymptomatic device-detected subclinical AF and elevated thromboembolic risk to prevent ischaemic stroke and thromboembolism, excluding patients at high risk of bleeding. ^{281,282}	IIb	B
Antiplatelet therapy is not recommended as an alternative to anticoagulation in patients with AF to prevent ischaemic stroke and thromboembolism. ^{242,283}	III	A
Using the temporal pattern of clinical AF (paroxysmal, persistent, or permanent) is not recommended to determine the need for oral anticoagulation. ^{284,285}	III	B

AF, atrial fibrillation; CHA₂DS₂-VA, congestive heart failure, hypertension, age ≥75 years (2 points), diabetes mellitus, prior stroke/transient ischaemic attack/arterial thromboembolism (2 points), vascular disease, age 65–74 years; DOAC, direct oral anticoagulant.

^aClass of recommendation.

^bLevel of evidence.

Table 10 Updated definitions for the CHA₂DS₂-VA score

CHA ₂ DS ₂ -VA component	Definition and comments	Points awarded ^a
C Chronic heart failure	Symptoms and signs of heart failure (irrespective of LVEF, thus including HFpEF, HFmrEF, and HFrEF), or the presence of asymptomatic LVEF ≤40%. ^{261–263}	1
H Hypertension	Resting blood pressure >140/90 mmHg on at least two occasions, or current antihypertensive treatment. The optimal BP target associated with lowest risk of major cardiovascular events is 120–129/70–79 mmHg (or keep as low as reasonably achievable). ^{162,264}	1
A Age 75 years or above	Age is an independent determinant of ischaemic stroke risk. ²⁶⁵ Age-related risk is a continuum, but for reasons of practicality, two points are given for age ≥75 years.	2
D Diabetes mellitus	Diabetes mellitus (type 1 or type 2), as defined by currently accepted criteria, ²⁶⁶ or treatment with glucose lowering therapy.	1
S Prior stroke, TIA, or arterial thromboembolism	Previous thromboembolism is associated with highly elevated risk of recurrence and therefore weighted 2 points.	2
V Vascular disease	Coronary artery disease, including prior myocardial infarction, angina, history of coronary revascularization (surgical or percutaneous), and significant CAD on angiography or cardiac imaging. ²⁶⁷ OR Peripheral vascular disease, including: intermittent claudication, previous revascularization for PVD, percutaneous or surgical intervention on the abdominal aorta, and complex aortic plaque on imaging (defined as features of mobility, ulceration, pedunculation, or thickness ≥4 mm). ^{268,269}	1
A Age 65–74 years	1 point is given for age between 65 and 74 years.	1

BP, blood pressure; CAD, coronary artery disease; CHA₂DS₂-VA, congestive heart failure, hypertension, age ≥75 years (2 points), diabetes mellitus, prior stroke/transient ischaemic attack/arterial thromboembolism (2 points), vascular disease, age 65–74 years; HFpEF, heart failure with mildly reduced ejection fraction; HFmrEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; PVD, peripheral vascular disease.

^aIn addition to these factors, other markers that modify an individual's risk for stroke and thromboembolism should be considered, including cancer, chronic kidney disease, ethnicity (black, Hispanic, Asian), biomarkers (troponin and BNP), and in specific groups, atrial enlargement, hyperlipidaemia, smoking, and obesity.

6.2. Oral anticoagulants

Vitamin K antagonists (VKA), predominantly warfarin but also other coumarin and indandione derivatives, have been the principal drugs to prevent thromboembolic events in the context of AF. As with any anticoagulant, a balance must be reached between preventing thromboembolism and preserving physiological haemostasis, with VKA-associated intracranial and other major haemorrhage the most critical limitation for acceptance of OAC. The global switch to DOACs as first-line therapy has changed this risk–benefit balance, allowing more widespread prescription with no need for routine monitoring (see [Supplementary data online, Additional Evidence Tables S5–S7](#)). This component of AF management may see substantive changes in the coming years, with a

number of factor XI inhibitors in various stages of clinical evaluation. A phase 2 trial of abelacimab in patients with AF has shown lower rates of bleeding compared with rivaroxaban²⁸⁶; however, a phase 3 trial of asundexian was terminated early due to lack of efficacy against apixaban (NCT05643573), despite favourable phase 2 results.²⁸⁷ Regardless of the type of OAC prescribed, healthcare teams should be aware of the potential for interactions with other drugs, foods, and supplements, and incorporate this information into the education provided to patients and their carers. The list of potential interactions with VKA is broad,^{288,289} but there are also some common cardiovascular and non-cardiovascular drugs that interact with DOACs.^{290,291} [Figure 9](#) highlights common and major interactions to consider for VKAs and DOACs.

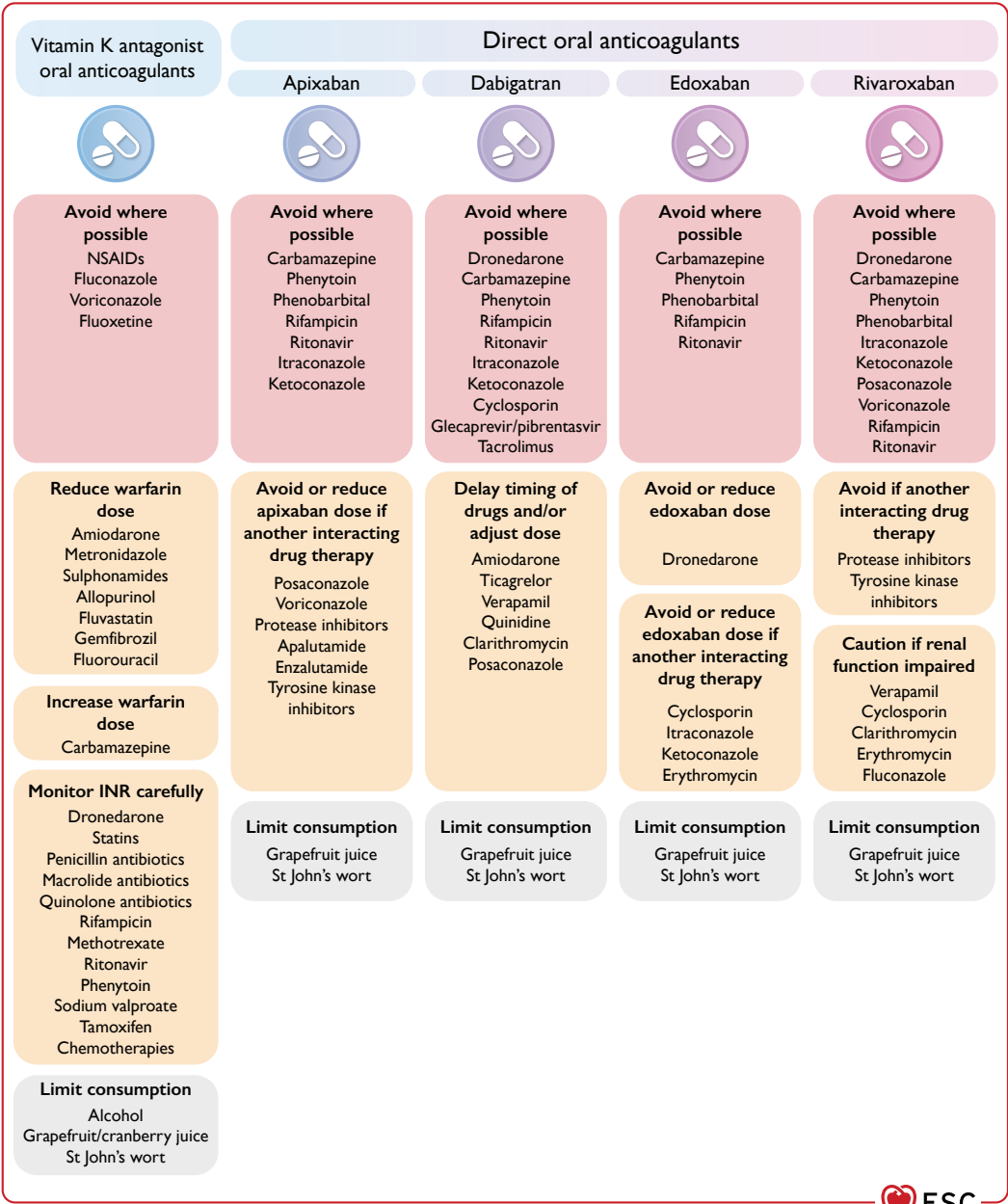


Figure 9 Common drug interactions with oral anticoagulants. INR, international normalized ratio of prothrombin time; NSAID, non-steroidal anti-inflammatory drug. This figure depicts only common or major interactions and is not an exhaustive list of all potential interactions. Please see the European Medicines Agency website or your local formulary for more information.

Recommendation Table 7 — Recommendations for oral anticoagulation in AF (see also Evidence Table 7)

Recommendations	Class ^a	Level ^b
Direct oral anticoagulants are recommended in preference to VKAs to prevent ischaemic stroke and thromboembolism, except in patients with mechanical heart valves or moderate-to-severe mitral stenosis. ^{25–28,292–294}	I	A
A target INR of 2.0–3.0 is recommended for patients with AF prescribed a VKA for stroke prevention to ensure safety and effectiveness. ^{295–298}	I	B
Switching to a DOAC is recommended for eligible patients that have failed to maintain an adequate time in therapeutic range on a VKA (TTR <70%) to prevent thromboembolism and intracranial haemorrhage. ^{299–303}	I	B
Keeping the time in therapeutic range above 70% should be considered in patients taking a VKA to ensure safety and effectiveness, with INR checks at appropriate frequency and patient-directed education and counselling. ^{304–308}	IIa	A
Maintaining VKA treatment rather than switching to a DOAC may be considered in patients aged ≥75 years on clinically stable therapeutic VKA with polypharmacy to prevent excess bleeding risk. ³⁰⁹	IIb	B
A reduced dose of DOAC therapy is not recommended, unless patients meet DOAC-specific criteria, ^c to prevent underdosing and avoidable thromboembolic events. ^{310–312}	III	B

AF, atrial fibrillation; DOAC, direct oral anticoagulant; INR, international normalized ratio of prothrombin time; TTR, time in therapeutic range; VKA, vitamin K antagonist.

^aClass of recommendation.

^bLevel of evidence.

^cSee Table 11.

6.2.1. Direct oral anticoagulants

The DOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) have all demonstrated at least non-inferior efficacy compared with warfarin for the prevention of thromboembolism, but with the added benefit of a 50% reduction in intracranial haemorrhage (ICH).^{25–28} Meta-analyses of individual data from 71 683 RCT patients showed that standard, full-dose DOAC treatment compared with warfarin reduces the risk of stroke or systemic embolism (HR, 0.81; 95% CI, 0.73–0.91), all-cause mortality (HR, 0.90; 95% CI, 0.85–0.95), and intracranial bleeding (HR, 0.48; 95% CI, 0.39–0.59), with no significant difference in other major bleeding (HR, 0.86; 95% CI, 0.73–1.00) and little or no between-trial heterogeneity.²⁹² Post-marketing observational data on the effectiveness and safety of dabigatran,^{313,314} rivaroxaban,^{315,316} apixaban,³¹⁷ and edoxaban³¹⁸ vs. warfarin show general consistency with the respective phase 3 RCTs.

For patients undergoing cardioversion, three underpowered trials showed non-significantly lower rates of cardiovascular events with DOACs compared with warfarin.^{319–321} In meta-analysis of these 5203 patients predominantly undergoing electrical cardioversion, the composite of stroke, systemic embolism, myocardial infarction (MI), and cardiovascular death was significantly lower at 0.42% in patients randomized to a DOAC vs. 0.98% in those allocated VKA

(risk ratio, 0.42; 95% CI, 0.21–0.86; *P* = .017), with no heterogeneity between trials and no significant difference in major bleeding.²⁹³

Specific patient subgroups show consistent benefit with DOACs vs. VKAs. For heart failure, major thromboembolic events were lower in DOAC-treated patients vs. warfarin in subgroup analysis of landmark RCTs,³²² confirmed in large-scale real-world data.³²³ In a retrospective cohort of patients aged over 80 years, DOAC use was associated with a lower risk of ischaemic stroke, dementia, mortality, and major bleeding than warfarin,³²⁴ but this may be confounded by prescription bias.

Direct oral anticoagulants retain their efficacy and safety over VKAs in patients with mild-to-moderate CKD (creatinine clearance [CrCl] >30 mL/min),³²⁵ although specific dosing adjustments apply.^{25–28,326} In Europe, reduced doses of rivaroxaban, apixaban, and edoxaban are approved in patients with severe CKD (CrCl 15–29 mL/min), although limited numbers of patients were included in the major RCTs against VKA.³²⁷ Dabigatran is more dependent on renal elimination and so is contraindicated with an estimated glomerular filtration rate <30 mL/min/1.73 m². Small trials have been performed in patients on haemodialysis, with two finding no difference between apixaban 2.5 mg twice daily and VKA for efficacy or safety outcomes,^{328,329} and one trial showing that rivaroxaban 10 mg led to significantly lower rates of cardiovascular events and major bleeding compared with VKA.³³⁰ Careful institution and regular follow-up are advised when instituting anticoagulants in any patient with impaired renal function (See [Supplementary data online, Additional Evidence Table 8](#)).³²⁶

Direct oral anticoagulants as a class should be avoided in specific patient groups, such as those with mechanical heart valves or moderate-to-severe mitral stenosis. In patients with mechanical heart valves, an excess of thromboembolic and major bleeding events among patients on dabigatran therapy vs. VKA was observed, with an RCT terminated prematurely.³³¹ A trial of apixaban vs. VKA after implantation of a mechanical aortic valve was also stopped due to excess thromboembolic events in the apixaban group.³³² The restriction on DOAC use does not apply to bioprosthetic heart valves (including mitral) or after transcatheter aortic valve implantation, where DOACs can be used and trial data show non-inferiority for clinical events compared with VKAs.^{304,333,334} With regards to mitral stenosis, the DOAC vs. VKA trials excluded patients with moderate-to-severe disease. In 4531 randomized patients with rheumatic heart disease and AF, VKAs led to a lower rate of composite cardiovascular events and death than rivaroxaban, without a higher rate of bleeding.²⁹⁴ Eighty-two per cent of the patients included had a mitral valve area ≤2 cm, supporting the restriction of DOAC use in patients with moderate-to-severe mitral stenosis. Note that patients with other types of valve disease (mitral regurgitation and others) should preferentially be prescribed a DOAC, and the term ‘valvular’ AF is obsolete and should be avoided.

Inappropriate dose reductions for DOACs are frequent in clinical practice,³¹¹ but need to be avoided as they increase the risk of stroke without decreasing bleeding risk.³¹⁰ Hence, DOAC therapy should be instituted according to the standard full dose as tested in phase 3 RCTs and approved by regulators ([Table 11](#)). The prescribed dosage should consider the individual patient’s profile.³³⁵ Drug interactions need to be considered in all patients taking or planned for DOACs (see [Figure 9](#) for common drug interactions).³³⁶ There is insufficient evidence currently to advise on routine laboratory testing for DOAC levels. However, in certain situations, measurement of DOAC levels (where available) may be helpful, such as severe bleeding, the need for urgent surgery, or thromboembolic events despite apparent DOAC compliance.^{337,338} Patients should always be involved in decision-making on anticoagulation,³³⁹ leading to better alignment with personal preferences that can help to increase understanding and adherence.

Table 11 Recommended doses for direct oral anticoagulant therapy

DOAC	Standard full dose	Criteria for dose reduction	Reduced dose only if criteria met
Apixaban	5 mg twice daily	Two out of three needed for dose reduction: (i) age ≥ 80 years (ii) body weight ≤ 60 kg (iii) serum creatinine ≥ 133 mmol/L.	2.5 mg twice daily
Dabigatran	150 mg twice daily	Dose reduction recommended if any apply: (i) age ≥ 80 years (ii) receiving concomitant verapamil. Dose reduction considered on an individual basis if any apply: (i) age 75–80 (ii) moderate renal impairment (creatinine clearance 30–50 mL/min) (iii) patients with gastritis, oesophagitis, or gastro-oesophageal reflux (iv) others at increased risk of bleeding.	110 mg twice daily
Edoxaban	60 mg once daily	Dose reduction if any apply: (i) moderate or severe renal impairment (creatinine clearance 15–50 mL/min) (ii) body weight ≤ 60 kg (iii) concomitant use of ciclosporin, dronedarone, erythromycin, or ketoconazole.	30 mg once daily
Rivaroxaban	20 mg once daily	Creatinine clearance 15–49 mL/min.	15 mg once daily

DOAC, direct oral anticoagulant.

Dose and dose adjustments are taken from the European Medicines Association Summary of Product Characteristics for each DOAC. There may be other patient-specific reasons for providing a reduced dose, but, in general, the standard full dose should be used to provide optimal prevention of thromboembolism related to AF. Note that antiplatelet agents should be stopped in most patients when commencing a DOAC (see Section 6.3). A number of drug interactions exist with each DOAC and should be taken into consideration (see Figure 9).

6.2.2. Vitamin K antagonists

Vitamin K antagonist therapy reduces stroke risk by 64% and mortality by 26% in patients with AF at elevated thromboembolic risk (mostly warfarin in trials, compared with placebo or no treatment).²³⁹ Vitamin K antagonists are still used in many patients worldwide, but prescriptions have declined sharply since the introduction of DOACs.^{340,341} Vitamin K antagonists are currently the only treatment option in AF patients with mechanical heart valves or moderate-to-severe mitral valve stenosis.^{294,331} The use of VKAs is not only limited by numerous drug and food interactions (Figure 9), but also a narrow therapeutic range. This requires frequent monitoring and dose adjustment according to the prothrombin time expressed as the international normalized ratio (INR).³⁴² If the time in therapeutic range (TTR) is maintained for long periods (e.g. $>70\%$ with INR 2.0–3.0), then VKA can be effective for thromboembolic protection with an acceptable safety profile.^{295–297,343} However, VKAs are associated with higher rates of intracranial bleeding,^{299,300} and also higher rates of other types of bleeding compared with DOACs.⁸³

In view of the potential safety benefits, switching from VKAs to a DOAC is justified where there are concerns about intracranial bleeding or for patient-choice reasons, and a switch is recommended where patients have failed to maintain an adequate TTR ($<70\%$). This depends on patients fulfilling eligibility criteria for DOACs and should take into account other correctable reasons for poor INR control. There is limited data on switching OAC in older patients (≥ 75 years) with polypharmacy or other markers of frailty. A recent trial in this patient group prematurely stopped for futility showed that switching from VKAs to DOACs led to a higher primary outcome rate of major or clinically relevant non-major bleeding events compared with continuing with INR-guided

VKA (17.8 vs. 10.5 per 100 patient-years, driven by non-major bleeds).³⁰⁹ Hence, in such patients who are clinically stable with good TTR, VKAs may be continued rather than switching to a DOAC after an open discussion with the patient and shared decision-making.

6.2.3. Clinical vs. device-detected subclinical AF

The known benefit of anticoagulation applies to clinical AF. Two RCTs have been published assessing the value of DOAC therapy in device-detected subclinical AF. The ARTESiA trial (Apixaban for the Reduction of Thromboembolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation) was completed with 4012 patients with device-detected subclinical AF and a mean follow-up of 3.5 years.²⁸² The primary efficacy outcome of stroke or systemic embolism was significantly less in those randomized to apixaban compared with aspirin (HR, 0.63; 95% CI, 0.45–0.88; $P = .007$). In the intention-to-treat analysis, the primary safety outcome of major bleeding was higher with apixaban (HR, 1.36; 95% CI, 1.01–1.82; $P = .04$). The NOAH trial (Non-vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes) was stopped prematurely due to safety concerns and futility for the efficacy of edoxaban, and hence provides limited information.²⁸¹ The analysis of 2536 patients with device-detected atrial high-rate episodes and a median follow-up of 21 months identified no difference in a composite of cardiovascular death, stroke, or embolism comparing edoxaban and placebo (HR, 0.81; 95% CI, 0.60–1.08; $P = .15$). Those randomized to edoxaban had a higher rate of the composite of death or major bleeding than placebo (HR, 1.31; 95% CI, 1.02–1.67; $P = .03$). Patients had a low burden of device-detected subclinical AF in both trials (median duration 1.5 h and

2.8 h, respectively), with lower rates of thromboembolism (around 1% per patient-year) than would be expected for an equivalent cohort of patients with clinical AF and a CHA₂DS₂-VASc score of 4.

Considering the trade-off between potential benefit and the risk of major bleeding, this task force concludes that DOAC therapy may be considered in subgroups of patients with asymptomatic device-detected subclinical AF who have high estimated stroke risk and an absence of major bleeding risk factors (see Section 6.7). The duration and burden of subclinical AF that could indicate potential benefit from OAC remains uncertain.³⁴⁴ Regardless of the initial decision on OAC, patients with subclinical AF should receive management and follow-up for all aspects of AF-CARE as the risk of developing clinical AF is high (6%–9% per year).

6.3. Antiplatelet drugs and combinations with anticoagulants

Antiplatelet drugs, such as aspirin and clopidogrel, are not an alternative to OAC. They should not be used for stroke prevention, and can lead to potential harm (especially among elderly patients with AF).^{345–347} In ACTIVE W (Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events), dual antiplatelet therapy (DAPT) with aspirin and clopidogrel was less effective than warfarin for the prevention of stroke, systemic embolism, MI, or vascular death (annual risk of events 5.6% vs. 3.9%, respectively; *P* = .0003), with similar rates of major bleeding.³⁴⁸ The AVERROES (Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) trial demonstrated a lower rate of stroke or systemic embolism with apixaban compared with aspirin (HR, 0.45; 95% CI, 0.32–0.62; *P* < .001), with no significant difference in major bleeding (there were 11 cases of intracranial bleeding with apixaban and 13 with aspirin).²⁴²

The combination of OAC with antiplatelet agents (especially aspirin) without an adequate indication occurs frequently in clinical practice (see Supplementary data online, Additional Evidence Table S9).^{349,350} Bleeding events are more common when antithrombotic agents are combined, and no clear benefit has been observed in terms of prevention of stroke or death.³⁴⁹ In general, combining antiplatelet drugs with anticoagulants (DOACs or VKAs) should only occur in selected patients with acute vascular disease (e.g. acute coronary syndromes; see Section 9.2). The combination of low-dose rivaroxaban (2.5 mg) with aspirin reduced the risk of stroke in patients with chronic vascular disease in a subanalysis of the COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial,^{351,352} but this cannot be generalized to AF patients because those with an indication for full-dose anticoagulants were excluded.

Recommendation Table 8 — Recommendations for combining antiplatelet drugs with anticoagulants for stroke prevention (see also Evidence Table 8)

Recommendation	Class ^a	Level ^b
Adding antiplatelet treatment to oral anticoagulation is not recommended in AF patients for the goal of preventing ischaemic stroke or thromboembolism. ^{345,347,353}	III	B

AF, atrial fibrillation.
^aClass of recommendation.
^bLevel of evidence.

6.4. Residual ischaemic stroke risk despite anticoagulation

Although OAC significantly reduces the risk of ischaemic stroke in patients with AF, there remains a residual risk.^{252,354} One-third of patients with AF presenting with an ischaemic stroke are already on anticoagulation,³⁵⁵ with heterogeneous aetiology.³⁵⁶ This may include non-AF-related competing stroke mechanisms (such as large artery and small vessel diseases), non-adherence to therapy, an inappropriately low dose of anticoagulant, or thromboembolism despite sufficient anticoagulation.³⁵⁷ Laboratory measurement of INR or DOAC levels may contribute to revealing an amenable cause of the stroke. Regardless of anticoagulation status, patients with ischaemic stroke are more likely to have cardiovascular risk factors.³⁵⁸ Many clinicians managing patients with an incident stroke despite taking anticoagulation will be tempted to switch their anticoagulant regimen. While there may be some advantage in switching from VKAs to DOACs for protection against future recurrent ischaemic or haemorrhagic stroke, this task force does not recommend routinely switching from one DOAC to another, or from a DOAC to a VKA, since this has no proven efficacy.^{252,356,359} There may be individual reasons for switching, including potential interactions with new drugs; however, there is no consistent data across countries that adherence or efficacy differs between once- and twice-daily approaches.^{360,361} Emerging, but observational evidence suggests that switching provides limited reduction in the risk of recurrent ischaemic stroke.^{252,356,359} The alternative strategy of adding antiplatelet therapy to OAC may lead to an increased risk of bleeding.^{356,359} Aside from thorough attention to underlying risk factors and comorbidities, the approach to management of patients with a stroke despite OAC remains a distinct challenge.

Recommendation Table 9 — Recommendations for thromboembolism despite anticoagulation (see also Evidence Table 9)

Recommendation	Class ^a	Level ^b
A thorough diagnostic work-up should be considered in patients taking an oral anticoagulant and presenting with ischaemic stroke or thromboembolism to prevent recurrent events, including assessment of non-cardioembolic causes, vascular risk factors, dosage, and adherence. ^{356,357}	IIa	B
Adding antiplatelet treatment to anticoagulation is not recommended in patients with AF to prevent recurrent embolic stroke. ^{356,359}	III	B
Switching from one DOAC to another, or from a DOAC to a VKA, without a clear indication is not recommended in patients with AF to prevent recurrent embolic stroke. ^{252,356,359}	III	B

AF, atrial fibrillation; DOAC, direct oral anticoagulant; VKA, vitamin K antagonist.
^aClass of recommendation.
^bLevel of evidence.

6.5. Percutaneous left atrial appendage occlusion

Percutaneous left atrial appendage occlusion (LAAO) is a device-based therapy that aims to prevent ischaemic stroke in patients with AF.^{362,363} In the VKA era, two RCTs compared warfarin with LAAO using the

Watchman device. The 5-year pooled outcomes demonstrated a similar rate of the composite endpoint (cardiovascular or unexplained death, systemic embolism, and stroke) between the LAAO and warfarin arms. Those randomized to LAAO had significantly lower rates of haemorrhagic stroke and all-cause death, but also a 71% non-significant increase in ischaemic stroke and systemic embolism.³⁶⁴ With DOACs demonstrating similar rates of major bleeding to aspirin,²⁴² warfarin in the control arms in these trials is no longer standard of care and hence the place of LAAO in current practice is unclear. The Amulet occluder is an alternative LAAO device which was non-inferior in an RCT to the Watchman device for safety events (procedure-related complications, death, or major bleeding) and thromboembolism.³⁶⁵ In the PRAGUE-17 trial, 402 AF patients were randomized to DOAC or LAAO (Watchman or Amulet), with non-inferiority reported for a broad composite primary endpoint of stroke, TIA, systemic embolism, cardiovascular death, major or non-major clinically relevant bleeding, and procedure/device-related complications.^{366,367} Larger trials^{368,369} are expected to provide more comprehensive data that can add to the current evidence base (see [Supplementary data online, Additional Evidence Table S10](#)).

Pending further RCTs (see [Supplementary data online, Table S4](#)), patients with a contraindication to all of the OAC options (the four DOACs and VKAs) have the most appropriate rationale for LAAO implantation, despite the paradox that the need for post-procedure antithrombotic treatment exposes the patient to a bleeding risk that may be equivalent to that of DOACs. Regulatory approvals based on RCT protocols suggest the need for 45 days of VKA plus aspirin after implantation, followed by 6 months of DAPT in patients with no major peri-device leaks, and then ongoing aspirin (see [Supplementary data online, Figure S2](#)).^{370–372} However, real-world practice is markedly different and also varied. Direct oral anticoagulant administration at full or reduced dose has been proposed as a treatment alternative to warfarin.³⁷³ Observational studies have also supported the use of antiplatelet therapy without associated increases in device-related thrombosis or stroke.^{374–376} In a propensity-matched comparison of patients receiving limited early OAC vs. antiplatelet treatment post-Watchman implantation, thromboembolic event rates and bleeding complications were similar.³⁷⁷ While waiting for solid RCT data (NCT03445949, NCT03568890),³⁷⁸ pertinent decisions on antithrombotic treatment are usually made on an individualized basis.^{379–381} Prevention of recurrent stroke, in addition to OAC, is another potential indication for LAAO. Only limited data are so far available from registries,³⁸² with ongoing trials expected to provide more insight (NCT03642509, NCT05963698).

Left atrial appendage occlusion device implantation is associated with procedural risk including stroke, major bleeding, device-related thrombus, pericardial effusion, vascular complications, and death.^{362,383–385} Voluntary registries enrolling patients considered ineligible for OAC have reported low peri-procedural risk,^{372,376,386,387} although national registries report in-hospital major adverse event rates of 9.5% in centres performing 5–15 LAAO cases per year, and 5.6% performing 32–211 cases per year ($P < .001$).³⁸⁸ Registries with new-generation devices report a lower complication rate compared with RCT data.^{389,390} Device-related thrombi occur with an incidence of 1.7%–7.2% and are associated with a higher risk of ischaemic stroke.^{386,391–397} Their detection can be documented as late as 1 year post-implantation in one-fifth of patients, thus mandating a late ‘rule-out’ imaging approach.³⁹¹ Likewise, follow-up screening for peri-device leaks is relevant, as small leaks (0–5 mm) are present in ~25% and have

been associated with higher thromboembolic and bleeding events during 1 year follow-up in a large observational registry of one particular device.³⁹⁸

Recommendation Table 10 — Recommendations for percutaneous left atrial appendage occlusion (see also Evidence Table 10)

Recommendation	Class ^a	Level ^b
Percutaneous LAA occlusion may be considered in patients with AF and contraindications for long-term anticoagulant treatment to prevent ischaemic stroke and thromboembolism. ^{372,376,386,387}	IIb	C

AF, atrial fibrillation; LAA, left atrial appendage.
^aClass of recommendation.
^bLevel of evidence.

6.6. Surgical left atrial appendage occlusion

Surgical occlusion or exclusion of the left atrial appendage (LAA) can contribute to stroke prevention in patients with AF undergoing cardiac surgery.^{399,400} The Left Atrial Appendage Occlusion Study (LAAOS III) randomized 4811 patients with AF to undergo or not undergo LAAO at the time of cardiac surgery for another indication. During a mean of 3.8 years follow-up, ischaemic stroke or systemic embolism occurred in 114 patients (4.8%) in the occlusion group and 168 (7.0%) in the control arm (HR, 0.67; 95% CI, 0.53–0.85; $P = .001$).⁴⁰¹ The LAAOS III trial did not compare appendage occlusion with anticoagulation (77% of participants continued to receive OAC), and therefore, surgical LAA closure should be considered as an adjunct therapy to prevent thromboembolism in addition to anticoagulation in patients with AF.

There are no RCT data showing a beneficial effect on ischaemic stroke or systemic embolism in patients with AF undergoing LAAO during endoscopic or hybrid AF ablation. A meta-analysis of RCT and observational data showed no differences in stroke prevention or all-cause mortality when comparing LAA clipping during thoracoscopic AF ablation with percutaneous LAAO and catheter ablation.⁴⁰² While the percutaneous LAAO/catheter ablation group showed a higher acute success rate, it was also associated with a higher risk of haemorrhage during the peri-operative period. In an observational study evaluating 222 AF patients undergoing LAA closure using a clipping device as a part of endoscopic or hybrid AF ablation, complete closure was achieved in 95% of patients.⁴⁰³ There were no intra-operative complications, and freedom from a combined endpoint of ischaemic stroke, haemorrhagic stroke, or TIA was 99.1% over 369 patient-years of follow-up. Trials evaluating the beneficial effect of surgical LAA closure in patients undergoing cardiac surgery but without a known history of AF are ongoing (NCT03724318, NCT02701062).⁴⁰⁴

There is a potential advantage for stand-alone epicardial over percutaneous LAA closure in patients with a contraindication for OAC, as there is no need for post-procedure anticoagulation after epicardial closure. Observational data show that stand-alone LAA closure using an epicardial clip is feasible and safe.⁴⁰⁵ A multidisciplinary team approach can facilitate the choice between epicardial or percutaneous LAA closure in such patients.⁴⁰⁶ The majority of safety data and experience in epicardial LAA closure originate from a single clipping device (AtriClip)^{403,407,408} (see [Supplementary data online, Additional Evidence Table S11](#)).

Recommendation Table 11 — Recommendations for surgical left atrial appendage occlusion (see also Evidence Table 11)

Recommendations	Class ^a	Level ^b
Surgical closure of the left atrial appendage is recommended as an adjunct to oral anticoagulation in patients with AF undergoing cardiac surgery to prevent ischaemic stroke and thromboembolism. ^{400,401,408–412}	I	B
Surgical closure of the left atrial appendage should be considered as an adjunct to oral anticoagulation in patients with AF undergoing endoscopic or hybrid AF ablation to prevent ischaemic stroke and thromboembolism. ^{402,403}	IIa	C
Stand-alone endoscopic surgical closure of the left atrial appendage may be considered in patients with AF and contraindications for long-term anticoagulant treatment to prevent ischaemic stroke and thromboembolism. ^{399,405,406,413}	IIb	C

AF, atrial fibrillation.

^aClass of recommendation.

^bLevel of evidence.

6.7. Bleeding risk

6.7.1. Assessment of bleeding risk

When initiating antithrombotic therapy, modifiable bleeding risk factors should be managed to improve safety (Figure 10).^{414–418} This includes strict control of hypertension, advice to reduce excess alcohol intake, avoidance of unnecessary antiplatelet or anti-inflammatory agents, and attention to OAC therapy (adherence, control of TTR if on VKAs, and review of interacting medications). Clinicians should consider the balance between stroke and bleeding risk—as factors for both are dynamic and overlapping, they should be re-assessed at each review depending on the individual patient.^{419–421} Bleeding risk factors are rarely a reason to withdraw or withhold OAC in eligible patients, as the risk of stroke without anticoagulation often outweighs the risk of major bleeding.^{422,423} Patients with non-modifiable risk factors should be reviewed more often, and where appropriate, a multidisciplinary team approach should be instituted to guide management.

Several bleeding risk scores have been developed to account for a wide range of clinical factors (see Supplementary data online, Table S5 and Additional Evidence Tables S12 and S13).⁴²⁴ Systematic reviews and validation studies in external cohorts have shown contrasting results and only modest predictive ability.^{244,425–434} This task force does not recommend a specific bleeding risk score given the uncertainty in accuracy and potential adverse implications of not providing appropriate OAC to those at thromboembolic risk. There are very few absolute contraindications to OAC (especially DOAC therapy). Whereas primary intracranial tumours⁴³⁵ or an intracerebral bleed related to cerebral amyloid angiopathy⁴³⁶ are examples where OAC should be avoided, many other contraindications are relative or temporary. For example, a DOAC can often be safely initiated or re-initiated after acute bleeding has stopped, as long as the source has been fully investigated and managed. Co-prescription of proton pump inhibitors is common in clinical practice for patients receiving

OAC that are at high risk of gastrointestinal bleeding. However, the evidence base is limited and not specifically in patients with AF. Whereas observational studies have shown potential benefit from proton pump inhibitors,⁴³⁷ a large RCT in patients receiving low-dose anticoagulation and/or aspirin for stable cardiovascular disease found that pantoprazole had no significant impact on upper gastrointestinal bleeding events compared with placebo (HR, 0.88; 95% CI, 0.67–1.15).⁴³⁸ Hence, the use of gastric protection should be individualized for each patient according to the totality of their perceived bleeding risk.

Recommendation Table 12 — Recommendations for assessment of bleeding risk (see also Evidence Table 12)

Recommendations	Class ^a	Level ^b
Assessment and management of modifiable bleeding risk factors is recommended in all patients eligible for oral anticoagulation, as part of shared decision-making to ensure safety and prevent bleeding. ^{439–444}	I	B
Use of bleeding risk scores to decide on starting or withdrawing oral anticoagulation is not recommended in patients with AF to avoid under-use of anticoagulation. ^{431,445,446}	III	B

AF, atrial fibrillation.

^aClass of recommendation.

^bLevel of evidence.

6.7.2. Management of bleeding on anticoagulant therapy

General management of bleeding in patients receiving OAC is outlined in Figure 11. Cause-specific management is beyond the scope of these guidelines, and will depend on the individual circumstances of the patient and the healthcare environment.⁴⁴⁷ Assessment of patients with active bleeding should include confirmation of the bleeding site, bleeding severity, type/dose/timepoint of last anticoagulant intake, concomitant use of other antithrombotic agents, and other factors influencing bleeding risk (renal function, platelet count, and medications such as non-steroidal anti-inflammatories). INR testing and information on recent results are invaluable for patients taking VKAs. Specific coagulation tests for DOACs include diluted thrombin time, ecarin clotting time, ecarin chromogenic assay for dabigatran, and chromogenic anti-factor Xa assay for rivaroxaban, apixaban, and edoxaban.^{447–449} Diagnostic and treatment interventions to identify and manage the cause of bleeding (e.g. gastroscopy) should be performed promptly.

In cases of minor bleeding, temporary withdrawal of OAC while the cause is managed is usually sufficient, noting that the reduction in anti-coagulant effect is dependent on the INR level for VKAs or the half-life of the particular DOAC.

For major bleeding events in patients taking VKAs, administration of fresh frozen plasma restores coagulation more rapidly than vitamin K, but prothrombin complex concentrates achieve even faster blood coagulation with fewer complications, and so are preferable to achieve haemostasis.⁴⁵⁰ In DOAC-treated patients where the last DOAC dose was taken within 2–4 h, charcoal administration and/or gastric lavage may reduce further exposure. If the patient is taking dabigatran, idarucizumab can fully reverse its anti-coagulant effect and help to achieve haemostasis within 2–4 h in

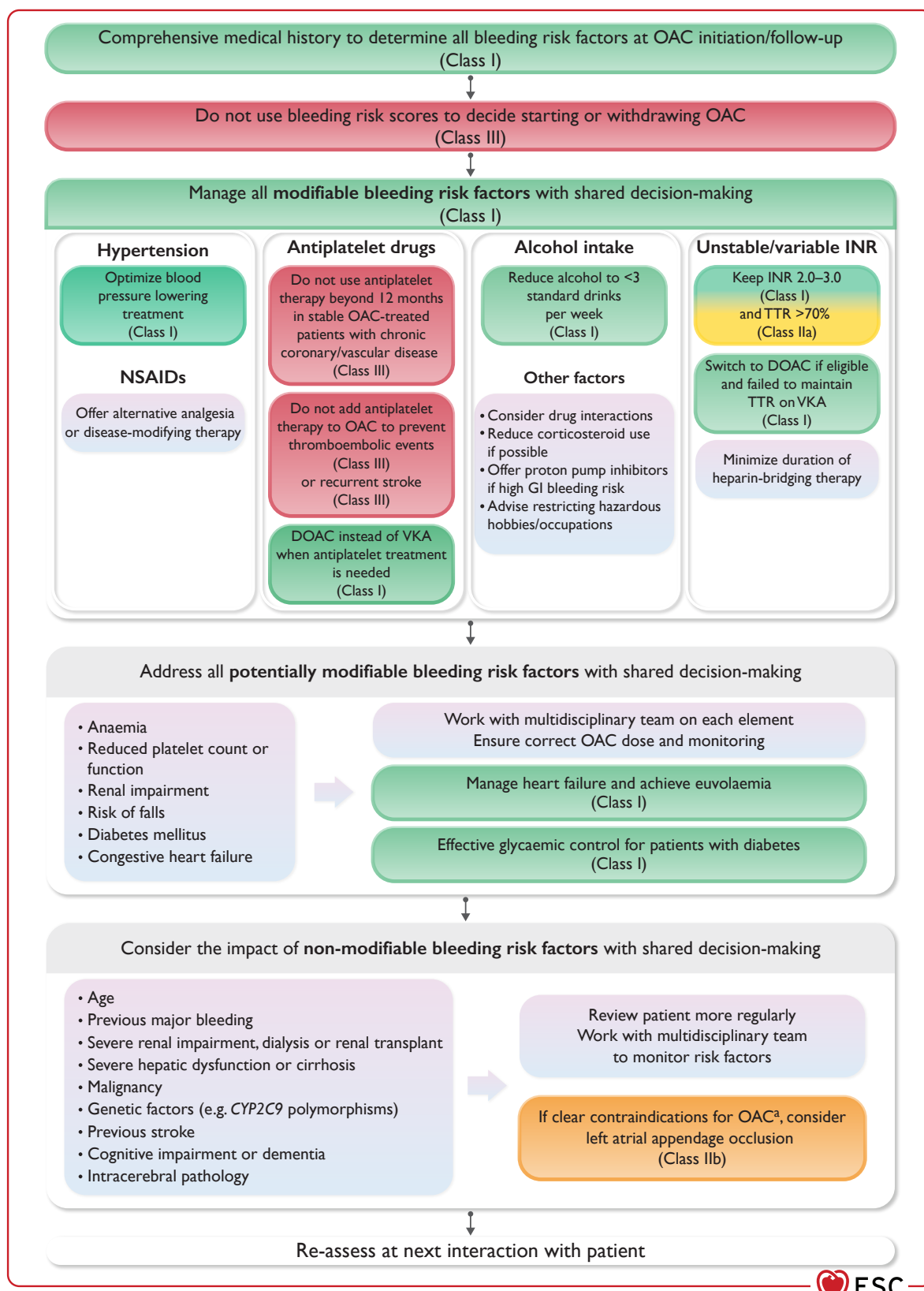


Figure 10 Modifying the risk of bleeding associated with OAC. DOAC, direct oral anticoagulant; GI, gastrointestinal; INR, international normalized ratio of prothrombin time; NSAID, non-steroidal anti-inflammatory drug; OAC, oral anticoagulant; TTR, time in therapeutic range; VKA, vitamin K antagonist. ^aAbsolute contraindications for OAC therapy are rare, and include primary intracranial tumours and intracerebral bleeds related to amyloid angiopathy. In most cases, contraindications may be relative or temporary. Left atrial appendage occlusion can be performed through a percutaneous or endoscopic approach.

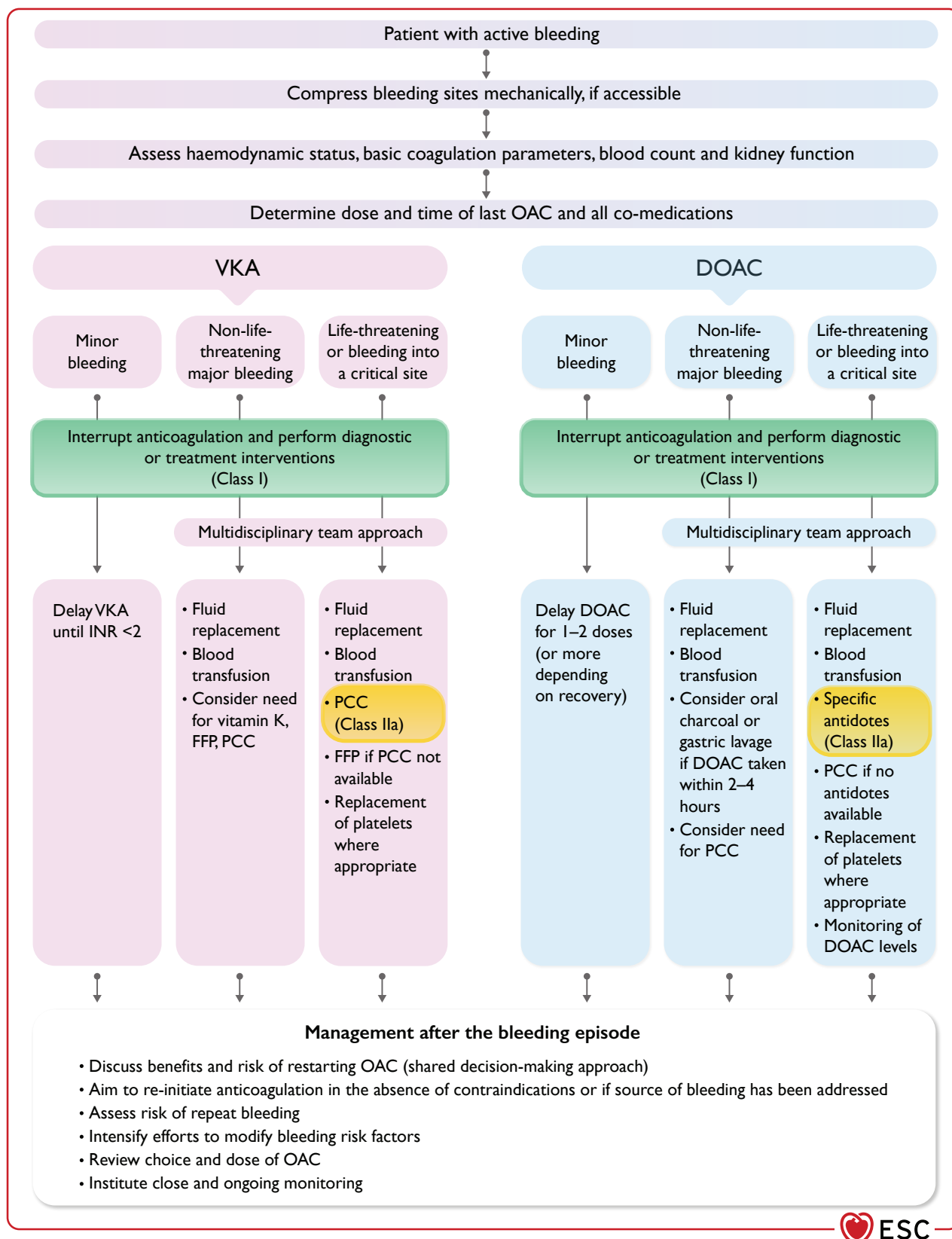


Figure 11 Management of oral anticoagulant-related bleeding in patients with AF. DOAC, direct oral anticoagulant; FFP, fresh frozen plasma; INR, international normalized ratio of prothrombin time; OAC, oral anticoagulant; PCC, prothrombin complex concentrate; VKA, vitamin K antagonist.

uncontrolled bleeding.⁴⁵¹ Dialysis can also be effective in reducing dabigatran concentration. Andexanet alfa rapidly reverses the activity of factor Xa inhibitors (apixaban, edoxaban, rivaroxaban) (see [Supplementary data online, Additional evidence Table S14](#)). An open-label RCT comparing andexanet alfa to usual care in patients presenting with acute ICH within 6 h of symptom onset was stopped early due to improved control of bleeding after 450 patients had been randomized.⁴⁵² As DOAC-specific antidotes are not yet available in all institutions, prothrombin complex concentrates are often used in cases of serious bleeding on factor Xa inhibitors, with evidence limited to observational studies.⁴⁵³

Due to the complexities of managing bleeding in patients taking OAC, it is advisable that each institution develop specific policies involving a multidisciplinary team that includes cardiologists, haematologists, emergency physicians/intensive care specialists, surgeons, and others. It is also important to educate patients taking anticoagulants on the signs and symptoms of bleeding events and to alert their healthcare provider when such events occur.³³⁵

The decision to reinstate OAC will be determined by the severity, cause, and subsequent management of bleeding, preferably by a multidisciplinary team and with close monitoring. Failure to reinstitute OAC after a bleed significantly increases the risk of MI, stroke, and death.⁴⁵⁴ However, if the cause of severe or life-threatening bleeds cannot be treated or reversed, the risk of ongoing bleeding may outweigh the benefit of thromboembolic protection.³³⁵

Recommendation Table 13 — Recommendations for management of bleeding in anticoagulated patients (see also Evidence Table 13)

Recommendations	Class ^a	Level ^b
Interrupting anticoagulation and performing diagnostic or treatment interventions is recommended in AF patients with active bleeding until the cause of bleeding is identified and resolved.	I	C
Prothrombin complex concentrates should be considered in AF patients on VKAs who develop a life-threatening bleed, or bleed into a critical site, to reverse the antithrombotic effect. ⁴⁵⁰	IIa	C
Specific antidotes should be considered in AF patients on a DOAC who develop a life-threatening bleed, or bleed into a critical site, to reverse the antithrombotic effect. ^{451,455,456}	IIa	B

© ESC 2024

AF, atrial fibrillation; DOAC, direct oral anticoagulant; VKA, vitamin K antagonist.

^aClass of recommendation.

^bLevel of evidence.

7. [R] Reduce symptoms by rate and rhythm control

Most patients diagnosed with AF will need therapies and/or interventions to control heart rate, revert to sinus rhythm, or maintain sinus rhythm to limit symptoms or improve outcomes. While the concept of choosing between rate and rhythm control is often discussed, in reality most patients require a combination approach which should be consciously re-evaluated during follow-up. Within a patient-centred and shared-management approach, rhythm control should be a consideration in all suitable AF patients, with explicit discussion of benefits and risks.

7.1. Management of heart rate in patients with AF

Limiting tachycardia is an integral part of AF management and is often sufficient to improve AF-related symptoms. Rate control is indicated as initial therapy in the acute setting, in combination with rhythm control therapies, or as the sole treatment strategy to control heart rate and reduce symptoms. Limited evidence exists to inform the best type and intensity of rate control treatment.⁴⁵⁷ The approach to heart rate control presented in [Figure 7](#) can be used for all types of AF, including paroxysmal, persistent, and permanent AF.

Recommendation Table 14 — Recommendations for heart rate control in patients with AF (see also Evidence Table 14)

Recommendations	Class ^a	Level ^b
Rate control therapy is recommended in patients with AF, as initial therapy in the acute setting, an adjunct to rhythm control therapies, or as a sole treatment strategy to control heart rate and reduce symptoms. ^{458–460}	I	B
Beta-blockers, diltiazem, verapamil, or digoxin are recommended as first-choice drugs in patients with AF and LVEF >40% to control heart rate and reduce symptoms. ^{48,461,462}	I	B
Beta-blockers and/or digoxin are recommended in patients with AF and LVEF ≤40% to control heart rate and reduce symptoms. ^{40,185,463–465}	I	B
Combination rate control therapy should be considered if a single drug does not control symptoms or heart rate in patients with AF, providing that bradycardia can be avoided, to control heart rate and reduce symptoms.	IIa	C
Lenient rate control with a resting heart rate of < 110 b.p.m. should be considered as the initial target for patients with AF, with stricter control reserved for those with continuing AF-related symptoms. ^{459,460,466}	IIa	B
Atrioventricular node ablation in combination with pacemaker implantation should be considered in patients unresponsive to, or ineligible for, intensive rate and rhythm control therapy to control heart rate and reduce symptoms. ^{467–469}	IIa	B
Atrioventricular node ablation combined with cardiac resynchronization therapy should be considered in severely symptomatic patients with permanent AF and at least one hospitalization for HF to reduce symptoms, physical limitations, recurrent HF hospitalization, and mortality. ^{470,471}	IIa	B
Intravenous amiodarone, digoxin, esmolol, or landiolol may be considered in patients with AF who have haemodynamic instability or severely depressed LVEF to achieve acute control of heart rate. ^{472,473}	IIb	B

© ESC 2024

AF, atrial fibrillation; b.p.m., beats per minute; HF, heart failure; LVEF, left ventricular ejection fraction.

^aClass of recommendation.

^bLevel of evidence.

7.1.1. Indications and target heart rate

The optimal heart rate target in AF patients depends on the setting, symptom burden, presence of heart failure, and whether rate control is combined with a rhythm control strategy. In the RACE II (Rate Control Efficacy in Permanent Atrial Fibrillation) RCT of patients with permanent AF, lenient rate control (target heart rate <110 [beats per minute] b.p.m.) was non-inferior to a strict approach (<80 b.p.m. at rest; <110 b.p.m. during exercise; Holter for safety) for a composite of clinical events, NYHA class, or hospitalization.^{186,459} Similar results were found in a post-hoc combined analysis from the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) and the RACE (Rate Control versus Electrical cardioversion) studies.⁴⁷⁴ Therefore, lenient rate control is an acceptable initial approach, unless there are ongoing symptoms or suspicion of tachycardia-induced cardiomyopathy, where stricter targets may be indicated.

7.1.2. Heart rate control in the acute setting

In acute settings, physicians should always evaluate and manage underlying causes for the initiation of AF prior to, or in parallel to, instituting acute rate and/or rhythm control. These include treating sepsis, addressing fluid overload, or managing cardiogenic shock. The choice of drug (Table 12) will depend on the patient's characteristics, presence of heart failure and LVEF, and haemodynamic profile (Figure 7). In general for acute rate control, beta-blockers (for all LVEF) and diltiazem/verapamil (for LVEF >40%) are preferred over digoxin because of their more rapid onset of action and dose-dependent effects.^{462,475,476} More selective beta-1 receptor blockers have a better efficacy and safety profile than unselective beta-blockers.⁴⁷⁷ Combination therapy with digoxin may be required in acute settings (combination of beta-blockers with diltiazem/verapamil should be avoided except in closely monitored situations).^{177,478} In selected patients who are haemodynamically unstable or with severely impaired LVEF, intravenous amiodarone, landiolol, or digoxin can be used.^{472,473,479}

7.1.3. Long-term heart rate control

Pharmacological rate control can be achieved with beta-blockers, diltiazem, verapamil, digoxin, or combination therapy (Table 12) (see Supplementary data online, Additional Evidence Table S15).⁴⁸⁰

The choice of rate control drugs depends on symptoms, comorbidities, and the potential for side effects and interactions. Combination therapy of different rate-controlling drugs should be considered only when needed to achieve the target heart rate, and careful follow-up to avoid bradycardia is advised. Combining beta-blockers with verapamil or diltiazem should only be performed in secondary care with regular monitoring of heart rate by 24 h ECG to check for bradycardia.⁴⁵⁹ Some antiarrhythmic drugs (AADs) also have rate-limiting properties (e.g. amiodarone, sotalol), but they should generally be used only for rhythm control. Dronedarone should not be instituted for rate control since it increases rates of heart failure, stroke, and cardiovascular death in permanent AF.⁴⁸¹

Beta-blockers, specifically beta-1 selective adrenoreceptor antagonists, are often first-line rate-controlling agents largely based on their acute effect on heart rate and the beneficial effects demonstrated in patients with chronic HFrEF. However, the prognostic benefit of beta-blockers seen in HFrEF patients with sinus rhythm may not be present in patients with AF.^{133,482}

Verapamil and diltiazem are non-dihydropyridine calcium channel blockers. They provide rate control⁴⁶¹ and have a different adverse effect profile, making verapamil or diltiazem useful for those experiencing side effects from beta-blockers.⁴⁸³ In a 60 patient crossover RCT, verapamil and diltiazem did not lead to the same reduction in exercise capacity as seen with beta-blockers, and had a beneficial impact on BNP.⁴⁸⁰

Digoxin and digitoxin are cardiac glycosides that inhibit the sodium–potassium adenosine triphosphatase and augment parasympathetic tone. In RCTs, there is no association between the use of digoxin and any increase in all-cause mortality.^{185,484} Lower doses of digoxin may be associated with better prognosis.¹⁸⁵ Serum digoxin concentrations can be monitored to avoid toxicity,⁴⁸⁵ especially in patients at higher risk due to older age, renal dysfunction, or use of interacting medications. In RATE-AF (RATE control Therapy Evaluation in permanent Atrial Fibrillation), a trial in patients with symptomatic permanent AF, there was no difference between low-dose digoxin and bisoprolol for patient-reported quality of life outcomes at 6 months. However, those randomized to digoxin demonstrated fewer adverse effects, a greater improvement in mEHRA and NYHA scores, and a reduction in BNP.⁴⁸ Two ongoing RCTs are addressing digoxin and digitoxin use in patients with HFrEF with and without AF (EudraCT-2013-005326-38, NCT03783429).⁴⁸⁶

Table 12 Drugs for rate control in AF

Agent ^a	Intravenous administration	Usual range for oral maintenance dose	Contraindicated
Beta-blockers^b			
Metoprolol tartrate	2.5–5 mg bolus over 2 mins; up to 15 mg maximal cumulative dose	25–100 mg twice daily	In case of asthma, non-selective beta-blockers should be avoided. Contraindicated in acute HF and history of severe bronchospasm.
Metoprolol XL (succinate)	N/A	50–200 mg once daily	
Bisoprolol	N/A	1.25–20 mg once daily	
Atenolol ^c	N/A	25–100 mg once daily	
Esmolol	500 µg/kg i.v. bolus over 1 min; followed by 50–300 µg/kg/min	N/A	
Landiolol	100 µg/kg i.v. bolus over 1 min; followed by 10–40 µg/kg/min	N/A	
Nebivolol	N/A	2.5–10 mg once daily	
Carvedilol	N/A	3.125–50 mg twice daily	

Continued

Non-dihydropyridine calcium channel antagonists			
Verapamil	2.5–10 mg i.v. bolus over 5 min	40 mg twice daily to 480 mg (extended release) once daily	Contraindicated if LVEF ≤40%. Adapt doses in hepatic and renal impairment.
Diltiazem	0.25 mg/kg i.v. bolus over 5 min, then 5–15 mg/h	60 mg three times daily to 360 mg (extended release) once daily	
Digitalis glycosides			
Digoxin	0.5 mg i.v. bolus (0.75–1.5 mg over 24 h in divided doses)	0.0625–0.25 mg once daily	High plasma levels associated with adverse events.
Digitoxin	0.4–0.6 mg	0.05–0.1 mg once daily	Check renal function before starting digoxin and adapt dose in CKD patients.
Other			
Amiodarone ^d	300 mg i.v. diluted in 250 mL 5% dextrose over 30–60 min (preferably via central venous cannula), followed by 900–1200 mg i.v. over 24 h diluted in 500–1000 mL via a central venous cannula	200 mg once daily after loading Loading: 200 mg three times daily for 4 weeks, then 200 mg daily or less as appropriate (reduce other rate control drugs according to heart rate)	Contraindicated in iodine sensitivity. Serious potential adverse effects (including pulmonary, ophthalmic, hepatic, and thyroid). Consider numerous drug interactions.

AF, atrial fibrillation; CKD, chronic kidney disease; HF, heart failure; i.v., intravenous; min, minutes; N/A, not available or not widely available. Maximum doses have been defined based on the summary of product characteristic of each drug.

^aAll rate control drugs are contraindicated in Wolff–Parkinson–White syndrome; also intravenous amiodarone.

^bOther beta-blockers are available but not recommended as specific rate control therapy in AF and therefore not mentioned here (e.g. propranolol and labetalol).

^cNo data on atenolol; should not be used in heart failure with reduced ejection fraction or in pregnancy.

^dLoading regimen may vary; i.v. dosage should be considered when calculating total load.

Due to its broad extracardiac adverse effect profile, **amiodarone** is reserved as a last option when heart rate cannot be controlled even with maximal tolerated combination therapy, or in patients who do not qualify for atrioventricular node ablation and pacing. Many of the adverse effects from amiodarone have a direct relationship with cumulative dose, restricting the long-term value of amiodarone for rate control.⁴⁸⁷

7.1.4. Atrioventricular node ablation and pacemaker implantation

Ablation of the atrioventricular node and pacemaker implantation (‘ablate and pace’) can lower and regularize heart rate in patients with AF (see [Supplementary data online, Additional Evidence Table S16](#)). The procedure has a low complication rate and a low long-term mortality risk.^{468,488} The pacemaker should be implanted a few weeks before the atrioventricular node ablation, with the initial pacing rate after ablation set at 70–90 b.p.m.^{489,490} This strategy does not worsen LV function,⁴⁹¹ and may even improve LVEF in selected patients.^{492,493} The evidence base has typically included older patients. For younger patients, ablate and pace should only be considered if heart rate remains uncontrolled despite consideration of other pharmacological and non-pharmacological treatment options. The choice of pacing therapy (right ventricular or biventricular pacing) depends on patient characteristics, presence of heart failure, and LVEF.^{187,494}

In severely symptomatic patients with permanent AF and at least one hospitalization for heart failure, atrioventricular node ablation combined with CRT should be considered. In the APAF-CRT (Ablate and Pace for Atrial Fibrillation-cardiac resynchronization therapy) trial in a population with narrow QRS complexes, atrioventricular node ablation combined with CRT was superior to rate control drugs for the primary outcomes (all-cause mortality, and death or hospitalization for heart failure), and secondary outcomes (symptom burden and physical limitation).^{470,471} Conduction system pacing may become a potentially useful alternate pacing mode when implementing a pace and ablate strategy, once safety and efficacy have been confirmed in larger RCTs.^{495,496} In CRT recipients, the presence (or occurrence) of AF is one of the main reasons for suboptimal biventricular pacing.¹⁸⁷ Improvement of biventricular pacing is indicated and can be reached by intensification of rate control drug regimens, atrioventricular node ablation, or rhythm control, depending on patient and AF characteristics.¹⁸⁷

7.2. Rhythm control strategies in patients with AF

7.2.1. General principles and anticoagulation

Rhythm control refers to therapies dedicated to restoring and maintaining sinus rhythm. These treatments include cardioversion, AADs, percutaneous catheter ablation, endoscopic and hybrid ablation, and open surgical approaches (see [Supplementary data online, Additional Evidence Table S17](#)). Rhythm control is never a strategy on its own; instead, it should always be part of the AF-CARE approach.

In patients with acute or worsening haemodynamic instability thought to be caused by AF, rapid electrical cardioversion is recommended. For other patients, a wait-and-see approach should be considered as an alternative to immediate cardioversion ([Figure 12](#)). The Rate Control versus Electrical Cardioversion Trial 7–Acute Cardioversion versus Wait and See (RACE 7 ACWAS) trial in patients with recent-onset symptomatic AF without haemodynamic compromise showed a wait-and-see approach for spontaneous conversion until 48 h after the onset of AF symptoms was non-inferior as compared with immediate cardioversion at 4 weeks follow-up.¹⁰

Since the publication of landmark trials more than 20 years ago, the main reason to consider longer-term rhythm control therapy has been the reduction in symptoms from AF.^{497–500} Older studies have shown that the institution of a rhythm control strategy using AADs does not reduce mortality and morbidity when compared with a rate control-only strategy,^{497–500} and may increase hospitalization.⁴⁵⁷ In contrast, multiple studies have shown that rhythm control strategies have a positive effect on quality of life once sinus rhythm is maintained.^{501,502} Therefore, in the case of uncertainty of the presence of symptoms associated with AF, an attempt to restore sinus rhythm is a rational first step. In patients with symptoms, patient factors that favour an attempt at rhythm control should be considered, including suspected tachycardiomyopathy, a brief AF history, non-dilated left atrium, or patient preference.

Rhythm control strategies have significantly evolved due to an increasing experience in the safe use of antiarrhythmic drugs,¹⁷ consistent use of OAC, improvements in ablation technology,^{503–509} and identification and management of risk factors and comorbidities.^{39,510,511} In the ATHENA trial (A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg twice daily for the Prevention of

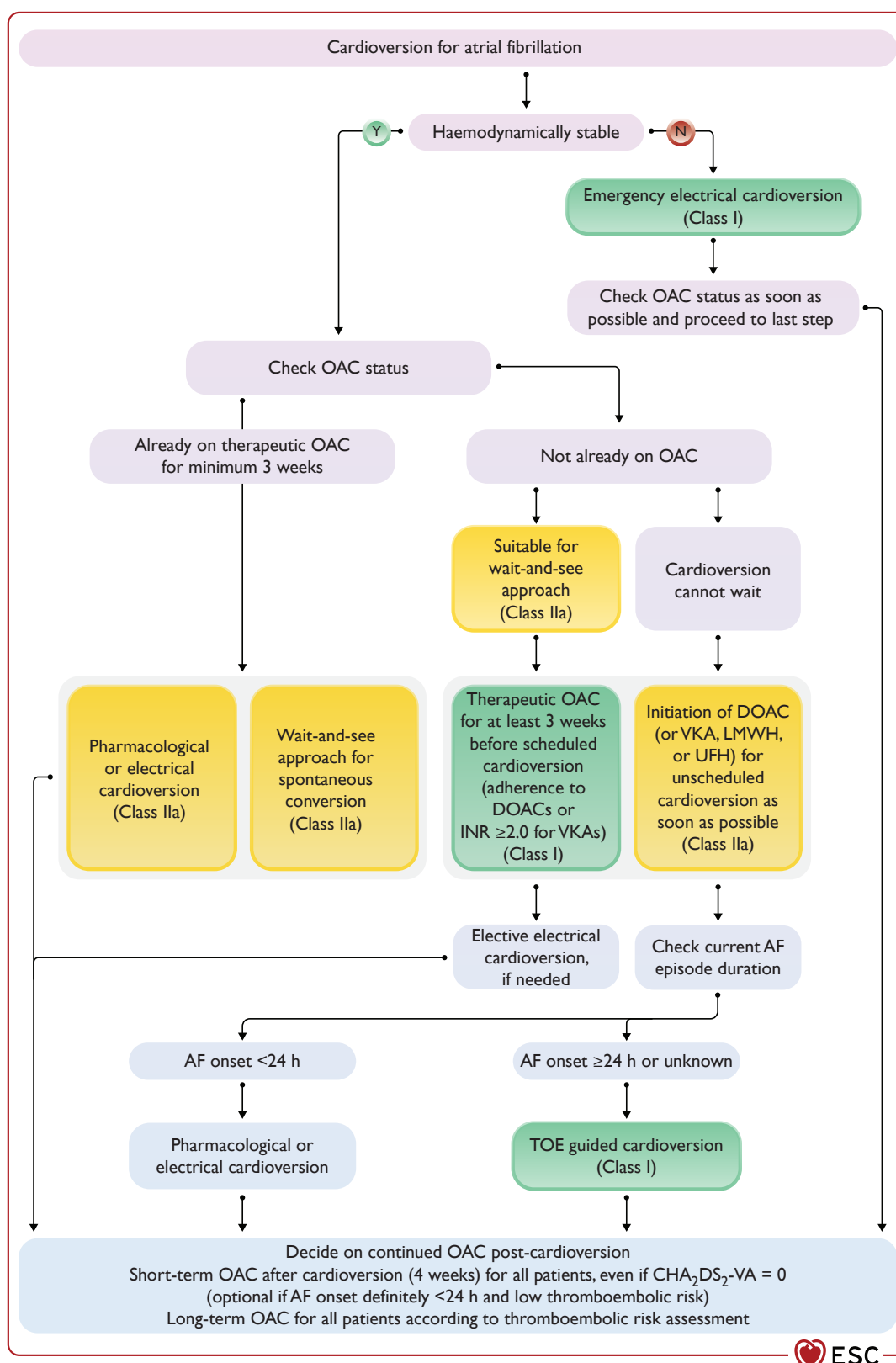


Figure 12 Approaches for cardioversion in patients with AF. AF, atrial fibrillation; CHA₂DS₂-VA, congestive heart failure, hypertension, age ≥75 years (2 points), diabetes mellitus, prior stroke/transient ischaemic attack/arterial thromboembolism (2 points), vascular disease, age 65–74 years; h, hour; LMWH, low molecular weight heparin; DOAC, direct oral anticoagulant; OAC, oral anticoagulant; TOE, transoesophageal echocardiography; UFH, unfractionated heparin; VKA, vitamin K antagonist. Flowchart for decision-making on cardioversion of AF depending on clinical presentation, AF onset, oral anticoagulation intake, and risk factors for stroke. ^aSee Section 6.

Cardiovascular Hospitalization or Death from Any Cause in Patients with Atrial Fibrillation/Atrial Flutter), dronedarone significantly reduced the risk of hospitalization due to cardiovascular events or death as compared with placebo in patients with paroxysmal or persistent AF.⁵¹² The CASTLE-AF trial (Catheter Ablation versus Standard Conventional Treatment in Patients With Left Ventricle Dysfunction and AF) demonstrated that a rhythm control strategy with catheter ablation can improve mortality and morbidity in selected patients with HFrEF and an implanted cardiac device.⁴ In end-stage HFrEF, the CASTLE-HTx trial (Catheter Ablation for Atrial Fibrillation in Patients With End-Stage Heart Failure and Eligibility for Heart Transplantation) found, in a single centre, that catheter ablation combined with guideline-directed medical therapy significantly reduced the composite of death from any cause, implantation of left ventricular assist device, or urgent heart transplantation compared with medical treatment.⁵¹³ At the same time, however, the CABANA trial (Catheter Ablation versus Anti-arrhythmic Drug Therapy for Atrial Fibrillation) could not demonstrate a significant difference in mortality and morbidity between catheter ablation and standard rhythm and/or rate control drugs in symptomatic AF patients older than 64 years, or younger than 65 years with risk factors for stroke.³ EAST-AFNET 4 (Early treatment of Atrial fibrillation for Stroke prevention Trial) reported that implementation of a rhythm control strategy within 1 year compared with usual care significantly reduced the risk of cardiovascular death, stroke, or hospitalization for heart failure or acute coronary syndrome in patients older than 75 years or with cardiovascular conditions.¹⁷ Of note, rhythm control was predominantly pursued with antiarrhythmic drugs (80% of patients in the intervention arm). Usual care consisted of rate control therapy; only when uncontrolled AF-related symptoms occurred was rhythm control considered. Patients in the EAST-AFNET 4 trial all had cardiovascular risk factors but were at an early stage of AF, with more than 50% being in sinus rhythm and 30% being asymptomatic at the start of the study.

Based on all of these studies, this task force concludes that implementation of a rhythm control strategy can be safely instituted and confers amelioration of AF-related symptoms. Beyond control of symptoms, sinus rhythm maintenance should also be pursued to reduce morbidity and mortality in selected groups of patients.^{4,17,502,513,514}

Any rhythm control procedure has an inherent risk of thromboembolism. Patients undergoing cardioversion require at least 3 weeks of therapeutic anticoagulation (adherence to DOACs or INR >2 if VKA) prior to the electrical or pharmacological procedure. In acute settings or when early cardioversion is needed, transoesophageal echocardiography (TOE) can be performed to exclude cardiac thrombus prior to cardioversion. These approaches have been tested in multiple RCTs.^{319–321} In the case of thrombus detection, therapeutic anticoagulation should be instituted for a minimum of 4 weeks followed by repeat TOE to ensure thrombus resolution. When the definite duration of AF is less than 48 hours, cardioversion has typically been considered without the need for pre-procedure OAC or TOE for thrombus exclusion. However, the 'definite' onset of AF is often not known, and observational data suggest that stroke/thromboembolism risk is lowest within a much shorter time period.^{515–519} This task force reached consensus that safety should come first. Cardioversion is not recommended if AF duration is longer than 24 hours, unless the patient has already received at least 3 weeks of therapeutic anticoagulation or a TOE is performed to exclude intracardiac thrombus. Most patients should continue OAC for at least 4 weeks post-cardioversion. Only for those without thromboembolic risk factors and sinus rhythm restoration within 24 h of AF onset is post-cardioversion OAC optional. In the presence of any thromboembolic risk factors, long-term OAC should be instituted irrespective of the rhythm outcome.

Recommendation Table 15 — Recommendations for general concepts in rhythm control (see also Evidence Table 15)

Recommendations	Class ^a	Level ^b
Electrical cardioversion is recommended in AF patients with acute or worsening haemodynamic instability to improve immediate patient outcomes. ⁵²⁰	I	C
Direct oral anticoagulants are recommended in preference to VKAs in eligible patients with AF undergoing cardioversion for thromboembolic risk reduction. ^{293,319–321,521}	I	A
Therapeutic oral anticoagulation for at least 3 weeks (adherence to DOACs or INR ≥2.0 for VKAs) is recommended before scheduled cardioversion of AF and atrial flutter to prevent procedure-related thromboembolism. ^{319–321}	I	B
Transoesophageal echocardiography is recommended if 3 weeks of therapeutic oral anticoagulation has not been provided, for exclusion of cardiac thrombus to enable early cardioversion. ^{319–321,522}	I	B
Oral anticoagulation is recommended to continue for at least 4 weeks in all patients after cardioversion and long-term in patients with thromboembolic risk factor(s) irrespective of whether sinus rhythm is achieved, to prevent thromboembolism. ^{239,319,320,523,524}	I	B
Cardioversion of AF (either electrical or pharmacological) should be considered in symptomatic patients with persistent AF as part of a rhythm control approach. ^{52,525,526}	IIa	B
A wait-and-see approach for spontaneous conversion to sinus rhythm within 48 h of AF onset should be considered in patients without haemodynamic compromise as an alternative to immediate cardioversion. ^{10,525}	IIa	B
Implementation of a rhythm control strategy should be considered within 12 months of diagnosis in selected patients with AF at risk of thromboembolic events to reduce the risk of cardiovascular death or hospitalization. ^{17,527}	IIa	B
Initiation of therapeutic anticoagulation should be considered as soon as possible in the setting of unscheduled cardioversion for AF or atrial flutter to prevent procedure-related thromboembolism. ^{319–321,528}	IIa	B
Repeat transoesophageal echocardiography should be considered before cardioversion if thrombus has been identified on initial imaging to ensure thrombus resolution and prevent peri-procedural thromboembolism. ⁵²⁹	IIa	C
Early cardioversion is not recommended without appropriate anticoagulation or transoesophageal echocardiography if AF duration is longer than 24 h, or there is scope to wait for spontaneous cardioversion. ⁵²²	III	C

AF, atrial fibrillation; DOAC, direct oral anticoagulant; INR, international normalized ratio of prothrombin time; VKA, vitamin K antagonist.

^aClass of recommendation.

^bLevel of evidence.

7.2.2. Electrical cardioversion

Electrical cardioversion (ECV) can be safely applied in the elective and acute setting (see [Supplementary data online, Additional Evidence Table S18](#)) with sedation by intravenous midazolam, propofol, or etomidate.⁵³⁰ Structured and integrated care for patients with acute-onset AF at the emergency department is associated with better outcomes without compromising safety.⁵³¹ Rates of major adverse clinical events after cardioversion are significantly lower with DOACs compared with warfarin.²⁹³

Blood pressure monitoring and oximetry should be used routinely. Intravenous atropine or isoproterenol, or temporary transcutaneous pacing, should be available in case of post-cardioversion bradycardia. Biphasic defibrillators are standard because of their superior efficacy compared with monophasic defibrillators.^{532–534} There is no single optimal position for electrodes, with a meta-analysis of 10 RCTs showing no difference in sinus rhythm restoration comparing anterior-posterior with antero-lateral electrode positioning.⁵³⁵ Applying active compression to the defibrillation pads is associated with lower defibrillation thresholds, lower total energy delivery, fewer shocks for successful ECV, and higher success rates.⁵³⁶ A randomized trial showed that maximum fixed-energy shocks were more effective than low-escalating energy for ECV.⁵³⁷

Immediate administration of vernakalant,⁵³⁸ or pre-treatment for 3–4 days with flecainide,^{539,540} ibutilide,^{541,542} propafenone,⁵⁴³ or amiodarone^{544–546} improves the rate of successful ECV and can facilitate long-term maintenance of sinus rhythm by preventing early recurrent AF.⁵⁴⁷ A meta-analysis demonstrated that pre-treatment with amiodarone (200–800 mg/day for 1–6 weeks pre-cardioversion) and post-treatment (200 mg/day) significantly improved the restoration and maintenance of sinus rhythm after ECV of AF.⁵⁴⁶

In some cases of persistent AF there is no clear relationship between the arrhythmia and symptoms. In these cases, restoring sinus rhythm by ECV might serve to confirm the impact of arrhythmia on symptoms and/or on heart failure symptoms and signs. Such an approach might be useful to identify truly asymptomatic individuals, to assess the impact of AF on LV function in patients with HFrEF, and to distinguish AF-related symptoms from heart failure symptoms.

Recommendation Table 16 — Recommendations for electrical cardioversion of AF (see also Evidence Table 16)

Recommendations	Class ^a	Level ^b
Electrical cardioversion as a diagnostic tool should be considered in patients with persistent AF where there is uncertainty about the value of sinus rhythm restoration on symptoms, or to assess improvement in left ventricular function. ⁵⁴⁸	IIa	C

AF, atrial fibrillation.

^aClass of recommendation.

^bLevel of evidence.

7.2.3. Pharmacological cardioversion

Pharmacological cardioversion to sinus rhythm is an elective procedure in haemodynamically stable patients. It is less effective than electrical cardioversion for restoration of sinus rhythm,⁵⁴⁹ with timing of cardioversion being a significant determinant of success.⁵⁵⁰ There are limited contemporary data on the true efficacy of pharmacological cardioversion, which are likely biased by the spontaneous restoration of sinus

rhythm in 76%–83% of patients with recent-onset AF (10%–18% within the first 3 h, 55%–66% within 24 h, and 69% within 48 h).^{10,119,445,551–555}

The choice of a specific drug is based on the type and severity of concomitant heart disease ([Table 13](#)). A meta-analysis demonstrated that intravenous vernakalant and flecainide have the highest conversion rate within 4 h, possibly allowing discharge from the emergency department and reducing hospital admissions. Intravenous and oral formulations of Class IC antiarrhythmics (flecainide more so than propafenone) are superior regarding conversion rates within 12 h, while amiodarone efficacy is exhibited in a delayed fashion (within 24 h).⁵⁵⁶ Pharmacological cardioversion does not require fasting, sedation, or anaesthesia. Anticoagulation should be started or continued according to a formal (re-)assessment of thromboembolic risk.^{554,557–559}

A single self-administered oral dose of flecainide or propafenone (pill-in-the-pocket) is effective in symptomatic patients with infrequent and recent-onset paroxysmal AF. Safe implementation of this strategy requires patient screening to exclude sinus node dysfunction, atrioventricular conduction defects, or Brugada syndrome, as well as prior in-hospital validation of its efficacy and safety.⁵⁶⁰ An atrioventricular node-blocking drug should be instituted in patients treated with Class IC AADs to avoid 1:1 conduction if the rhythm transforms to AFL.⁵⁶¹

Recommendation Table 17 — Recommendations for pharmacological cardioversion of AF (see also Evidence Table 17)

Recommendations	Class ^a	Level ^b
Intravenous flecainide or propafenone is recommended when pharmacological cardioversion of recent-onset AF is desired, excluding patients with severe left ventricular hypertrophy, HFrEF, or coronary artery disease. ^{562–566}	I	A
Intravenous vernakalant is recommended when pharmacological cardioversion of recent-onset AF is desired, excluding patients with recent ACS, HFrEF, or severe aortic stenosis. ^{562–568}	I	A
Intravenous amiodarone is recommended when cardioversion of AF in patients with severe left ventricular hypertrophy, HFrEF, or coronary artery disease is desired, accepting there may be a delay in cardioversion. ^{473,569,570}	I	A
A single self-administered oral dose of flecainide or propafenone (pill-in-the-pocket) should be considered for patient-led cardioversion in selected patients with infrequent paroxysmal AF, after efficacy and safety assessment and excluding those with severe left ventricular hypertrophy, HFrEF, or coronary artery disease. ^{560,571–573}	IIa	B
Pharmacological cardioversion is not recommended for patients with sinus node dysfunction, atrioventricular conduction disturbances, or prolonged QTc (>500 ms), unless risks for proarrhythmia and bradycardia have been considered.	III	C

ACS, acute coronary syndromes; AF, atrial fibrillation; HFrEF, heart failure with reduced ejection fraction.

^aClass of recommendation.

^bLevel of evidence.

Table 13 Antiarrhythmic drugs for sinus rhythm restoration

Drug	Administration route	Initial dosing	Subsequent dosing [long-term approach]	Acute success rate and time to sinus rhythm	Contraindications and precautions
Flecainide	Oral	200–300 mg	[long-term 50–150 mg twice daily]	50%–60% at 3 h and 75%–85% at 6–8 h (3–8 h)	• Should not be used in patients with severe structural or coronary artery disease, Brugada syndrome, or severe renal failure (CrCl <35 mL/min/1.73 m²). • Prior documentation of safety and efficacy in an inpatient setting is recommended prior to pill-in-the-pocket use. • An AVN-blocking agent should be administered to avoid 1:1 conduction if transformation to AFL. • Drug infusion should be discontinued in case of QRS widening >25% or bundle branch block occurrence. • Caution is needed in patients with sinus node disease and AVN dysfunction. • Do NOT use for conversion of atrial flutter.
	Intravenous	1–2 mg/kg over 10 min		52%–95% (Up to 6 h)	
Propafenone	Oral	450–600 mg	[long-term 150–300 mg three times daily]	45%–55% at 3 h, 69%–78% at 8 h (3–8 h)	
	Intravenous	1.5–2 mg/kg over 10 min		43%–89% (Up to 6 h)	
Amiodarone	Intravenous (/oral)	300 mg intravenous over 30–60 min	900–1200 mg intravenous over 24 hours (or 200 mg oral three times daily for 4 weeks). [long-term 200 mg oral daily]	44% (8–12 h to several days)	• May cause phlebitis (use a large peripheral vein, avoid i.v. administration >24 h and use preferably volumetric pump). • May cause hypotension, bradycardia/atrioventricular block, QT prolongation. • Only if no other option in patients with hyperthyroidism (risk of thyrotoxicosis). • Consider the broad range of drug interactions.
Ibutilide	Intravenous	1 mg over 10 min (0.01 mg/kg if body weight <60 kg)	1 mg over 10 min (10–20 min after the initial dose)	31%–51% (30–90 min) in AF 60–75% in AFL (60 min)	• Should be used in the setting of a cardiac care unit as it may cause QT prolongation and torsades de pointes. • ECG monitoring for at least 4 h after administration to detect any proarrhythmic effects. • Should not be used in patients with prolonged QT, severe LVH, or low LVEF.
Vernakalant	Intravenous	3 mg/kg over 10 min (maximum 339 mg)	2 mg/kg over 10 min (10–15 min after the initial dose) (maximum 226 mg)	50% within 10 min	• Should not be used in patients with arterial hypotension (SBP <100 mmHg), recent ACS (within 1 month), NYHA III or IV HF, QT prolongation or severe aortic stenosis. • May cause arterial hypotension, QT prolongation, QRS widening, or non-sustained ventricular tachycardia.

ACS, acute coronary syndromes; AF, atrial fibrillation; AFL, atrial flutter; AVN, atrioventricular node; CrCl, creatinine clearance; ECG, electrocardiogram; HF, heart failure; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; NYHA, New York Heart Association; QT, QT interval; SBP, systolic blood pressure. Long-term dosage for maintenance of sinus rhythm is indicated in [square brackets]. Long-term oral dosing for dronedarone is 400 mg twice daily, and for sotalol 80–160 mg twice daily.

7.2.4. Antiarrhythmic drugs

The aims of long-term rhythm control are to maintain sinus rhythm, improve quality of life, slow the progression of AF, and potentially reduce morbidity related to AF episodes (see [Supplementary data online, Additional Evidence Table S19](#)).^{17,445,574,575} Antiarrhythmic drugs do not eliminate recurrences of AF, but in patients with paroxysmal or persistent AF, a recurrence is not equivalent to treatment

failure if episodes are less frequent, briefer, or less symptomatic. Antiarrhythmic drugs also have a role for long-term rhythm control in AF patients that are considered ineligible or unwilling to undergo catheter or surgical ablation.

Before starting AAD treatment, reversible triggers should be identified and underlying comorbidities treated to reduce the arrhythmogenic substrate, prevent progression of AF, and facilitate maintenance of sinus

rhythm.^{39,128} The RACE 3 trial, including patients with early persistent AF and mild-to-moderate heart failure (predominantly HFpEF and HFmrEF), showed that targeted therapy of underlying conditions improved sinus rhythm maintenance at 1 year (75% vs. 63% as compared with standard care).³⁹ The selection of an AAD for long-term rhythm control requires careful evaluation that takes into account AF type, patient parameters, and safety profile.⁴⁴⁵ It also includes shared decision-making, balancing the benefit/risk ratio of AADs in comparison with other strategies. Notably, recent evidence has shown that careful institution of AADs can be performed safely.¹⁷

The long-term effectiveness of AADs is limited. In a meta-analysis of 59 RCTs, AADs reduced AF recurrences by 20%–50% compared with no treatment, placebo, or drugs for rate control.^{576,577} When one AAD fails to reduce AF recurrences, a clinically acceptable response may be achieved with another drug, particularly if from a different class.⁵⁷⁸ Combinations of AADs are not recommended. The data available suggest that AADs do not produce an appreciable effect on mortality or other cardiovascular complications with the exception of increased mortality signals for sotalol^{574,579,580} and amiodarone.⁵⁸¹ In contrast, use of AADs within a rhythm control strategy can be associated with reduction of morbidity and mortality in selected patients.⁵⁸²

All AADs may produce serious cardiac (proarrhythmia, negative inotropism, hypotension) and extracardiac adverse effects (organ toxicity, predominantly amiodarone). Drug safety, rather than efficacy, should determine the choice of drug. The risk of proarrhythmia increases in patients with structural heart disease. Suggested doses for long-term oral AAD are presented in [Table 13](#).^{577,583,584}

Recommendation Table 18 — Recommendations for antiarrhythmic drugs for long-term maintenance of sinus rhythm (see also Evidence Table 18)

Recommendations	Class ^a	Level ^b
Amiodarone is recommended in patients with AF and HFrEF requiring long-term antiarrhythmic drug therapy to prevent recurrence and progression of AF, with careful consideration and monitoring for extracardiac toxicity. ^{577,585–587}	I	A
Dronedarone is recommended in patients with AF requiring long-term rhythm control, including those with HFmrEF, HFpEF, ischaemic heart disease, or valvular disease to prevent recurrence and progression of AF. ^{512,577,588,589}	I	A
Flecainide or propafenone is recommended in patients with AF requiring long-term rhythm control to prevent recurrence and progression of AF, excluding those with impaired left ventricular systolic function, severe left ventricular hypertrophy, or coronary artery disease. ^{526,577,585,590}	I	A
Concomitant use of a beta-blocker, diltiazem, or verapamil should be considered in AF patients treated with flecainide or propafenone, to prevent 1:1 conduction if their rhythm is transformed to atrial flutter.	IIa	C

Continued

Sotalol may be considered in patients with AF requiring long-term rhythm control with normal LVEF or coronary artery disease to prevent recurrence and progression of AF, but requires close monitoring of QT interval, serum potassium levels, renal function, and other proarrhythmia risk factors.^{585,587}

Antiarrhythmic drug therapy is not recommended in patients with advanced conduction disturbances unless antibradycardia pacing is provided.

IIb

A

III

C

AF, atrial fibrillation; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction.

^aClass of recommendation.

^bLevel of evidence.

7.2.5. Catheter ablation

Catheter ablation prevents AF recurrences, reduces AF burden, and improves quality of life in symptomatic paroxysmal or persistent AF where the patient is intolerant or does not respond to AAD.^{503–509}

Multiple RCTs have provided evidence in favour of catheter ablation as a first-line approach for rhythm control in patients with paroxysmal AF, with a similar risk of adverse events as compared with initial AAD treatment (see [Supplementary data online, Additional Evidence Table S20](#)).^{15,16,591–594} In contrast, it is not clear whether first-line ablation is superior to drug therapy in persistent AF. Catheter ablation may also have a role in patients with symptoms due to prolonged pauses upon AF termination, where non-randomized data have shown improved symptoms, and avoidance of pacemaker implantation.^{595–598}

Pulmonary vein isolation (PVI) remains the cornerstone of AF catheter ablation,^{503,508,593,599} but the optimal ablation strategy has not been clarified in the non-paroxysmal AF population.⁶⁰⁰ New technologies are emerging, such as pulsed field ablation, in which high-amplitude electrical pulses are used to ablate the myocardium by electroporation with high tissue specificity. In a single-blind RCT of 607 patients, pulsed field ablation was non-inferior for efficacy and safety endpoints compared with conventional radiofrequency or cryoballoon ablation.⁶⁰¹ Regarding timing of ablation, a small RCT found that delaying catheter ablation in patients with paroxysmal or persistent AF by 12 months (while on optimized medical therapy) did not impact on arrhythmia-free survival compared with ablation within 1 month.⁶⁰²

As with any type of rhythm control, many patients in clinical practice will not be suitable for catheter ablation due to factors that reduce the likelihood of a positive response, such as left atrial dilatation. Definitive evidence that supports the prognostic benefit of catheter ablation is needed before this invasive treatment can be considered for truly asymptomatic patients. As previously noted, the CABANA trial did not confirm a benefit of catheter ablation compared with medical therapy, although high crossover rates and low event rates may have diluted the treatment effect.³ Therefore, only highly selected asymptomatic patients could be candidates for catheter ablation, and only after detailed discussion of associated risks and potential benefit of delaying AF progression.^{4,603} Randomized trials have shown that AF catheter ablation in patients with HFmrEF significantly reduces arrhythmia recurrence and increases ejection fraction, with improvement in clinical outcomes and mortality also observed in selected patients.^{4,513,514,604–612} Several

characteristics, including but not limited to AF type, left atrial dilatation, and the presence of atrial and/or ventricular fibrosis, could refine patient selection to maximize outcome benefit from AF catheter ablation in patients with HFrEF.^{604,608,613–617} The prognostic value of catheter ablation in patients with HFpEF is less well established than for HFrEF.^{617–626}

Recent registries and trials report varying rates of peri-procedural serious adverse events associated with catheter ablation (2.9%–7.2%) with a very low 30 day mortality rate (<0.1%). Operator experience and procedural volume at the ablation centre are critical, since they are associated with complication rates and 30 day mortality.^{627–631}

Intermittent rhythm monitoring has typically been used to detect AF relapses following catheter ablation. Recent technology developments such as smartwatch or smartphone photoplethysmography and wearable patches may have an emerging role in post-ablation monitoring.^{632,633} In addition, implantable loop recorders have been used to quantify AF burden before and after ablation as an additional endpoint beyond binary AF elimination.⁶³⁴ Management of arrhythmia recurrence post-ablation is an informed, shared decision-making process driven by available options for symptom control. In the post-AF ablation context, there is data supporting a role for AAD continuation or re-initiation, even for previously ineffective drugs.⁶³⁵ A short-term AAD treatment (2–3 months) following ablation reduces early recurrences of AF,^{554,635–639} but does not affect late recurrences^{636,637,640–642} or 1 year clinical outcomes.⁶⁴² Repeat PVI should be offered in patients with AF recurrence if symptom improvement was demonstrated after the first ablation, with shared decision-making and clear goals of treatment.^{643–645}

Recommendation Table 19 — Recommendations for catheter ablation of AF (see also Evidence Table 19)

Recommendations	Class ^a	Level ^b
Shared decision-making		
Shared decision-making is recommended when considering catheter ablation for AF, taking into account procedural risks, likely benefits, and risk factors for AF recurrence. ^{128,210,503,646}	I	C
AF patients resistant or intolerant to antiarrhythmic drug therapy		
Catheter ablation is recommended in patients with paroxysmal or persistent AF resistant or intolerant to antiarrhythmic drug therapy to reduce symptoms, recurrence, and progression of AF. ^{3,15,503,505,506,508}	I	A
First-line rhythm control therapy		
Catheter ablation is recommended as a first-line option within a shared decision-making rhythm control strategy in patients with paroxysmal AF, to reduce symptoms, recurrence, and progression of AF. ^{16,591–594}	I	A
Catheter ablation may be considered as a first-line option within a shared decision-making rhythm control strategy in selected patients with persistent AF to reduce symptoms, recurrence, and progression of AF.	IIb	C

Continued

Patients with heart failure		
AF catheter ablation is recommended in patients with AF and HFrEF with high probability of tachycardia-induced cardiomyopathy to reverse left ventricular dysfunction. ^{604,611}	I	B
AF catheter ablation should be considered in selected AF patients with HFrEF to reduce HF hospitalization and prolong survival. ^{4,513,514,604,610,612}	IIa	B
Sinus node disease/tachycardia–bradycardia syndrome		
AF catheter ablation should be considered in patients with AF-related bradycardia or sinus pauses on AF termination to improve symptoms and avoid pacemaker implantation. ^{595–598}	IIa	C
Recurrence after catheter ablation		
Repeat AF catheter ablation should be considered in patients with AF recurrence after initial catheter ablation, provided the patient’s symptoms were improved after the initial PVI or after failed initial PVI, to reduce symptoms, recurrence, and progression of AF. ^{643–645}	IIa	B

AF, atrial fibrillation; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; PVI, pulmonary vein isolation.
^aClass of recommendation.
^bLevel of evidence.

7.2.6. Anticoagulation in patients undergoing catheter ablation

The presence of left atrial thrombus is a contraindication to catheter-based AF ablation due to the risk of thrombus dislodgement leading to ischaemic stroke. Patients planned for catheter ablation of AF with an increased risk of thromboembolism should be on OAC for at least 3 full weeks prior to the procedure.^{554,647}

There is a wide range in practice for visualization of intra-atrial thrombi prior to catheter ablation, including TOE, intracardiac echocardiography, or delayed phase cardiac computed tomography (CT).^{554,648} The prevalence of left atrial thrombus was 1.3% and 2.7% in two meta-analyses of observational studies in patients planned for catheter ablation of AF on adequate OAC.^{649,650} The prevalence of left atrial thrombus was higher in patients with elevated stroke risk scores, and in patients with non-paroxysmal compared with paroxysmal AF.⁶⁵⁰ In addition, several patient subgroups with AF have increased risk of ischaemic stroke and intracardiac thrombus even if treated with adequate anticoagulation, including those with cardiac amyloidosis, rheumatic heart disease, and hypertrophic cardiomyopathy (HCM). Cardiac imaging before catheter ablation should be considered in these high-risk patient groups regardless of preceding effective OAC. Observational studies suggest that patients with a low thromboembolic risk profile may be managed without visualization of the LAA,^{651–653} but no RCTs have been performed (see [Supplementary data online, Additional Evidence Table S21](#)).

For patients who have been anticoagulated prior to the ablation procedure it is recommended to avoid interruption of OAC (see [Supplementary data online, Additional Evidence Table S22](#)).^{654–656} Patients with interrupted OAC showed an increase in silent stroke detected by brain magnetic resonance imaging (MRI) as compared with those with uninterrupted OAC.^{657–659} In a true uninterrupted

DOAC strategy for once-daily dosing, a pre-procedural shift to evening intake might be considered to mitigate bleeding risk. Randomized trials show comparable safety and efficacy with minimally interrupted OAC (withholding the morning DOAC dose on the day of the procedure) and a totally uninterrupted peri-ablation OAC strategy.⁶⁵⁵

Anticoagulation with heparin during AF ablation is common practice.⁵⁵⁴ Post-ablation DOACs should be continued as per the dosing regimen when haemostasis has been achieved.^{335,554,647} All patients should be kept on an OAC for at least 2 months after an AF ablation procedure irrespective of estimated thromboembolic risk (see [Supplementary data online, Additional Evidence Table S23](#)).⁶⁴⁷ Meta-analyses of observational studies have tried to assess the safety of stopping OAC treatment after catheter ablation for AF, but the results have been heterogenous.^{660–663} Until the completion of relevant RCTs (e.g. NCT02168829), it is recommended to continue OAC therapy post-AF ablation according to the patient's CHA₂DS₂-VA score and not the perceived success of the ablation procedure.⁵⁵⁴

Recommendation Table 20 — Recommendations for anticoagulation in patients undergoing catheter ablation (see also Evidence Table 20)

Recommendations	Class ^a	Level ^b
Initiation of oral anticoagulation is recommended at least 3 weeks prior to catheter-based ablation in AF patients at elevated thromboembolic risk, to prevent peri-procedural ischaemic stroke and thromboembolism. ^{554,647}	I	C
Uninterrupted oral anticoagulation is recommended in patients undergoing AF catheter ablation to prevent peri-procedural ischaemic stroke and thromboembolism. ^{664,665}	I	A
Continuation of oral anticoagulation is recommended for at least 2 months after AF ablation in all patients, irrespective of rhythm outcome or CHA ₂ DS ₂ -VA score, to reduce the risk of peri-procedural ischaemic stroke and thromboembolism. ^{554,663}	I	C
Continuation of oral anticoagulation is recommended after AF ablation according to the patient's CHA ₂ DS ₂ -VA score, and not the perceived success of the ablation procedure, to prevent ischaemic stroke and thromboembolism. ⁵⁵⁴	I	C
Cardiac imaging should be considered prior to catheter ablation of AF in patients at high risk of ischaemic stroke and thromboembolism despite taking oral anticoagulation to exclude thrombus. ^{649,650}	IIa	B

AF, atrial fibrillation; CHA₂DS₂-VA, congestive heart failure, hypertension, age ≥75 years (2 points), diabetes mellitus, prior stroke/transient ischaemic attack/arterial thromboembolism (2 points), vascular disease, age 65–74 years.

^aClass of recommendation.

^bLevel of evidence.

7.2.7. Endoscopic and hybrid AF ablation

Minimally invasive surgical AF ablation can be performed via a thoracoscopic approach or a subxiphoid approach. The term endoscopic covers both strategies. Hybrid ablation approaches have been developed where endoscopic epicardial ablation on the beating heart is performed in combination with endocardial catheter ablation, either in a simultaneous or sequential procedure. The rationale for combining an endocardial with an epicardial approach is that a more effective transmural ablation strategy can be pursued.^{666,667}

For paroxysmal AF, an endoscopic or hybrid ablation approach may be considered after a failed percutaneous catheter ablation strategy.^{668–670} Long-term follow-up of the FAST RCT (mean of 7.0 years), which included patients with paroxysmal and persistent AF, found arrhythmia recurrence was common but substantially lower with thoracoscopic ablation than catheter ablation: 34/61 patients (56%) compared with 55/63 patients (87%), with $P < .001$ for the comparison.⁶⁶⁹ For persistent AF, endoscopic or hybrid ablation approaches are suitable as a first procedure to maintain long-term sinus rhythm in selected patients.^{667–672} A meta-analysis of three RCTs confirmed a lower rate of atrial arrhythmia recurrence after thoracoscopic vs. catheter ablation (incidence rate ratio, 0.55; 95% CI, 0.38–0.78; with no heterogeneity between trials).⁶⁶⁹ An RCT with 12 month follow-up published after the meta-analysis in patients with long-standing persistent AF found no difference in arrhythmia freedom comparing thoracoscopic with catheter ablation.⁶⁷³ Although overall morbidity and mortality of both techniques is low, endoscopic and hybrid ablation have higher complication rates than catheter ablation, but similar long-term rates of the composite of mortality, MI, or stroke.^{667,669}

More recent trials have assessed the efficacy and safety of the hybrid epicardial-plus-endocardial approach in persistent AF refractory to AAD therapy, including a single-centre RCT⁶⁷⁰ and two multicentre RCTs.^{671,674} Across these trials, hybrid ablation was consistently superior to catheter ablation alone for maintaining long-term sinus rhythm, without significant differences in major adverse events. Notably, these studies were typically performed in highly experienced centres (see [Supplementary data online, Additional Evidence Table S24](#)).

Similar to other rhythm control approaches, this task force recommends that OAC are continued in all patients who have a risk of thromboembolism, irrespective of rhythm outcome, and regardless of LAA exclusion performed as part of the surgical procedure.

Recommendation Table 21 — Recommendations for endoscopic and hybrid AF ablation (see also Evidence Table 21)

Recommendations	Class ^a	Level ^b
Continuation of oral anticoagulation is recommended in patients with AF at elevated thromboembolic risk after concomitant, endoscopic, or hybrid AF ablation, independent of rhythm outcome or LAA exclusion, to prevent ischaemic stroke and thromboembolism.	I	C

Continued

Endoscopic and hybrid ablation procedures should be considered in patients with symptomatic persistent AF refractory to AAD therapy to prevent symptoms, recurrence, and progression of AF, within a shared decision-making rhythm control team of electrophysiologists and surgeons. ^{667–671,674}	IIa	A
Endoscopic and hybrid ablation procedures may be considered in patients with symptomatic paroxysmal AF refractory to AAD therapy and failed percutaneous catheter ablation strategy to prevent symptoms, recurrence, and progression of AF, within a shared decision-making rhythm control team of electrophysiologists and surgeons. ^{668,669}	IIb	B

AAD, antiarrhythmic drugs; AF, atrial fibrillation; LAA, left atrial appendage.
^aClass of recommendation.
^bLevel of evidence.

7.2.8. AF ablation during cardiac surgery

Atrial fibrillation is a significant risk factor for early mortality, late mortality, and stroke in patients referred for cardiac surgery.^{675–677} The best validated method of surgical ablation is the Maze procedure, consisting of a pattern of transmural lesions including PVI, with subsequent modifications using bipolar radiofrequency and/or cryotherapy ablation with LAA amputation (see [Supplementary data online, Additional Evidence Table S25](#)).^{678–681} Education and training, close co-operation within a multidisciplinary team, and shared decision-making can improve the quality and outcomes of surgical ablation.⁶⁸²

A number of RCTs have shown that surgical AF ablation during cardiac surgery increases freedom from arrhythmia recurrence.^{683–688} Performing surgical AF ablation, mainly targeting those patients needing mitral valve surgery, is not associated with increased morbidity or mortality.^{678,683–685} Observational data, including large registries, have supported the potential value of surgical AF ablation,^{689–700} but further RCTs are needed to evaluate which patients should be selected, and whether this approach contributes to the prevention of stroke, thromboembolism, and death.

Data on pacemaker implantation rates after surgical AF ablation are variable and are likely influenced by centre experience and the patients treated (e.g. underlying sinus node disease). In a systematic review of 22 RCTs (1726 patients), permanent pacemaker implantation rates were higher with surgical AF ablation than without concomitant AF surgery (6.0% vs. 4.1%; RR, 1.69; 95% CI, 1.12–2.54).⁷⁰¹ Observational registry data from contemporary cohorts (2011–2020) suggest an overall pacemaker rate post-operatively of 2.1% in patients selected for surgical AF ablation, with no discernible impact of surgical ablation on the need for a pacemaker, but higher rates in those needing multivalve surgery.⁷⁰² With a safety-first approach in mind, imaging is advised during surgical AF ablation to exclude thrombus and help to plan the surgical approach (e.g. with TOE), regardless of effective pre-procedural anticoagulant use.

Recommendation Table 22 — Recommendations for AF ablation during cardiac surgery (see also Evidence Table 22)

Recommendations	Class ^a	Level ^b
Concomitant surgical ablation is recommended in patients undergoing mitral valve surgery and AF suitable for a rhythm control strategy to prevent symptoms and recurrence of AF, with shared decision-making supported by an experienced team of electrophysiologists and arrhythmia surgeons. ^{683–685,701}	I	A
Intraprocedural imaging for detection of left atrial thrombus in patients undergoing surgical ablation is recommended to guide surgical strategy, independent of oral anticoagulant use, to prevent peri-procedural ischaemic stroke and thromboembolism.	I	C
Concomitant surgical ablation should be considered in patients undergoing non-mitral valve cardiac surgery and AF suitable for a rhythm control strategy to prevent symptoms and recurrence of AF, with shared decision-making supported by an experienced team of electrophysiologists and arrhythmia surgeons. ^{701,703–707}	IIa	B

AF, atrial fibrillation.
^aClass of recommendation.
^bLevel of evidence.

7.2.9. Atrial tachycardia after pulmonary vein isolation

After any ablation for AF, recurrent arrhythmias may manifest as AF, but also as atrial tachycardia (AT). Although AT may be perceived as a step in the right direction by the treating physician, this view is often not shared by the patient because AT can be equally or more symptomatic than the original AF. Conventionally, an early arrhythmia recurrence post-PVI (whether AT, AF, or flutter) is considered potentially transitory.⁷⁰⁸ Recent trials using continuous implantable loop recorders for peri-procedural monitoring have provided insight into the incidence and significance of early arrhythmia recurrences, and have confirmed a link between early and later recurrence.⁷⁰⁹ Discussion of management options for AT post-ablation should ideally involve a multidisciplinary team with experience in interventional management of complex arrhythmias, considering technical challenges, procedural efficacy, and safety, in the context of patient preferences.

8. [E] Evaluation and dynamic reassessment

The development and progression of AF results from continuous interactions between underlying mechanisms (electrical, cellular, neurohormonal, and haemodynamic), coupled with a broad range of clinical factors and associated comorbidities. Each individual factor

has considerable variability over time, affecting its contribution to the AF-promoting substrate. The risk profile of each patient is also far from static, and requires a dynamic mode of care to ensure optimal AF management.^{710,711} Patients with AF require periodic reassessment of therapy based on this changing risk status if we are to improve the overall quality of care. Timely attention to modifiable factors and underpinning comorbidities has the potential to slow or reverse the progression of AF, increase quality of life, and prevent adverse outcomes such as heart failure, thromboembolism, and major bleeding.

The [E] in AF-CARE encompasses the range of activity needed by healthcare professionals and patients to: (i) thoroughly evaluate associated comorbidities and risk factors that can guide treatment; and (ii) provide the dynamic assessment needed to ensure that treatment plans remain suited to that particular patient. This task force recommends an adaptive strategy that not only reacts to changes notified by a patient, but also proactively seeks out issues where altering management could impact on patient wellbeing. Avoidance of unnecessary and costly follow-up is also inherent in this framework, with educated and empowered patients contributing to identifying the need for access to specialist care or an escalation of management. The patient-centred, shared decision philosophy is embedded to improve efficiency in models of care and to address the needs of patients with AF.

Medical history and the results of any tests should be regularly re-evaluated to address the dynamic nature of comorbidities and risk factors.⁷¹² This may have impact on therapeutic decisions; e.g. resumption of full-dose DOAC therapy after improvement in the patient's renal function. The timing of review of the AF-CARE pathway is patient specific and should respond to changes in clinical status. In most cases, this task force advises re-evaluation 6 months after initial presentation, and then at least annually by a healthcare professional in primary or secondary care (see [Figure 3](#)).

8.1. Implementation of dynamic care

A multidisciplinary-based approach is advocated to improve implementation of dynamic AF-CARE (see [Figure 2](#)); although potentially resource intensive, this is preferred to more simplistic or opportunistic methods. For example, in a pragmatic trial of 47 333 AF patients identified through health insurance claims, there was no difference in OAC initiation at 1 year in those randomized to a single mailout of patient and clinician education, compared with those in the usual care group.⁷¹³ For co-ordination of care there is a core role for cardiologists, general practitioners, specialized nurses, and pharmacists.⁷¹⁴ If needed, and depending on local resources, others may also be involved (cardiac surgeons, physiotherapists, neurologists, psychologists, and other allied health professionals). It is strongly advocated that one core team member coordinates care, and that additional team members become involved according to the needs of the individual patient throughout their AF trajectory.

Several organizational models of integrated care for AF have been evaluated, but which components are most useful remains unclear. Some models include a multidisciplinary team,^{715,716} while others are nurse-led^{79,122,124,717} or cardiologist-led.^{79,122,124,717} Several published models used computerized decision support systems or electronic health applications.^{79,122,715,718} Evaluation within RCTs has demonstrated mixed results due to the variety of methods tested and differences in regional care. Several studies report significant improvements with respect to adherence to anticoagulation, cardiovascular mortality, and hospitalization relative to standard of care.^{121–123} However, the

RACE 4 (IntegRAteD Chronic Care Program at Specialized AF Clinic Versus Usual CarE in Patients with Atrial Fibrillation) trial, which included 1375 patients, failed to demonstrate superiority of nurse-led over usual care.⁷⁹ New studies of the components and optimal models for delivery for integrated care approaches in routine practice are ongoing (ACTRN12616001109493, NCT03924739).

8.2. Improving treatment adherence

Advances in the care of patients with AF can only be effective if appropriate tools are available to support the implementation of the treatment regimen.⁷¹⁹ A number of factors are related to the optimal implementation of care at the level of: (i) the individual patient (culture, cognitive impairment, and psychological status); (ii) the treatment (complexity, side effects, polypharmacy, impact on daily life, and cost); (iii) the healthcare system (access to treatment and multidisciplinary approach); and (iv) the healthcare professional (knowledge, awareness of guidelines, expertise, and communication skills). A collaborative approach to patient care, based upon shared decision-making and goals tailored to individual patient needs, is crucial in promoting ongoing patient adherence to the agreed treatment regimen.⁷²⁰ Even when treatment seems feasible for the individual, patients often lack access to reliable and up-to-date information about risks and benefits of various treatment options, and consequently are not empowered to engage in their own management. A sense of ownership that promotes the achievement of joint goals can be encouraged through the use of educational programmes, websites (such as <https://afibmatters.org>), app-based tools, and individually tailored treatment protocols which take into account gender, ethnic, socioeconomic, environmental, and work factors. In addition, practical tools (e.g. schedules, apps, brochures, reminders, pillboxes) can help to implement treatment in daily life.^{721,722} Regular review by members of the multidisciplinary team enables the evolution of a flexible and responsive management regimen that the patient will find easier to follow.

8.3. Cardiac imaging

A TTE is a valuable asset across all four AF-CARE domains when there are changes in the clinical status of an individual patient ([Figure 13](#)).^{723–725} The key findings to consider from an echocardiogram are any structural heart disease (e.g. valvular disease or left ventricular hypertrophy), impairment of left ventricular function (systolic and/or diastolic to classify heart failure subtype), left atrial dilatation, and right heart dysfunction.^{59,67,726} To counter irregularity when in AF, obtaining measurements in cardiac cycles that follow two similar RR intervals can improve the value of parameters compared with sequential averaging of cardiac cycles.^{723,727} Contrast TTE or alternative imaging modalities may be required where image quality is poor, and quantification of left ventricular systolic function is needed for decisions on rate or rhythm control. Other cardiac imaging techniques, such as cardiac magnetic resonance (CMR), CT, TOE, and nuclear imaging can be valuable when: (i) TTE quality is suboptimal for diagnostic purposes; (ii) additional information is needed on structure, substrate, or function; and (iii) to support decisions on interventional procedures (see [Supplementary data online, Figure S1](#)).^{59,724,725,728} As with TTE, other types of cardiac imaging can be challenging in the context of AF irregularity or with rapid heart rate, requiring technique-specific modifications when acquiring ECG-gated sequences.^{729–731}

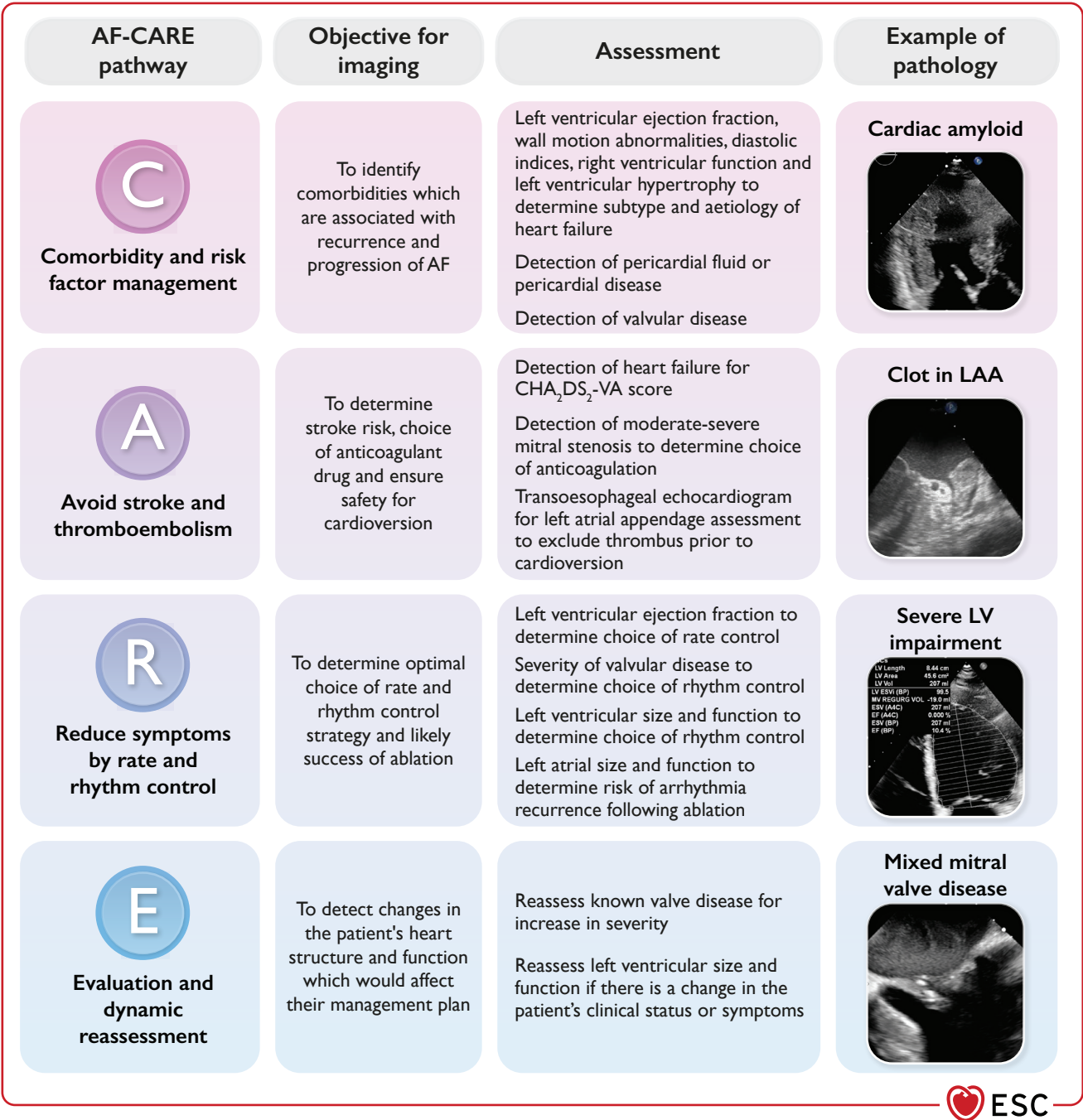


Figure 13 Relevance of echocardiography in the AF-CARE pathway. AF, atrial fibrillation; AF-CARE, atrial fibrillation—[C] Comorbidity and risk factor management, [A] Avoid stroke and thromboembolism, [R] Reduce symptoms by rate and rhythm control, [E] Evaluation and dynamic reassessment; CHA₂DS₂-VA, congestive heart failure, hypertension, age ≥75 years (2 points), diabetes mellitus, prior stroke/transient ischaemic attack/arterial thromboembolism (2 points), vascular disease, age 65–74 years; LAA, left atrial appendage; LV, left ventricle.

8.4. Patient-reported outcome measures

Patients with AF have a lower quality of life compared with the general population.⁷³² Improvement in quality of life and functional status should play a key role in assessing and reassessing treatment decisions (see [Supplementary data online, Additional Evidence Table S26](#)).³⁶ Patient-reported outcome measures are valuable to measure quality of life, functional status, symptoms, and treatment burden for patients

with AF over time.^{55,733–735} Patient-reported outcome measures are playing an increasing role in clinical trials to assess the success of treatment; however, they remain under-utilized.^{736,737} They can be divided into generic or disease-specific tools, with the latter helping to provide insight into AF-related impacts.⁷³⁸ However, multimorbidity can still confound the sensitivity of all PROMs, impacting on association with other established metrics of treatment performance such as mEHRA symptom

class and natriuretic peptides.⁴⁸ Intervention studies have demonstrated an association between improvement in PROM scores and reduction in AF burden and symptoms.^{48,738}

Atrial fibrillation-specific questionnaires include the AF 6 (AF6),⁷³⁹ Atrial Fibrillation Effect on QualiTy-of-Life (AFEQT),⁷⁴⁰ the Atrial Fibrillation Quality of Life Questionnaire (AFQLQ),⁷⁴¹ the Atrial Fibrillation Quality of Life (AF-QoL),⁷⁴² and the Quality of Life in Atrial Fibrillation (QLAF).⁷⁴³ The measurement properties of most of these tools lack sufficient validation.⁴⁹ The International Consortium for Health Outcomes Measurement (ICHOM) working group recommends the use of the AFEQT PROM or a symptom questionnaire called the Atrial Fibrillation Severity Scale (AFSS) for measuring exercise tolerance and the impact of symptoms in AF.⁷⁴⁴ Through wider use of patient experience measures, there is an opportunity at the institutional level to improve the quality of care delivered to patients with AF.^{49–55}

Recommendation Table 23 — Recommendations to improve patient experience (see also Evidence Table 23)

Recommendations	Class ^a	Level ^b
Evaluating quality of care and identifying opportunities for improved treatment of AF should be considered by practitioners and institutions to improve patient experiences. ^{49–55}	IIa	B

AF, atrial fibrillation.
^aClass of recommendation.
^bLevel of evidence.

9. The AF-CARE pathway in specific clinical settings

The following sections detail specific clinical settings where approaches to AF-CARE may vary. Unless specially discussed, measures for [C] comorbidity and risk factor management, [A] avoidance of stroke and thromboembolism, [R] rate and rhythm control, and [E] evaluation and dynamic reassessment should follow the standard pathways introduced in Section 4.

9.1. AF-CARE in unstable patients

Unstable patients with AF include those with haemodynamic instability caused by the arrhythmia or acute cardiac conditions, and severely ill patients who develop AF (sepsis, trauma, surgery, and particularly cancer-related surgery). Conditions such as sepsis, adrenergic overstimulation, and electrolyte disturbances contribute to onset and recurrence of AF in these patients. Spontaneous restoration of sinus rhythm has been reported in up to 83% during the first 48 h after appropriate treatment of the underlying cause.^{551,745}

Emergency electrical cardioversion is still considered the first-choice treatment if sinus rhythm is thought to be beneficial, despite the limitation of having a high rate of immediate relapse.⁷⁴⁶ Amiodarone is a second-line option because of its delayed activity; however, it may be an appropriate alternative in the acute setting.^{747,748} In a multicentre cohort study carried out in the United Kingdom and the United States of America, amiodarone and beta-blockers were similarly effective for

rate control in intensive care patients, and superior to digoxin and calcium channel blockers.⁷⁴⁹ The ultra-short acting and highly selective beta-blocker landiolol can safely control rapid AF in patients with low ejection fraction and acutely decompensated heart failure, with a limited impact on myocardial contractility or blood pressure.^{477,750,751}

9.2. AF-CARE in acute and chronic coronary syndromes

The incidence of AF in acute coronary syndromes (ACS) ranges from 2% to 23%.⁷⁵² The risk of new-onset AF is increased by 60%–77% in patients suffering an MI,⁷⁵³ and AF may be associated with an increased risk of ST-segment elevation myocardial infarction (STEMI) or non-STEMI ACS.⁷⁵⁴ Overall, 10%–15% of AF patients undergo percutaneous intervention (PCI) for CAD.⁷⁵⁵ In addition, AF is a common precipitant for type 2 MI.⁷⁵⁶ Observational studies show that patients with both ACS and AF are less likely to receive appropriate antithrombotic therapy⁷⁵⁷ and more likely to experience adverse outcomes.⁷⁵⁸ Peri-procedural management of patients with ACS or chronic coronary syndromes (CCS) are detailed in the 2023 ESC Guidelines for the management of acute coronary syndromes and 2024 ESC Guidelines for the management of chronic coronary syndromes.^{759,760}

The combination of AF with ACS is the area where use of multiple antithrombotic drugs is most frequently indicated, consisting of antiplatelet agents plus OAC (Figure 14) (see Supplementary data online, Additional Evidence Table S27). There is a general trend to decrease the duration of DAPT to reduce bleeding; however, this may increase ischaemic events and stent thrombosis.^{761,762} In ACS there is a high risk of predominantly platelet-driven atherothrombosis and thus of coronary ischaemic events. Acute coronary syndromes treated by PCI require DAPT for improved short- and long-term prognosis. Therefore, a peri-procedural triple antithrombotic regimen including an OAC, aspirin, and a P2Y₁₂ inhibitor should be the default strategy for most patients. Major thrombotic events vs. major bleeding risk need to be balanced when prescribing antiplatelet therapy and OAC after the acute phase and/or after PCI. The combination of OAC (preferably a DOAC) and a P2Y₁₂ inhibitor results in less major bleeding than triple therapy that includes aspirin. Clopidogrel is the preferred P2Y₁₂ inhibitor, as the evidence for ticagrelor and prasugrel is less clear with higher bleeding risk.^{763–769} Ongoing trials will add to our knowledge about safely combining DOACs with antiplatelet agents (NCT04981041, NCT04436978). When using VKAs with antiplatelet agents, there is consensus opinion to use an INR range of 2.0–2.5 to mitigate excess bleeding risk.

Short-term triple therapy (≤1 week) is recommended for all patients without diabetes after ACS or PCI. In pooled analyses of RCTs, omitting aspirin in patients with ACS undergoing PCI has the potential for higher rates of ischaemic/stent thrombosis, without impact on incident stroke.^{761,762,770–772} None of the trials were powered for ischaemic events. All patients in AUGUSTUS (an open-label, 2 × 2 factorial, randomized controlled clinical trial to evaluate the safety of apixaban vs. vitamin k antagonist and aspirin vs. aspirin placebo in patients with AF and ACS or PCI) received aspirin plus a P2Y₁₂ inhibitor for a median time of 6 days.⁷⁷³ At the end of the trial, apixaban and a P2Y₁₂ inhibitor without aspirin was the optimal treatment regimen for most patients with AF and ACS and/or PCI, irrespective of the patient’s baseline bleeding and stroke risk.^{774,775}

Prolonged triple therapy up to 1 month after ACS/PCI should be considered in patients at high ischaemic risk, e.g. STEMI, prior stent thrombosis, complex coronary procedures, and prolonged cardiac instability, even though these patients were not adequately represented in the RCTs so far available.⁷⁷⁶ In AF

patients with ACS or CCS and diabetes mellitus undergoing coronary stent implantation, prolonging triple therapy with low-dose aspirin, clopidogrel, and an OAC up to 3 months may be of benefit if thrombotic risk outweighs bleeding risk in the individual patient.²⁰⁷

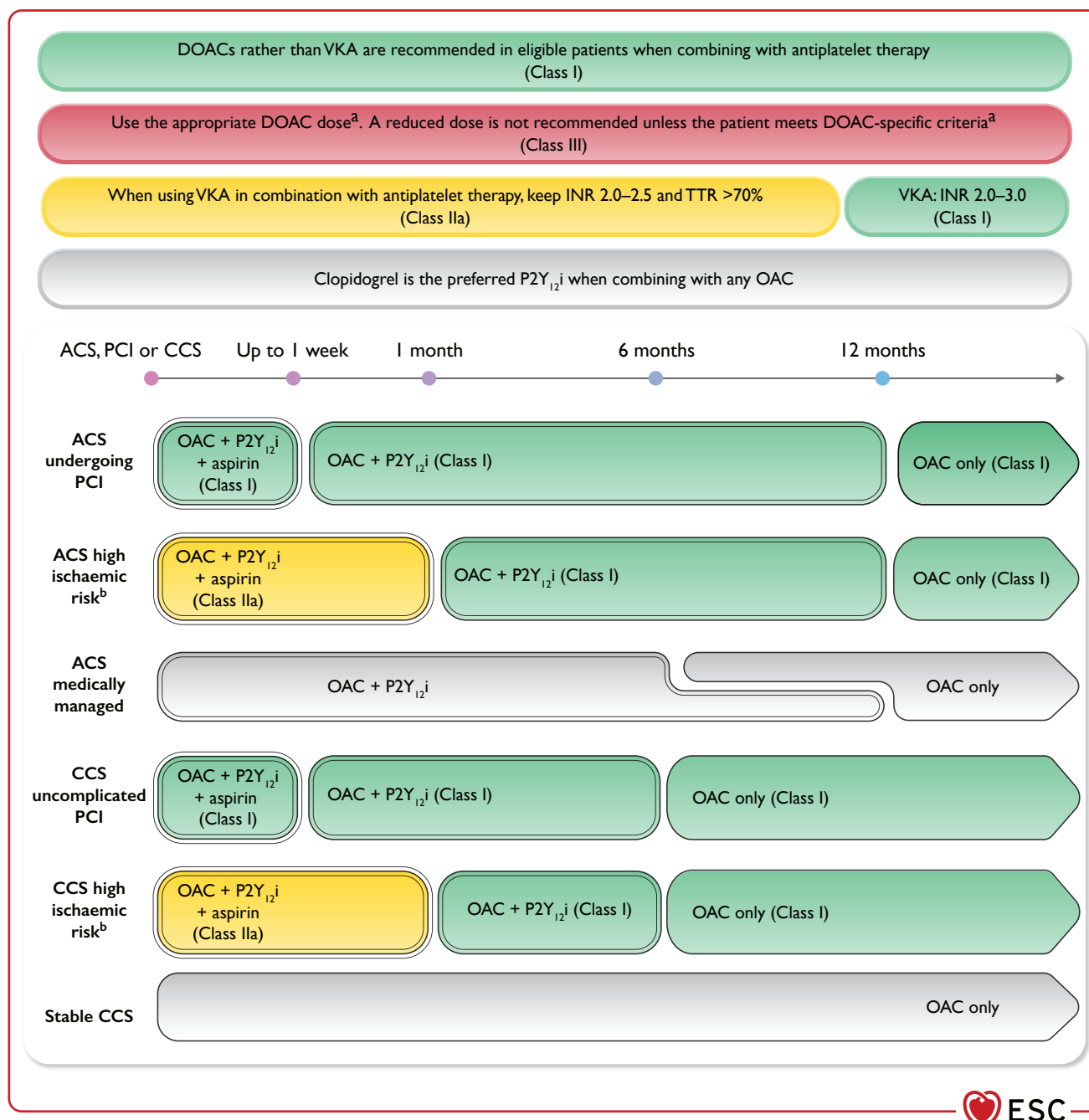


Figure 14 Antithrombotic therapy in patients with AF and acute or chronic coronary syndromes. ACS, acute coronary syndromes; CCS, chronic coronary syndrome; DOAC, direct oral anticoagulant; INR, international normalized ratio of prothrombin time; OAC, oral anticoagulant; P2Y₁₂i, P2Y₁₂-receptor inhibitor antiplatelet agents (clopidogrel, prasugrel, ticagrelor); PCI, percutaneous intervention; TTR, time in therapeutic range; VKA, vitamin K antagonist. The flowchart applies to those patients with an indication for oral anticoagulant therapy. ^aThe full standard dose of DOACs should be used unless the patient fulfils dose-reduction criteria (Table 11). When rivaroxaban or dabigatran are used as the DOAC and concerns about bleeding risk prevail over stent thrombosis or ischaemic stroke, the reduced dose should be considered (15 mg and 110 mg respectively; Class IIa). ^bIn patients with diabetes mellitus undergoing coronary stent implantation, prolonging triple antithrombotic therapy for up to 3 months may be of value if thrombotic risk outweighs the bleeding risk.

The evidence for ACS treated without revascularization is limited. Six to 12 months of a single antiplatelet agent in addition to a long-term DOAC is usually sufficient and can minimize bleeding risk.^{760,764,774} Although there are no head-to-head comparisons between aspirin and clopidogrel, studies have typically used clopidogrel. In patients with stable CCS for more than 12 months, sole therapy with a DOAC is sufficient and no additional antiplatelet therapy is required.³⁵³ In patients at potential risk of gastrointestinal bleeding, use of proton pump inhibitors is reasonable during combined antithrombotic therapy, although evidence in AF patients is limited.^{437,777–779} Multimorbid patients with ACS or CCS need careful assessment of ischaemic risk and management of modifiable bleeding risk factors, with a comprehensive work-up to individually adapt antithrombotic therapy.

Recommendation Table 24 — Recommendations for patients with acute coronary syndromes or undergoing percutaneous intervention (see also Evidence Table 24)

Recommendations	Class ^a	Level ^b
General recommendations for patients with AF and an indication for concomitant antiplatelet therapy		
For combinations with antiplatelet therapy, a DOAC is recommended in eligible patients in preference to a VKA to mitigate bleeding risk and prevent thromboembolism. ^{764,766}	I	A
Rivaroxaban 15 mg once daily should be considered in preference to rivaroxaban 20 mg once daily when combined with antiplatelet therapy in patients where concerns about bleeding risk prevail over concerns about stent thrombosis or ischaemic stroke. ⁷⁶⁵	IIa	B
Dabigatran 110 mg twice daily should be considered in preference to dabigatran 150 mg twice daily when combined with antiplatelet therapy in patients where concerns about bleeding risk prevail over concerns about stent thrombosis or ischaemic stroke. ⁷⁶⁶	IIa	B
Carefully regulated VKA dosing with a target INR of 2.0–2.5 and TTR >70% should be considered when combined with antiplatelet therapy in AF patients to mitigate bleeding risk.	IIa	C
Recommendations for AF patients with ACS		
Early cessation (≤1 week) of aspirin and continuation of an oral anticoagulant (preferably DOAC) with a P2Y ₁₂ inhibitor (preferably clopidogrel) for up to 12 months is recommended in AF patients with ACS undergoing an uncomplicated PCI to avoid major bleeding, if the risk of thrombosis is low or bleeding risk is high. ^{764–767}	I	A
Triple therapy with aspirin, clopidogrel, and oral anticoagulation for longer than 1 week after an ACS should be considered in patients with AF when ischaemic risk outweighs the bleeding risk, with the total duration (≤1 month) decided according to assessment of these risks and clear documentation of the discharge treatment plan. ⁷⁷⁶	IIa	C

Continued

Recommendations for AF patients undergoing PCI		
After uncomplicated PCI, early cessation (≤1 week) of aspirin and continuation of an oral anticoagulant and a P2Y ₁₂ inhibitor (preferably clopidogrel) for up to 6 months is recommended to avoid major bleeding, if ischaemic risk is low. ^{763–766,776,780}	I	A
Triple therapy with aspirin, clopidogrel, and an oral anticoagulant for longer than 1 week should be considered after PCI when the risk of stent thrombosis outweighs the bleeding risk, with the total duration (≤1 month) decided according to assessment of these risks and clear documentation. ⁷⁷⁶	IIa	B
Recommendations for AF patients with chronic coronary or vascular disease		
Antiplatelet therapy beyond 12 months is not recommended in stable patients with chronic coronary or vascular disease treated with oral anticoagulation, due to lack of efficacy and to avoid major bleeding. ^{353,781,782}	III	B

ACS, acute coronary syndromes; AF, atrial fibrillation; DOAC, direct oral anticoagulant; INR, international normalized ratio of prothrombin time; PCI, percutaneous intervention; TTR, time in therapeutic range; VKA, vitamin K antagonist.

^aClass of recommendation.

^bLevel of evidence.

9.3. AF-CARE in vascular disease

Peripheral arterial disease (PAD) is common in patients with AF, ranging from 6.7% to 14% of patients.^{783,784} Manifest PAD is associated with incident AF.⁷⁸⁵ PAD predicts a higher mortality in patients with AF and is an independent predictor of stroke in those not on OAC.^{783,786} Patients with lower extremity artery disease and AF also have a higher overall mortality and risk of major cardiac events.^{784,787,788} A public health database of >40 000 patients hospitalized for PAD or critical limb ischaemia showed AF to be an independent predictor for mortality (HR, 1.46; 95% CI, 1.39–1.52) and ischaemic stroke (HR, 1.63; 95% CI, 1.44–1.85) as compared with propensity-matched controls.⁷⁸⁴ Similarly, in patients undergoing carotid endarterectomy or stenting, the presence of AF is associated with higher mortality (OR, 1.59; 95% CI, 1.11–2.26).⁷⁸⁹

Anticoagulation alone is usually sufficient in the chronic disease phase, with DOACs being the preferred agents despite one RCT sub-analysis showing a higher risk of bleeding as compared with warfarin.⁷⁹⁰ In the case of recent endovascular revascularization, a period of combination with single antiplatelet therapy should be considered, weighing bleeding and thrombotic risks and keeping the period of combination antithrombotic therapy as brief as possible (ranging between 1 month for peripheral⁷⁹¹ and 90 days for neuro-interventional procedures).⁷⁹²

9.4. AF-CARE in acute stroke or intracranial haemorrhage

9.4.1. Management of acute ischaemic stroke

Management of acute stroke in patients with AF is beyond the scope of these guidelines. In AF patients presenting with acute ischaemic stroke while taking OAC, acute therapy depends on the treatment regimen and intensity of OAC. Management should be co-ordinated by a specialist neurologist team according to relevant guidelines.⁷⁹³

9.4.2. Introduction or re-introduction of anticoagulation after ischaemic stroke

The optimal time for administering OAC in patients with acute cardio-embolic stroke and AF remains unclear. Randomized control trials have been unable to provide any evidence to support the administration of anticoagulants or heparin in patients with acute ischaemic stroke within 48 h from stroke onset. This suggests that low-dose aspirin should be administered to all patients during this timeframe.⁷⁹⁴

Two trials have examined the use of DOAC therapy early after stroke, with no difference in clinical outcomes compared with delayed DOAC prescription. The ELAN (Early versus Late initiation of direct oral Anticoagulants in post-ischaemic stroke patients with atrial fibrillation) trial randomized 2013 patients with acute ischaemic stroke and AF to open-label early use of DOACs (<48 h after minor/moderate stroke; day 6–7 after major stroke) vs. later DOAC prescription (day 3–4 after minor stroke; day 6–7 after moderate stroke; day 12–14 after major stroke). There was no significant difference in the composite thromboembolic, bleeding, and vascular death outcome at 30 days (risk difference early vs. late, –1.18%; 95% CI, –2.84 to 0.47).⁷⁹⁵ The TIMING (Timing of Oral Anticoagulant Therapy in Acute Ischemic Stroke With Atrial Fibrillation) trial, a registry-based, non-inferiority, open-label, blinded endpoint trial randomized 888 patients within 72 h of ischaemic stroke onset to early (≤4 days) or delayed (5–10 days) DOAC initiation. Early DOAC use was non-inferior to the delayed strategy for the composite of thromboembolism, bleeding and all-cause mortality at 90 days (risk difference, –1.79%; 95% CI, –5.31% to 1.74%).⁷⁹⁶ Two ongoing trials will provide further guidance on the most appropriate timing of DOAC therapy after ischaemic stroke (NCT03759938, NCT03021928).

9.4.3. Introduction or re-introduction of anticoagulation after haemorrhagic stroke

There is insufficient evidence currently to recommend whether OAC should be started or re-started after ICH to protect against the high risk of ischaemic stroke in these patients (see [Supplementary data online, Additional Evidence Table S28](#)). Data from two pilot trials are available. The APACHE-AF (Apixaban After Anticoagulation-associated Intracerebral Haemorrhage in Patients With Atrial Fibrillation) trial was a prospective, randomized, open-label trial with masked endpoint assessment; 101 patients who survived 7–90 days after anticoagulation-associated ICH were randomized to apixaban or no OAC. During a median of 1.9 years follow-up (222 person-years), there was no difference in non-fatal stroke or vascular death, with an annual event rate of 12.6% with apixaban and 11.9% with no OAC (adjusted HR, 1.05; 95% CI, 0.48–2.31; *P* = .90).⁷⁹⁷ SoSTART (Start or STop Anticoagulants Randomised Trial) was an open-label RCT in 203 patients with AF after symptomatic spontaneous ICH. Starting OAC was not non-inferior to avoiding long-term (≥1 year) OAC, with ICH recurrence in 8/101 (8%) vs. 4/102 (4%) patients (adjusted HR, 2.42; 95% CI, 0.72–8.09). Mortality occurred in 22/101 (22%) patients in the OAC group vs. 11/102 (11%) patients where OAC were avoided.⁷⁹⁸

Until additional trials report on the clinical challenge of post-ICH anticoagulation (NCT03950076, NCT03996772), an individualized multi-disciplinary approach is advised led by an expert neurology team.

9.5. AF-CARE for trigger-induced AF

Trigger-induced AF is defined as new AF in the immediate association of a precipitating and potentially reversible factor. Also known as ‘secondary’ AF, this task force prefer the term trigger-induced as there are almost

always underlying factors in individual patients that can benefit from full consideration of the AF-CARE pathway. The most common precipitant unmasking a tendency to AF is acute sepsis, where AF prevalence is between 9% and 20% and has been associated with a worse prognosis.^{11–14} The degree of inflammation correlates with the incidence of AF,⁷⁹⁹ which may partly explain the wide variability across studies in prevalence, as well as recurrence of AF. Longer-term data suggest that AF triggered by sepsis recurs after discharge in between a third to a half of patients.^{12,800–807} In addition to other acute triggers which may be causal (such as alcohol^{808,809} and illicit drug use⁸¹⁰), numerous conditions are also associated with chronic inflammation leading to subacute stimuli for AF ([Table 14](#)). The specific trigger of an operative procedure is discussed in [Section 9.6](#).

After meeting the diagnostic criteria for AF (see [Section 3.2](#)), the management of trigger-induced AF is recommended to follow the AF-CARE principles, with critical consideration of underlying risk factors and comorbidities. Based on retrospective and observational data, patients with AF and trigger-induced AF seem to carry the same thromboembolic risk as patients with primary AF.^{811,812} In the acute phase of sepsis, patients show an unclear risk–benefit profile with anticoagulation therapy.^{813,814} Prospective studies on anticoagulation in patients with triggered AF episodes are lacking.^{802,812,815} Acknowledging that there are no RCTs specifically available in this population to assess trigger-induced AF, long-term OAC therapy should be considered in suitable patients with trigger-induced AF who are at elevated risk of thromboembolism, starting OAC after the acute trigger has been corrected and considering the anticipated net clinical benefit and informed patient preferences. As with any decision on OAC, not all patients will be suitable for OAC, depending on relative and absolute contraindications and the risk of major bleeding. The approach to rate and rhythm control will depend on subsequent recurrence of AF or any associated symptoms, and re-evaluation should be individualized to take account of the often high AF recurrence rate.

Table 14 Non-cardiac conditions associated with trigger-induced AF

Acute conditions
Infections (bacterial and viral)
Pericarditis, myocarditis
Emergency conditions (burn injury, severe trauma, shock)
Binge alcohol consumption
Drug use, including methamphetamines, cocaine, opiates, and cannabis
Acute interventions, procedures, and surgery
Endocrine disorders (thyroid, adrenal, pituitary, others)
Chronic conditions with inflammation and enhanced AF substrate
Immune-mediated diseases (rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, coeliac disease, psoriasis, others)
Obesity
Chronic obstructive airways disease
Obstructive sleep apnoea
Cancer
Fatty liver disease
Stress
Endocrine disorders (see Section 9.10)

Recommendation Table 25 — Recommendations for trigger-induced AF (see also Evidence Table 25)

Recommendation	Class ^a	Level ^b
Long-term oral anticoagulation should be considered in suitable patients with trigger-induced AF at elevated thromboembolic risk to prevent ischaemic stroke and systemic thromboembolism. ^{13,800,806,807,815}	IIa	C

AF, atrial fibrillation.

^aClass of recommendation.

^bLevel of evidence.

© ESC 2024

9.6. AF-CARE in post-operative patients

Peri-operative AF describes the onset of the arrhythmia during an ongoing intervention. Post-operative AF (POAF), defined as new-onset AF in the immediate post-operative period, is a common complication with clinical impact that occurs in 30%–50% of patients undergoing cardiac surgery,^{816–818} and in 5%–30% of patients undergoing non-cardiac surgery. Intra- and post-operative changes and specific AF triggers (including peri-operative complications) and pre-existing AF-related risk factors and comorbidities increase the susceptibility to POAF.⁸¹⁹ Although POAF episodes may be self-terminating, POAF is associated with 4–5 times increase in recurrent AF during the next 5 years,^{820,821} and is a risk factor for stroke, MI, heart failure, and death.^{822–827} Other adverse events associated with POAF include haemodynamic instability, prolonged hospital stay, infections, renal complications, bleeding, increased in-hospital death, and greater healthcare cost.^{828–830}

While multiple strategies to prevent POAF with pre-treatment or acute drug treatment have been described, there is a lack of evidence from large RCTs. Pre-operative use of propranolol or carvedilol plus N-acetyl cysteine in cardiac and non-cardiac surgery is associated with a reduced incidence of POAF,^{831–834} but not major adverse events.⁸³⁵ An umbrella review of 89 RCTs from 23 meta-analyses (19 211 patients, but not necessarily in AF) showed no benefit from beta-blockers in cardiac surgery for mortality, MI, or stroke. In non-cardiac surgery, beta-blockers were associated with reduced rates of MI after surgery (RR range, 0.08–0.92), but higher mortality (RR range, 1.03–1.31), and increased risk of stroke (RR range, 1.33–7.72).⁸³⁶ Prevention of peri-operative AF can also be achieved with amiodarone. In a meta-analyses, amiodarone (oral or intravenous [i.v.]) and beta-blockers were equally effective in reducing post-operative AF,⁸³⁷ but their combination was better than beta-blockers alone.⁸³⁸ Lower cumulative doses of amiodarone (<3000 mg during the loading phase) could be effective, with fewer adverse events.^{837,839,840} Withdrawal of beta-blockers should be avoided due to increased risk of POAF.⁸⁴¹ Other treatment strategies (steroids, magnesium, sotalol, (bi)atrial pacing, and botulinum injection into the epicardial fat pad) lack scientific evidence for the prevention of peri-operative AF.^{842,843} Peri-operative posterior pericardiotomy, due to the reduction of post-operative pericardial effusion, showed a significant decrease in POAF in patients undergoing cardiac surgery (OR, 0.44; 95% CI, 0.27–0.70; *P* = .0005).^{844–846} In 3209 patients undergoing non-cardiac thoracic surgery, colchicine did not lead to any significant reduction in AF compared with placebo (HR, 0.85; 95% CI, 0.65–1.10; *P* = .22).⁸⁴⁷

The evidence for prevention of ischaemic stroke in POAF by OAC is limited.^{822,827} Oral anticoagulant therapy is associated with a high

bleeding risk soon after cardiac surgery or major non-cardiac interventions.⁸²⁷ Conversely, meta-analyses of observational cohort studies suggest a possible protective impact of OAC in POAF for all-cause mortality⁸⁴⁸ and a lower risk of thromboembolic events following cardiac surgery, accompanied by higher rates of bleeding.⁸⁴⁹ This task force recommends to treat post-operative AF according to the AF-CARE pathway as discussed for trigger-induced AF (with the [R] pathway the same as for first-diagnosed AF). Ongoing RCTs in cardiac surgery (NCT04045665) and non-cardiac surgery (NCT03968393) will inform optimal long-term OAC use among patients with POAF. While awaiting the results of these trials, this task force recommends that after acute bleeding risk has settled, long-term OAC should be considered in patients with POAF according to their thromboembolic risk factors.

Recommendation Table 26 — Recommendations for management of post-operative AF (see also Evidence Table 26)

Recommendations	Class ^a	Level ^b
Peri-operative amiodarone therapy is recommended where drug therapy is desired to prevent post-operative AF after cardiac surgery. ^{838,839,850,851}	I	A
Concomitant posterior peri-cardiotomy should be considered in patients undergoing cardiac surgery to prevent post-operative AF. ^{845,846}	IIa	B
Long-term oral anticoagulation should be considered in patients with post-operative AF after cardiac and non-cardiac surgery at elevated thromboembolic risk, to prevent ischaemic stroke and thromboembolism. ^{811,852–854}	IIa	B
Routine use of beta-blockers is not recommended in patients undergoing non-cardiac surgery for the prevention of post-operative AF. ^{836,855}	III	B

AF, atrial fibrillation.

^aClass of recommendation.

^bLevel of evidence.

© ESC 2024

9.7. AF-CARE in embolic stroke of unknown source

The term ‘embolic stroke of undetermined source’ (ESUS) was introduced to identify non-lacunar strokes whose mechanism is likely to be embolic, but the source remains unidentified.⁸⁵⁶ Of note, these patients have a recurrent risk of stroke of 4%–5% per year.⁸⁵⁶ The main embolic sources associated with ESUS are concealed AF, atrial cardiomyopathy, left ventricular disease, atherosclerotic plaques, patent foramen ovale (PFO), valvular diseases, and cancer. Atrial cardiomyopathy and left ventricular disease are the most prevalent causes.⁸⁵⁶ AF is reported to be the underlying mechanism in 30% of ESUS patients.^{857–859} The detection of AF among ESUS patients increases the longer cardiac monitoring is provided (see [Supplementary data online, Additional Evidence Table S29](#)).^{857,860–864} This also holds for the duration of implantable cardiac monitoring, with probability of AF detection ranging from 2% with 1 week to over 20% by 3 years.⁸⁶⁵ In patients with ESUS, factors associated with an increased detection of AF are increasing age,^{866,867} left atrial enlargement,⁸⁶⁶ cortical location of stroke,⁸⁶⁸ large or small vessel disease,⁸⁶³ an increased number of

atrial premature beats per 24 h,⁸⁶⁸ rhythm irregularity,⁸⁵⁹ and risk stratification scores (such as CHA₂DS₂-VASc,⁸⁶⁹ Brown ESUS-AF,⁸⁷⁰ HAVOC,⁸⁷¹ and C₂HES⁸⁷²). This task force recommends prolonged monitoring depending on the presence of the above-mentioned risk markers.^{865,873,874}

Currently available evidence, including two completed RCTs and one stopped for futility, do not support the use of DOACs compared with aspirin in patients with acute ESUS without documented AF.^{875–877} Ongoing trials will provide further guidance (NCT05134454, NCT05293080, NCT04371055).

Recommendation Table 27 — Recommendations for patients with embolic stroke of unknown source (see also Evidence Table 27)

Recommendations	Class ^a	Level ^b
Prolonged monitoring for AF is recommended in patients with ESUS to inform on AF treatment decisions. ^{861–863}	I	B
Initiation of oral anticoagulation in ESUS patients without documented AF is not recommended due to lack of efficacy in preventing ischaemic stroke and thromboembolism. ^{875,876}	III	A

AF, atrial fibrillation; ESUS, embolic stroke of undetermined source.
^aClass of recommendation.
^bLevel of evidence.

9.8. AF-CARE during pregnancy

Atrial fibrillation is one of the most common arrhythmias during pregnancy, with prevalence increasing due to higher maternal age and changes in lifestyle, and because more women with congenital heart disease survive to childbearing age.^{878–881} Rapid atrioventricular conduction of AF may have serious haemodynamic consequences for mother and foetus. AF during pregnancy is associated with an increased risk of death.⁸⁸² A multidisciplinary approach is essential to prevent maternal and foetal complications, bringing together gynaecologists, neonatologists, anaesthesiologists, and cardiologists experienced in maternal medicine.⁸⁸³

Pregnancy is associated with a hypercoagulable state and increased thromboembolic risk.⁸⁸⁴ The same rules for risk assessment of thromboembolism should be used as in non-pregnant women, as detailed in the 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy.⁸⁸⁵ The preferred agents for anticoagulation of AF during pregnancy are unfractionated or low molecular weight heparins (LMWHs), which do not cross the placenta. Vitamin K antagonists should be avoided in the first trimester (risk of miscarriage, teratogenicity) and from week 36 onwards (risk of foetal intracranial bleeding if early unexpected delivery). Direct oral anticoagulants are not recommended during pregnancy due to concerns about safety.⁸⁸⁶ However, an accidental exposure during pregnancy should not lead to a recommendation for termination of the pregnancy.⁸⁸⁷ Vaginal delivery should be advised for most women, but is contraindicated during VKA treatment because of the risk of foetal intracranial bleeding.⁸⁸⁵

Intravenous selective beta-1 receptor blockers are recommended as first choice for acute heart rate control of AF.⁸⁸⁸ This does not include atenolol, which can lead to intrauterine growth retardation.⁸⁸⁹ If beta-blockers fail, digoxin and verapamil can be considered for rate control

(verapamil should be avoided in the first trimester). Rhythm control is the preferred strategy during pregnancy. Electrical cardioversion is recommended if there is haemodynamic instability, considerable risk to mother or foetus, or with concomitant HCM. Electrical cardioversion can be performed safely without compromising foetal blood flow, and the consequent risk for foetal arrhythmias or pre-term labour is low. The foetal heart rate should be closely monitored throughout and after cardioversion, which should generally be preceded by anticoagulation.⁸⁸⁵ In haemodynamically stable women without structural heart disease, intravenous ibutilide or flecainide may be considered for termination of AF, but experience is limited.⁸⁹⁰ Catheter ablation is normally avoided during pregnancy,⁸⁸³ but is technically feasible without radiation in refractory symptomatic cases with a minimal/zero fluoroscopy approach.⁸⁸³

Counselling is important in women of childbearing potential prior to pregnancy, highlighting the potential risks of anticoagulation and rate or rhythm control drugs (including teratogenic risk, where relevant). Contraception and timely switch to safe drugs should be proactively discussed.

Recommendation Table 28 — Recommendations for patients with AF during pregnancy (see also Evidence Table 28)

Recommendations	Class ^a	Level ^b
Immediate electrical cardioversion is recommended in patients with AF during pregnancy and haemodynamic instability or pre-excited AF to improve maternal and foetal outcomes. ^{885,891–893}	I	C
Therapeutic anticoagulation with LMWHs or VKAs (except VKAs for the first trimester or beyond Week 36) is recommended for pregnant patients with AF at elevated thromboembolic risk to prevent ischaemic stroke and thromboembolism. ⁸⁸⁵	I	C
Beta-1 selective blockers are recommended for heart rate control of AF in pregnancy to reduce symptoms and improve maternal and foetal outcomes, excluding atenolol. ⁸⁸⁸	I	C
Electrical cardioversion should be considered for persistent AF in pregnant women with HCM to improve maternal and foetal outcomes. ^{885,894}	IIa	C
Digoxin should be considered for heart rate control of AF in pregnancy, if beta-blockers are ineffective or not tolerated, to reduce symptoms and improve maternal and foetal outcomes. ⁸⁸⁵	IIa	C
Intravenous ibutilide or flecainide may be considered for termination of AF in stable pregnant patients with a structurally normal heart to improve maternal and foetal outcomes. ^{895,896}	IIb	C
Flecainide or propafenone may be considered for longer-term rhythm control in pregnancy, if rate controlling drugs are ineffective or not tolerated, to reduce symptoms and improve maternal and foetal outcomes. ⁸⁸⁵	IIb	C

AF, atrial fibrillation; HCM, hypertrophic cardiomyopathy; LMWH, low molecular weight heparin; VKA, vitamin K antagonist.
^aClass of recommendation.
^bLevel of evidence.

9.9. AF-CARE in congenital heart disease

Survival of patients with congenital heart disease has increased over time, but robust data on the management of AF are missing and available evidence is derived mainly from observational studies. Oral anti-coagulants are recommended for all patients with AF and intracardiac repair, cyanotic congenital heart disease, Fontan palliation, or systemic right ventricle irrespective of the individuals' thromboembolic risk factors.⁸⁹⁷ Patients with AF and other congenital heart diseases should follow the general risk stratification for OAC use in AF (i.e. depending on the thromboembolic risk or CHA₂DS₂-VA score). Direct oral anticoagulants are contraindicated in patients with mechanical heart valves,³³¹ but appear safe in patients with congenital heart disease,^{898,899} or those with a valvular bioprosthesis.^{900,901}

Rate control drugs such as selective beta-1 receptor blockers, verapamil, diltiazem, and digoxin can be used with caution, with monitoring for bradycardia and hypotension. Rhythm control strategies such as amiodarone may be effective, but warrant monitoring for bradycardia. When cardioversion is planned, both 3 weeks of OAC and TOE should be considered because thrombi are common in patients with congenital heart disease and atrial arrhythmias.^{902,903} Ablation approaches can be successful in patients with congenital heart disease, but AF recurrence rates may be high (see [Supplementary data online, Additional Evidence Table S30](#)).

In patients with atrial septal defect, closure may be performed before the fourth decade of life to decrease the risk of AF or AFL.⁹⁰⁴ Patients with stroke who underwent closure of their PFO may have an increased risk of AF,⁹⁰⁵ but in patients with PFO and AF, PFO closure is not recommended for stroke prevention. AF surgery or catheter ablation can be considered at the time of closure of the atrial septal defect within a multidisciplinary team.^{906–908} AF catheter ablation of late atrial arrhythmias is likely to be effective after surgical atrial septal closure.⁹⁰⁹

Recommendation Table 29 — Recommendations for patients with AF and congenital heart disease (see also Evidence Table 29)

Recommendation	Class ^a	Level ^b
Oral anticoagulation should be considered in all adult congenital heart disease patients with AF/AFL and intracardiac repair, cyanosis, Fontan palliation, or systemic right ventricle to prevent ischaemic stroke and thromboembolism, regardless of other thromboembolic risk factors. ⁸⁹⁷	Ila	C

AF, atrial fibrillation; AFL, atrial flutter.

^aClass of recommendation.

^bLevel of evidence.

9.10. AF-CARE in endocrine disorders

Endocrine dysfunction is closely related to AF, both as the direct action of endocrine hormones and as a consequence of treatments for endocrine disease. Optimal management of endocrine disorders is therefore part of the AF-CARE pathway.^{910,911}

Clinical and subclinical hyperthyroidism, as well as subclinical hypothyroidism, are associated with an increased risk of AF.^{912,913} Patients presenting with new-onset or recurrent AF should be tested for thyroid-stimulating hormone (TSH) levels. The risk of AF is enhanced

in vulnerable patients, including the elderly and those with structural atrial diseases,^{914,915} as well as cancer patients on immune checkpoint inhibitors.^{916,917} In hyperthyroidism, and even in the euthyroid range, the risk of AF increases according to the reduction in TSH and elevated levels of thyroxine.^{918,919} Moreover, the risk of stroke is higher in patients with hyperthyroidism, which can be mitigated by treating the thyroid disorder.^{920,921} Amiodarone induces thyroid dysfunction in 15%–20% of treated patients, leading to both hypo- and hyperthyroidism,^{922,923} which warrants referral to an endocrinologist (see [Supplementary data online](#) for further details).

Hypercalcaemia may also induce arrhythmias, but the role of primary hyperparathyroidism in incident AF is poorly studied. Surgical parathyroidectomy has been found to reduce both supraventricular and ventricular premature beats.^{924–926} Primary aldosteronism is related to an increased risk of AF through direct actions and vascular effects,^{927,928} with a three-fold higher rate of incident AF compared with patients with essential hypertension.⁹²⁹ Increases in genetically predicted plasma cortisol are associated with greater risk of AF, and patients with adrenal incidentalomas with subclinical cortisol secretion have a higher prevalence of AF.^{930,931} Acromegaly may predispose to an increased substrate for AF, with incident AF rates significantly higher than controls in long-term follow-up, even after adjusting for AF risk factors.⁹³²

The association between type 2 diabetes and AF is discussed in [Sections 5.3](#) (AF recurrence) and [Section 10.5](#) (incident AF). In addition to insulin-resistance mechanisms typical of type 2 diabetes, the loss of insulin signalling has recently been associated with electrical changes that can lead to AF. Type 1 diabetes is associated with an increased risk of several cardiovascular diseases including AF.^{933–937}

9.11. AF-CARE in inherited cardiomyopathies and primary arrhythmia syndromes

A higher incidence and prevalence of AF have been described in patients with inherited cardiomyopathies and primary arrhythmia syndromes.^{271,938–970} AF can be the presenting or only clinically overt feature.^{969,971–975} AF in these patients is associated with adverse clinical outcomes,^{947,954,959,963,965,976–978} and has important implications on management (see [Supplementary data online, Additional Evidence Table S31](#)). When AF presents at a young age, there should be a careful interrogation about family history and a search for underlying disease.⁹⁷⁹

Rhythm control approaches may be challenging in patients with inherited cardiomyopathies and primary arrhythmia syndromes. For example, many drugs have a higher risk of adverse events or may be contraindicated (e.g. amiodarone and sotalol in congenital long QT syndrome, and Class IC AADs in Brugada syndrome) (see [Supplementary Data online, Table S6](#)). Owing to long-term adverse effects, chronic use of amiodarone is problematic in these typically young individuals. In patients with an implantable cardioverter defibrillator, AF is a common cause of inappropriate shocks.^{959,966,980,981} Programming a single high-rate ventricular fibrillation zone ≥210–220 b.p.m. with long detection time is safe,^{950,953,982} and is suggested in patients without documented slow monomorphic ventricular tachycardia. Implantation of an atrial lead may be considered in the case of significant bradycardia with beta-blocker treatment.

Patients with Wolff–Parkinson–White syndrome and AF are at risk of fast ventricular rates from rapid conduction of atrial electrical activity to the ventricles via the accessory pathway, potentially leading to ventricular fibrillation and sudden death.^{983,984} Immediate electrical cardioversion is needed for haemodynamically compromised patients with

pre-excited AF, and atrioventricular node-modulating drugs should be avoided.^{985,986} Pharmacological cardioversion can be attempted using ibutilide⁹⁸⁷ or flecainide, while propafenone should be used with caution due to effects on the atrioventricular node.^{988,989} Amiodarone should be avoided in pre-excited AF due to its delayed action. Further details on inherited cardiomyopathies can be found in the 2023 ESC Guidelines for the management of cardiomyopathies.⁹⁹⁰

9.12. AF-CARE in cancer

All types of cancer show an increased risk of AF, with prevalence varying from 2% to 28%.^{991–995} The occurrence of AF may often be related to a pre-existing atrial substrate with vulnerability to AF. AF may be an indicator of an occult cancer, but also can appear in the context of concomitant surgery, chemotherapy, or radiotherapy.^{916,994,996} Risk of AF is dependent on, among other factors, the cancer type and stage,⁹⁹⁷ and is greater in older patients with pre-existing cardiovascular disease.^{991,993,994} Some procedures are associated with higher incidence of AF, including lung surgery (from 6% to 32%) and non-thoracic surgery such as a colectomy (4%–5%).⁹⁹⁴

Atrial fibrillation in the context of cancer is associated with a two-fold higher risk of systemic thromboembolism and stroke, and six-fold increased risk of heart failure.^{991,994} On the other hand, the coexistence of cancer increases the risk of all-cause mortality and major bleeding in patients with AF.⁹⁹⁸ Bleeding in those receiving OAC can also unmask the presence of cancer.⁹⁹⁹

Stroke risk scores may underestimate thromboembolic risk in cancer patients.¹⁰⁰⁰ The association between cancer, AF, and ischaemic stroke also differs between cancer types. In some types of cancer, the risk of bleeding seems to exceed the risk of thromboembolism.⁹⁹⁸ Risk stratification is therefore complex in this population, and should be performed on an individual basis considering cancer type, stage, prognosis, bleeding risk, and other risk factors. These aspects can change within a short period of time, requiring dynamic assessment and management.

As with non-cancer patients, DOACs in those with cancer have similar efficacy and better safety compared with VKAs.^{1001–1010} Low molecular weight heparin is a short-term anticoagulation option, mostly during some cancer treatments, recent active bleeding, or thrombocytopenia.¹⁰¹¹ Decision-making on AF management, including on rhythm control, is best performed within a cardio-oncology multidisciplinary team.^{916,1012} Attention is required on interactions with cancer treatments, in particular QT-interval prolongation with AADs.

9.13. AF-CARE in older, multimorbid, or frail patients

Atrial fibrillation increases with age, and older patients more frequently have multimorbidity and frailty which are associated with worse clinical outcomes.^{1013–1016} Multimorbidity is the coexistence of two or more medically diagnosed diseases in the same individual. Frailty is defined as a person more vulnerable and less able to respond to a stressor or acute event, increasing the risk of adverse outcomes.^{1016,1017} The prevalence of frailty in AF varies due to different methods of assessment from 4.4% to 75.4%, and AF prevalence in the frail population ranges from 48.2% to 75.4%.¹⁰¹⁸ Frailty status is a strong independent risk factor for new-onset AF among older adults with hypertension.¹⁰¹⁹

Atrial fibrillation in frail patients is associated with less use of OAC and lower rates of management with a rhythm control strategy.^{1015,1018,1020} Oral anticoagulation initiation in older, frail

multimorbid AF patients has improved since the introduction of DOACs, but is still lower in AF patients at older age (OR, 0.98 per year; 95% CI, 0.98–0.98), with dementia (OR, 0.57; 95% CI, 0.55–0.58), or frailty (OR, 0.74; 95% CI, 0.72–0.76).¹⁰²¹ The value of observational data which show potential benefit from OAC (in particular, DOACs) is limited due to prescription biases.^{1022–1027} Frail patients aged ≥75 years with polypharmacy and stable on a VKA may remain on the VKA rather than switching to a DOAC (Section 6.2).³⁰⁹

9.14. AF-CARE in atrial flutter

Due to the association between AFL and thromboembolic outcomes, and the frequent development of AF in patients with AFL, the management of comorbidities and risk factors in AFL should mirror that for AF (see Section 5). Similarly, the approach to prevent thromboembolism in AFL includes peri-procedural and long-term OAC (see Section 6). Rate control can be difficult to achieve in AFL, despite combination therapy. Rhythm control is often the first-line approach,⁹⁸³ with small randomized trials showing that cavo-tricuspid isthmus (CTI) ablation is superior to AADs.^{1028,1029} Recurrence of AFL is uncommon after achieving and confirming bidirectional block in typical CTI-dependent AFL. However, the majority of patients (50%–70%) have manifested AF during long-term follow-up in observational studies after AFL ablation.^{1030,1031} Hence the necessity for long-term dynamic re-evaluation in all patients with AFL in keeping with the AF-CARE approach. More detail on the management of AFL and other atrial arrhythmias is described in the 2019 ESC Guidelines for the management of patients with supraventricular tachycardia.⁹⁸³

Recommendation Table 30 — Recommendations for prevention of thromboembolism in atrial flutter (see also Evidence Table 30)

Recommendation	Class ^a	Level ^b
Oral anticoagulation is recommended in patients with atrial flutter at elevated thromboembolic risk to prevent ischaemic stroke and thromboembolism. ^{86,1032}	I	B

AF, atrial fibrillation; AFL, atrial flutter.
^aClass of recommendation.
^bLevel of evidence.

10. Screening and prevention of AF

10.1. Epidemiology of AF

Atrial fibrillation is the most common sustained arrhythmia worldwide, with an estimated global prevalence in 2019 of 59.7 million persons with AF.¹⁰³³ Incident cases of AF are doubling every few decades.¹⁰³⁴ Future increases are anticipated, in particular in middle-income countries.¹⁰³⁴ In community-based individuals, the prevalence of AF in a United States of America cohort was up to 5.9%.¹⁰³⁵ The age-standardized prevalence and incidence rates have remained constant over time.^{1033,1036} The increase in overall prevalence is largely attributable to population growth, ageing, and survival from other cardiac conditions. In parallel, increases in risk factor burden, better awareness, and improved detection of AF have been observed.¹⁰³⁷ The lifetime risk

of AF has been estimated to be as high as 1 in 3 for older individuals,¹⁰³⁸ with age-standardized incidence rates higher for men than women. Populations of European ancestry are typically found to have higher AF prevalence, individuals of African ancestry have worse outcomes, and other groups may have less access to interventions.^{1039–1041} Socioeconomic and other factors likely play a role in racial and ethnic differences in AF, but studies are also limited due to differences in how groups access healthcare. Greater deprivation in socioeconomic and living status is associated with higher AF incidence.¹⁰⁴²

10.2. Screening tools for AF

In recent years, an abundance of novel devices that can monitor heart rhythm have come to the market, including fitness bands and smart-watches. Although the evidence for clinical effectiveness of digital devices is limited, they may be useful in detecting AF, and their clinical, economic, legal, and policy implications merit further investigation.^{1043,1044} Devices for AF detection can broadly be divided into those that provide an ECG, and those with non-ECG approaches such as photoplethysmography (Figure 15 and Table 15).

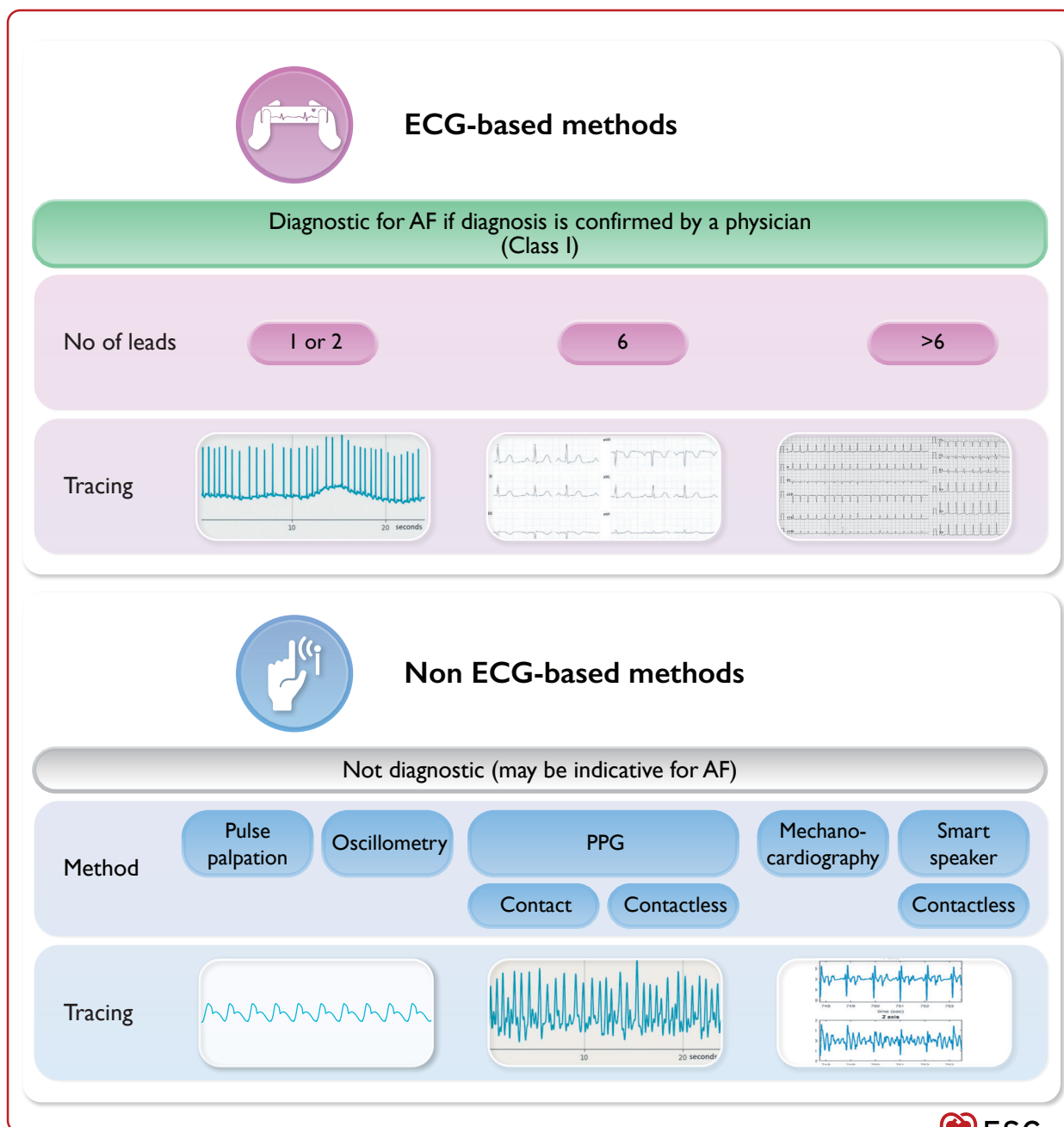


Figure 15 Non-invasive diagnostic methods for AF screening. AF, atrial fibrillation; BP, blood pressure; ECG, electrocardiogram; PPG, photoplethysmography.

Table 15 Tools for AF screening**Tools for AF screening**

- (i) Pulse palpation¹⁰⁴⁵
- (ii) Use of artificial intelligence algorithms to identify patients at risk¹⁰⁴⁶
- (iii) ECG-based devices
 - (a) Conventional ECG devices
 - (1) Classic 12-lead ECG¹⁰⁴⁷
 - (2) Holter monitoring (from 24 h to a week or more)¹⁰⁴⁸
 - (3) Mobile cardiac telemetry (during hospitalization)¹⁰⁴⁹
 - (4) Handheld devices^{1050–1052}
 - (5) Wearable patches (up to 14 days)^{1053–1067}
 - (6) Biotextiles (up to 30 days)^{1068–1072}
 - (7) Smart devices (30 s)^{1073–1091}
 - (b) Implantable loop recorders (3–5 years)^{1092–1099}
- (iv) Non-ECG-based devices
 - (a) Photoplethysmography and automatic algorithms: contact (fingertip, smart device, band) and contactless (video)^{1100–1106}
 - (b) Oscillometry (blood pressure monitors that derive heart rhythm regularity algorithmically)^{1107–1110}
 - (c) Mechanocardiography (accelerometers and gyroscopes to sense the mechanical activity of the heart)¹¹¹¹
 - (d) Contactless video plethysmography (through video monitoring)^{1112–1115}
 - (e) Smart speakers (through the identification of abnormal heart rate patterns)¹¹¹⁶

ECG, electrocardiogram.

Most consumer-based devices use photoplethysmography, and several large studies have been performed typically in low-risk individuals.^{633,1076,1117,1118} In an RCT of 5551 participants invited by their health insurer, smartphone-based photoplethysmography increased the odds of OAC-treated new AF by 2.12 (95% CI, 1.19–3.76; $P=.01$) compared with usual care.⁶⁰⁵ RCTs powered for assessment of clinical outcomes are still lacking for consumer-based AF screening. Further head-to-head comparisons between novel digital devices and those commonly used in healthcare settings are needed to establish their comparative effectiveness in the clinical setting and account for different populations and settings.¹¹¹⁹ In a systematic review of smartphone-based photoplethysmography compared with a reference ECG, unrealistically high sensitivity and specificity were noted, likely due to small, low-quality studies with a high degree of patient selection bias.¹¹²⁰ Hence, when AF is suggested by a photoplethysmography device or any other screening tool, a single-lead or continuous ECG tracing of >30 s or 12-lead ECG showing AF analysed by a physician with expertise in ECG rhythm interpretation is recommended to establish a definitive diagnosis of AF.^{1091,1121–1125}

The combination of big data and artificial intelligence (AI) is having an increasing impact on the field of electrophysiology. Algorithms have been created to improve automated AF diagnosis and several algorithms to aid diagnostics are being investigated.¹⁰⁴⁶ However, the clinical performance and broad applicability of these solutions are not yet known. The use of AI may enable future treatment changes to be assessed with dynamic and continuous patient-directed monitoring using wearable devices.¹¹²⁶ There are still challenges in the field that need clarification, such as data acquisition, model performance, external validity, clinical implementation, algorithm interpretation, and confidence, as well as the ethical aspects.¹¹²⁷

10.3. Screening strategies for AF

Screening can be performed systematically, with an invitation issued to a patient, or opportunistically, at the time of an *ad hoc* meeting with a healthcare professional. Regardless of the mode of invitation, screening should be part of a structured programme¹¹²⁸ and is not the same as identification of AF during a routine healthcare visit or secondary to arrhythmia symptoms.

Screening can be done at a single timepoint (snapshot of the heart rhythm), e.g. using pulse palpation or a 12-lead ECG. Screening can also be of an extended duration, i.e. prolonged, using either intermittent or continuous monitoring of heart rhythm. Most studies using an opportunistic strategy have screened for AF at a single timepoint with short duration (such as a single timepoint ECG), compared with systematic screening studies that have mainly used prolonged (repeated or continuous) rhythm assessment.¹¹²⁹ The optimal screening method will vary depending on the population being studied (Figure 16) (see [Supplementary data online, Additional Evidence Table S32](#)). More sensitive methods will detect more AF but may lead to an increased risk of false positives and an increased detection of low burden AF, whereas more specific methods result in less false positives, at the risk of missing AF.

Invasive monitoring of heart rhythm in high-risk populations extended for several years has been shown to result in device-detected AF prevalence of around 30%, albeit most of whom have a low burden of AF.^{5,857,1130,1131} Pacemaker studies have shown that patients with a low burden of device-detected subclinical AF have a lower risk of ischaemic stroke.^{5,24,1131,1132} This has been confirmed in RCTs assessing DOAC use in patients with device-detected subclinical AF (see [Section 6.1.1](#)).^{5,281,282} The burden needed for device-detected subclinical AF to translate into stroke risk is not known, and further studies are clearly needed.^{1133,1134} Benefit and cost-effectiveness of screening are discussed in the [Supplementary data online](#).

Recommendation Table 31 — Recommendations for screening for AF (see also Evidence Table 31)

Recommendations	Class ^a	Level ^b
Review of an ECG (12-lead, single, or multiple leads) by a physician is recommended to provide a definite diagnosis of AF and commence appropriate management. ^{1091,1121–1123,1125}	I	B
Routine heart rhythm assessment during healthcare contact is recommended in all individuals aged ≥65 years for earlier detection of AF.	I	C
Population-based screening for AF using a prolonged non-invasive ECG-based approach should be considered in individuals aged ≥75 years, or ≥65 years with additional CHA ₂ DS ₂ -VA risk factors to ensure earlier detection of AF. ^{6,1135–1137}	IIa	B

AF, atrial fibrillation; CHA₂DS₂-VA, congestive heart failure, hypertension, age ≥75 years (2 points), diabetes mellitus, prior stroke/transient ischaemic attack/arterial thromboembolism (2 points), vascular disease, age 65–74 years; ECG, electrocardiogram.
^aClass of recommendation.
^bLevel of evidence.

10.3.1. Single timepoint screening ‘snapshot’

Several cluster RCTs in primary care settings have explored whether screening performed as a snapshot of the heart rhythm at one timepoint can detect more AF compared with usual care in individuals aged ≥65 years.^{1138–1140} No increased detection of AF was seen in groups randomized to single timepoint screening.^{1138–1140} These findings were confirmed in a meta-analysis of RCTs showing that screening as a one-time event did not increase detection of AF compared with usual care.¹¹³⁵ Notably, these studies were performed in healthcare settings where the detection of AF in the population might be high, hence the results might not be generalizable to healthcare settings with a lower spontaneous AF detection. There are no RCTs addressing clinical outcomes in patients with AF detected by single timepoint screening.^{1123,1135}

10.3.2. Prolonged screening

Studies using prolonged screening have shown an increased detection of AF leading to initiation of OAC.^{1129,1135,1141} Two RCTs have investigated the effect on clinical outcomes in prolonged screening for AF.^{5,6} In the STROKESTOP trial (Systematic ECG Screening for Atrial Fibrillation Among 75 Year Old Subjects in the Region of Stockholm

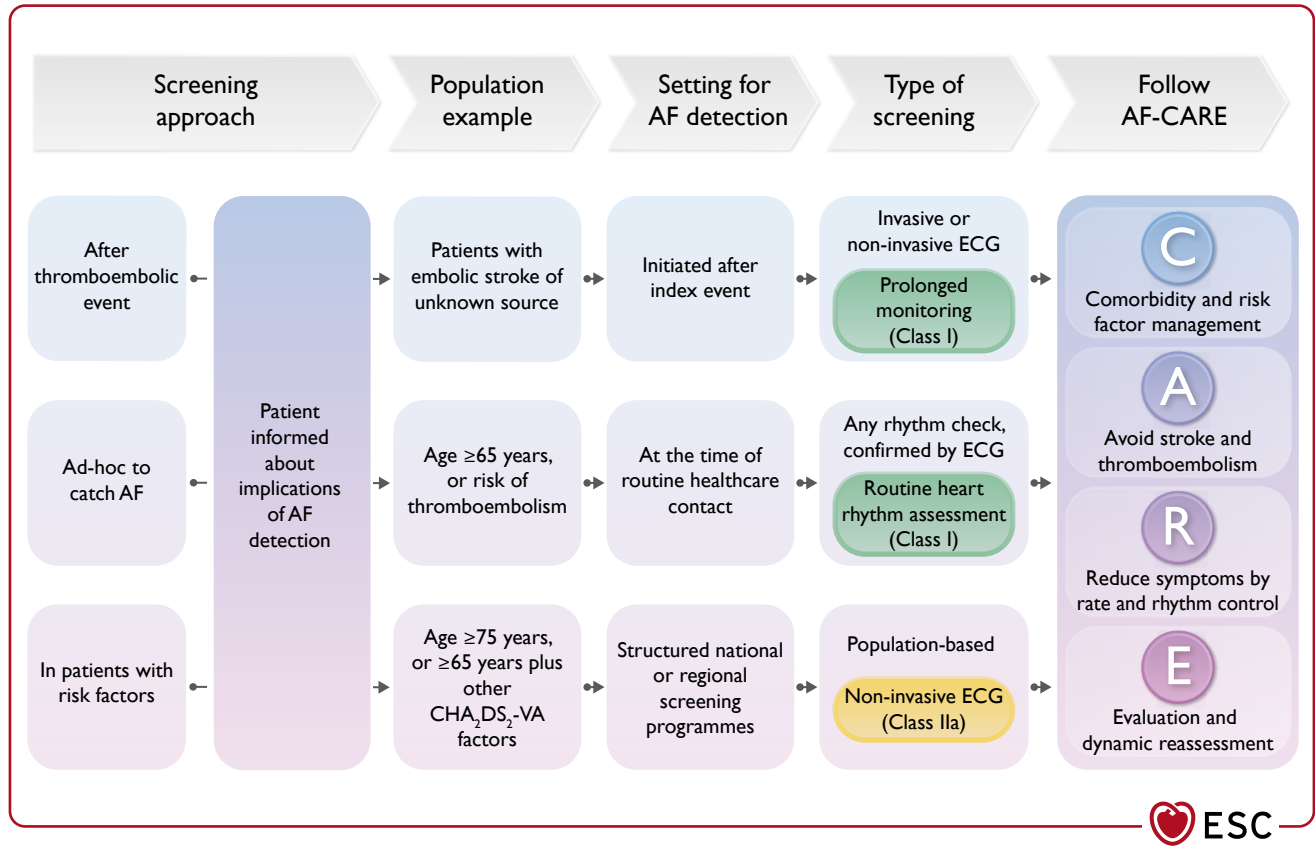


Figure 16 Approaches to screening for AF. AF, atrial fibrillation; AF-CARE, atrial fibrillation—[C] Comorbidity and risk factor management, [A] Avoid stroke and thromboembolism, [R] Reduce symptoms by rate and rhythm control, [E] Evaluation and dynamic reassessment; CHA₂DS₂-VA, congestive heart failure, hypertension, age ≥75 years (2 points), diabetes mellitus, prior stroke/TIA/arterial thromboembolism (2 points), vascular disease, age 65–74 years; ECG, electrocardiogram. See Figure 15 for non-invasive ECG methods.

and Halland, Sweden), 75- and 76-year-olds were randomized to be invited to prolonged screening for AF using single-lead ECGs twice daily for 2 weeks, or to standard of care. After a median of 6.9 years there was a small reduction in the primary combined endpoint of all-cause mortality, stroke, systematic embolism, and severe bleeding in favour of prolonged screening (HR, 0.96; 95% CI, 0.92–1.00; $P = .045$).⁶ In the LOOP (Atrial Fibrillation Detected by Continuous ECG Monitoring) trial, individuals at increased risk of stroke were randomized to receive an implantable loop recorder that monitored heart rhythm for an average of 3.3 years, or to a control group receiving standard of care. Although there was a higher detection of AF (31.8%) and subsequent initiation of OAC in the loop recorder group compared with standard of care (12.2%), this was not accompanied by a difference in the primary outcome of stroke or systemic embolism.⁵ In a meta-analysis of recent RCTs on the outcome of stroke, a small but significant benefit was seen in favour of prolonged screening (RR, 0.91; 95% CI, 0.84–0.99).¹¹³⁶ This was not repeated in a second meta-analysis including older RCTs, where no risk reduction was seen with regard to mortality or stroke.¹¹³⁵ Notably, both these meta-analyses are likely underpowered to assess clinical outcomes.

10.4. Factors associated with incident AF

The most common risk predictors for incident (new-onset) AF are shown in Table 16. While the factors listed are robustly associated with incident AF in observational studies, it is not known whether the relationships are causal. Studies using Mendelian randomization (genetic proxies for risk factors to estimate causal effects) robustly implicate systolic BP and higher BMI as causal risk factors for incident AF.¹¹⁴²

A high degree of interaction occurs between all factors related to AF development (see Supplementary data online, Additional Evidence Table S33).^{1038,1039,1143–1145} For ease of clinical application, risk prediction tools have combined various factors, and have recently employed machine learning algorithms for prediction.^{1146,1147} Classical risk scores are also available with variable predictive ability and model performance (see Supplementary data online, Table S7).¹¹⁴⁸ Improved outcomes when using these risk scores have yet to be demonstrated. Although knowledge is rapidly increasing about the genetic basis for AF in some patients, the value of genetic screening is limited at the present time (see Supplementary data online).

Table 16 Factors associated with incident AF

Demographic factors	Age ^{1149–1151}
	Male sex ^{1149–1152}
	European ancestry ^{1149,1150}
	Lower socioeconomic status ¹¹⁵⁰
Lifestyle behaviours	Smoking/tobacco use ^{1149–1151}
	Alcohol intake ^{1149,1150}
	Physical inactivity ^{1149,1150}
	Vigorous exercise ^{1153–1156}
	Competitive or athlete-level endurance sports ^{1151,1157}
	Caffeine ^{1158–1160}

Continued

Comorbidities and risk factors	Hypertension ^{1149–1151}
	Heart failure ^{178,1149–1151,1161}
	Valvular disease ^{1149,1151,1162–1164}
	Coronary artery disease ^{1149,1151,1161,1165}
	Peripheral arterial disease ⁷⁸⁵
	Congenital heart disease ^{1149,1166}
	Heart rate, heart rate variability ^{1167,1168}
	Total cholesterol ^{1149,1150}
	Low-density lipoprotein cholesterol ¹¹⁵⁰
	High-density lipoprotein cholesterol ¹¹⁵⁰
	Triglycerides ¹¹⁵⁰
	Impaired glucose tolerance, ^{1169–1172} diabetes mellitus ^{1149–1151,1169}
	Renal dysfunction/CKD ^{1149–1151,1173,1174}
	Obesity ^{1149–1151,1175,1176}
	Body mass index, weight ^{1149–1151}
	Height ¹¹⁵⁰
Subclinical atherosclerosis	Sleep apnoea ^{1149,1151,1177,1178}
	Chronic obstructive pulmonary disease ¹¹⁷⁹
	Coronary artery calcification ^{1149,1151,1180}
ECG abnormalities	Carotid IMT and carotid plaque ^{1149,1151,1181,1182}
	PR interval prolongation ^{1149,1151,1183}
	Sick sinus syndrome ^{1149,1184,1185}
Genetic factors	Wolff–Parkinson–White ^{1149,1186}
	Family history of AF ^{1149,1151,1187–1190}
	AF-susceptible loci identified by GWAS ^{1149,1151,1191,1192}
	Short QT syndrome ¹¹⁴⁹
Biomarkers	Genetic cardiomyopathies ^{990,1193}
	C-reactive protein ^{1150,1151}
	Fibrinogen ¹¹⁵⁰
	Growth differentiation factor-15 ¹¹⁹⁴
	Natriuretic peptides (atrial and B-type) ^{1195–1200}
	Cardiac troponins ¹¹⁹⁹
Others	Inflammatory biomarkers ^{1149,1151}
	Thyroid dysfunction ^{912,1149–1151}
	Autoimmune diseases ¹¹⁵⁰
	Air pollution ^{1149,1201}
	Sepsis ^{1149,1202}
	Psychological factors ^{1203,1204}

AF, atrial fibrillation; CKD, chronic kidney disease; GWAS, genome-wide association studies; HF, heart failure; IMT, intima-media thickness.

10.5. Primary prevention of AF

Preventing the onset of AF before clinical manifestation has clear potential to improve the lives of the general population and reduce the considerable health and social care costs associated with development of AF. Whereas the [C] in AF-CARE is focused on the effective management of risk factors and comorbidities to limit AF recurrence and progression, there is also evidence they can be targeted to prevent AF. Available data are presented below for hypertension, heart failure, type 2 diabetes mellitus, obesity, sleep apnoea syndrome,

physical activity, and alcohol, although many other risk markers can also be targeted. Further information on each factor’s attributable risk for AF is provided in the [Supplementary data online](#) (see [Supplementary data online, Evidence Table 32](#) and [additional Evidence Tables S34–S39](#)).

Recommendation Table 32 — Recommendations for primary prevention of AF (see also Evidence Table 32)

Recommendation	Class ^a	Level ^b
Maintaining optimal blood pressure is recommended in the general population to prevent AF, with ACE inhibitors or ARBs as first-line therapy. ^{1205–1207}	I	B
Appropriate medical HF therapy is recommended in individuals with HFrEF to prevent AF. ^{133,136,1208–1211}	I	B
Maintaining normal weight (BMI 20–25 kg/m ²) is recommended for the general population to prevent AF. ^{208,1212,1213}	I	B
Maintaining an active lifestyle is recommended to prevent AF, with the equivalent of 150–300 min per week of moderate intensity or 75–150 min per week of vigorous intensity aerobic physical activity. ^{1214–1219}	I	B
Avoidance of binge drinking and alcohol excess is recommended in the general population to prevent AF. ^{1220–1223}	I	B
Metformin or SGLT2 inhibitors should be considered for individuals needing pharmacological management of diabetes mellitus to prevent AF. ^{1210,1211,1224–1226}	IIa	B
Weight reduction should be considered in obese individuals to prevent AF. ^{1212,1227–1231}	IIa	B

ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; SGLT2, sodium-glucose cotransporter-2.
^aClass of recommendation.
^bLevel of evidence.

10.5.1. Hypertension

Management of hypertension has been associated with a reduction in incident AF.^{1205–1207,1232} In the LIFE (Losartan Intervention for End point reduction in hypertension) trial, a 10 mmHg reduction in systolic BP was associated with a 17% reduction in incident AF.¹²⁰⁷ Secondary analysis of RCTs and observational studies suggest that ACE inhibitors or ARBs may be superior to beta-blockers, calcium channel blockers, or diuretics for the prevention of incident AF.^{1233–1236}

10.5.2. Heart failure

Long-standing established pharmacological treatments for HFrEF have been associated with a reduction in incident AF. The use of ACE inhibitors or ARBs in patients with known HFrEF was associated with a 44% reduction in incidence of AF.¹²⁰⁸ Similarly, beta-blockers in HFrEF led to a 33% reduction in the odds of incident AF.¹³³ Mineralocorticoid receptor antagonists have also been shown to reduce the risk of new-onset AF by 42% in patients with HFrEF.¹²⁰⁹ Although there have been variable effects of SGLT2 inhibitors on

incident AF, several meta-analyses have demonstrated that there is an 18%–37% reduction in incident AF.^{136,1210,1211,1237} However, treatment of HFrEF with sacubitril/valsartan has not yet been shown to confer any adjunctive benefit in reducing new-onset AF when compared with ACE inhibitors/ARBs alone.¹²³⁸ There is some evidence to suggest that effective CRT in eligible patients with HFrEF reduces the risk of incident AF.¹²³⁹ To date, no treatments in HFpEF have been shown to reduce incident AF.

10.5.3. Type 2 diabetes mellitus

The integrated care of type 2 diabetes, based on lifestyle and pharmacological treatments for comorbidities such as obesity, hypertension, and dyslipidaemia, are useful steps in preventing atrial remodelling and subsequent AF. Intensive glucose-lowering therapy targeting an HbA1c level of <6.0% (<42 mmol/mol) failed to show a protective effect on incident AF.¹²⁴⁰ More than glycaemic control *per se*, the class of glucose-lowering agent may influence the risk of AF.¹²⁴⁰ Insulin promotes adipogenesis and cardiac fibrosis, and sulfonylureas have been consistently associated with an increased risk of AF.¹⁹³ Observational studies have associated metformin with lower rates of incident AF.^{1224,1225,1241–1243} Various recent studies and meta-analyses point to the positive role of SGLT2 inhibitors to reduce the risk of incident AF in diabetic and non-diabetic patients.^{136,1226,1244–1246} Pooled data from 22 trials including 52 951 patients with type 2 diabetes and heart failure showed that SGLT2 inhibitors compared with placebo can significantly reduce the incidence of AF by 18% in studies on diabetes, and up to 37% in heart failure with or without type 2 diabetes.^{1210,1211}

10.5.4. Obesity

Management of weight is important in the prevention of AF. In a large population-based cohort study, normal weight was associated with a reduced risk of incident AF compared with those who were obese (4.7% increase in the risk of incident AF for each 1 kg/m² increase of BMI).²⁰⁸ In the Women’s Health Study, participants who became obese had a 41% increased risk of incident AF compared with those who maintained their BMI <30 kg/m².¹²¹² Similarly, observational studies in populations using bariatric surgery for weight loss in morbidly obese individuals (BMI ≥40 kg/m²) have observed a lower risk of incident AF.^{1227–1231}

10.5.5. Sleep apnoea syndrome

Although it would seem rational to optimize sleep habits, to date there is no conclusive evidence to support this for the primary prevention of AF. The SAVE (Sleep Apnea cardioVascular Endpoints) trial failed to demonstrate a difference in clinical outcomes in those randomized to CPAP therapy or placebo.²³⁰ There was no difference in incident AF, albeit the analysis of AF was not based on systematic screening but rather on clinically documented AF.

10.5.6. Physical activity

Several studies have demonstrated beneficial effects of moderate physical activity on cardiovascular health.¹²⁴⁷ Moderate aerobic exercise may also reduce the risk of new-onset AF.^{1214–1219} It should be noted that the incidence of AF appears to be increased among athletes, with a meta-analysis of observational studies showing a 2.5-fold increased risk of AF compared with non-athlete controls.¹²⁴⁸

10.5.7. Alcohol intake

The premise that reducing alcohol intake can prevent AF is based on observational studies linking alcohol to an excess risk of incident AF in a dose-dependent manner (see [Supplementary data online](#)).^{1220–1222} In addition, a population cohort study of those with high alcohol consumption (>60 g/day for men and >40 g/day for women) found that abstinence from alcohol was associated with a lower incidence of AF compared with patients who continued heavy drinking.¹²²³

11. Key messages

- (1) General management: optimal treatment according to the AF-CARE pathway, which includes: [C] Comorbidity and risk factor management; [A] Avoid stroke and thromboembolism; [R] Reduce symptoms by rate and rhythm control; and [E] Evaluation and dynamic reassessment.
- (2) Shared care: patient-centred AF management with joint decision-making and a multidisciplinary team.
- (3) Equal care: avoid health inequalities based on gender, ethnicity, disability, and socioeconomic factors.
- (4) Education: for patients, family members, caregivers, and health-care professionals to aid shared decision-making.
- (5) Diagnosis: clinical AF requires confirmation on an ECG device to initiate risk stratification and AF management.
- (6) Initial evaluation: medical history, assessment of symptoms and their impact, blood tests, echocardiography/other imaging, patient-reported outcome measures, and risk factors for thromboembolism and bleeding.
- (7) Comorbidities and risk factors: thorough evaluation and management critical to all aspects of care for patients with AF to avoid recurrence and progression of AF, improve success of AF treatments, and prevent AF-related adverse outcomes.
- (8) Focus on conditions associated with AF: including hypertension, heart failure, diabetes mellitus, obesity, obstructive sleep apnoea, physical inactivity, and high alcohol intake.
- (9) Assessing the risk of thromboembolism: use locally validated risk tools or the CHA₂DS₂-VA score and assessment of other risk factors, with reassessment at periodic intervals to assist in decisions on anticoagulant prescription.
- (10) Oral anticoagulants: recommended for all eligible patients, except those at low risk of incident stroke or thromboembolism (CHA₂DS₂-VA = 1 anticoagulation should be considered; CHA₂DS₂-VA ≥ 2 anticoagulation recommended).
- (11) Choice of anticoagulant: DOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) are preferred over VKAs (warfarin and others), except in patients with mechanical heart valves and mitral stenosis.
- (12) Dose/range of anticoagulant: use full standard doses for DOACs unless the patient meets specific dose-reduction criteria; for VKAs, keep INR generally 2.0–3.0, and in range for >70% of the time.
- (13) Switching anticoagulants: switch from a VKA to DOAC if risk of intracranial haemorrhage or poor control of INR levels.
- (14) Bleeding risk: modifiable bleeding risk factors should be managed to improve safety; bleeding risk scores should not be used to decide on starting or withdrawing anticoagulants.
- (15) Antiplatelet therapy: avoid combining anticoagulants and antiplatelet agents, unless the patient has an acute vascular event or needs interim treatment for procedures.

- (16) Rate control therapy: use beta-blockers (any ejection fraction), digoxin (any ejection fraction), or diltiazem/verapamil (LVEF >40%) as initial therapy in the acute setting, an adjunct to rhythm control therapies, or as a sole treatment strategy to control heart rate and symptoms.
- (17) Rhythm control: consider in all suitable AF patients, explicitly discussing with patients all potential benefits and risks of cardioversion, antiarrhythmic drugs, and catheter or surgical ablation to reduce symptoms and morbidity.
- (18) Safety first: keep safety and anticoagulation in mind when considering rhythm control; e.g. delay cardioversion and provide at least 3 weeks of anticoagulation beforehand if AF duration >24 h, and consider toxicity and drug interactions for antiarrhythmic therapy.
- (19) Cardioversion: use electrical cardioversion in cases of haemodynamic instability; otherwise choose electrical or pharmacological cardioversion based on patient characteristics and preferences.
- (20) Indication for long-term rhythm control: the primary indication should be reduction in AF-related symptoms and improvement in quality of life; for selected patient groups, sinus rhythm maintenance can be pursued to reduce morbidity and mortality.
- (21) Success or failure of rhythm control: continue anticoagulation according to the patient's individual risk of thromboembolism, irrespective of whether they are in AF or sinus rhythm.
- (22) Catheter ablation: consider as second-line option if antiarrhythmic drugs fail to control AF, or first-line option in patients with paroxysmal AF.
- (23) Endoscopic or hybrid ablation: consider if catheter ablation fails, or an alternative to catheter ablation in persistent AF despite antiarrhythmic drugs.
- (24) Atrial fibrillation ablation during cardiac surgery: perform in centres with experienced teams, especially for patients undergoing mitral valve surgery.
- (25) Dynamic evaluation: periodically reassess therapy and give attention to new modifiable risk factors that could slow/reverse the progression of AF, increase quality of life, and prevent adverse outcomes.

12. Gaps in evidence

The following bullet list gives the most important gaps in evidence where new clinical trials could substantially aid the patient pathway:

Definition and clinical impact of AF

- Paroxysmal AF is not one entity, and patterns of AF progression and regression are highly variable. It is uncertain what the relevance is for treatment strategies and management decisions.
- Thirty seconds as definition for clinical AF needs validation and evaluation whether it is related to AF-related outcomes.
- Definition, clinical features, diagnosis, and implementation for treatment choices of atrial cardiomyopathy in patients with AF is unsettled.
- Diversity in AF presentation, underlying pathophysiological mechanisms, and associated comorbidities is incompletely understood with regard to differences in sex, gender, race/ethnicity, socioeconomic state, education, and differences between low-, moderate-, and high-income countries.
- Personalized risk prediction for AF incidence, AF progression, and associated outcomes remains challenging.

- Insights into psychosocial and environmental factors and risk of AF and adverse outcomes in AF are understudied.

Patient-centred, multidisciplinary AF management

- The benefit of additional education directed to patients, to family members, and to healthcare professionals in order to optimize shared decision-making still needs to be proved.
- Access to patient-centred management according to the AF-CARE principles to ensure equality in healthcare provision and improve outcomes warrants evidence.
- The place of remote monitoring and telemedicine for identification and follow-up of patients with AF, or its subgroups is non-established, though widely applied.

[C] Comorbidity and risk factor management

- Methods to achieve consistent and reproducible weight loss in patients with AF requires substantial improvement. Despite some evidence demonstrating the benefits of weight loss, widespread adoption has been limited by the need for reproducible strategies.
- The importance of sleep apnoea syndrome and its treatment on AF-related outcomes remains to be elucidated.

[A] Avoid stroke and thromboembolism

- Data are lacking on how to treat patients with low risk of stroke (with a CHA₂DS₂-VA score of 0 or 1), as these patients were excluded from large RCTs.
- Not enough evidence is available for OAC in elderly patients, frail polypharmacy patients, those with cognitive impairment/dementia, recent bleeding, previous ICH, severe end-stage renal failure, liver impairment, cancer, or severe obesity.
- In elderly patients, routinely switching VKAs to DOACs is associated with increased bleeding risk; however, the reasons why this happens are unclear.
- The selection of which patients with asymptomatic device-detected subclinical AF benefit from OAC therapy needs to be defined.
- There is a lack of evidence whether and when to (re)start anticoagulation after intracranial haemorrhage.
- There is lack of evidence about optimal anticoagulation in patients with ischaemic stroke or left atrial thrombus while being treated with OAC.
- There is uncertainty about the place of LAA closure and how to manage antithrombotic post-procedural management when LAAO is performed.
- Balance of thromboembolism and bleeding is unclear in patients with AF and incidental cerebral artery aneurysms identified on brain MRI.

[R] Reduce symptoms by rate and rhythm control

- In some patients, AF can be benign in terms of symptoms and outcomes. In which patients rhythm control is not needed warrants investigation.
- Application of antiarrhythmic drugs has been hampered by poor effectiveness and side effects; however, new antiarrhythmic drugs are needed to increase the therapeutic arsenal for AF patients.

- The amount of AF reduction obtained by rhythm control to improve outcomes is unknown.
- Large catheter ablation studies showed no improved outcome of patients with AF. Some small studies in specific subpopulations have observed an improved outcome. This warrants further investigation to provide each patient with AF with personalized treatment goals.
- Uncertainty exists on the time of duration of AF and risk of stroke when performing a cardioversion.
- The value of diagnostic cardioversion for persistent AF in steering management of AF is unknown.
- Decisions on continuation of OAC are completely based on stroke risk scores and irrespective of having (episodes) of AF; whether this holds for patients undergoing successful catheter ablation is uncertain.
- Large variability in ablation strategies and techniques exist for patients with persistent AF, or after first failed catheter ablation for paroxysmal AF. The optimal catheter ablation strategy and techniques, however, are unknown.
- Sham-controlled intervention studies are lacking to determine the effects on AF symptoms, quality of life, and PROMS, accounting for the placebo effect that is associated with interventions.

The AF-CARE pathway in specific clinical settings

- The optimal duration of triple therapy in patients with AF at high risk of recurrent coronary events after acute coronary syndrome is unclear.
- The role of the coronary vessel involved and whether this should impact on the duration of combined OAC and antiplatelet treatment needs further study.
- The role of antiplatelet therapy in patients with AF and peripheral artery disease on OAC is uncertain.
- The use of DOACs in patients with congenital heart disease, particularly in patients with complex corrected congenital defects, is poorly studied.
- Improved risk stratification for stroke in patients with AF and cancer, or with post-operative or trigger-induced AF is needed to inform on OAC treatment decisions.

Screening and prevention of AF

- There are a lack of adequately powered randomized controlled studies on ischaemic stroke rate in patients screened for AF, both in the primary prevention setting and in secondary prevention (post-stroke), and its cost-effectiveness.
- Population selection that might benefit the most from screening, the optimal duration of screening, and the burden of AF that might increase the risk for patients with screening-detected AF are uncertain.
- Evaluation of strategies to support longer-term use of technologies for AF detection are awaited.
- The role of photoplethysmography technology for AF screening in an effort to assess AF burden and reduce stroke is still unclear.
- How new consumer devices and wearable technology can be used for diagnostic and monitoring purposes in routine clinical practice needs to be clarified.

13. 'What to do' and 'What not to do' messages from the guidelines

Table 17 lists all Class I and Class III recommendations from the text alongside their level of evidence.

Table 17 'What to do' and 'what not to do'

Recommendations	Class ^a	Level ^b
Recommendations for the diagnosis of AF		
Confirmation by an electrocardiogram (12-lead, multiple, or single leads) is recommended to establish the diagnosis of clinical AF and commence risk stratification and treatment.	I	A
Recommendations for symptom evaluation in patients with AF		
Evaluating the impact of AF-related symptoms is recommended before and after major changes in treatment to inform shared decision-making and guide treatment choices.	I	B
Recommendations for diagnostic evaluation in patients with new AF		
A transthoracic echocardiogram is recommended in patients with an AF diagnosis where this will guide treatment decisions.	I	C
Recommendations for patient-centred care and education		
Education directed to patients, family members, caregivers, and healthcare professionals is recommended to optimize shared decision-making, facilitating open discussion of both the benefit and risk associated with each treatment option.	I	C
Access to patient-centred management according to the AF-CARE principles is recommended in all patients with AF, regardless of gender, ethnicity, and socioeconomic status, to ensure equality in healthcare provision and improve outcomes.	I	C
Recommendations for comorbidity and risk factor management in AF		
Identification and management of risk factors and comorbidities is recommended as an integral part of AF care.	I	B
Blood pressure lowering treatment is recommended in patients with AF and hypertension to reduce recurrence and progression of AF and prevent adverse cardiovascular events.	I	B
Diuretics are recommended in patients with AF, HF, and congestion to alleviate symptoms and facilitate better AF management.	I	C
Appropriate medical therapy for HF is recommended in AF patients with HF and impaired LVEF to reduce symptoms and/or HF hospitalization and prevent AF recurrence.	I	B
Sodium-glucose cotransporter-2 inhibitors are recommended for patients with HF and AF regardless of left ventricular ejection fraction to reduce the risk of HF hospitalization and cardiovascular death.	I	A
Effective glycaemic control is recommended as part of comprehensive risk factor management in individuals with diabetes mellitus and AF, to reduce burden, recurrence, and progression of AF.	I	C
Weight loss is recommended as part of comprehensive risk factor management in overweight and obese individuals with AF to reduce symptoms and AF burden, with a target of 10% or more reduction in body weight.	I	B
A tailored exercise programme is recommended in individuals with paroxysmal or persistent AF to improve cardiorespiratory fitness and reduce AF recurrence.	I	B
Reducing alcohol consumption to ≤3 standard drinks (≤30 grams of alcohol) per week is recommended as part of comprehensive risk factor management to reduce AF recurrence.	I	B
When screening for obstructive sleep apnoea in individuals with AF, using only symptom-based questionnaires is not recommended.	III	B
Recommendations to assess and manage thromboembolic risk in AF		
Oral anticoagulation is recommended in patients with clinical AF at elevated thromboembolic risk to prevent ischaemic stroke and thromboembolism.	I	A
A CHA ₂ DS ₂ -VA score of 2 or more is recommended as an indicator of elevated thromboembolic risk for decisions on initiating oral anticoagulation.	I	C
Oral anticoagulation is recommended in all patients with AF and hypertrophic cardiomyopathy or cardiac amyloidosis, regardless of CHA ₂ DS ₂ -VA score, to prevent ischaemic stroke and thromboembolism.	I	B
Individualized reassessment of thromboembolic risk is recommended at periodic intervals in patients with AF to ensure anticoagulation is started in appropriate patients.	I	B
Antiplatelet therapy is not recommended as an alternative to anticoagulation in patients with AF to prevent ischaemic stroke and thromboembolism.	III	A
Using the temporal pattern of clinical AF (paroxysmal, persistent, or permanent) is not recommended to determine the need for oral anticoagulation.	III	B

Continued

Recommendations for oral anticoagulation in AF		
Direct oral anticoagulants are recommended in preference to VKAs to prevent ischaemic stroke and thromboembolism, except in patients with mechanical heart valves or moderate-to-severe mitral stenosis.	I	A
A target INR of 2.0–3.0 is recommended for patients with AF prescribed a VKA for stroke prevention to ensure safety and effectiveness.	I	B
Switching to a DOAC is recommended for eligible patients that have failed to maintain an adequate time in therapeutic range on a VKA (TTR <70%) to prevent thromboembolism and intracranial haemorrhage.	I	B
A reduced dose of DOAC therapy is not recommended, unless patients meet DOAC-specific criteria, to prevent underdosing and avoidable thromboembolic events.	III	B
Recommendations for combining antiplatelet drugs with anticoagulants for stroke prevention		
Adding antiplatelet treatment to oral anticoagulation is not recommended in AF patients for the goal of preventing ischaemic stroke or thromboembolism.	III	B
Recommendations for thromboembolism despite anticoagulation		
Adding antiplatelet treatment to anticoagulation is not recommended in patients with AF to prevent recurrent embolic stroke.	III	B
Switching from one DOAC to another, or from a DOAC to a VKA, without a clear indication is not recommended in patients with AF to prevent recurrent embolic stroke.	III	B
Recommendations for surgical left atrial appendage occlusion		
Surgical closure of the left atrial appendage is recommended as an adjunct to oral anticoagulation in patients with AF undergoing cardiac surgery to prevent ischaemic stroke and thromboembolism.	I	B
Recommendations for assessment of bleeding risk		
Assessment and management of modifiable bleeding risk factors is recommended in all patients eligible for oral anticoagulation, as part of shared decision-making to ensure safety and prevent bleeding.	I	B
Use of bleeding risk scores to decide on starting or withdrawing oral anticoagulation is not recommended in patients with AF to avoid under-use of anticoagulation.	III	B
Recommendations for management of bleeding in anticoagulated patients		
Interrupting anticoagulation and performing diagnostic or treatment interventions is recommended in AF patients with active bleeding until the cause of bleeding is identified and resolved.	I	C
Recommendations for heart rate control in patients with AF		
Rate control therapy is recommended in patients with AF, as initial therapy in the acute setting, an adjunct to rhythm control therapies, or as a sole treatment strategy to control heart rate and reduce symptoms.	I	B
Beta-blockers, diltiazem, verapamil, or digoxin are recommended as first-choice drugs in patients with AF and LVEF >40% to control heart rate and reduce symptoms.	I	B
Beta-blockers and/or digoxin are recommended in patients with AF and LVEF ≤40% to control heart rate and reduce symptoms.	I	B
Recommendations for general concepts in rhythm control		
Electrical cardioversion is recommended in AF patients with acute or worsening haemodynamic instability to improve immediate patient outcomes.	I	C
Direct oral anticoagulants are recommended in preference to VKAs in eligible patients with AF undergoing cardioversion for thromboembolic risk reduction.	I	A
Therapeutic oral anticoagulation for at least 3 weeks (adherence to DOACs or INR ≥2.0 for VKAs) is recommended before scheduled cardioversion of AF and atrial flutter to prevent procedure-related thromboembolism.	I	B
Transoesophageal echocardiography is recommended if 3 weeks of therapeutic oral anticoagulation has not been provided, for exclusion of cardiac thrombus to enable early cardioversion.	I	B
Oral anticoagulation is recommended to continue for at least 4 weeks in all patients after cardioversion and long-term in patients with thromboembolic risk factor(s) irrespective of whether sinus rhythm is achieved, to prevent thromboembolism.	I	B
Early cardioversion is not recommended without appropriate anticoagulation or transoesophageal echocardiography if AF duration is longer than 24 h, or there is scope to wait for spontaneous cardioversion.	III	C
Recommendations for pharmacological cardioversion of AF		
Intravenous flecainide or propafenone is recommended when pharmacological cardioversion of recent-onset AF is desired, excluding patients with severe left ventricular hypertrophy, HFrEF, or coronary artery disease.	I	A
Intravenous vernakalant is recommended when pharmacological cardioversion of recent-onset AF is desired, excluding patients with recent ACS, HFrEF, or severe aortic stenosis.	I	A
Intravenous amiodarone is recommended when cardioversion of AF in patients with severe left ventricular hypertrophy, HFrEF, or coronary artery disease is desired, accepting there may be a delay in cardioversion.	I	A
Pharmacological cardioversion is not recommended for patients with sinus node dysfunction, atrioventricular conduction disturbances, or prolonged QTc (>500 ms), unless risks for proarrhythmia and bradycardia have been considered.	III	C

Continued

Recommendations for antiarrhythmic drugs for long-term maintenance of sinus rhythm		
Amiodarone is recommended in patients with AF and HFrEF requiring long-term antiarrhythmic drug therapy to prevent recurrence and progression of AF, with careful consideration and monitoring for extracardiac toxicity.	I	A
Dronedarone is recommended in patients with AF requiring long-term rhythm control, including those with HFmrEF, HFpEF, ischaemic heart disease, or valvular disease to prevent recurrence and progression of AF.	I	A
Flecainide or propafenone is recommended in patients with AF requiring long-term rhythm control to prevent recurrence and progression of AF, excluding those with impaired left ventricular systolic function, severe left ventricular hypertrophy, or coronary artery disease.	I	A
Antiarrhythmic drug therapy is not recommended in patients with advanced conduction disturbances unless antibradycardia pacing is provided.	III	C
Recommendations for catheter ablation of AF		
Shared decision-making		
Shared decision-making is recommended when considering catheter ablation for AF, taking into account procedural risks, likely benefits, and risk factors for AF recurrence.	I	C
Atrial fibrillation patients resistant or intolerant to antiarrhythmic drug therapy		
Catheter ablation is recommended in patients with paroxysmal or persistent AF resistant or intolerant to antiarrhythmic drug therapy to reduce symptoms, recurrence, and progression of AF.	I	A
First-line rhythm control therapy		
Catheter ablation is recommended as a first-line option within a shared decision-making rhythm control strategy in patients with paroxysmal AF, to reduce symptoms, recurrence, and progression of AF.	I	A
Patients with heart failure		
Atrial fibrillation catheter ablation is recommended in patients with AF and HFrEF with high probability of tachycardia-induced cardiomyopathy to reverse left ventricular dysfunction.	I	B
Recommendations for anticoagulation in patients undergoing catheter ablation		
Initiation of oral anticoagulation is recommended at least 3 weeks prior to catheter-based ablation in AF patients at elevated thromboembolic risk, to prevent peri-procedural ischaemic stroke and thromboembolism.	I	C
Uninterrupted oral anticoagulation is recommended in patients undergoing AF catheter ablation to prevent peri-procedural ischaemic stroke and thromboembolism.	I	A
Continuation of oral anticoagulation is recommended for at least 2 months after AF ablation in all patients, irrespective of rhythm outcome or CHA ₂ DS ₂ -VA score, to reduce the risk of peri-procedural ischaemic stroke and thromboembolism.	I	C
Continuation of oral anticoagulation is recommended after AF ablation according to the patient's CHA ₂ DS ₂ -VA score, and not the perceived success of the ablation procedure, to prevent ischaemic stroke and thromboembolism.	I	C
Recommendations for endoscopic and hybrid AF ablation		
Continuation of oral anticoagulation is recommended in patients with AF at elevated thromboembolic risk after concomitant, endoscopic, or hybrid AF ablation, independent of rhythm outcome or LAA exclusion, to prevent ischaemic stroke and thromboembolism.	I	C
Recommendations for AF ablation during cardiac surgery		
Concomitant surgical ablation is recommended in patients undergoing mitral valve surgery and AF suitable for a rhythm control strategy to prevent symptoms and recurrence of AF, with shared decision-making supported by an experienced team of electrophysiologists and arrhythmia surgeons.	I	A
Intraprocedural imaging for detection of left atrial thrombus in patients undergoing surgical ablation is recommended to guide surgical strategy, independent of oral anticoagulant use, to prevent peri-procedural ischaemic stroke and thromboembolism.	I	C
Recommendations for patients with acute coronary syndromes or undergoing percutaneous intervention		
General recommendations for patients with AF and an indication for concomitant antiplatelet therapy		
For combinations with antiplatelet therapy, a DOAC is recommended in eligible patients in preference to a VKA to mitigate bleeding risk and prevent thromboembolism.	I	A
Recommendations for AF patients with ACS		
Early cessation (≤ 1 week) of aspirin and continuation of an oral anticoagulant (preferably DOAC) with a P2Y ₁₂ inhibitor (preferably clopidogrel) for up to 12 months is recommended in AF patients with ACS undergoing an uncomplicated PCI to avoid major bleeding, if the risk of thrombosis is low or bleeding risk is high.	I	A
Recommendations for AF patients undergoing PCI		
After uncomplicated PCI, early cessation (≤ 1 week) of aspirin and continuation of an oral anticoagulant and a P2Y ₁₂ inhibitor (preferably clopidogrel) for up to 6 months is recommended to avoid major bleeding, if ischaemic risk is low.	I	A

Continued

Recommendations for AF patients with chronic coronary or vascular disease		
Antiplatelet therapy beyond 12 months is not recommended in stable patients with chronic coronary or vascular disease treated with oral anticoagulation, due to lack of efficacy and to avoid major bleeding.	III	B
Recommendations for management of post-operative AF		
Peri-operative amiodarone therapy is recommended where drug therapy is desired to prevent post-operative AF after cardiac surgery.	I	A
Routine use of beta-blockers is not recommended in patients undergoing non-cardiac surgery for the prevention of post-operative AF.	III	B
Recommendations for patients with embolic stroke of unknown source		
Prolonged monitoring for AF is recommended in patients with ESUS to inform on AF treatment decisions.	I	B
Initiation of oral anticoagulation in ESUS patients without documented AF is not recommended due to lack of efficacy in preventing ischaemic stroke and thromboembolism.	III	A
Recommendations for patients with AF during pregnancy		
Immediate electrical cardioversion is recommended in patients with AF during pregnancy and haemodynamic instability or pre-excited AF to improve maternal and foetal outcomes.	I	C
Therapeutic anticoagulation with LMWHs or VKAs (except VKAs for the first trimester or beyond Week 36) is recommended for pregnant patients with AF at elevated thromboembolic risk to prevent ischaemic stroke and thromboembolism.	I	C
Beta-1 selective blockers are recommended for heart rate control of AF in pregnancy to reduce symptoms and improve maternal and foetal outcomes, excluding atenolol.	I	C
Recommendations for prevention of thromboembolism in atrial flutter		
Oral anticoagulation is recommended in patients with atrial flutter at elevated thromboembolic risk to prevent ischaemic stroke and thromboembolism.	I	B
Recommendations for screening for AF		
Review of an ECG (12-lead, single, or multiple leads) by a physician is recommended to provide a definite diagnosis of AF and commence appropriate management.	I	B
Routine heart rhythm assessment during healthcare contact is recommended in all individuals aged ≥ 65 years for earlier detection of AF.	I	C
Recommendations for primary prevention of AF		
Maintaining optimal blood pressure is recommended in the general population to prevent AF, with ACE inhibitors or ARBs as first-line therapy.	I	B
Appropriate medical HF therapy is recommended in individuals with HFrEF to prevent AF.	I	B
Maintaining normal weight (BMI 20–25 kg/m ²) is recommended for the general population to prevent AF.	I	B
Maintaining an active lifestyle is recommended to prevent AF, with the equivalent of 150–300 min per week of moderate intensity or 75–150 min per week of vigorous intensity aerobic physical activity.	I	B
Avoidance of binge drinking and alcohol excess is recommended in the general population to prevent AF.	I	B

AAD, antiarrhythmic drugs; ACEi, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndromes; AF, atrial fibrillation; AF-CARE, atrial fibrillation—[C] Comorbidity and risk factor management, [A] Avoid stroke and thromboembolism, [R] Reduce symptoms by rate and rhythm control, [E] Evaluation and dynamic reassessment; AFL, atrial flutter; ARB, angiotensin receptor blocker; BMI, body mass index; CHA₂DS₂-VA, congestive heart failure, hypertension, age ≥ 75 years (2 points), diabetes mellitus, prior stroke/transient ischaemic attack/arterial thromboembolism (2 points), vascular disease, age 65–74 years; DOAC, direct oral anticoagulant; ECG, electrocardiogram; ESUS, embolic stroke of undetermined source; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; INR, international normalized ratio of prothrombin time; LAA, left atrial appendage; LMWH, low molecular weight heparin; LVEF, left ventricular ejection fraction; PCI, percutaneous intervention; SGLT2, sodium-glucose cotransporter-2; TTR, time in therapeutic range; VKA, vitamin K antagonist.

^aClass of recommendation.

^bLevel of evidence.

14. Evidence tables

Evidence tables are available at *European Heart Journal* online.

15. Data availability statement

No new data were generated or analysed in support of this research.

16. Author information

Author/Task Force Member Affiliations: Michiel Rienstra, Department of Cardiology, University of Groningen, University

Medical Center Groningen, Groningen, Netherlands; **Karina V. Bunting**, Institute of Cardiovascular Sciences, University of Birmingham, Birmingham, United Kingdom, Cardiology Department, Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom; **Ruben Casado-Arroyo**, Department of Cardiology, H.U.B.-Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium; **Valeria Caso**, Stroke Unit, Santa della Misericordia Hospital, Perugia, Italy; **Harry J.G.M. Crijns**, Cardiology Maastricht University Medical Centre, Maastricht, Netherlands, Cardiology Cardiovascular Research Institute Maastricht, Maastricht University, Maastricht, Netherlands; **Tom J. R. De Potter**, Department of Cardiology, OLV Hospital,

Aalst, Belgium; **Jeremy Dwight** (United Kingdom), ESC Patient Forum, Sophia Antipolis, France; **Luigina Guasti**, Department of Medicine and Surgery, University of Insubria, Varese, Italy, Division of Geriatrics and Clinical Gerontology, ASST-Settelaghi, Varese, Italy; **Thorsten Hanke**, Clinic For Cardiac Surgery, Asklepios Klinikum, Harburg, Hamburg, Germany; **Tiny Jaarsma**, Department of Cardiology, Linköping University, Linköping, Sweden, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, Netherlands; **Maddalena Lettino**, Department for Cardiac, Thoracic and Vascular Diseases, Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy; **Maja-Lisa Løchen**, Department of Clinical Medicine UiT, The Arctic University of Norway, Tromsø, Norway, Department of Cardiology, University Hospital of North Norway, Tromsø, Norway; **R. Thomas Lumbers**, Institute of Health Informatics, University College London, London, United Kingdom, Saint Bartholomew's Hospital, Barts Health NHS Trust, London, United Kingdom, University College Hospital, University College London Hospitals NHS Trust, London, United Kingdom; **Bart Maesen**, Department of Cardiothoracic Surgery, Maastricht University Medical Centre+, Maastricht, Netherlands, Cardiovascular Research Institute Maastricht, Maastricht University, Maastricht, Netherlands; **Inge Mølgaard** (Denmark), ESC Patient Forum, Sophia Antipolis, France; **Giuseppe M.C. Rosano**, Department of Human Sciences and Promotion of Quality of Life, Chair of Pharmacology, San Raffaele University of Rome, Rome, Italy, Cardiology, San Raffaele Cassino Hospital, Cassino, Italy, Cardiovascular Academic Group, St George's University Medical School, London, United Kingdom; **Prashanthan Sanders**, Centre for Heart Rhythm Disorders, University of Adelaide, Adelaide, Australia, Department of Cardiology, Royal Adelaide Hospital, Adelaide, Australia; **Renate B. Schnabel**, Cardiology University Heart & Vascular Center Hamburg, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, German Center for Cardiovascular Research (DZHK) Partner site Hamburg/Kiel/Lübeck, Germany; **Piotr Suwalski**, Department of Cardiac Surgery and Transplantation, National Medical Institute of the Ministry of Interior and Administration, Centre of Postgraduate Medical Education, Warsaw, Poland; **Emma Svennberg**, Department of Medicine, Karolinska University Hospital Huddinge, Karolinska Institutet, Stockholm, Sweden, Department of Cardiology, Karolinska University Hospital, Stockholm, Sweden; **Juan Tamargo**, Pharmacology and Toxicology School of Medicine, Universidad Complutense, Madrid, Spain; **Otilia Tica**, Department of Cardiology, Emergency County Clinical Hospital of Bihor, Oradea, Romania, Institute of Cardiovascular Sciences, University of Birmingham, Birmingham, United Kingdom; **Vassil Traykov**, Department of Invasive Electrophysiology, Acibadem City Clinic Tokuda University Hospital, Sofia, Bulgaria; and **Stylianios Tzeis**, Cardiology Department, Mitera Hospital, Athens, Greece.

17. Appendix

ESC Scientific Document Group

Includes Document Reviewers and ESC National Cardiac Societies.

Document Reviewers: Nikolaos Dagres (CPG Review Co-ordinator) (Germany), Bianca Rocca (CPG Review Co-ordinator) (Italy), Syed Ahsan (United Kingdom), Pietro Ameri (Italy), Elena Arbelo (Spain), Axel Bauer (Austria), Michael A. Borger (Germany), Sergio Buccheri (Sweden), Barbara Casadei (United Kingdom), Ovidiu Chioncel (Romania), Dobromir Dobrev (Germany), Laurent Fauchier

(France), Bruna Gigante (Sweden), Michael Glikson (Israel), Ziad Hijazi (Sweden), Gerhard Hindricks (Germany), Daniela Husser (Germany), Borja Ibanez (Spain), Stefan James (Sweden), Stefan Kaab (Germany), Paulus Kirchhof (Germany), Lars Køber (Denmark), Konstantinos C. Koskinas (Switzerland), Thomas Kumler (Denmark), Gregory Y.H. Lip (United Kingdom), John Mandrolia (United States of America), Nikolaus Marx (Germany), John William Mcevoy (Ireland), Borislava Mihaylova (United Kingdom), Richard Mindham (United Kingdom), Denisa Muraru (Italy), Lis Neubeck (United Kingdom), Jens Cosedis Nielsen (Denmark), Jonas Oldgren (Sweden), Maurizio Paciaroni (Italy), Agnes A. Pasquet (Belgium), Eva Prescott (Denmark), Filip Rega (Belgium), Francisco Javier Rossello (Spain), Marcin Rucinski (Poland), Sacha P. Salzberg (Switzerland), Sam Schulman (Canada), Philipp Sommer (Germany), Jesper Hastrup Svendsen (Denmark), Jurrien M. ten Berg (Netherlands), Hugo Ten Cate (Netherlands), Ilonca Vaartjes (Netherlands), Christiaan Jm. Vrints (Belgium), Adam Witkowski (Poland), and Katja Zeppenfeld (Netherlands).

ESC National Cardiac Societies actively involved in the review process of the 2024 ESC Guidelines for the management of atrial fibrillation:

Albania: Albanian Society of Cardiology, Leonard Simoni; **Algeria:** Algerian Society of Cardiology, Brahim Kichou; **Armenia:** Armenian Cardiologists Association, Hamayak S. Sisakian; **Austria:** Austrian Society of Cardiology, Daniel Scherr; **Belgium:** Belgian Society of Cardiology, Frank Cools; **Bosnia and Herzegovina:** Association of Cardiologists of Bosnia and Herzegovina, Elnur Smajić; **Bulgaria:** Bulgarian Society of Cardiology, Tchavdar Shalganov; **Croatia:** Croatian Cardiac Society, Sime Manola; **Cyprus:** Cyprus Society of Cardiology, Panayiotis Avraamides; **Czechia:** Czech Society of Cardiology, Milos Taborsky; **Denmark:** Danish Society of Cardiology, Axel Brandes; **Egypt:** Egyptian Society of Cardiology, Ahmed M. El-Damaty; **Estonia:** Estonian Society of Cardiology, Priit Kampus; **Finland:** Finnish Cardiac Society, Pekka Raatikainen; **France:** French Society of Cardiology, Rodrigue Garcia; **Georgia:** Georgian Society of Cardiology, Kakhaber Etsadashvili; **Germany:** German Cardiac Society, Lars Eckardt; **Greece:** Hellenic Society of Cardiology, Eleftherios Kallergis; **Hungary:** Hungarian Society of Cardiology, László Gellér; **Iceland:** Icelandic Society of Cardiology, Kristján Guðmundsson; **Ireland:** Irish Cardiac Society, Jonathan Lyne; **Israel:** Israel Heart Society, Ibrahim Marai; **Italy:** Italian Federation of Cardiology, Furio Colivicchi; **Kazakhstan:** Association of Cardiologists of Kazakhstan, Ayan Suleimenovich Abdrakhmanov; **Kosovo (Republic of):** Kosovo Society of Cardiology, Ibadete Bytyci; **Kyrgyzstan:** Kyrgyz Society of Cardiology, Alina Kerimkulova; **Latvia:** Latvian Society of Cardiology, Kaspars Kupics; **Lebanon:** Lebanese Society of Cardiology, Marwan Refaat; **Libya:** Libyan Cardiac Society, Osama Abdulmajed Bheleel; **Lithuania:** Lithuanian Society of Cardiology, Jūratė Barysienė; **Luxembourg:** Luxembourg Society of Cardiology, Patrick Leitz; **Malta:** Maltese Cardiac Society, Mark A. Sammut; **Moldova (Republic of):** Moldavian Society of Cardiology, Aurel Grosu; **Montenegro:** Montenegro Society of Cardiology, Nikola Pavlovic; **Morocco:** Moroccan Society of Cardiology, Abdelhamid Moustaghfir; **Netherlands:** Netherlands Society of Cardiology, Sing-Chien Yap; **North Macedonia:** National Society of Cardiology of North Macedonia, Jane Taleski; **Norway:** Norwegian Society of Cardiology, Trine Fink; **Poland:** Polish Cardiac Society, Jaroslaw Kazmierczak; **Portugal:** Portuguese Society of Cardiology, Victor M. Sanfins; **Romania:** Romanian Society of Cardiology, Dragos Cozma; **San**

Marino: San Marino Society of Cardiology, Marco Zavatta; **Serbia:** Cardiology Society of Serbia, Dragan V. Kovačević; **Slovakia:** Slovak Society of Cardiology, Peter Hlivak; **Slovenia:** Slovenian Society of Cardiology, Igor Zupan; **Spain:** Spanish Society of Cardiology, David Calvo; **Sweden:** Swedish Society of Cardiology, Anna Björkenheim; **Switzerland:** Swiss Society of Cardiology, Michael Kühne; **Tunisia:** Tunisian Society of Cardiology and Cardiovascular Surgery, Sana Ouali; **Turkey:** Turkish Society of Cardiology, Sabri Demircan; **Ukraine:** Ukrainian Association of Cardiology, Oleg S. Sychoy; **United Kingdom of Great Britain and Northern Ireland:** British Cardiovascular Society, Andre Ng; and **Uzbekistan:** Association of Cardiologists of Uzbekistan, Husniddin Kuchkarov.

ESC Clinical Practice Guidelines (CPG) Committee: Eva Prescott (Chairperson) (Denmark), Stefan James (Co-Chairperson) (Sweden), Elena Arbelo (Spain), Colin Baigent (United Kingdom), Michael A. Borger (Germany), Sergio Burcheri (Sweden), Borja Ibanez (Spain), Lars Køber (Denmark), Konstantinos C. Koskinas (Switzerland), John William McEvoy (Ireland), Borislava Mihaylova (United Kingdom), Richard Mindham (United Kingdom), Lis Neubeck (United Kingdom), Jens Cosedis Nielsen (Denmark), Agnes A. Pasquet (Belgium), Amina Rakisheva (Kazakhstan), Bianca Rocca (Italy), Xavier Rossello (Spain), Ilonca Vaartjes (Netherlands), Christiaan Vrints (Belgium), Adam Witkowski (Poland), and Katja Zeppenfeld (Netherlands). Andrea Sarkozy* (Belgium) *Contributor either stepped down or was engaged in only a part of the review process.

18. References

- Alam M, Bandea SJ, Shahzad SA, Lakkis N. Real-life global survey evaluating patients with atrial fibrillation (REALISE-AF): results of an international observational registry. *Expert Rev Cardiovasc Ther* 2012;**10**:283–91. <https://doi.org/10.1586/erc.12.8>
- De With RR, Erkün Ö, Rienstra M, Nguyen BO, Körver FWJ, Linz D, et al. Temporal patterns and short-term progression of paroxysmal atrial fibrillation: data from RACE V. *Europace* 2020;**22**:1162–72. <https://doi.org/10.1093/europace/euaa123>
- Packer DL, Mark DB, Robb RA, Monahan KH, Bahnson TD, Poole JE, et al. Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation: the CABANA randomized clinical trial. *JAMA* 2019;**321**:1261–74. <https://doi.org/10.1001/jama.2019.0693>
- Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, et al. Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med* 2018;**378**:417–27. <https://doi.org/10.1056/NEJMoa1707855>
- Svensen JH, Diederichsen SZ, Højberg S, Krieger DW, Graff C, Kronborg C, et al. Implantable loop recorder detection of atrial fibrillation to prevent stroke (The LOOP Study): a randomised controlled trial. *Lancet* 2021;**398**:1507–16. [https://doi.org/10.1016/S0140-6736\(21\)01698-6](https://doi.org/10.1016/S0140-6736(21)01698-6)
- Svensen E, Friberg L, Frykman V, Al-Khalili F, Engdahl J, Rosenqvist M. Clinical outcomes in systematic screening for atrial fibrillation (STROKESTOP): a multicentre, parallel group, unmasked, randomised controlled trial. *Lancet* 2021;**398**:1498–506. [https://doi.org/10.1016/S0140-6736\(21\)01637-8](https://doi.org/10.1016/S0140-6736(21)01637-8)
- Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, et al. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med* 2012;**366**:120–9. <https://doi.org/10.1056/NEJMoa1105575>
- McIntyre WF, Healey JS, Bhatnagar AK, Wang P, Gordon JA, Baranchuk A, et al. Vernakalant for cardioversion of recent-onset atrial fibrillation: a systematic review and meta-analysis. *Europace* 2019;**21**:1159–66. <https://doi.org/10.1093/europace/euz175>
- Bager JE, Martín A, Carbajosa Dalmau J, Simon A, Merino JL, Ritz B, et al. Vernakalant for cardioversion of recent-onset atrial fibrillation in the emergency department: the SPECTRUM study. *Cardiology* 2022;**147**:566–77. <https://doi.org/10.1159/000526831>
- Pluymaekers N, Dudink E, Luermans J, Meeder JG, Lenderink T, Widdershoven J, et al. Early or delayed cardioversion in recent-onset atrial fibrillation. *N Engl J Med* 2019;**380**:1499–508. <https://doi.org/10.1056/NEJMoa1900353>
- Lubitz SA, Yin X, Rienstra M, Schnabel RB, Walkey AJ, Magnani JW, et al. Long-term outcomes of secondary atrial fibrillation in the community: the Framingham Heart Study. *Circulation* 2015;**131**:1648–55. <https://doi.org/10.1161/CIRCULATIONAHA.114.014058>
- Wang EY, Hulme OL, Khurshid S, Weng LC, Choi SH, Walkey AJ, et al. Initial precipitants and recurrence of atrial fibrillation. *Circ Arrhythm Electrophysiol* 2020;**13**:e007716. <https://doi.org/10.1161/CIRCEP.119.007716>
- Corica B, Romiti GF, Basili S, Proietti M. Prevalence of new-onset atrial fibrillation and associated outcomes in patients with sepsis: a systematic review and meta-analysis. *J Pers Med* 2022;**12**:547. <https://doi.org/10.3390/jpm12040547>
- Bedford JP, Ferrando-Vivas P, Redfern O, Rajappan K, Harrison DA, Watkinson PJ, et al. New-onset atrial fibrillation in intensive care: epidemiology and outcomes. *Eur Heart J Acute Cardiovasc Care* 2022;**11**:620–8. <https://doi.org/10.1093/ehjacc/zuac080>
- Wazni OM, Marrouche NF, Martin DO, Verma A, Bhargava M, Saliba W, et al. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of symptomatic atrial fibrillation: a randomized trial. *JAMA* 2005;**293**:2634–40. <https://doi.org/10.1001/jama.293.21.2634>
- Andrade JG, Wells GA, Deyell MW, Bennett M, Essebag V, Champagne J, et al. Cryoablation or drug therapy for initial treatment of atrial fibrillation. *N Engl J Med* 2021;**384**:305–15. <https://doi.org/10.1056/NEJMoa2029980>
- Kirchhof P, Camm AJ, Goette A, Brandes A, Eckardt L, Elvan A, et al. Early rhythm-control therapy in patients with atrial fibrillation. *N Engl J Med* 2020;**383**:1305–16. <https://doi.org/10.1056/NEJMoa2019422>
- Coats AJS, Heymans S, Farmakis D, Anker SD, Backs J, Bauersachs J, et al. Atrial disease and heart failure: the common soil hypothesis proposed by the heart failure association of the European Society of Cardiology. *Eur Heart J* 2022;**43**:863–7. <https://doi.org/10.1093/eurheartj/ehab834>
- Schnabel RB, Marinelli EA, Arbelo E, Boriani G, Boveda S, Buckley CM, et al. Early diagnosis and better rhythm management to improve outcomes in patients with atrial fibrillation: the 8th AFNET/EHRA consensus conference. *Europace* 2023;**25**:6–27. <https://doi.org/10.1093/europace/euac062>
- Goette A, Kalman JM, Aguinaga L, Akar J, Cabrera JA, Chen SA, et al. EHRA/HRS/APHS/SOLACE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication. *Europace* 2016;**18**:1455–90. <https://doi.org/10.1093/europace/euw161>
- Sagris D, Georgiopoulos G, Pateras K, Perlepe K, Korompoki E, Milonis H, et al. Atrial high-rate episode duration thresholds and thromboembolic risk: a systematic review and meta-analysis. *J Am Heart Assoc* 2021;**10**:e022487. <https://doi.org/10.1161/JAHA.121.022487>
- Kaufman ES, Israel CW, Nair GM, Armaganian L, Divakaramenon S, Mairesse GH, et al. Positive predictive value of device-detected atrial high-rate episodes at different rates and durations: an analysis from ASSERT. *Heart Rhythm* 2012;**9**:1241–6. <https://doi.org/10.1016/j.hrthm.2012.03.017>
- Miyazawa K, Pastori D, Martin DT, Choucair WK, Halperin JL, Lip GYH. Characteristics of patients with atrial high rate episodes detected by implanted defibrillator and resynchronization devices. *Europace* 2022;**24**:375–83. <https://doi.org/10.1093/europace/euab186>
- Vitolo M, Imberti JF, Maisano A, Albini A, Bonini N, Valenti AC, et al. Device-detected atrial high rate episodes and the risk of stroke/thromboembolism and atrial fibrillation incidence: a systematic review and meta-analysis. *Eur J Intern Med* 2021;**92**:100–6. <https://doi.org/10.1016/j.ejim.2021.05.038>
- Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;**361**:1139–51. <https://doi.org/10.1056/NEJMoa0905561>
- Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;**369**:2093–104. <https://doi.org/10.1056/NEJMoa1310907>
- Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;**365**:981–92. <https://doi.org/10.1056/NEJMoa1107039>
- Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;**365**:883–91. <https://doi.org/10.1056/NEJMoa1009638>
- Stroke prevention in atrial fibrillation study. Final results. *Circulation* 1991;**84**:527–39. <https://doi.org/10.1161/01.CIR.84.2.527>
- Mannina C, Jin Z, Matsumoto K, Ito K, Biviano A, Elkind MSV, et al. Frequency of cardiac arrhythmias in older adults: findings from the subclinical atrial fibrillation and risk of ischemic stroke (SAFARIS) study. *Int J Cardiol* 2021;**337**:64–70. <https://doi.org/10.1016/j.ijcard.2021.05.006>
- Schnabel RB, Pecun L, Ojeda FM, Lucerna M, Rzaeva N, Blankenberg S, et al. Gender differences in clinical presentation and 1-year outcomes in atrial fibrillation. *Heart* 2017;**103**:1024–30. <https://doi.org/10.1136/heartjnl-2016-310406>
- Simantirakis EN, Papakonstantinou PE, Chlouverakis GI, Kanoupakis EM, Mavrikis HE, Kallergis EM, et al. Asymptomatic versus symptomatic episodes in patients with paroxysmal atrial fibrillation via long-term monitoring with implantable loop recorders. *Int J Cardiol* 2017;**231**:125–30. <https://doi.org/10.1016/j.ijcard.2016.12.025>
- Verma A, Champagne J, Sapp J, Essebag V, Novak P, Skanes A, et al. Discerning the incidence of symptomatic and asymptomatic episodes of atrial fibrillation before and after catheter ablation (DISCERN AF): a prospective, multicenter study. *JAMA Intern Med* 2013;**173**:149–56. <https://doi.org/10.1001/jamainternmed.2013.1561>

34. Sgreccia D, Manicardi M, Malavasi VL, Vitolo M, Valenti AC, Proietti M, et al. Comparing outcomes in asymptomatic and symptomatic atrial fibrillation: a systematic review and meta-analysis of 81,462 patients. *J Clin Med* 2021;**10**:3979. <https://doi.org/10.3390/jcm10173979>
35. Holmes DN, Piccini JP, Allen LA, Fonarow GC, Gersh BJ, Kowey PR, et al. Defining clinically important difference in the atrial fibrillation effect on quality-of-life score. *Circ Cardiovasc Qual Outcomes* 2019;**12**:e005358. <https://doi.org/10.1161/CIRCOUTCOMES.118.005358>
36. Jones J, Stanbury M, Haynes S, Bunting KV, Lobban T, Camm AJ, et al. Importance and assessment of quality of life in symptomatic permanent atrial fibrillation: patient focus groups from the RATE-AF trial. *Cardiology* 2020;**145**:666–75. <https://doi.org/10.1159/000511048>
37. Abu HO, Wang W, Otabil EM, Saczynski JS, Mehawej J, Mishra A, et al. Perception of atrial fibrillation symptoms: impact on quality of life and treatment in older adults. *J Am Geriatr Soc* 2022;**70**:2805–17. <https://doi.org/10.1111/jgs.17954>
38. Rienstra M, Vermond RA, Crijns HJ, Tijssen JG, Van Gelder IC; RACE Investigators. Asymptomatic persistent atrial fibrillation and outcome: results of the RACE study. *Heart Rhythm* 2014;**11**:939–45. <https://doi.org/10.1016/j.hrthm.2014.03.016>
39. Rienstra M, Hobbelt AH, Alings M, Tijssen JGP, Smit MD, Brugemann J, et al. Targeted therapy of underlying conditions improves sinus rhythm maintenance in patients with persistent atrial fibrillation: results of the RACE 3 trial. *Eur Heart J* 2018;**39**:2987–96. <https://doi.org/10.1093/eurheartj/ehx739>
40. Mulder BA, Van Veldhuisen DJ, Crijns HJ, Tijssen JG, Hillege HL, Alings M, et al. Digoxin in patients with permanent atrial fibrillation: data from the RACE II study. *Heart Rhythm* 2014;**11**:1543–50. <https://doi.org/10.1016/j.hrthm.2014.06.007>
41. Kloosterman M, Crijns H, Mulder BA, Groenewald HF, Van Veldhuisen DJ, Rienstra M, et al. Sex-related differences in risk factors, outcome, and quality of life in patients with permanent atrial fibrillation: results from the RACE II study. *Europace* 2020;**22**:1619–27. <https://doi.org/10.1093/eurheartj/ehz300>
42. Park YJ, Park JW, Yu HT, Kim TH, Uhm JS, Joung B, et al. Sex difference in atrial fibrillation recurrence after catheter ablation and antiarrhythmic drugs. *Heart* 2023;**109**:519–26. <https://doi.org/10.1136/heartjnl-2021-320601>
43. Kupper N, van den Broek KC, Widdershoven J, Denollet J. Subjectively reported symptoms in patients with persistent atrial fibrillation and emotional distress. *Front Psychol* 2013;**4**:192. <https://doi.org/10.3389/fpsyg.2013.00192>
44. Schnabel RB, Michal M, Wilde S, Wiltink J, Wild PS, Sinning CR, et al. Depression in atrial fibrillation in the general population. *PLoS One* 2013;**8**:e79109. <https://doi.org/10.1371/journal.pone.0079109>
45. Gleason KT, Dennison Himmelfarb CR, Ford DE, Lehmann H, Samuel L, Han HR, et al. Association of sex, age and education level with patient reported outcomes in atrial fibrillation. *BMC Cardiovasc Disord* 2019;**19**:85. <https://doi.org/10.1186/s12872-019-1059-6>
46. Schnabel RB, Pecun L, Rzaeva N, Lucerna M, Purmah Y, Ojeda FM, et al. Symptom burden of atrial fibrillation and its relation to interventions and outcome in Europe. *J Am Heart Assoc* 2018;**7**:e007559. <https://doi.org/10.1161/JAHA.117.007559>
47. Wynn GJ, Todd DM, Webber M, Bonnett L, McShane J, Kirchhof P, et al. The European Heart Rhythm Association symptom classification for atrial fibrillation: validation and improvement through a simple modification. *Europace* 2014;**16**:965–72. <https://doi.org/10.1093/eurheartj/eut395>
48. Kotecha D, Bunting KV, Gill SK, Mehta S, Stanbury M, Jones JC, et al. Effect of digoxin vs bisoprolol for heart rate control in atrial fibrillation on patient-reported quality of life: the RATE-AF randomized clinical trial. *JAMA* 2020;**324**:2497–508. <https://doi.org/10.1001/jama.2020.23138>
49. Kotecha D, Ahmed A, Calvert M, Lencioni M, Terwee CB, Lane DA. Patient-reported outcomes for quality of life assessment in atrial fibrillation: a systematic review of measurement properties. *PLoS One* 2016;**11**:e0165790. <https://doi.org/10.1371/journal.pone.0165790>
50. Mantovan R, Macle L, De Martino G, Chen J, Morillo CA, Novak P, et al. Relationship of quality of life with procedural success of atrial fibrillation (AF) ablation and postablation AF burden: substudy of the STAR AF randomized trial. *Can J Cardiol* 2013;**29**:1211–7. <https://doi.org/10.1016/j.cjca.2013.06.006>
51. Samuel M, Khairy P, Champagne J, Deyell MW, Macle L, Leong-Sit P, et al. Association of atrial fibrillation burden with health-related quality of life after atrial fibrillation ablation: substudy of the cryoballoon vs contact-force atrial fibrillation ablation (CIRCA-DOSE) randomized clinical trial. *JAMA Cardiol* 2021;**6**:1324–8. <https://doi.org/10.1001/jamacardio.2021.3063>
52. Sandhu RK, Smigrowsky M, Lockwood E, Savu A, Kaul P, McAlister FA. Impact of electrical cardioversion on quality of life for the treatment of atrial fibrillation. *Can J Cardiol* 2017;**33**:450–5. <https://doi.org/10.1016/j.cjca.2016.11.013>
53. Terricabras M, Mantovan R, Jiang CY, Betts TR, Chen J, Deisenhofer I, et al. Association between quality of life and procedural outcome after catheter ablation for atrial fibrillation: a secondary analysis of a randomized clinical trial. *JAMA Netw Open* 2020;**3**:e2025473. <https://doi.org/10.1001/jamanetworkopen.2020.25473>
54. Zenger B, Zhang M, Lyons A, Bunch TJ, Fang JC, Freedman RA, et al. Patient-reported outcomes and subsequent management in atrial fibrillation clinical practice: results from the Utah mEVAL AF program. *J Cardiovasc Electrophysiol* 2020;**31**:3187–95. <https://doi.org/10.1111/jce.14795>
55. Arbelo E, Aktaa S, Bollmann A, D'Avila A, Drossart I, Dwight J, et al. Quality indicators for the care and outcomes of adults with atrial fibrillation. *Europace* 2021;**23**:494–5. <https://doi.org/10.1093/eurheartj/ehaa253>
56. Kvist LM, Vinter N, Urbonaviciene G, Lindholt JS, Diederichsen ACP, Frost L. Diagnostic accuracies of screening for atrial fibrillation by cardiac nurses versus radiographers. *Open Heart* 2019;**6**:e000942. <https://doi.org/10.1136/openhrt-2018-000942>
57. Hijazi Z, Oldgren J, Siegbahn A, Granger CB, Wallentin L. Biomarkers in atrial fibrillation: a clinical review. *Eur Heart J* 2013;**34**:1475–80. <https://doi.org/10.1093/eurheartj/ehs024>
58. Berg DD, Ruff CT, Morrow DA. Biomarkers for risk assessment in atrial fibrillation. *Clin Chem* 2021;**67**:87–95. <https://doi.org/10.1093/clinchem/hvaa298>
59. Tops LF, Schalij MJ, Bax JJ. Imaging and atrial fibrillation: the role of multimodality imaging in patient evaluation and management of atrial fibrillation. *Eur Heart J* 2010;**31**:542–51. <https://doi.org/10.1093/eurheartj/ehq005>
60. Obeng-Gyimah E, Nazarian S. Advancements in imaging for atrial fibrillation ablation: is there a potential to improve procedural outcomes? *J Innov Card Rhythm Manag* 2020;**11**:4172–8. <https://doi.org/10.19102/icrm.2020.110701>
61. Romero J, Husain SA, Kelesidis I, Sanz J, Medina HM, Garcia MJ. Detection of left atrial appendage thrombus by cardiac computed tomography in patients with atrial fibrillation: a meta-analysis. *Circ Cardiovasc Imaging* 2013;**6**:185–94. <https://doi.org/10.1161/CIRCIMAGING.112.000153>
62. Bisbal F, Benito E, Teis A, Alarcón F, Sarrias A, Caixal G, et al. Magnetic resonance imaging-guided fibrosis ablation for the treatment of atrial fibrillation: the ALICIA trial. *Circ Arrhythm Electrophysiol* 2020;**13**:e008707. <https://doi.org/10.1161/CIRCEP.120.008707>
63. Khurram IM, Habibi M, Gucuk Ipek E, Chrispin J, Yang E, Fukumoto K, et al. Left atrial LGE and arrhythmia recurrence following pulmonary vein isolation for paroxysmal and persistent AF. *JACC Cardiovasc Imaging* 2016;**9**:142–8. <https://doi.org/10.1016/j.jcmg.2015.10.015>
64. Marrouche NF, Wilber D, Hindricks G, Jais P, Akoum N, Marchlinski F, et al. Association of atrial tissue fibrosis identified by delayed enhancement MRI and atrial fibrillation catheter ablation: the DECAAF study. *JAMA* 2014;**311**:498–506. <https://doi.org/10.1001/jama.2014.3>
65. Roney CH, Sillett C, Whitaker J, Lemus JAS, Sim I, Kotadia I, et al. Applications of multimodality imaging for left atrial catheter ablation. *Eur Heart J Cardiovasc Imaging* 2021;**23**:31–41. <https://doi.org/10.1093/ehjci/ehab205>
66. Potter A, Augustine DX, Ingram TE. Referring for echocardiography: when not to test. *Br J Gen Pract* 2021;**71**:333–4. <https://doi.org/10.3399/bjgp21X716441>
67. Troughton RV, Asher CR, Klein AL. The role of echocardiography in atrial fibrillation and cardioversion. *Heart* 2003;**89**:1447–54. <https://doi.org/10.1136/heart.89.12.1447>
68. Odutayo A, Wong CX, Hsiao AJ, Hopewell S, Altman DG, Emdin CA. Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis. *BMJ* 2016;**354**:i4482. <https://doi.org/10.1136/bmj.i4482>
69. Ruddox V, Sandven I, Munkhaugen J, Skattebu J, Edvardsen T, Otterstad JE. Atrial fibrillation and the risk for myocardial infarction, all-cause mortality and heart failure: a systematic review and meta-analysis. *Eur J Prev Cardiol* 2017;**24**:1555–66. <https://doi.org/10.1177/2047487317715769>
70. Bassand JP, Accetta G, Al Mahmeed W, Corbalan R, Eikelboom J, Fitzmaurice DA, et al. Risk factors for death, stroke, and bleeding in 28,628 patients from the GARFIELD-AF registry: rationale for comprehensive management of atrial fibrillation. *PLoS One* 2018;**13**:e0191592. <https://doi.org/10.1371/journal.pone.0191592>
71. Bassand JP, Accetta G, Camm AJ, Cools F, Fitzmaurice DA, Fox KA, et al. Two-year outcomes of patients with newly diagnosed atrial fibrillation: results from GARFIELD-AF. *Eur Heart J* 2016;**37**:2882–9. <https://doi.org/10.1093/eurheartj/ehw233>
72. Hornestam B, Adiels M, Wai Giang K, Hansson PO, Björck L, Rosengren A. Atrial fibrillation and risk of venous thromboembolism: a Swedish nationwide registry study. *Europace* 2021;**23**:1913–21. <https://doi.org/10.1093/eurheartj/ehab180>
73. Lutsey PL, Norby FL, Alonso A, Cushman M, Chen LY, Michos ED, et al. Atrial fibrillation and venous thromboembolism: evidence of bidirectionality in the atherosclerosis risk in communities study. *J Thromb Haemost* 2018;**16**:670–9. <https://doi.org/10.1111/jth.13974>
74. Koh YH, Lew LZW, Franke KB, Elliott AD, Lau DH, Thiyagarajah A, et al. Predictive role of atrial fibrillation in cognitive decline: a systematic review and meta-analysis of 2.8 million individuals. *Europace* 2022;**24**:1229–39. <https://doi.org/10.1093/eurheartj/ehac003>
75. Papanastasiou CA, Theochari CA, Zareifopoulos N, Arfaras-Melainis A, Giannakoulas G, Karamitsos TD, et al. Atrial fibrillation is associated with cognitive impairment, all-cause dementia, vascular dementia, and Alzheimer's disease: a systematic review and meta-analysis. *J Gen Intern Med* 2021;**36**:3122–35. <https://doi.org/10.1007/s11606-021-06954-8>
76. Giannone ME, Filippini T, Whelton PK, Chiari A, Vitolo M, Boriani G, et al. Atrial fibrillation and the risk of early-onset dementia: a systematic review and meta-analysis. *J Am Heart Assoc* 2022;**11**:e025653. <https://doi.org/10.1161/JAHA.122.025653>

77. Zuin M, Roncon L, Passaro A, Bosi C, Cervellati C, Zuliani G. Risk of dementia in patients with atrial fibrillation: short versus long follow-up. A systematic review and meta-analysis. *Int J Geriatr Psychiatry* 2021;**36**:1488–500. <https://doi.org/10.1002/gps.5582>
78. Mobley AR, Subramanian A, Champai A, Wang X, Myles P, McGreavy P, et al. Thromboembolic events and vascular dementia in patients with atrial fibrillation and low apparent stroke risk. *Nat Med* 2024. <https://doi.org/10.1038/s41591-024-03049-9>.
79. Wijnvliet E, Tieleman RG, van Gelder IC, Pluymaekers N, Rienstra M, Folkeringa RJ, et al. Nurse-led vs. usual-care for atrial fibrillation. *Eur Heart J* 2020;**41**:634–41. <https://doi.org/10.1093/eurheartj/ehz666>
80. Wong CX, Brooks AG, Lau DH, Leong DP, Sun MT, Sullivan T, et al. Factors associated with the epidemic of hospitalizations due to atrial fibrillation. *Am J Cardiol* 2012;**110**:1496–9. <https://doi.org/10.1016/j.amjcard.2012.07.011>
81. Dai H, Zhang Q, Much AA, Maor E, Segev A, Beinart R, et al. Global, regional, and national prevalence, incidence, mortality, and risk factors for atrial fibrillation, 1990–2017: results from the Global Burden of Disease Study 2017. *Eur Heart J Qual Care Clin Outcomes* 2021;**7**:574–82. <https://doi.org/10.1093/ehjqcco/qcaa061>
82. Tica O, Tica O, Bunting KV, deBono J, Gkoutos GV, Popescu MI, et al. Post-mortem examination of high mortality in patients with heart failure and atrial fibrillation. *BMC Med* 2022;**20**:331. <https://doi.org/10.1186/s12916-022-02533-8>
83. Bassand JP, Virdone S, Badoz M, Verheugt FWA, Camm AJ, Cools F, et al. Bleeding and related mortality with NOACs and VKAs in newly diagnosed atrial fibrillation: results from the GARFIELD-AF registry. *Blood Adv* 2021;**5**:1081–91. <https://doi.org/10.1182/bloodadvances.2020003560>
84. Pokorney SD, Piccini JP, Stevens SR, Patel MR, Pieper KS, Halperin JL, et al. Cause of death and predictors of all-cause mortality in anticoagulated patients with nonvalvular atrial fibrillation: data from ROCKET AF. *J Am Heart Assoc* 2016;**5**:e002197. <https://doi.org/10.1161/JAHA.115.002197>
85. Granada J, Uribe W, Chyou PH, Maassen K, Vierkant R, Smith PN, et al. Incidence and predictors of atrial flutter in the general population. *J Am Coll Cardiol* 2000;**36**:2242–6. [https://doi.org/10.1016/S0735-1097\(00\)00982-7](https://doi.org/10.1016/S0735-1097(00)00982-7)
86. Vadmann H, Nielsen PB, Hjortshøj SP, Riahi S, Rasmussen LH, Lip GY, et al. Atrial flutter and thromboembolic risk: a systematic review. *Heart* 2015;**101**:1446–55. <https://doi.org/10.1136/heartjnl-2015-037550>
87. Leloirier P, Humphries KH, Krahm A, Connolly SJ, Talajic M, Green M, et al. Prognostic differences between atrial fibrillation and atrial flutter. *Am J Cardiol* 2004;**93**:647–9. <https://doi.org/10.1016/j.amjcard.2003.11.042>
88. Biblo LA, Yuan Z, Quan KJ, Mackall JA, Rimm AA. Risk of stroke in patients with atrial flutter. *Am J Cardiol* 2001;**87**:346–9. [https://doi.org/10.1016/S0002-9149\(00\)01374-6](https://doi.org/10.1016/S0002-9149(00)01374-6)
89. Corrado G, Sgalambro A, Mantero A, Gentile F, Gasparini M, Bufalino R, et al. Thromboembolic risk in atrial flutter. The FLASIEC (Flutter Atriale Società Italiana di Ecografia Cardiovascolare) multicentre study. *Eur Heart J* 2001;**22**:1042–51. <https://doi.org/10.1053/ehj.2000.2427>
90. Lin YS, Chen TH, Chi CC, Lin MS, Tung TH, Liu CH, et al. Different implications of heart failure, ischemic stroke, and mortality between nonvalvular atrial fibrillation and atrial flutter—a view from a national cohort study. *J Am Heart Assoc* 2017;**6**:e006406. <https://doi.org/10.1161/JAHA.117.006406>
91. Giehm-Reese M, Johansen MN, Kronborg MB, Jensen HK, Gerdes C, Kristensen J, et al. Discontinuation of oral anticoagulation and risk of stroke and death after ablation for typical atrial flutter: a nation-wide Danish cohort study. *Int J Cardiol* 2021;**333**:110–6. <https://doi.org/10.1016/j.ijcard.2021.02.057>
92. Gallagher C, Rowett D, Nyfort-Hansen K, Simmons S, Brooks AG, Moss JR, et al. Patient-centered educational resources for atrial fibrillation. *JACC Clin Electrophysiol* 2019;**5**:1101–14. <https://doi.org/10.1016/j.jacep.2019.08.007>
93. Chung MK, Fagerlin A, Wang PJ, Ajayi TB, Allen LA, Baykaner T, et al. Shared decision making in cardiac electrophysiology procedures and arrhythmia management. *Circ Arrhythm Electrophysiol* 2021;**14**:e007958. <https://doi.org/10.1161/CIRCEP.121.007958>
94. Wang PJ, Lu Y, Mahaffey KW, Lin A, Morin DP, Sears SF, et al. A randomized clinical trial to evaluate an atrial fibrillation stroke prevention shared decision-making pathway. *J Am Heart Assoc* 2022;**12**:e028562. <https://doi.org/10.1161/JAHA.122.028562>
95. Seaburg L, Hess EP, Coylewright M, Ting HH, McLeod CJ, Montori VM. Shared decision making in atrial fibrillation: where we are and where we should be going. *Circulation* 2014;**129**:704–10. <https://doi.org/10.1161/CIRCULATIONAHA.113.004498>
96. Zhang J, Lenarczyk R, Marin F, Malaczynska-Rajpold K, Kosiuk J, Doehner W, et al. The interpretation of CHA2DS2-VASc score components in clinical practice: a joint survey by the European Heart Rhythm Association (EHRA) scientific initiatives committee, the EHRA young electrophysiologists, the Association of Cardiovascular Nursing and Allied Professionals, and the European Society of Cardiology council on stroke. *Europace* 2021;**23**:314–22. <https://doi.org/10.1093/eurpace/euraa358>
97. Omoush A, Aloush S, Albashtawy M, Rayan A, Alkhaldeh A, Eshah N, et al. Nurses' knowledge of anticoagulation therapy for atrial fibrillation patients: effectiveness of an educational course. *Nurs Forum* 2022;**57**:825–32. <https://doi.org/10.1111/nuf.12770>
98. Heidbuchel H, Dagres N, Antz M, Kuck KH, Lazure P, Murray S, et al. Major knowledge gaps and system barriers to guideline implementation among European physicians treating patients with atrial fibrillation: a European Society of Cardiology international educational needs assessment. *Europace* 2018;**20**:1919–28. <https://doi.org/10.1093/eurpace/euray039>
99. Bunting KV, Van Gelder IC, Kotecha D. STEER-AF: a cluster-randomized education trial from the ESC. *Eur Heart J* 2020;**41**:1952–4. <https://doi.org/10.1093/eurheartj/ehaa421>
100. Tanner FC, Brooks N, Fox KF, Gonçalves L, Kearney P, Michalis L, et al. ESC core curriculum for the cardiologist. *Eur Heart J* 2020;**41**:3605–92. <https://doi.org/10.1093/eurheartj/ehaa641>
101. Astin F, Carroll D, De Geest S, Fernandez-Oliver AL, Holt J, Hinterbuchner L, et al. A core curriculum for the continuing professional development of nurses working in cardiovascular settings: developed by the education committee of the Council on Cardiovascular Nursing and Allied Professions (CCNAP) on behalf of the European Society of Cardiology. *Eur J Cardiovasc Nurs* 2015;**14**:S1–17. <https://doi.org/10.1177/1474515115580905>
102. Sterlinski M, Bunting KV, Boriani G, Boveda S, Guasch E, Mont L, et al. STEER-AF Trial Team. Design and deployment of the STEER-AF trial to evaluate and improve guideline adherence: a cluster-randomised trial by the European Society of Cardiology and European Heart Rhythm Association. *Europace* 2024;euae178. <https://doi.org/10.1093/eurpace/eurae178>
103. Vinereanu D, Lopes RD, Bahit MC, Xavier D, Jiang J, Al-Khalidi HR, et al. A multifaceted intervention to improve treatment with oral anticoagulants in atrial fibrillation (IMPACT-AF): an international, cluster-randomised trial. *Lancet* 2017;**390**:1737–46. [https://doi.org/10.1016/S0140-6736\(17\)32165-7](https://doi.org/10.1016/S0140-6736(17)32165-7)
104. Franchi C, Antoniazzi S, Ardoino I, Proietti M, Marcucci M, Santalucia P, et al. Simulation-based education for physicians to increase oral anticoagulants in hospitalized elderly patients with atrial fibrillation. *Am J Med* 2019;**132**:e634–47. <https://doi.org/10.1016/j.amjmed.2019.03.052>
105. Baicus C, Delcea C, Dima A, Oprisan E, Jurcut C, Dan GA. Influence of decision aids on oral anticoagulant prescribing among physicians: a randomised trial. *Eur J Clin Invest* 2017;**47**:649–58. <https://doi.org/10.1111/eci.12786>
106. Ono F, Akiyama S, Suzuki A, Ikeda Y, Takahashi A, Matsuoka H, et al. Impact of care coordination on oral anticoagulant therapy among patients with atrial fibrillation in routine clinical practice in Japan: a prospective, observational study. *BMC Cardiovasc Disord* 2019;**19**:235. <https://doi.org/10.1186/s12872-019-1216-y>
107. Ferguson C, Hickman LD, Phillips J, Newton PJ, Inglis SC, Lam L, et al. An mHealth intervention to improve nurses' atrial fibrillation and anticoagulation knowledge and practice: the EVICOAG study. *Eur J Cardiovasc Nurs* 2019;**18**:7–15. <https://doi.org/10.1177/1474515118793051>
108. Lip GY, Laroche C, Popescu MI, Rasmussen LH, Vitali-Serdoz L, Dan GA, et al. Improved outcomes with European Society of Cardiology guideline-adherent antithrombotic treatment in high-risk patients with atrial fibrillation: a report from the EORP-AF general pilot registry. *Europace* 2015;**17**:1777–86. <https://doi.org/10.1093/eurpace/eurv269>
109. Linde C, Bongioni MG, Birgersdotter-Green U, Curtis AB, Deisenhofer I, Furokawa T, et al. Sex differences in cardiac arrhythmia: a consensus document of the European Heart Rhythm Association, endorsed by the Heart Rhythm Society and Asia Pacific Heart Rhythm Society. *Europace* 2018;**20**:1565–1565a. <https://doi.org/10.1093/eurpace/euray067>
110. Camm AJ, Accetta G, Al Mahmeed W, Ambrosio G, Goldhaber SZ, Haas S, et al. Impact of gender on event rates at 1 year in patients with newly diagnosed non-valvular atrial fibrillation: contemporary perspective from the GARFIELD-AF registry. *BMJ Open* 2017;**7**:e014579. <https://doi.org/10.1136/bmjopen-2016-014579>
111. Emdin CA, Wong CX, Hsiao AJ, Altman DG, Peters SA, Woodward M, et al. Atrial fibrillation as risk factor for cardiovascular disease and death in women compared with men: systematic review and meta-analysis of cohort studies. *BMJ* 2016;**352**:h7013. <https://doi.org/10.1136/bmj.h7013>
112. Tomasdottir M, Friberg L, Hijazi Z, Lindback J, Oldgren J. Risk of ischemic stroke and utility of CHA2DS2-VASc score in women and men with atrial fibrillation. *Clin Cardiol* 2019;**42**:1003–9. <https://doi.org/10.1002/clc.23257>
113. Kloosterman M, Chua W, Fabritz L, Al-Khalidi HR, Schotten U, Nielsen JC, et al. Sex differences in catheter ablation of atrial fibrillation: results from AXAFA-AFNET 5. *Europace* 2020;**22**:1026–35. <https://doi.org/10.1093/eurpace/euraa015>
114. Benjamin EJ, Thomas KL, Go AS, Desvigne-Nickens P, Albert CM, Alonso A, et al. Transforming atrial fibrillation research to integrate social determinants of health: a national heart, lung, and blood institute workshop report. *JAMA Cardiol* 2023;**8**:182–91. <https://doi.org/10.1001/jamacardio.2022.4091>
115. Karlsson LO, Nilsson S, Bang M, Nilsson L, Charitakis E, Janzon M. A clinical decision support tool for improving adherence to guidelines on anticoagulant therapy in patients with atrial fibrillation at risk of stroke: a cluster-randomized trial in a Swedish primary care setting (the CDS-AF study). *PLoS Med* 2018;**15**:e1002528. <https://doi.org/10.1371/journal.pmed.1002528>

116. Biersteker TE, Schalij MJ, Treskes RW. Impact of mobile health devices for the detection of atrial fibrillation: systematic review. *JMIR Mhealth Uhealth* 2021;**9**:e26161. <https://doi.org/10.2196/26161>
117. Romiti GF, Pastori D, Rivera-Caravaca JM, Ding WY, Gue YX, Menichelli D, et al. Adherence to the 'atrial fibrillation better care' pathway in patients with atrial fibrillation: impact on clinical outcomes—a systematic review and meta-analysis of 285,000 patients. *Thromb Haemost* 2022;**122**:406–14. <https://doi.org/10.1055/a-1515-9630>
118. Gallagher C, Elliott AD, Wong CX, Rangnekar G, Middeldorp ME, Mahajan R, et al. Integrated care in atrial fibrillation: a systematic review and meta-analysis. *Heart* 2017;**103**:1947–53. <https://doi.org/10.1136/heartjnl-2016-310952>
119. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;**37**:2893–962. <https://doi.org/10.1093/eurheartj/ehw210>
120. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the task force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021;**42**:373–498. <https://doi.org/10.1093/eurheartj/ehaa612>
121. Qvist I, Hendriks JM, Møller DS, Albertsen AE, Mogensen HM, Oddershede GD, et al. Effectiveness of structured, hospital-based, nurse-led atrial fibrillation clinics: a comparison between a real-world population and a clinical trial population. *Open Heart* 2016;**3**:e000335. <https://doi.org/10.1136/openhrt-2015-000335>
122. Hendriks JM, de Wit R, Crijns HJ, Vrijhoef HJ, Prins MH, Pisters R, et al. Nurse-led care vs. usual care for patients with atrial fibrillation: results of a randomized trial of integrated chronic care vs. routine clinical care in ambulatory patients with atrial fibrillation. *Eur Heart J* 2012;**33**:2692–9. <https://doi.org/10.1093/eurheartj/ehs071>
123. Carter L, Gardner M, Magee K, Fearon A, Morgulis I, Doucette S, et al. An integrated management approach to atrial fibrillation. *J Am Heart Assoc* 2016;**5**:e002950. <https://doi.org/10.1161/JAHA.115.002950>
124. van den Dries CJ, van Doorn S, Rutten FH, Oudega R, van de Leur S, Elvan A, et al. Integrated management of atrial fibrillation in primary care: results of the ALL-IN cluster randomized trial. *Eur Heart J* 2020;**41**:2836–44. <https://doi.org/10.1093/eurheartj/ehaa055>
125. Abed HS, Wittert GA, Leong DP, Shirazi MG, Bahrami B, Middeldorp ME, et al. Effect of weight reduction and cardiometabolic risk factor management on symptom burden and severity in patients with atrial fibrillation: a randomized clinical trial. *JAMA* 2013;**310**:2050–60. <https://doi.org/10.1001/jama.2013.280521>
126. Pathak RK, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Wong CX, et al. Long-term effect of goal-directed weight management in an atrial fibrillation cohort: a long-term follow-up study (LEGACY). *J Am Coll Cardiol* 2015;**65**:2159–69. <https://doi.org/10.1016/j.jacc.2015.03.002>
127. Middeldorp ME, Pathak RK, Meredith M, Mehta AB, Elliott AD, Mahajan R, et al. PREVENTion and regReSSive effect of weight-loss and risk factor modification on atrial fibrillation: the REVERSE-AF study. *Europace* 2018;**20**:1929–35. <https://doi.org/10.1093/europace/euy117>
128. Pathak RK, Middeldorp ME, Lau DH, Mehta AB, Mahajan R, Twomey D, et al. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. *J Am Coll Cardiol* 2014;**64**:2222–31. <https://doi.org/10.1016/j.jacc.2014.09.028>
129. Pinho-Gomes AC, Azevedo L, Copland E, Canoy D, Nazarzadeh M, Ramakrishnan R, et al. Blood pressure-lowering treatment for the prevention of cardiovascular events in patients with atrial fibrillation: an individual participant data meta-analysis. *PLoS Med* 2021;**18**:e1003599. <https://doi.org/10.1371/journal.pmed.1003599>
130. Parkash R, Wells GA, Sapp JL, Healey JS, Tardif J-C, Greiss I, et al. Effect of aggressive blood pressure control on the recurrence of atrial fibrillation after catheter ablation: a randomized, open-label clinical trial (SMAC-AF [Substrate Modification with Aggressive Blood Pressure Control]). *Circulation* 2017;**135**:1788–98. <https://doi.org/10.1161/CIRCULATIONAHA.116.026230>
131. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2012;**33**:1787–847. <https://doi.org/10.1093/eurheartj/ehs104>
132. Olsson LG, Swedberg K, Ducharme A, Granger CB, Michelson EL, McMurray JJ, et al. Atrial fibrillation and risk of clinical events in chronic heart failure with and without left ventricular systolic dysfunction: results from the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) program. *J Am Coll Cardiol* 2006;**47**:1997–2004. <https://doi.org/10.1016/j.jacc.2006.01.060>
133. Kotecha D, Holmes J, Krum H, Altman DG, Manzano L, Cleland JG, et al. Efficacy of beta blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. *Lancet* 2014;**384**:2235–43. [https://doi.org/10.1016/S0140-6736\(14\)61373-8](https://doi.org/10.1016/S0140-6736(14)61373-8)
134. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011;**364**:11–21. <https://doi.org/10.1056/NEJMoa1009492>
135. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;**371**:993–1004. <https://doi.org/10.1056/NEJMoa1409077>
136. Pandey AK, Okaj I, Kaur H, Belley-Cote EP, Wang J, Orsai A, et al. Sodium-glucose co-transporter inhibitors and atrial fibrillation: a systematic review and meta-analysis of randomized controlled trials. *J Am Heart Assoc* 2021;**10**:e022222. <https://doi.org/10.1161/JAHA.121.022222>
137. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumach A, Bohm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021;**42**:3599–726. <https://doi.org/10.1093/eurheartj/ehab368>
138. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med* 2022;**387**:1089–98. <https://doi.org/10.1056/NEJMoa2206286>
139. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med* 2021;**385**:1451–61. <https://doi.org/10.1056/NEJMoa2107038>
140. Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med* 2021;**384**:117–28. <https://doi.org/10.1056/NEJMoa2030183>
141. Pathak RK, Elliott A, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, et al. Impact of CARDIOrespiratory FITness on arrhythmia recurrence in obese individuals with atrial fibrillation: the CARDIO-FIT study. *J Am Coll Cardiol* 2015;**66**:985–96. <https://doi.org/10.1016/j.jacc.2015.06.488>
142. Hegbom F, Stavem K, Sire S, Høidal M, Orning OM, Gjesdal K. Effects of short-term exercise training on symptoms and quality of life in patients with chronic atrial fibrillation. *Int J Cardiol* 2007;**116**:86–92. <https://doi.org/10.1016/j.ijcard.2006.03.034>
143. Osbak PS, Mourier M, Kjaer A, Henriksen JH, Kofoed KF, Jensen GB. A randomized study of the effects of exercise training on patients with atrial fibrillation. *Am Heart J* 2011;**162**:1080–7. <https://doi.org/10.1016/j.ahj.2011.09.013>
144. Malmø V, Nes BM, Amundsen BH, Tjønnå AE, Støylen A, Rossvoll O, et al. Aerobic interval training reduces the burden of atrial fibrillation in the short term: a randomized trial. *Circulation* 2016;**133**:466–73. <https://doi.org/10.1161/CIRCULATIONAHA.115.018220>
145. Oesterle A, Giancaterino S, Van Noord MG, Pellegrini CN, Fan D, Srivatsa UN, et al. Effects of supervised exercise training on atrial fibrillation: a meta-analysis of randomized controlled trials. *J Cardiopulm Rehabil Prev* 2022;**42**:258–65. <https://doi.org/10.1097/HCR.0000000000000665>
146. Elliott AD, Verdicchio CV, Mahajan R, Middeldorp ME, Gallagher C, Mishima RS, et al. An exercise and physical activity program in patients with atrial fibrillation: the ACTIVE-AF randomized controlled trial. *JACC Clin Electrophysiol* 2023;**9**:455–65. <https://doi.org/10.1016/j.jacep.2022.12.002>
147. Voskoboinik A, Kalman JM, De Silva A, Nicholls T, Costello B, Nanayakkara S, et al. Alcohol abstinence in drinkers with atrial fibrillation. *N Engl J Med* 2020;**382**:20–8. <https://doi.org/10.1056/NEJMoa1817591>
148. Holmqvist F, Guan N, Zhu Z, Kowey PR, Allen LA, Fonarow GC, et al. Impact of obstructive sleep apnea and continuous positive airway pressure therapy on outcomes in patients with atrial fibrillation—results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *Am Heart J* 2015;**169**:647–654.e2. <https://doi.org/10.1016/j.ahj.2014.12.024>
149. Fein AS, Shvilkin A, Shah D, Haffajee CI, Das S, Kumar K, et al. Treatment of obstructive sleep apnea reduces the risk of atrial fibrillation recurrence after catheter ablation. *J Am Coll Cardiol* 2013;**62**:300–5. <https://doi.org/10.1016/j.jacc.2013.03.052>
150. Li L, Wang ZV, Li J, Ge X, Guo LZ, Wang Y, et al. Efficacy of catheter ablation of atrial fibrillation in patients with obstructive sleep apnoea with and without continuous positive airway pressure treatment: a meta-analysis of observational studies. *Europace* 2014;**16**:1309–14. <https://doi.org/10.1093/europace/euu066>
151. Naruse Y, Tada H, Satoh M, Yanagihara M, Tsunoka H, Hirata Y, et al. Concomitant obstructive sleep apnea increases the recurrence of atrial fibrillation following radio-frequency catheter ablation of atrial fibrillation: clinical impact of continuous positive airway pressure therapy. *Heart Rhythm* 2013;**10**:331–7. <https://doi.org/10.1016/j.hrthm.2012.11.015>
152. Qureshi WT, Nasir UB, Alqalyoobi S, O'Neal WT, Mawri S, Sabbagh S, et al. Meta-analysis of continuous positive airway pressure as a therapy of atrial fibrillation in obstructive sleep apnea. *Am J Cardiol* 2015;**116**:1767–73. <https://doi.org/10.1016/j.amjcard.2015.08.046>
153. Shukla A, Aizer A, Holmes D, Fowler S, Park DS, Bernstein S, et al. Effect of obstructive sleep apnea treatment on atrial fibrillation recurrence: a meta-analysis. *JACC Clin Electrophysiol* 2015;**1**:41–51. <https://doi.org/10.1016/j.jacep.2015.02.014>
154. Nalliah CJ, Wong GR, Lee G, Voskoboinik A, Kee K, Goldin J, et al. Impact of CPAP on the atrial fibrillation substrate in obstructive sleep apnea: the SLEEP-AF study. *JACC Clin Electrophysiol* 2022;**8**:869–77. <https://doi.org/10.1016/j.jacep.2022.04.015>
155. Kadhim K, Middeldorp ME, Elliott AD, Jones D, Hendriks JML, Gallagher C, et al. Self-reported daytime sleepiness and sleep-disordered breathing in patients with atrial

- fibrillation: SNOozE-AF. *Can J Cardiol* 2019;**35**:1457–64. <https://doi.org/10.1016/j.cjca.2019.07.627>
156. Traaen GM, Overland B, Aakeroy L, Hunt TE, Bendz C, Sande L, et al. Prevalence, risk factors, and type of sleep apnea in patients with paroxysmal atrial fibrillation. *Int J Cardiol Heart Vasc* 2020;**26**:100447. <https://doi.org/10.1016/j.ijcha.2019.100447>
 157. Kadhim K, Middeldorp ME, Elliott AD, Agbaedeng T, Gallagher C, Malik V, et al. Prevalence and assessment of sleep-disordered breathing in patients with atrial fibrillation: a systematic review and meta-analysis. *Can J Cardiol* 2021;**37**:1846–56. <https://doi.org/10.1016/j.cjca.2021.09.026>
 158. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish atrial fibrillation cohort study. *Eur Heart J* 2012;**33**:1500–10. <https://doi.org/10.1093/eurheartj/ehs488>
 159. Lopes LC, Spencer FA, Neumann I, Ventresca M, Ebrahim S, Zhou Q, et al. Systematic review of observational studies assessing bleeding risk in patients with atrial fibrillation not using anticoagulants. *PLoS One* 2014;**9**:e88131. <https://doi.org/10.1371/journal.pone.0088131>
 160. Potpara TS, Polovina MM, Licina MM, Marinkovic JM, Lip GY. Predictors and prognostic implications of incident heart failure following the first diagnosis of atrial fibrillation in patients with structurally normal hearts: the Belgrade atrial fibrillation study. *Eur J Heart Fail* 2013;**15**:415–24. <https://doi.org/10.1093/eurjhf/hft004>
 161. Noubiap JJ, Fetei VF, Middeldorp ME, Fitzgerald JL, Thomas G, Kleinig T, et al. A meta-analysis of clinical risk factors for stroke in anticoagulant-naïve patients with atrial fibrillation. *Europace* 2021;**23**:1528–38. <https://doi.org/10.1093/europace/euab087>
 162. McEvoy JW, Touyz RM, McCarthy CP, Bruno RM, Brouwers S, Canavan MD, et al. 2024 ESC Guidelines for the management of elevated blood pressure and hypertension. *Eur Heart J* 2024. <https://doi.org/10.1093/eurheartj/ehae178>
 163. Santoro F, Di Biase L, Trivedi C, Burkhardt JD, Paoletti Perini A, Sanchez J, et al. Impact of uncontrolled hypertension on atrial fibrillation ablation outcome. *JACC Clin Electrophysiol* 2015;**1**:164–73. <https://doi.org/10.1016/j.jacep.2015.04.002>
 164. Trines SA, Stabile G, Arbelo E, Dagnes N, Brugada J, Kautzner J, et al. Influence of risk factors in the ESC-EHRA EORP atrial fibrillation ablation long-term registry. *Pacing Clin Electrophysiol* 2019;**42**:1365–73. <https://doi.org/10.1111/pace.13763>
 165. Shah AN, Mittal S, Sichrovsky TC, Cotiga D, Arshad A, Maleki K, et al. Long-term outcome following successful pulmonary vein isolation: pattern and prediction of very late recurrence. *J Cardiovasc Electrophysiol* 2008;**19**:661–7. <https://doi.org/10.1111/j.1540-8167.2008.01101.x>
 166. Berruezo A, Tamborero D, Mont L, Benito B, Tolosana JM, Sitges M, et al. Pre-procedural predictors of atrial fibrillation recurrence after circumferential pulmonary vein ablation. *Eur Heart J* 2007;**28**:836–41. <https://doi.org/10.1093/eurheartj/ehm027>
 167. Themistoclakis S, Schweikert RA, Saliba WJ, Bonso A, Rossillo A, Bader G, et al. Clinical predictors and relationship between early and late atrial tachyarrhythmias after pulmonary vein antrum isolation. *Heart Rhythm* 2008;**5**:679–85. <https://doi.org/10.1016/j.hrthm.2008.01.031>
 168. Letsas KP, Weber R, Burkle G, Mihos CC, Minners J, Kalusche D, et al. Pre-ablative predictors of atrial fibrillation recurrence following pulmonary vein isolation: the potential role of inflammation. *Europace* 2009;**11**:158–63. <https://doi.org/10.1093/europace/eun309>
 169. Khaykin Y, Oosthuizen R, Zarnett L, Essebag V, Parkash R, Seabrook C, et al. Clinical predictors of arrhythmia recurrences following pulmonary vein antrum isolation for atrial fibrillation: predicting arrhythmia recurrence post-PVAI. *J Cardiovasc Electrophysiol* 2011;**22**:1206–14. <https://doi.org/10.1111/j.1540-8167.2011.02108.x>
 170. Kamioka M, Hijioka N, Matsumoto Y, Nodera M, Kaneshiro T, Suzuki H, et al. Uncontrolled blood pressure affects atrial remodeling and adverse clinical outcome in paroxysmal atrial fibrillation. *Pacing Clin Electrophysiol* 2018;**41**:402–10. <https://doi.org/10.1111/pace.13311>
 171. Zylla MM, Hochadel M, Andresen D, Brachmann J, Eckardt L, Hoffmann E, et al. Ablation of atrial fibrillation in patients with hypertension—an analysis from the German ablation registry. *J Clin Med* 2020;**9**:1–14. <https://doi.org/10.3390/jcm9082402>
 172. Galzerano D, Di Michele S, Paolisso G, Tuccillo B, Lama D, Carbotta S, et al. A multi-centre, randomized study of telmisartan versus carvedilol for prevention of atrial fibrillation recurrence in hypertensive patients. *J Renin Angiotensin Aldosterone Syst* 2012;**13**:496–503. <https://doi.org/10.1177/1470320312443909>
 173. Du H, Fan J, Ling Z, Woo K, Su L, Chen S, et al. Effect of nifedipine versus telmisartan on prevention of atrial fibrillation recurrence in hypertensive patients. *Hypertension* 2013;**61**:786–92. <https://doi.org/10.1161/HYPERTENSIONAHA.111.202309>
 174. Giannopoulos G, Kossyvakis C, Efremidis M, Katsivas A, Panagopoulou V, Doudoumis K, et al. Central sympathetic inhibition to reduce postablation atrial fibrillation recurrences in hypertensive patients: a randomized, controlled study. *Circulation* 2014;**130**:1346–52. <https://doi.org/10.1161/CIRCULATIONAHA.114.010999>
 175. Schneider MP, Hua TA, Bohm M, Wachtell K, Kjeldsen SE, Schmieder RE. Prevention of atrial fibrillation by renin-angiotensin system inhibition: a meta-analysis. *J Am Coll Cardiol* 2010;**55**:2299–307. <https://doi.org/10.1016/j.jacc.2010.01.043>
 176. Blum S, Aeschbacher S, Meyre P, Zwimpfer L, Reichlin T, Beer JH, et al. Incidence and predictors of atrial fibrillation progression. *J Am Heart Assoc* 2019;**8**:e012554. <https://doi.org/10.1161/JAHA.119.012554>
 177. Kotecha D, Piccini JP. Atrial fibrillation in heart failure: what should we do? *Eur Heart J* 2015;**36**:3250–7. <https://doi.org/10.1093/eurheartj/ehv513>
 178. Santhanakrishnan R, Wang N, Larson MG, Magnani JW, McManus DD, Lubitz SA, et al. Atrial fibrillation begets heart failure and vice versa: temporal associations and differences in preserved versus reduced ejection fraction. *Circulation* 2016;**133**:484–92. <https://doi.org/10.1161/CIRCULATIONAHA.115.018614>
 179. Rossello X, Gil V, Escoda R, Jacob J, Aguirre A, Martín-Sánchez FJ, et al. Editor's choice – impact of identifying precipitating factors on 30-day mortality in acute heart failure patients. *Eur Heart J Acute Cardiovasc Care* 2019;**8**:667–80. <https://doi.org/10.1177/2048872619869328>
 180. Atrial Fibrillation Investigators. Echocardiographic predictors of stroke in patients with atrial fibrillation: a prospective study of 1066 patients from 3 clinical trials. *Arch Intern Med* 1998;**158**:1316–20. <https://doi.org/10.1001/archinte.158.12.1316>
 181. Rohla M, Weiss TW, Pecan L, Patti G, Siller-Matula JM, Schnabel RB, et al. Risk factors for thromboembolic and bleeding events in anticoagulated patients with atrial fibrillation: the prospective, multicentre observational PREvention of thromboembolic events—European Registry in Atrial Fibrillation (PREFER in AF). *BMJ Open* 2019;**9**:e022478. <https://doi.org/10.1136/bmjopen-2018-022478>
 182. Kotecha D, Chudasama R, Lane DA, Kirchhof P, Lip GY. Atrial fibrillation and heart failure due to reduced versus preserved ejection fraction: a systematic review and meta-analysis of death and adverse outcomes. *Int J Cardiol* 2016;**203**:660–6. <https://doi.org/10.1016/j.ijcard.2015.10.220>
 183. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2023 focused update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2023;**44**:3627–39. <https://doi.org/10.1093/eurheartj/ehad195>
 184. ACTIVE I Investigators; Yusuf S, Healey JS, Pogue J, Chrolavicius S, Flather M, et al. Irbesartan in patients with atrial fibrillation. *N Engl J Med* 2011;**364**:928–38. <https://doi.org/10.1056/NEJMoa1008816>
 185. Ziff OJ, Lane DA, Samra M, Griffith M, Kirchhof P, Lip GY, et al. Safety and efficacy of digoxin: systematic review and meta-analysis of observational and controlled trial data. *BMJ* 2015;**351**:h4451. <https://doi.org/10.1136/bmj.h4451>
 186. Groenveld HF, Crijns HJ, Van den Berg MP, Van Sonderen E, Alings AM, Tijssen JG, et al. The effect of rate control on quality of life in patients with permanent atrial fibrillation: data from the RACE II (Rate Control Efficacy in Permanent Atrial Fibrillation II) study. *J Am Coll Cardiol* 2011;**58**:1795–803. <https://doi.org/10.1016/j.jacc.2011.06.055>
 187. Glikson M, Nielsen JC, Kronborg MB, Michowitz Y, Auricchio A, Barbash IM, et al. 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J* 2021;**42**:3427–520. <https://doi.org/10.1093/eurheartj/ehab364>
 188. Solomon SD, Claggett B, Lewis EF, Desai A, Anand I, Sweitzer NK, et al. Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. *Eur Heart J* 2016;**37**:455–62. <https://doi.org/10.1093/eurheartj/ehv464>
 189. Lund LH, Claggett B, Liu J, Lam CS, Jhund PS, Rosano GM, et al. Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum. *Eur J Heart Fail* 2018;**20**:1230–9. <https://doi.org/10.1002/ehf.1149>
 190. Cleland JGF, Bunting KV, Flather MD, Altman DG, Holmes J, Coats AJS, et al. Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials. *Eur Heart J* 2018;**39**:26–35. <https://doi.org/10.1093/eurheartj/ehx564>
 191. Tica O, Khambo W, Kotecha D. Breaking the cycle of heart failure with preserved ejection fraction and atrial fibrillation. *Card Fail Rev* 2022;**8**:e32. <https://doi.org/10.15420/cfr.2022.03>
 192. Nguyen BO, Crijns H, Tijssen JGP, Geelhoed B, Hobbelt AH, Hemels MEW, et al. Long-term outcome of targeted therapy of underlying conditions in patients with early persistent atrial fibrillation and heart failure: data of the RACE 3 trial. *Europace* 2022;**24**:910–20. <https://doi.org/10.1093/europace/euab270>
 193. Wang A, Green JB, Halperin JL, Piccini JP, Sr. Atrial fibrillation and diabetes mellitus: JACC review topic of the week. *J Am Coll Cardiol* 2019;**74**:1107–15. <https://doi.org/10.1016/j.jacc.2019.07.020>
 194. Aljila F, Buttia C, Reichlin T, Razvi S, Minder B, Wilhelm M, et al. Association of diabetes with atrial fibrillation types: a systematic review and meta-analysis. *Cardiovasc Diabetol* 2021;**20**:230. <https://doi.org/10.1186/s12933-021-01423-2>
 195. Ding WY, Kotalczyk A, Boriani G, Marin F, Blomstrom-Lundqvist C, Potpara TS, et al. Impact of diabetes on the management and outcomes in atrial fibrillation: an analysis from the ESC-EHRA EORP-AF long-term general registry. *Eur J Intern Med* 2022;**103**:41–9. <https://doi.org/10.1016/j.ejim.2022.04.026>
 196. Proietti M, Romiti GF, Basili S. The case of diabetes mellitus and atrial fibrillation: underlining the importance of non-cardiovascular comorbidities. *Eur J Intern Med* 2022;**103**:38–40. <https://doi.org/10.1016/j.ejim.2022.06.017>

197. Karayiannis S, Norhammar A, Landstedt-Hallin L, Friberg L, Lundman P. Prognostic impact of type 1 and type 2 diabetes mellitus in atrial fibrillation and the effect of severe hypoglycaemia: a nationwide cohort study. *Eur J Prev Cardiol* 2022;**29**:1759–69. <https://doi.org/10.1093/eurjpc/zwac093>
198. Lip GY, Nieuwlaet R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on atrial fibrillation. *Chest* 2010;**137**: 263–72. <https://doi.org/10.1378/chest.09-1584>
199. Abdel-Qadir H, Gunn M, Lega IC, Pang A, Austin PC, Singh SM, et al. Association of diabetes duration and glycemic control with stroke rate in patients with atrial fibrillation and diabetes: a population-based cohort study. *J Am Heart Assoc* 2022;**11**: e023643. <https://doi.org/10.1161/JAHA.121.023643>
200. Donnellan E, Aagaard P, Kanj M, Jaber W, Elshazly M, Hoosien M, et al. Association between pre-ablation glycemic control and outcomes among patients with diabetes undergoing atrial fibrillation ablation. *JACC Clin Electrophysiol* 2019;**5**:897–903. <https://doi.org/10.1016/j.jacep.2019.05.018>
201. D'Souza S, Elshazly MB, Dargham SR, Donnellan E, Asaad N, Hayat S, et al. Atrial fibrillation catheter ablation complications in obese and diabetic patients: insights from the US nationwide inpatient sample 2005–2013. *Clin Cardiol* 2021;**44**:1151–60. <https://doi.org/10.1002/clc.23667>
202. Creta A, Providencia R, Adragao P, de Asmundis C, Chun J, Chierchia G, et al. Impact of type-2 diabetes mellitus on the outcomes of catheter ablation of atrial fibrillation (European Observational Multicentre Study). *Am J Cardiol* 2020;**125**:901–6. <https://doi.org/10.1016/j.amjcard.2019.12.037>
203. Wang Z, Wang YJ, Liu ZY, Li Q, Kong YW, Chen YW, et al. Effect of insulin resistance on recurrence after radiofrequency catheter ablation in patients with atrial fibrillation. *Cardiovasc Drugs Ther* 2023;**37**:705–13. <https://doi.org/10.1007/s10557-022-07317-z>
204. Papazoglou AS, Kartsas A, Moysidis DV, Tsagkaris C, Papadakis SP, Bekiaridou A, et al. Glycemic control and atrial fibrillation: an intricate relationship, yet under investigation. *Cardiovasc Diabetol* 2022;**21**:39. <https://doi.org/10.1186/s12933-022-01473-0>
205. Zhang Z, Zhang X, Korantzopoulos P, Letsas KP, Tse G, Gong M, et al. Thiazolidinedione use and atrial fibrillation in diabetic patients: a meta-analysis. *BMC Cardiovasc Disord* 2017;**17**:96. <https://doi.org/10.1186/s12872-017-0531-4>
206. Bell DSH, Goncalves E. Atrial fibrillation and type 2 diabetes: prevalence, etiology, pathophysiology and effect of anti-diabetic therapies. *Diabetes Obes Metab* 2019;**21**: 210–7. <https://doi.org/10.1111/dom.13512>
207. Marx N, Federici M, Schütt K, Müller-Wieland D, Ajjan RA, Antunes MJ, et al. 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes. *Eur Heart J* 2023;**44**:4043–140. <https://doi.org/10.1093/eurheartj/ehad192>
208. Di Benedetto L, Michels G, Luben R, Khaw KT, Pfister R. Individual and combined impact of lifestyle factors on atrial fibrillation in apparently healthy men and women: the EPIC-Norfolk prospective population study. *Eur J Prev Cardiol* 2018;**25**:1374–83. <https://doi.org/10.1177/2047487318782379>
209. Grundvold I, Bodegard J, Nilsson PM, Svennblad B, Johansson G, Ostgren CJ, et al. Body weight and risk of atrial fibrillation in 7,169 patients with newly diagnosed type 2 diabetes: an observational study. *Cardiovasc Diabetol* 2015;**14**:5. <https://doi.org/10.1186/s12933-014-0170-3>
210. Wong CX, Sullivan T, Sun MT, Mahajan R, Pathak RK, Middeldorp M, et al. Obesity and the risk of incident, post-operative, and post-ablation atrial fibrillation: a meta-analysis of 626,603 individuals in 51 studies. *JACC Clin Electrophysiol* 2015;**1**:139–52. <https://doi.org/10.1016/j.jacep.2015.04.004>
211. Providencia R, Adragao P, de Asmundis C, Chun J, Chierchia G, Defaye P, et al. Impact of body mass index on the outcomes of catheter ablation of atrial fibrillation: a European observational multicenter study. *J Am Heart Assoc* 2019;**8**:e012253. <https://doi.org/10.1161/JAHA.119.012253>
212. Glover BM, Hong KL, Dagres N, Arbelo E, Laroche C, Riahi S, et al. Impact of body mass index on the outcome of catheter ablation of atrial fibrillation. *Heart* 2019;**105**:244–50. <https://doi.org/10.1136/heartjnl-2018-313490>
213. Gessler N, Willems S, Steven D, Aberle J, Akbulak RO, Gosau N, et al. Supervised obesity reduction trial for AF ablation patients: results from the SORT-AF trial. *Europace* 2021;**23**:1548–58. <https://doi.org/10.1093/eurpace/eurab122>
214. Mohanty S, Mohanty P, Natale V, Trivedi C, Gianni C, Burkhardt JD, et al. Impact of weight loss on ablation outcome in obese patients with longstanding persistent atrial fibrillation. *J Cardiovasc Electrophysiol* 2018;**29**:246–53. <https://doi.org/10.1111/jce.13394>
215. Donnellan E, Wazni OM, Kanj M, Elshazly M, Hussein AA, Patel DR, et al. Impact of risk-factor modification on arrhythmia recurrence among morbidly obese patients undergoing atrial fibrillation ablation. *J Cardiovasc Electrophysiol* 2020;**31**:1979–86. <https://doi.org/10.1111/jce.14607>
216. Donnellan E, Wazni OM, Kanj M, Baranowski B, Cremer P, Harb S, et al. Association between pre-ablation bariatric surgery and atrial fibrillation recurrence in morbidly obese patients undergoing atrial fibrillation ablation. *Europace* 2019;**21**:1476–83. <https://doi.org/10.1093/eurpace/eurz183>
217. Donnellan E, Wazni O, Kanj M, Hussein A, Baranowski B, Lindsay B, et al. Outcomes of atrial fibrillation ablation in morbidly obese patients following bariatric surgery compared with a nonobese cohort. *Circ Arrhythm Electrophysiol* 2019;**12**:e007598. <https://doi.org/10.1161/CIRCEP.119.007598>
218. Moulai AI, Parrini I, Tetta C, Lucà F, Parise G, Rao CM, et al. Obstructive sleep apnea and atrial fibrillation. *J Clin Med* 2022;**11**:1242. <https://doi.org/10.3390/jcm11051242>
219. Kapur VK, Auckley DH, Chowdhuri S, Kuhlmann DC, Mehra R, Ramar K, et al. Clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: an American academy of sleep medicine clinical practice guideline. *J Clin Sleep Med* 2017;**13**: 479–504. <https://doi.org/10.5664/jcsm.6506>
220. Linz D, Brooks AG, Elliott AD, Nalliah CJ, Hendriks JML, Middeldorp ME, et al. Variability of sleep apnea severity and risk of atrial fibrillation: the VARIOS-AF study. *JACC Clin Electrophysiol* 2019;**5**:692–701. <https://doi.org/10.1016/j.jacep.2019.03.005>
221. Linz D, Linz B, Dobrev D, Baumert M, Hendriks JM, Pepin JL, et al. Personalized management of sleep apnea in patients with atrial fibrillation: an interdisciplinary and translational challenge. *Int J Cardiol Heart Vasc* 2021;**35**:100843. <https://doi.org/10.1016/j.ijcha.2021.100843>
222. Kanagala R, Murali NS, Friedman PA, Ammash NM, Gersh BJ, Ballman KV, et al. Obstructive sleep apnea and the recurrence of atrial fibrillation. *Circulation* 2003;**107**:2589–94. <https://doi.org/10.1161/01.CIR.0000068337.25994.21>
223. Abumumar AM, Newman D, Dorian P, Shapiro CM. Cardiac effects of CPAP treatment in patients with obstructive sleep apnea and atrial fibrillation. *J Interv Card Electrophysiol* 2019;**54**:289–97. <https://doi.org/10.1007/s10840-018-0482-4>
224. Mittal S, Golombek D, Pimienta J. Sleep apnoea and AF: where do we stand? Practical advice for clinicians. *Arrhythm Electrophysiol Rev* 2021;**10**:140–6. <https://doi.org/10.15420/aer.2021.05>
225. Hunt TE, Traaen GM, Aakeroy L, Bendz C, Overland B, Akre H, et al. Effect of continuous positive airway pressure therapy on recurrence of atrial fibrillation after pulmonary vein isolation in patients with obstructive sleep apnea: a randomized controlled trial. *Heart Rhythm* 2022;**19**:1433–41. <https://doi.org/10.1016/j.hrthm.2022.06.016>
226. Caples SM, Mansukhani MP, Friedman PA, Somers VK. The impact of continuous positive airway pressure treatment on the recurrence of atrial fibrillation post cardioversion: a randomized controlled trial. *Int J Cardiol* 2019;**278**:133–6. <https://doi.org/10.1016/j.ijcard.2018.11.100>
227. Labarca G, Dreyse J, Drake L, Jorquera J, Barbe F. Efficacy of continuous positive airway pressure (CPAP) in the prevention of cardiovascular events in patients with obstructive sleep apnea: systematic review and meta-analysis. *Sleep Med Rev* 2020;**52**:101312. <https://doi.org/10.1016/j.smrv.2020.101312>
228. Abuzaid AS, Al Ashry HS, Elbadawi A, Ld H, Saad M, Elgendy IY, et al. Meta-analysis of cardiovascular outcomes with continuous positive airway pressure therapy in patients with obstructive sleep apnea. *Am J Cardiol* 2017;**120**:693–9. <https://doi.org/10.1016/j.amjcard.2017.05.042>
229. Yu J, Zhou Z, McEvoy RD, Anderson CS, Rodgers A, Perkovic V, et al. Association of positive airway pressure with cardiovascular events and death in adults with sleep apnea: a systematic review and meta-analysis. *JAMA* 2017;**318**:156–66. <https://doi.org/10.1001/jama.2017.7967>
230. McEvoy RD, Antic NA, Heeley E, Luo Y, Ou Q, Zhang X, et al. CPAP for prevention of cardiovascular events in obstructive sleep apnea. *N Engl J Med* 2016;**375**:919–31. <https://doi.org/10.1056/NEJMoa1606599>
231. Overvad TF, Rasmussen LH, Skjøth F, Overvad K, Albersen IE, Lane DA, et al. Alcohol intake and prognosis of atrial fibrillation. *Heart* 2013;**99**:1093–9. <https://doi.org/10.1136/heartjnl-2013-304036>
232. Lim C, Kim T-H, Yu HT, Lee S-R, Cha M-J, Lee J-M, et al. Effect of alcohol consumption on the risk of adverse events in atrial fibrillation: from the COMPARISON study of Drugs for symptom control and complication prevention of Atrial Fibrillation (CODE-AF) registry. *EP Europace* 2021;**23**:548–56. <https://doi.org/10.1093/eurpace/eurab340>
233. Lee SR, Choi EK, Jung JH, Han KD, Oh S, Lip GYH. Lower risk of stroke after alcohol abstinence in patients with incident atrial fibrillation: a nationwide population-based cohort study. *Eur Heart J* 2021;**42**:4759–68. <https://doi.org/10.1093/eurheartj/ehab315>
234. Pisters R, Lane DA, Nieuwlaet R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010;**138**:1093–100. <https://doi.org/10.1378/chest.10-0134>
235. Takahashi Y, Nitta J, Kobori A, Sakamoto Y, Nagata Y, Tanimoto K, et al. Alcohol consumption reduction and clinical outcomes of catheter ablation for atrial fibrillation. *Circ Arrhythm Electrophysiol* 2021;**14**:e009770. <https://doi.org/10.1161/CIRCEP.121.009770>
236. Friberg L, Hammar N, Rosenqvist M. Stroke in paroxysmal atrial fibrillation: report from the Stockholm cohort of atrial fibrillation. *Eur Heart J* 2010;**31**:967–75. <https://doi.org/10.1093/eurheartj/ehn599>
237. Banerjee A, Taillandier S, Olesen JB, Lane DA, Lallemand B, Lip GY, et al. Pattern of atrial fibrillation and risk of outcomes: the Loire valley atrial fibrillation project. *Int J Cardiol* 2013;**167**:2682–7. <https://doi.org/10.1016/j.ijcard.2012.06.118>
238. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham study. *Stroke* 1991;**22**:983–8. <https://doi.org/10.1161/01.STR.22.8.983>

239. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;**146**: 857–67. <https://doi.org/10.7326/0003-4819-146-12-200706190-00007>
240. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014;**383**: 955–62. [https://doi.org/10.1016/S0140-6736\(13\)62343-0](https://doi.org/10.1016/S0140-6736(13)62343-0)
241. Sjalander S, Sjalander A, Svensson PJ, Friberg L. Atrial fibrillation patients do not benefit from acetylsalicylic acid. *Europace* 2014;**16**:631–8. <https://doi.org/10.1093/eurpace/eut333>
242. Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, et al. Apixaban in patients with atrial fibrillation. *N Engl J Med* 2011;**364**:806–17. <https://doi.org/10.1056/NEJMoa1007432>
243. van Doorn S, Rutten FH, O'Flynn CM, Oudega R, Hoes AW, Moons KGM, et al. Effectiveness of CHA2DS2-VASc based decision support on stroke prevention in atrial fibrillation: a cluster randomised trial in general practice. *Int J Cardiol* 2018;**273**:123–9. <https://doi.org/10.1016/j.ijcard.2018.08.096>
244. Borre ED, Goode A, Raitz G, Shah B, Lowenstern A, Chatterjee R, et al. Predicting thromboembolic and bleeding event risk in patients with non-valvular atrial fibrillation: a systematic review. *Thromb Haemost* 2018;**118**:2171–87. <https://doi.org/10.1055/s-0038-1675400>
245. van der Endt VHW, Milders J, de Vries BBLP, Trines SA, Groenewold RHH, Dekkers OM, et al. Comprehensive comparison of stroke risk score performance: a systematic review and meta-analysis among 6 267 728 patients with atrial fibrillation. *Europace* 2022;**24**:1739–53. <https://doi.org/10.1093/eurpace/eurac096>
246. Quinn GR, Severdija ON, Chang Y, Singer DE. Wide variation in reported rates of stroke across cohorts of patients with atrial fibrillation. *Circulation* 2017;**135**: 208–19. <https://doi.org/10.1161/CIRCULATIONAHA.116.024057>
247. Pisters R, Lane DA, Marin F, Camm AJ, Lip GY. Stroke and thromboembolism in atrial fibrillation. *Circ J* 2012;**76**:2289–304. <https://doi.org/10.1253/circj.CJ-12-1036>
248. Hohnloser SH, Hijazi Z, Thomas L, Alexander JH, Amerena J, Hanna M, et al. Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial. *Eur Heart J* 2012;**33**:2821–30. <https://doi.org/10.1093/eurheartj/ehs274>
249. Fox KA, Piccini JP, Wojdyla D, Becker RC, Halperin JL, Nessel CC, et al. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. *Eur Heart J* 2011;**32**:2387–94. <https://doi.org/10.1093/eurheartj/ehr342>
250. Yaghi S, Henninger N, Giles JA, Leon Guerrero C, Mistry E, Liberman AL, et al. Ischaemic stroke on anticoagulation therapy and early recurrence in acute cardioembolic stroke: the IAC study. *J Neurol Neurosurg Psychiatry* 2021;**92**:1062–7. <https://doi.org/10.1136/jnnp-2021-326166>
251. Ocak G, Khairoun M, Khairoun O, Bos WJW, Fu EL, Cramer MJ, et al. Chronic kidney disease and atrial fibrillation: a dangerous combination. *PLoS One* 2022;**17**:e0266046. <https://doi.org/10.1371/journal.pone.0266046>
252. Seiffge DJ, De Marchis GM, Koga M, Paciaroni M, Wilson D, Cappellari M, et al. Ischemic stroke despite oral anticoagulant therapy in patients with atrial fibrillation. *Ann Neurol* 2020;**87**:677–87. <https://doi.org/10.1002/ana.25700>
253. Paciaroni M, Agnelli G, Falocci N, Caso V, Becattini C, Marcheselli S, et al. Prognostic value of trans-thoracic echocardiography in patients with acute stroke and atrial fibrillation: findings from the RAF study. *J Neurol* 2016;**263**:231–7. <https://doi.org/10.1007/s00415-015-7957-3>
254. Hijazi Z, Oldgren J, Siegbahn A, Wallentin L. Application of biomarkers for risk stratification in patients with atrial fibrillation. *Clin Chem* 2017;**63**:152–64. <https://doi.org/10.1373/clinchem.2016.255182>
255. Singleton MJ, Yuan Y, Dawood FZ, Howard G, Judd SE, Zakai NA, et al. Multiple blood biomarkers and stroke risk in atrial fibrillation: the REGARDs study. *J Am Heart Assoc* 2021;**10**:e020157. <https://doi.org/10.1161/JAHA.120.020157>
256. Wu VC, Wu M, Aboyans V, Chang SH, Chen SW, Chen MC, et al. Female sex as a risk factor for ischaemic stroke varies with age in patients with atrial fibrillation. *Heart* 2020;**106**:534–40. <https://doi.org/10.1136/heartjnl-2019-315065>
257. Mikkelsen AP, Lindhardtsen J, Lip GY, Gislason GH, Torp-Pedersen C, Olesen JB. Female sex as a risk factor for stroke in atrial fibrillation: a nationwide cohort study. *J Thromb Haemost* 2012;**10**:1745–51. <https://doi.org/10.1111/j.1538-7836.2012.04853.x>
258. Antonenko K, Paciaroni M, Agnelli G, Falocci N, Becattini C, Marcheselli S, et al. Sex-related differences in risk factors, type of treatment received and outcomes in patients with atrial fibrillation and acute stroke: results from the RAF study (early recurrence and cerebral bleeding in patients with acute ischemic stroke and atrial fibrillation). *Eur Stroke J* 2017;**2**:46–53. <https://doi.org/10.1177/2396987316679577>
259. Wang X, Mobley AR, Tica O, Okoth K, Ghosh RE, Myles P, et al. Systematic approach to outcome assessment from coded electronic healthcare records in the DaRe2THINK NHS-embedded randomized trial. *Eur Heart J - Dig Health* 2022;**3**: 426–36. <https://doi.org/10.1093/ehjdh/ztac046>
260. Rivard L, Khairy P, Talajic M, Tardif JC, Nattel S, Bherer L, et al. Blinded randomized trial of anticoagulation to prevent ischemic stroke and neurocognitive impairment in atrial fibrillation (BRAIN-AF): methods and design. *Can J Cardiol* 2019;**35**:1069–77. <https://doi.org/10.1016/j.cjca.2019.04.022>
261. Chung S, Kim TH, Uhm JS, Cha MJ, Lee JM, Park J, et al. Stroke and systemic embolism and other adverse outcomes of heart failure with preserved and reduced ejection fraction in patients with atrial fibrillation (from the COMPARISON study of Drugs for symptom control and complication prEvention of Atrial Fibrillation [CODE-AF]). *Am J Cardiol* 2020;**125**:68–75. <https://doi.org/10.1016/j.amjcard.2019.09.035>
262. Uhm JS, Kim J, Yu HT, Kim TH, Lee SR, Cha MJ, et al. Stroke and systemic embolism in patients with atrial fibrillation and heart failure according to heart failure type. *ESC Heart Fail* 2021;**8**:1582–9. <https://doi.org/10.1002/ehf2.13264>
263. McMurray JJ, Ezekowitz JA, Lewis BS, Gersh BJ, van Diepen S, Amerena J, et al. Left ventricular systolic dysfunction, heart failure, and the risk of stroke and systemic embolism in patients with atrial fibrillation: insights from the ARISTOTLE trial. *Circ Heart Fail* 2013;**6**:451–60. <https://doi.org/10.1161/CIRCHEARTFAILURE.112.000143>
264. Kim D, Yang PS, Kim TH, Jang E, Shin H, Kim HY, et al. Ideal blood pressure in patients with atrial fibrillation. *J Am Coll Cardiol* 2018;**72**:1233–45. <https://doi.org/10.1016/j.jacc.2018.05.076>
265. Lip GY, Clementy N, Pericart L, Banerjee A, Fauchier L. Stroke and major bleeding risk in elderly patients aged ≥75 years with atrial fibrillation: the Loire valley atrial fibrillation project. *Stroke* 2015;**46**:143–50. <https://doi.org/10.1161/STROKEAHA.114.007199>
266. American Diabetes Association Professional Practice Committee. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes—2022. *Diabetes Care* 2022;**45**:S17–38. <https://doi.org/10.2337/dc22-S002>
267. Steensig K, Olesen KKW, Thim T, Nielsen JC, Jensen SE, Jensen LO, et al. Should the presence or extent of coronary artery disease be quantified in the CHA2DS2-VASc score in atrial fibrillation? A report from the western Denmark heart registry. *Thromb Haemost* 2018;**118**:2162–70. <https://doi.org/10.1055/s-0038-1675401>
268. Zabalgoitia M, Halperin JL, Pearce LA, Blackshear JL, Asinger RV, Hart RG. Transesophageal echocardiographic correlates of clinical risk of thromboembolism in nonvalvular atrial fibrillation. Stroke prevention in atrial fibrillation III investigators. *J Am Coll Cardiol* 1998;**31**:1622–6. [https://doi.org/10.1016/S0735-1097\(98\)00146-6](https://doi.org/10.1016/S0735-1097(98)00146-6)
269. Stroke Prevention in Atrial Fibrillation Investigators Committee on Echocardiography. Transesophageal echocardiography in atrial fibrillation: standards for acquisition and interpretation and assessment of interobserver variability. Stroke prevention in atrial fibrillation investigators committee on echocardiography. *J Am Soc Echocardiogr* 1996;**9**:556–66. [https://doi.org/10.1016/S0894-7317\(96\)90127-3](https://doi.org/10.1016/S0894-7317(96)90127-3)
270. Lozier MR, Sanchez AM, Lee JJ, Donath EM, Font VE, Escobar E. Thromboembolic outcomes of different anticoagulation strategies for patients with atrial fibrillation in the setting of hypertrophic cardiomyopathy: a systematic review. *J Atr Fibrillation* 2019;**12**:2207. <https://doi.org/10.4022/jafb.2207>
271. Guttman OP, Rahman MS, O'Mahony C, Anastakis A, Elliott PM. Atrial fibrillation and thromboembolism in patients with hypertrophic cardiomyopathy: systematic review. *Heart* 2014;**100**:465–72. <https://doi.org/10.1136/heartjnl-2013-304276>
272. Guttman OP, Pavlou M, O'Mahony C, Monserrat L, Anastakis A, Rapezzi C, et al. Prediction of thromboembolic risk in patients with hypertrophic cardiomyopathy (HCM risk-CVA). *Eur J Heart Fail* 2015;**17**:837–45. <https://doi.org/10.1002/ehf.316>
273. Vilches S, Fontana M, Gonzalez-Lopez E, Mitran L, Satriu G, Renju M, et al. Systemic embolism in amyloid transthyretin cardiomyopathy. *Eur J Heart Fail* 2022;**24**: 1387–96. <https://doi.org/10.1002/ehf.2566>
274. Lee SE, Park JK, Uhm JS, Kim JY, Pak HN, Lee MH, et al. Impact of atrial fibrillation on the clinical course of apical hypertrophic cardiomyopathy. *Heart* 2017;**103**:1496–501. <https://doi.org/10.1136/heartjnl-2016-310720>
275. Hirota T, Kubo T, Baba Y, Ochi Y, Takahashi A, Yamasaki N, et al. Clinical profile of thromboembolic events in patients with hypertrophic cardiomyopathy in a regional Japanese cohort—results from Kochi RYOMA study. *Circ J* 2019;**83**:1747–54. <https://doi.org/10.1253/circj.CJ-19-0186>
276. Hsu JC, Huang YT, Lin LY. Stroke risk in hypertrophic cardiomyopathy patients with atrial fibrillation: a nationwide database study. *Aging (Albany NY)* 2020;**12**:24219–27. <https://doi.org/10.18632/aging.104133>
277. Chao TF, Lip GYH, Liu CJ, Lin YJ, Chang SL, Lo LW, et al. Relationship of aging and incident comorbidities to stroke risk in patients with atrial fibrillation. *J Am Coll Cardiol* 2018;**71**:122–32. <https://doi.org/10.1016/j.jacc.2017.10.085>
278. Weijls B, Dudink E, de Vos CB, Limantoro I, Tieleman RG, Pisters R, et al. Idiopathic atrial fibrillation patients rapidly outgrow their low thromboembolic risk: a 10-year follow-up study. *Neth Heart J* 2019;**27**:487–97. <https://doi.org/10.1007/s12471-019-1272-z>
279. Bezabhe WM, Bereznicki LR, Radford J, Wimmer BC, Salahudeen MS, Garrahy E, et al. Stroke risk reassessment and oral anticoagulant initiation in primary care patients with atrial fibrillation: A ten-year follow-up. *Eur J Clin Invest* 2021;**51**:e13489. <https://doi.org/10.1111/eci.13489>
280. Fauchier L, Bodin A, Bisson A, Herbert J, Spiesser P, Clementy N, et al. Incident comorbidities, aging and the risk of stroke in 608,108 patients with atrial fibrillation: a nationwide analysis. *J Clin Med* 2020;**9**:1234. <https://doi.org/10.3390/jcm9041234>

281. Kirchhof P, Toennis T, Goette A, Camm AJ, Diener HC, Becher N, et al. Anticoagulation with edoxaban in patients with atrial high-rate episodes. *N Engl J Med* 2023;**389**:1167–79. <https://doi.org/10.1056/NEJMoa2303062>
282. Healey JS, Lopes RD, Granger CB, Alings M, Rivard L, McIntyre VF, et al. Apixaban for stroke prevention in subclinical atrial fibrillation. *N Engl J Med* 2024;**390**:107–17. <https://doi.org/10.1056/NEJMoa2310234>
283. van Walraven C, Hart RG, Singer DE, Laupacis A, Connolly S, Petersen P, et al. Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation: an individual patient meta-analysis. *JAMA* 2002;**288**:2441–8. <https://doi.org/10.1001/jama.288.19.2441>
284. Hart RG, Pearce LA, Rothbart RM, McAnulty JH, Asinger RV, Halperin JL. Stroke with intermittent atrial fibrillation: incidence and predictors during aspirin therapy. Stroke prevention in atrial fibrillation investigators. *J Am Coll Cardiol* 2000;**35**:183–7. [https://doi.org/10.1016/S0735-1097\(99\)00489-1](https://doi.org/10.1016/S0735-1097(99)00489-1)
285. Nieuwlaat R, Dinh T, Olsson SB, Camm AJ, Capucci A, Tieleman RG, et al. Should we abandon the common practice of withholding oral anticoagulation in paroxysmal atrial fibrillation? *Eur Heart J* 2008;**29**:915–22. <https://doi.org/10.1093/eurheartj/ehh101>
286. Ruff CT. AZALEA-TIMI 71 Steering Committee. Abecimab, a novel factor XI/XIIa inhibitor, vs rivaroxaban in patients with atrial fibrillation: primary results of the AZALEA-TIMI 71 randomized trial. *Circulation* 2024;**148**:e282–317. <https://doi.org/10.1161/CIR.0000000000001200>
287. Piccini JP, Caso V, Connolly SJ, Fox KAA, Oldgren J, Jones WS, et al. Safety of the oral factor Xla inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): a multicentre, randomised, double-blind, double-dummy, dose-finding phase 2 study. *Lancet* 2022;**399**:1383–90. [https://doi.org/10.1016/S0140-6736\(22\)00456-1](https://doi.org/10.1016/S0140-6736(22)00456-1)
288. Tan CSS, Lee SWH. Warfarin and food, herbal or dietary supplement interactions: a systematic review. *Br J Clin Pharmacol* 2021;**87**:352–74. <https://doi.org/10.1111/bcp.14404>
289. Holbrook AM, Pereira JA, Labiris R, McDonald H, Douketis JD, Crowther M, et al. Systematic overview of warfarin and its drug and food interactions. *Arch Intern Med* 2005;**165**:1095–106. <https://doi.org/10.1001/archinte.165.10.1095>
290. Ferri N, Colombo E, Tenconi M, Baldessin L, Corsini A. Drug-drug interactions of direct oral anticoagulants (DOACs): from pharmacological to clinical practice. *Pharmaceutics* 2022;**14**:1120. <https://doi.org/10.3390/pharmaceutics14061120>
291. Mar PL, Gopinathannair R, Gengler BE, Chung MK, Perez A, Dukes J, et al. Drug interactions affecting oral anticoagulant use. *Circ Arrhythm Electrophysiol* 2022;**15**:e007956. <https://doi.org/10.1161/CIRCEP.121.007956>
292. Carnicelli AP, Hong H, Connolly SJ, Eikelboom J, Giugliano RP, Morrow DA, et al. Direct oral anticoagulants versus warfarin in patients with atrial fibrillation: patient-level network meta-analyses of randomized clinical trials with interaction testing by age and sex. *Circulation* 2022;**145**:242–55. <https://doi.org/10.1161/CIRCULATIONAHA.121.056355>
293. Kotecha D, Pollack CV, Jr, De Caterina R, Renda G, Kirchhof P. Direct oral anticoagulants halve thromboembolic events after cardioversion of AF compared with warfarin. *J Am Coll Cardiol* 2018;**72**:1984–6. <https://doi.org/10.1016/j.jacc.2018.07.083>
294. Connolly SJ, Karthikeyan G, Ntsekhe M, Haileamlak A, El Sayed A, El Ghamrawy A, et al. Rivaroxaban in rheumatic heart disease-associated atrial fibrillation. *N Engl J Med* 2022;**387**:978–88. <https://doi.org/10.1056/NEJMoa2209051>
295. Halperin JL, Hart RG, Kronmal RA, McBride R. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: stroke prevention in atrial fibrillation II study. *Lancet* 1994;**343**:687–91. [https://doi.org/10.1016/S0140-6736\(94\)91577-6](https://doi.org/10.1016/S0140-6736(94)91577-6)
296. Singer DE, Hughes RA, Gress DR, Sheehan MA, Oertel LB, Maraventano SV, et al. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. *N Engl J Med* 1990;**323**:1505–11. <https://doi.org/10.1056/NEJM199011293232201>
297. Gulløv AL, Koefoed BG, Petersen P, Pedersen TS, Andersen ED, Godtfredsen J, et al. Fixed minidose warfarin and aspirin alone and in combination vs adjusted-dose warfarin for stroke prevention in atrial fibrillation: second Copenhagen atrial fibrillation, aspirin, and anticoagulation study. *Arch Intern Med* 1998;**158**:1513–21. <https://doi.org/10.1001/archinte.158.14.1513>
298. Blackshear JL, Halperin JL, Hart RG, Laupacis A. Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: stroke prevention in atrial fibrillation III randomised clinical trial. *Lancet* 1996;**348**:633–8. [https://doi.org/10.1016/S0140-6736\(96\)03487-3](https://doi.org/10.1016/S0140-6736(96)03487-3)
299. Amin A, Deitelzweig S, Jing Y, Makenbaeva D, Wiederkehr D, Lin J, et al. Estimation of the impact of warfarin's time-in-therapeutic range on stroke and major bleeding rates and its influence on the medical cost avoidance associated with novel oral anticoagulant use—learnings from ARISTOTLE, ROCKET-AF, and RE-LY trials. *J Thromb Thrombolysis* 2014;**38**:150–9. <https://doi.org/10.1007/s11239-013-1048-z>
300. Sjalander S, Sjögren V, Renlund H, Norrving B, Sjalander A. Dabigatran, rivaroxaban and apixaban vs. high TTR warfarin in atrial fibrillation. *Thromb Res* 2018;**167**:113–8. <https://doi.org/10.1016/j.thromres.2018.05.022>
301. van Miert JHA, Kooistra HAM, Veegeer N, Westerterp A, Piersma-Wichers M, Meijer K. Choosing between continuing vitamin K antagonists (VKA) or switching to a direct oral anticoagulant in currently well-controlled patients on VKA for atrial fibrillation: a randomised controlled trial (GAINN). *Br J Haematol* 2019;**186**:e21–3. <https://doi.org/10.1111/bjh.15856>
302. Kittayaphong R, Chantrarat T, Rojarekarnai P, Jittham P, Sairat P, Lip GYH. Poor time in therapeutic range control is associated with adverse clinical outcomes in patients with non-valvular atrial fibrillation: a report from the nationwide COOL-AF registry. *J Clin Med* 2020;**9**:1698. <https://doi.org/10.3390/jcm9061698>
303. Szummer K, Gasparini A, Eliasson S, Årnlöv J, Qureshi AR, Bárány P, et al. Time in therapeutic range and outcomes after warfarin initiation in newly diagnosed atrial fibrillation patients with renal dysfunction. *J Am Heart Assoc* 2017;**6**:e004925. <https://doi.org/10.1161/JAHA.116.004925>
304. Cardoso R, Ternes CMP, Justino GB, Fernandes A, Rocha AV, Knijnik L, et al. Non-vitamin K antagonists versus warfarin in patients with atrial fibrillation and bio-prosthetic valves: a systematic review and meta-analysis. *Am J Med* 2022;**135**:228–234.e1. <https://doi.org/10.1016/j.amjmed.2021.08.026>
305. Wan Y, Heneghan C, Perera R, Roberts N, Hollowell J, Glasziou P, et al. Anticoagulation control and prediction of adverse events in patients with atrial fibrillation: a systematic review. *Circ Cardiovasc Qual Outcomes* 2008;**1**:84–91. <https://doi.org/10.1161/CIRCOUTCOMES.108.796185>
306. Vestergaard AS, Skjøth F, Larsen TB, Ehlers LH. The importance of mean time in therapeutic range for complication rates in warfarin therapy of patients with atrial fibrillation: a systematic review and meta-regression analysis. *PLoS One* 2017;**12**:e0188482. <https://doi.org/10.1371/journal.pone.0188482>
307. Macaluso GP, Pagani FD, Slaughter MS, Milano CA, Feller ED, Tatoes AJ, et al. Time in therapeutic range significantly impacts survival and adverse events in destination therapy patients. *ASAIO J* 2022;**68**:14–20. <https://doi.org/10.1097/MAT.0000000000001572>
308. Heneghan C, Ward A, Perera R, Bankhead C, Fuller A, Stevens R, et al. Self-monitoring of oral anticoagulation: systematic review and meta-analysis of individual patient data. *Lancet* 2012;**379**:322–34. [https://doi.org/10.1016/S0140-6736\(11\)61294-4](https://doi.org/10.1016/S0140-6736(11)61294-4)
309. Joosten LPT, van Doorn S, van de Ven PM, Köhler BTG, Niernan MC, Koek HL, et al. Safety of switching from a vitamin K antagonist to a non-vitamin K antagonist oral anticoagulant in frail older patients with atrial fibrillation: results of the FRAIL-AF randomized controlled trial. *Circulation* 2024;**149**:279–89. <https://doi.org/10.1161/CIRCULATIONAHA.123.066485>
310. Yao X, Shah ND, Sangaralingham LR, Gersh BJ, Noseworthy PA. Non-vitamin K antagonist oral anticoagulant dosing in patients with atrial fibrillation and renal dysfunction. *J Am Coll Cardiol* 2017;**69**:2779–90. <https://doi.org/10.1016/j.jacc.2017.03.600>
311. Steinberg BA, Shrader P, Thomas L, Ansell J, Fonarow GC, Gersh BJ, et al. Off-label dosing of non-vitamin K antagonist oral anticoagulants and adverse outcomes: the ORBIT-AF II registry. *J Am Coll Cardiol* 2016;**68**:2597–604. <https://doi.org/10.1016/j.jacc.2016.09.966>
312. Alexander JH, Andersson U, Lopes RD, Hijazi Z, Hohnloser SH, Ezekowitz JA, et al. Apixaban 5 mg twice daily and clinical outcomes in patients with atrial fibrillation and advanced age, low body weight, or high creatinine: a secondary analysis of a randomized clinical trial. *JAMA Cardiol* 2016;**1**:673–81. <https://doi.org/10.1001/jamacardio.2016.1829>
313. Carmo J, Moscoso Costa F, Ferreira J, Mendes M. Dabigatran in real-world atrial fibrillation. Meta-analysis of observational comparison studies with vitamin K antagonists. *Thromb Haemost* 2016;**116**:754–63. <https://doi.org/10.1160/TH16-03-0203>
314. Huisman MV, Rothman KJ, Paquette M, Teutsch C, Diener HC, Dubner SJ, et al. Two-year follow-up of patients treated with dabigatran for stroke prevention in atrial fibrillation: global registry on long-term antithrombotic treatment in patients with atrial fibrillation (GLORIA-AF) registry. *Am Heart J* 2018;**198**:55–63. <https://doi.org/10.1016/j.ahj.2017.08.018>
315. Camm AJ, Amarencio P, Haas S, Hess S, Kirchhof P, Kuhls S, et al. XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation. *Eur Heart J* 2016;**37**:1145–53. <https://doi.org/10.1093/eurheartj/ehv466>
316. Martinez CAA, Lanás F, Radaideh G, Kharabsheh SM, Lambelet M, Viaud MAL, et al. XANTUS-EL: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation in Eastern Europe, Middle East, Africa and Latin America. *Egypt Heart J* 2018;**70**:307–13. <https://doi.org/10.1016/j.ehj.2018.09.002>
317. Li XS, Deitelzweig S, Keshishian A, Hamilton M, Horblyuk R, Gupta K, et al. Effectiveness and safety of apixaban versus warfarin in non-valvular atrial fibrillation patients in “real-world” clinical practice. A propensity-matched analysis of 76,940 patients. *Thromb Haemost* 2017;**117**:1072–82. <https://doi.org/10.1160/TH17-01-0068>
318. Lee SR, Choi EK, Han KD, Jung JH, Oh S, Lip GYH. Edoxaban in Asian patients with atrial fibrillation: effectiveness and safety. *J Am Coll Cardiol* 2018;**72**:838–53. <https://doi.org/10.1016/j.jacc.2018.05.066>
319. Cappato R, Ezekowitz MD, Klein AL, Camm AJ, Ma CS, Le Heuzey JY, et al. Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial fibrillation. *Eur Heart J* 2014;**35**:3346–55. <https://doi.org/10.1093/eurheartj/ehu367>
320. Goette A, Merino JL, Ezekowitz MD, Zamoryakhin D, Melino M, Jin J, et al. Edoxaban versus enoxaparin-warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): a randomised, open-label, phase 3b trial. *Lancet* 2016;**388**:1995–2003. [https://doi.org/10.1016/S0140-6736\(16\)31474-X](https://doi.org/10.1016/S0140-6736(16)31474-X)

321. Ezekowitz MD, Pollack CV, Jr, Halperin JL, England RD, VanPelt Nguyen S, Spahr J, et al. Apixaban compared to heparin/vitamin K antagonist in patients with atrial fibrillation scheduled for cardioversion: the EMANATE trial. *Eur Heart J* 2018;**39**:2959–71. <https://doi.org/10.1093/eurheartj/ehy148>
322. Savarese G, Giugliano RP, Rosano GM, McMurray J, Magnani G, Filippatos G, et al. Efficacy and safety of novel oral anticoagulants in patients with atrial fibrillation and heart failure: a meta-analysis. *JACC Heart Fail* 2016;**4**:870–80. <https://doi.org/10.1016/j.jchf.2016.07.012>
323. von Lueder TG, Atar D, Agewall S, Jensen JK, Hopper I, Kotecha D, et al. All-cause mortality and cardiovascular outcomes with non-vitamin K oral anticoagulants versus warfarin in patients with heart failure in the food and drug administration adverse event reporting system. *Am J Ther* 2019;**26**:e671–8. <https://doi.org/10.1097/MJT.0000000000000883>
324. Harrison SL, Buckley BJR, Ritchie LA, Proietti R, Underhill P, Lane DA, et al. Oral anticoagulants and outcomes in adults ≥ 80 years with atrial fibrillation: a global federated health network analysis. *J Am Geriatr Soc* 2022;**70**:2386–92. <https://doi.org/10.1111/jgs.17884>
325. Malhotra K, Ishfaq MF, Goyal N, Katsanos AH, Parissis J, Alexandrov AWW, et al. Oral anticoagulation in patients with chronic kidney disease: a systematic review and meta-analysis. *Neurology* 2019;**92**:e2421–31. <https://doi.org/10.1212/WNL.00000000000007534>
326. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, et al. The 2018 European heart rhythm association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Eur Heart J* 2018;**39**:1330–93. <https://doi.org/10.1093/eurheartj/ehy136>
327. Rhee TM, Lee SR, Choi EK, Oh S, Lip GYH. Efficacy and safety of oral anticoagulants for atrial fibrillation patients with chronic kidney disease: a systematic review and meta-analysis. *Front Cardiovasc Med* 2022;**9**:885548. <https://doi.org/10.3389/fcvm.2022.885548>
328. Reinecke H, Engelbertz C, Bauersachs R, Breithardt G, Echtermoff HH, Gerß J, et al. A randomized controlled trial comparing apixaban with the vitamin K antagonist phenprocoumon in patients on chronic hemodialysis: the AXADIA-AFNET 8 study. *Circulation* 2023;**147**:296–309. <https://doi.org/10.1161/CIRCULATIONAHA.122.062779>
329. Pokorney SD, Chertow GM, Al-Khalidi HR, Gallup D, Dignacco P, Mussina K, et al. Apixaban for patients with atrial fibrillation on hemodialysis: a multicenter randomized controlled trial. *Circulation* 2022;**146**:1735–45. <https://doi.org/10.1161/CIRCULATIONAHA.121.054990>
330. De Vriese AS, Caluwé R, Van Der Meersch H, De Boeck K, De Bacquer D. Safety and efficacy of vitamin K antagonists versus rivaroxaban in hemodialysis patients with atrial fibrillation: a multicenter randomized controlled trial. *J Am Soc Nephrol* 2021;**32**:1474–83. <https://doi.org/10.1681/ASN.2020111566>
331. Eikelboom JW, Connolly SJ, Brueckmann M, Granger CB, Kappetein AP, Mack MJ, et al. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med* 2013;**369**:1206–14. <https://doi.org/10.1056/NEJMoa1300615>
332. Wang TY, Svensson LG, Wen J, Vekstein A, Gerdtsch M, Rao VU, et al. Apixaban or warfarin in patients with an on-X mechanical aortic valve. *NEJM Evid* 2023;**2**:EVID02300067. <https://doi.org/10.1056/EVID02300067>
333. Guimarães HP, Lopes RD, de Barros ESPGM, Liporace IL, Sampaio RO, Tarasoutchi F, et al. Rivaroxaban in patients with atrial fibrillation and a bioprosthetic mitral valve. *N Engl J Med* 2020;**383**:2117–26. <https://doi.org/10.1056/NEJMoa2029603>
334. Collet JP, Van Belle E, Thiele H, Berti S, Lhermusier T, Manigold T, et al. Apixaban vs. standard of care after transcatheter aortic valve implantation: the ATLANTIS trial. *Eur Heart J* 2022;**43**:2783–97. <https://doi.org/10.1093/eurheartj/ehac242>
335. Steffel J, Collins R, Antz M, Cornu P, Desteghe L, Haeusler KG, et al. 2021 European heart rhythm association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Europace* 2021;**23**:1612–76. <https://doi.org/10.1093/eurpace/ehab065>
336. Grynmonprez M, Carnoy L, Capiou A, Boussery K, Mehuis E, De Backer TL, et al. Impact of P-glycoprotein and CYP3A4-interacting drugs on clinical outcomes in patients with atrial fibrillation using non-vitamin K antagonist oral anticoagulants: a nationwide cohort study. *Eur Heart J Cardiovasc Pharmacother* 2023;**9**:722–30. <https://doi.org/10.1093/ehjcvp/pvad070>
337. Testa S, Legnani C, Antonucci E, Paoletti O, Dellanoce C, Cosmi B, et al. Drug levels and bleeding complications in atrial fibrillation patients treated with direct oral anticoagulants. *J Thromb Haemost* 2019;**17**:1064–72. <https://doi.org/10.1111/jth.14457>
338. Suwa M, Nohara Y, Morii I, Kino M. Safety and efficacy re-evaluation of edoxaban and rivaroxaban dosing with plasma concentration monitoring in non-valvular atrial fibrillation: with observations of on-label and off-label dosing. *Circ Rep* 2023;**5**:80–9. <https://doi.org/10.1253/circrep.CR-22-0076>
339. Song D, Zhou J, Fan T, Chang J, Qiu Y, Zhuang Z, et al. Decision aids for shared decision-making and appropriate anticoagulation therapy in patients with atrial fibrillation: a systematic review and meta-analysis. *Eur J Cardiovasc Nurs* 2022;**21**:97–106. <https://doi.org/10.1093/ejcn/zvab085>
340. Vora P, Morgan Stewart H, Russell B, Asimwe A, Brobert G. Time trends and treatment pathways in prescribing individual oral anticoagulants in patients with nonvalvular atrial fibrillation: an observational study of more than three million patients from Europe and the United States. *Int J Clin Pract* 2022;**2022**:6707985. <https://doi.org/10.1155/2022/6707985>
341. Grynmonprez M, Simoons C, Steurbaut S, De Backer TL, Lahousse L. Worldwide trends in oral anticoagulant use in patients with atrial fibrillation from 2010 to 2018: a systematic review and meta-analysis. *Europace* 2022;**24**:887–98. <https://doi.org/10.1093/eurpace/ehab303>
342. De Caterina R, Husted S, Wallentin L, Andreotti F, Arnesen H, Bachmann F, et al. Vitamin K antagonists in heart disease: current status and perspectives (section III). Position paper of the ESC working group on thrombosis—task force on anticoagulants in heart disease. *Thromb Haemost* 2013;**110**:1087–107. <https://doi.org/10.1160/TH13-06-0443>
343. Pandey AK, Xu K, Zhang L, Gupta S, Eikelboom J, Cook O, et al. Lower versus standard INR targets in atrial fibrillation: a systematic review and meta-analysis of randomized controlled trials. *Thromb Haemost* 2020;**120**:484–94. <https://doi.org/10.1055/s-0039-3401823>
344. Sanders P, Svennberg E, Diederichsen SZ, Crijns HJGM, Lambiasi PD, Boriani G, et al. Great debate: device-detected subclinical atrial fibrillation should be treated like clinical atrial fibrillation. *Eur Heart J* 2024;ehae365. <https://doi.org/10.1093/eurheartj/ehae365>
345. ACTIVE Investigators; Connolly SJ, Pogue J, Hart RG, Hohnloser SH, Pfeffer M, et al. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med* 2009;**360**:2066–78. <https://doi.org/10.1056/NEJMoa0901301>
346. Mant J, Hobbs FD, Fletcher K, Roaloe A, Fitzmaurice D, Lip GY, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet* 2007;**370**:493–503. [https://doi.org/10.1016/S0140-6736\(07\)61233-1](https://doi.org/10.1016/S0140-6736(07)61233-1)
347. Lip GY. The role of aspirin for stroke prevention in atrial fibrillation. *Nat Rev Cardiol* 2011;**8**:602–6. <https://doi.org/10.1038/nrcardio.2011.112>
348. ACTIVE Writing Group of the ACTIVE Investigators; Connolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet* 2006;**367**:1903–12. [https://doi.org/10.1016/S0140-6736\(06\)68845-4](https://doi.org/10.1016/S0140-6736(06)68845-4)
349. Fox KAA, Velentgas P, Camm AJ, Bassand JP, Fitzmaurice DA, Gersh BJ, et al. Outcomes associated with oral anticoagulants plus antiplatelets in patients with newly diagnosed atrial fibrillation. *JAMA Netw Open* 2020;**3**:e200107. <https://doi.org/10.1001/jamanetworkopen.2020.0107>
350. Verheugt FWA, Gao H, Al Mahmeed W, Ambrosio G, Angchaisuksiri P, Atar D, et al. Characteristics of patients with atrial fibrillation prescribed antiplatelet monotherapy compared with those on anticoagulants: insights from the GARFIELD-AF registry. *Eur Heart J* 2018;**39**:464–73. <https://doi.org/10.1093/eurheartj/ehx730>
351. Steffel J, Eikelboom JW, Anand SS, Shestakovska O, Yusuf S, Fox KAA. The COMPASS trial: net clinical benefit of low-dose rivaroxaban plus aspirin as compared with aspirin in patients with chronic vascular disease. *Circulation* 2020;**142**:40–8. <https://doi.org/10.1161/CIRCULATIONAHA.120.046048>
352. Sharma M, Hart RG, Connolly SJ, Bosch J, Shestakovska O, Ng KKH, et al. Stroke outcomes in the COMPASS trial. *Circulation* 2019;**139**:1134–45. <https://doi.org/10.1161/CIRCULATIONAHA.118.035864>
353. Yasuda S, Kaikita K, Akao M, Ako J, Matoba T, Nakamura M, et al. Antithrombotic therapy for atrial fibrillation with stable coronary disease. *N Engl J Med* 2019;**381**:1103–13. <https://doi.org/10.1056/NEJMoa1904143>
354. Senoo K, Lip GY, Lane DA, Büller HR, Kotecha D. Residual risk of stroke and death in anticoagulated patients according to the type of atrial fibrillation: AMADEUS trial. *Stroke* 2015;**46**:2523–8. <https://doi.org/10.1161/STROKEAHA.115.009487>
355. Meinel TR, Branca M, De Marchis GM, Nedeltchev K, Kahles T, Bonati L, et al. Prior anticoagulation in patients with ischemic stroke and atrial fibrillation. *Ann Neurol* 2021;**89**:42–53. <https://doi.org/10.1002/ana.25917>
356. Polymeris AA, Meinel TR, Oehler H, Hölscher K, Zietz A, Scheitz JF, et al. Aetiology, secondary prevention strategies and outcomes of ischaemic stroke despite oral anticoagulant therapy in patients with atrial fibrillation. *J Neurol Neurosurg Psychiatry* 2022;**93**:588–98. <https://doi.org/10.1136/jnnp-2021-328391>
357. Paciaroni M, Agnelli G, Caso V, Silvestrelli G, Seiffge DJ, Engelter S, et al. Causes and risk factors of cerebral ischemic events in patients with atrial fibrillation treated with non-vitamin K antagonist oral anticoagulants for stroke prevention. *Stroke* 2019;**50**:2168–74. <https://doi.org/10.1161/STROKEAHA.119.025350>
358. Purruccer JC, Hölscher K, Kollmer J, Ringleb PA. Etiology of ischemic strokes of patients with atrial fibrillation and therapy with anticoagulants. *J Clin Med* 2020;**9**:2938. <https://doi.org/10.3390/jcm9092938>
359. Paciaroni M, Caso V, Agnelli G, Mosconi MG, Giustozzi M, Seiffge DJ, et al. Recurrent ischemic stroke and bleeding in patients with atrial fibrillation who suffered an acute stroke while on treatment with nonvitamin K antagonist oral anticoagulants: the RENO-EXTEND study. *Stroke* 2022;**53**:2620–7. <https://doi.org/10.1161/STROKEAHA.121.038239>
360. Smits E, Andreotti F, Houben E, Crijns H, Haas S, Spentzouris G, et al. Adherence and persistence with once-daily vs twice-daily direct oral anticoagulants among patients

- with atrial fibrillation: real-world analyses from The Netherlands, Italy and Germany. *Drugs Real World Outcomes* 2022;**9**:199–209. <https://doi.org/10.1007/s40801-021-00289-w>
361. Polymeris AA, Zietz A, Schaub F, Meya L, Traenka C, Thilemann S, et al. Once versus twice daily direct oral anticoagulants in patients with recent stroke and atrial fibrillation. *Eur Stroke J* 2022;**7**:221–9. <https://doi.org/10.1177/23969873221099477>
 362. Glikson M, Wolff R, Hindricks G, Mandrola J, Camm AJ, Lip GYH, et al. EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion—an update. *Europace* 2020;**22**:184. <https://doi.org/10.1093/eurpace/euz258>
 363. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. *Ann Thorac Surg* 1996;**61**:755–9. [https://doi.org/10.1016/0003-4975\(95\)00887-X](https://doi.org/10.1016/0003-4975(95)00887-X)
 364. Reddy VY, Doshi SK, Kar S, Gibson DN, Price MJ, Huber K, et al. 5-Year outcomes after left atrial appendage closure: from the PREVAIL and PROTECT AF trials. *J Am Coll Cardiol* 2017;**70**:2964–75. <https://doi.org/10.1016/j.jacc.2017.10.021>
 365. Lakkireddy D, Thaler D, Ellis CR, Swarup V, Sondergaard L, Carroll J, et al. Amplatzer amulet left atrial appendage occluder versus watchman device for stroke prophylaxis (amulet IDE): a randomized, controlled trial. *Circulation* 2021;**144**:1543–52. <https://doi.org/10.1161/CIRCULATIONAHA.121.057063>
 366. Osmancik P, Herman D, Neuzil P, Hala P, Taborsky M, Kala P, et al. Left atrial appendage closure versus direct oral anticoagulants in high-risk patients with atrial fibrillation. *J Am Coll Cardiol* 2020;**75**:3122–35. <https://doi.org/10.1016/j.jacc.2020.04.067>
 367. Osmancik P, Herman D, Neuzil P, Hala P, Taborsky M, Kala P, et al. 4-Year outcomes after left atrial appendage closure versus nonwarfarin oral anticoagulation for atrial fibrillation. *J Am Coll Cardiol* 2022;**79**:1–14. <https://doi.org/10.1016/j.jacc.2021.10.023>
 368. Korsholm K, Damgaard D, Valentin JB, Packer EJS, Odenstedt J, Sinisalo J, et al. Left atrial appendage occlusion vs novel oral anticoagulation for stroke prevention in atrial fibrillation: rationale and design of the multicenter randomized occlusion-AF trial. *Am Heart J* 2022;**243**:28–38. <https://doi.org/10.1016/j.ahj.2021.08.020>
 369. Huijboom M, Maarse M, Aarnink E, van Dijk V, Swaans M, van der Heijden J, et al. COMPARE LAO: rationale and design of the randomized controlled trial “COMPARing Effectiveness and safety of Left Atrial Appendage Occlusion to standard of care for atrial fibrillation patients at high stroke risk and ineligible to use oral anticoagulation therapy”. *Am Heart J* 2022;**250**:45–56. <https://doi.org/10.1016/j.ahj.2022.05.001>
 370. Freeman JV, Higgins AY, Wang Y, Du C, Friedman DJ, Daimee UA, et al. Antithrombotic therapy after left atrial appendage occlusion in patients with atrial fibrillation. *J Am Coll Cardiol* 2022;**79**:1785–98. <https://doi.org/10.1016/j.jacc.2022.02.047>
 371. Patti G, Sticchi A, Verolino G, Pasceri V, Vizzi V, Brcsic E, et al. Safety and efficacy of single versus dual antiplatelet therapy after left atrial appendage occlusion. *Am J Cardiol* 2020;**134**:83–90. <https://doi.org/10.1016/j.amjcard.2020.08.013>
 372. Boersma LV, Schmidt B, Betts TR, Sievert H, Tamburino C, Teiger E, et al. Implant success and safety of left atrial appendage closure with the WATCHMAN device: periprocedural outcomes from the EVOLUTION registry. *Eur Heart J* 2016;**37**:2465–74. <https://doi.org/10.1093/eurheartj/ehv730>
 373. Garg J, Shah S, Shah K, Turagam MK, Tzou W, Natale A, et al. Direct oral anticoagulant versus warfarin for watchman left atrial appendage occlusion—systematic review. *JACC Clin Electrophysiol* 2020;**6**:1735–7. <https://doi.org/10.1016/j.jacep.2020.08.020>
 374. Osman M, Busu T, Osman K, Khan SU, Daniels M, Holmes DR, et al. Short-term antiplatelet versus anticoagulant therapy after left atrial appendage occlusion: a systematic review and meta-analysis. *JACC Clin Electrophysiol* 2020;**6**:494–506. <https://doi.org/10.1016/j.jacep.2019.11.009>
 375. Hildick-Smith D, Landmesser U, Camm AJ, Diener HC, Paul V, Schmidt B, et al. Left atrial appendage occlusion with the Amplatzer Amulet device: full results of the prospective global observational study. *Eur Heart J* 2020;**41**:2894–901. <https://doi.org/10.1093/eurheartj/ehaa169>
 376. Reddy VY, Mobius-Winkler S, Miller MA, Neuzil P, Schuler G, Wiebe J, et al. Left atrial appendage closure with the Watchman device in patients with a contraindication for oral anticoagulation: the ASAP study (ASA Plavix Feasibility Study with Watchman Left Atrial Appendage Closure Technology). *J Am Coll Cardiol* 2013;**61**:2551–6. <https://doi.org/10.1016/j.jacc.2013.03.035>
 377. Sondergaard L, Wong YH, Reddy VY, Boersma LVA, Bergmann MW, Doshi S, et al. Propensity-matched comparison of oral anticoagulation versus antiplatelet therapy after left atrial appendage closure with Watchman. *JACC Cardiovasc Interv* 2019;**12**:1055–63. <https://doi.org/10.1016/j.jcin.2019.04.004>
 378. Flores-Umanzor EJ, Cepas-Guillen PL, Arzamendi D, Cruz-Gonzalez I, Regueiro A, Freixa X. Rationale and design of a randomized clinical trial to compare two antithrombotic strategies after left atrial appendage occlusion: double antiplatelet therapy vs. apixaban (ADALA study). *J Interv Card Electrophysiol* 2020;**59**:471–7. <https://doi.org/10.1007/s10840-020-00884-x>
 379. Aminian A, Schmidt B, Mazzone P, Berti S, Fischer S, Montorfano M, et al. Incidence, characterization, and clinical impact of device-related thrombus following left atrial appendage occlusion in the prospective global AMPLATZER amulet observational study. *JACC Cardiovasc Interv* 2019;**12**:1003–14. <https://doi.org/10.1016/j.jcin.2019.02.003>
 380. Kany S, Metzner A, Lubos E, Kirchhof P. The atrial fibrillation heart team-guiding therapy in left atrial appendage occlusion with increasingly complex patients and little evidence. *Eur Heart J* 2022;**43**:1691–2. <https://doi.org/10.1093/eurheartj/ehab744>
 381. Saw J, Holmes DR, Cavalcante JL, Freeman JV, Goldsweig AM, Kavinsky CJ, et al. SCAI/HRS expert consensus statement on transcatheter left atrial appendage closure. *Heart Rhythm* 2023;**20**:e1–16. <https://doi.org/10.1016/j.hrthm.2023.01.007>
 382. Cruz-González I, González-Ferreiro R, Freixa X, Gafoor S, Omran H, et al. Left atrial appendage occlusion for stroke despite oral anticoagulation (resistant stroke). Results from the Amplatzer Cardiac Plug registry. *Rev Esp Cardiol (Engl Ed)* 2020;**73**:28–34. <https://doi.org/10.1016/j.rec.2019.02.013>
 383. Willits I, Keltie K, Linker N, de Belder M, Henderson R, Patrick H, et al. Left atrial appendage occlusion in the UK: prospective registry and data linkage to hospital episode statistics. *Eur Heart J Qual Care Clin Outcomes* 2021;**7**:468–75. <https://doi.org/10.1093/ehjcc/qcab042>
 384. Price MJ, Valderrabano M, Zimmerman S, Friedman DJ, Kar S, Curtis JP, et al. Periprocedural pericardial effusion complicating transcatheter left atrial appendage occlusion: a report from the NCDR LAO registry. *Circ Cardiovasc Interv* 2022;**15**:e011718. <https://doi.org/10.1161/CIRCINTERVENTIONS.121.011718>
 385. Aminian A, De Backer O, Nielsen-Kudsk JE, Mazzone P, Berti S, Fischer S, et al. Incidence and clinical impact of major bleeding following left atrial appendage occlusion: insights from the amplatzer amulet observational post-market study. *EuroIntervention* 2021;**17**:774–82. <https://doi.org/10.4244/EIJ-D-20-01309>
 386. Boersma LV, Ince H, Kische S, Pokushalov E, Schmitz T, Schmidt B, et al. Evaluating real-world clinical outcomes in atrial fibrillation patients receiving the WATCHMAN left atrial appendage closure technology: final 2-year outcome data of the EVOLUTION trial focusing on history of stroke and hemorrhage. *Circ Arrhythm Electrophysiol* 2019;**12**:e006841. <https://doi.org/10.1161/CIRCEP.118.006841>
 387. Tzikas A, Shakir S, Gafoor S, Omran H, Berti S, Santoro G, et al. Left atrial appendage occlusion for stroke prevention in atrial fibrillation: multicentre experience with the AMPLATZER cardiac plug. *EuroIntervention* 2016;**11**:1170–9. https://doi.org/10.4244/EIJY15M01_06
 388. Nazir S, Ahuja KR, Kolte D, Isogai T, Michihata N, Saad AM, et al. Association of hospital procedural volume with outcomes of percutaneous left atrial appendage occlusion. *JACC Cardiovasc Interv* 2021;**14**:554–61. <https://doi.org/10.1016/j.jcin.2020.11.029>
 389. Freeman JV, Varosy P, Price MJ, Slotwiner D, Kusumoto FM, Rammohan C, et al. The NCDR left atrial appendage occlusion registry. *J Am Coll Cardiol* 2020;**75**:1503–18. <https://doi.org/10.1016/j.jacc.2019.12.040>
 390. Cruz-Gonzalez I, Korsholm K, Trejo-Velasco B, Thambo JB, Mazzone P, Rioufol G, et al. Procedural and short-term results with the new watchman FLX left atrial appendage occlusion device. *JACC Cardiovasc Interv* 2020;**13**:2732–41. <https://doi.org/10.1016/j.jcin.2020.06.056>
 391. Simard T, Jung RG, Lehenbauer K, Piayda K, Pracon R, Jackson GG, et al. Predictors of device-related thrombus following percutaneous left atrial appendage occlusion. *J Am Coll Cardiol* 2021;**78**:297–313. <https://doi.org/10.1016/j.jacc.2021.04.098>
 392. Simard TJ, Hibbert B, Alkhouli MA, Abraham NS, Holmes DR, Jr. Device-related thrombus following left atrial appendage occlusion. *EuroIntervention* 2022;**18**:224–32. <https://doi.org/10.4244/EIJ-D-21-01010>
 393. Lempereur M, Aminian A, Freixa X, Gafoor S, Kefer J, Tzikas A, et al. Device-associated thrombus formation after left atrial appendage occlusion: a systematic review of events reported with the Watchman, the Amplatzer Cardiac Plug and the Amulet. *Catheter Cardiovasc Interv* 2017;**90**:E111–21. <https://doi.org/10.1002/ccd.26903>
 394. Saw J, Tzikas A, Shakir S, Gafoor S, Omran H, Nielsen-Kudsk JE, et al. Incidence and clinical impact of device-associated thrombus and peri-device leak following left atrial appendage closure with the amplatzer cardiac plug. *JACC Cardiovasc Interv* 2017;**10**:391–9. <https://doi.org/10.1016/j.jcin.2016.11.029>
 395. Fauchier L, Cinaud A, Brigadeau F, Lepillier A, Pierre B, Abbey S, et al. Device-related thrombosis after percutaneous left atrial appendage occlusion for atrial fibrillation. *J Am Coll Cardiol* 2018;**71**:1528–36. <https://doi.org/10.1016/j.jacc.2018.01.076>
 396. Dukkkipati SR, Kar S, Holmes DR, Doshi SK, Swarup V, Gibson DN, et al. Device-related thrombus after left atrial appendage closure: incidence, predictors, and outcomes. *Circulation* 2018;**138**:874–85. <https://doi.org/10.1161/CIRCULATIONAHA.118.035090>
 397. Kar S, Doshi SK, Sadhu A, Horton R, Osorio J, Ellis C, et al. Primary outcome evaluation of a next-generation left atrial appendage closure device: results from the PINNACLE FLX trial. *Circulation* 2021;**143**:1754–62. <https://doi.org/10.1161/CIRCULATIONAHA.120.050117>
 398. Alkhouli M, Du C, Killu A, Simard T, Noseworthy PA, Friedman PA, et al. Clinical impact of residual leaks following left atrial appendage occlusion: insights from the NCDR LAO registry. *JACC Clin Electrophysiol* 2022;**8**:766–78. <https://doi.org/10.1016/j.jacep.2022.03.001>
 399. Tsai YC, Phan K, Munkholm-Larsen S, Tian DH, La Meir M, Yan TD. Surgical left atrial appendage occlusion during cardiac surgery for patients with atrial fibrillation: a meta-analysis. *Eur J Cardiothorac Surg* 2015;**47**:847–54. <https://doi.org/10.1093/ejcts/ezu291>

400. Whitlock RP, Vincent J, Blackall MH, Hirsh J, Fremes S, Novick R, et al. Left atrial appendage occlusion study II (LAAOS II). *Can J Cardiol* 2013;**29**:1443–7. <https://doi.org/10.1016/j.cjca.2013.06.015>
401. Whitlock RP, Belley-Cote EP, Paparella D, Healey JS, Brady K, Sharma M, et al. Left atrial appendage occlusion during cardiac surgery to prevent stroke. *N Engl J Med* 2021;**384**:2081–91. <https://doi.org/10.1056/NEJMoa2101897>
402. Zhang S, Cui Y, Li J, Tian H, Yun Y, Zhou X, et al. Concomitant transcatheter occlusion versus thoracoscopic surgical clipping for left atrial appendage in patients undergoing ablation for atrial fibrillation: a meta-analysis. *Front Cardiovasc Med* 2022;**9**:970847. <https://doi.org/10.3389/fcvm.2022.970847>
403. van Laar C, Verberkmoes NJ, van Es HW, Lewalter T, Dunnington G, Stark S, et al. Thoracoscopic left atrial appendage clipping: a multicenter cohort analysis. *JACC Clin Electrophysiol* 2018;**4**:893–901. <https://doi.org/10.1016/j.jacep.2018.03.009>
404. Kiviniemi T, Bustamante-Munguira J, Olsson C, Jeppsson A, Halfwerk FR, Hartikainen J, et al. A randomized prospective multicenter trial for stroke prevention by prophylactic surgical closure of the left atrial appendage in patients undergoing bioprosthetic aortic valve surgery—LAA-CLOSURE trial protocol. *Am Heart J* 2021;**237**:127–34. <https://doi.org/10.1016/j.ahj.2021.03.014>
405. Cartledge R, Suwalski G, Witkowska A, Gottlieb G, Cioci A, Chidiac G, et al. Standalone epicardial left atrial appendage exclusion for thromboembolism prevention in atrial fibrillation. *Interact Cardiovasc Thorac Surg* 2022;**34**:548–55. <https://doi.org/10.1093/icvts/ivab334>
406. Branzoli S, Guarracini F, Marini M, D'Onghia G, Penzo D, Piffer S, et al. Heart team for left atrial appendage occlusion: a patient-tailored approach. *J Clin Med* 2022;**11**:176. <https://doi.org/10.3390/jcm11010176>
407. Toale C, Fitzmaurice GJ, Eaton D, Lyne J, Redmond KC. Outcomes of left atrial appendage occlusion using the AtriClip device: a systematic review. *Interact Cardiovasc Thorac Surg* 2019;**29**:655–62. <https://doi.org/10.1093/icvts/ivz156>
408. Caliskan E, Sahin A, Yilmaz M, Seifert B, Hinzpeter R, Alkadhhi H, et al. Epicardial left atrial appendage AtriClip occlusion reduces the incidence of stroke in patients with atrial fibrillation undergoing cardiac surgery. *Europace* 2018;**20**:e105–14. <https://doi.org/10.1093/europace/eux211>
409. Nso N, Nassar M, Zirkiyeva M, Lakhdar S, Shaikat T, Guzman L, et al. Outcomes of cardiac surgery with left atrial appendage occlusion versus no occlusion, direct oral anticoagulants, and vitamin K antagonists: a systematic review with meta-analysis. *Int J Cardiol Heart Vasc* 2022;**40**:100998. <https://doi.org/10.1016/j.ijcha.2022.100998>
410. Ibrahim AM, Tandan N, Koester C, Al-Akchar M, Bhandari B, Botchway A, et al. Meta-analysis evaluating outcomes of surgical left atrial appendage occlusion during cardiac surgery. *Am J Cardiol* 2019;**124**:1218–25. <https://doi.org/10.1016/j.amjcard.2019.07.032>
411. Park-Hansen J, Holme SJV, Irmukhamedov A, Carranza CL, Greve AM, Al-Farra G, et al. Adding left atrial appendage closure to open heart surgery provides protection from ischemic brain injury six years after surgery independently of atrial fibrillation history: the LAACS randomized study. *J Cardiothorac Surg* 2018;**13**:53. <https://doi.org/10.1186/s13019-018-0740-7>
412. Soltész EG, Dewan KC, Anderson LH, Ferguson MA, Gillinov AM. Improved outcomes in CABG patients with atrial fibrillation associated with surgical left atrial appendage exclusion. *J Card Surg* 2021;**36**:1201–8. <https://doi.org/10.1111/jocs.15335>
413. Fu M, Qin Z, Zheng S, Li Y, Yang S, Zhao Y, et al. Thoracoscopic left atrial appendage occlusion for stroke prevention compared with long-term warfarin therapy in patients with nonvalvular atrial fibrillation. *Am J Cardiol* 2019;**123**:50–6. <https://doi.org/10.1016/j.amjcard.2018.09.025>
414. Peterson D, Geison E. Pharmacist interventions to reduce modifiable bleeding risk factors using HAS-BLED in patients taking warfarin. *Fed Pract* 2017;**34**:S16–20.
415. Chao TF, Lip GYH, Lin YJ, Chang SL, Lo LW, Hu YF, et al. Incident risk factors and major bleeding in patients with atrial fibrillation treated with oral anticoagulants: a comparison of baseline, follow-up and Delta HAS-BLED scores with an approach focused on modifiable bleeding risk factors. *Thromb Haemost* 2018;**47**:768–77. <https://doi.org/10.1055/s-0038-1636534>
416. Linkins LA, Choi PT, Douketis JD. Clinical impact of bleeding in patients taking oral anticoagulant therapy for venous thromboembolism: a meta-analysis. *Ann Intern Med* 2003;**139**:893–900. <https://doi.org/10.7326/0003-4819-139-11-200312020-00007>
417. Kirchhof P, Haas S, Amarenco P, Hess S, Lambellet M, van Eickels M, et al. Impact of modifiable bleeding risk factors on major bleeding in patients with atrial fibrillation anticoagulated with rivaroxaban. *J Am Heart Assoc* 2020;**9**:e009530. <https://doi.org/10.1161/JAHA.118.009530>
418. Guo Y, Lane DA, Chen Y, Lip GYH; mAF-App II Trial investigators. Regular bleeding risk assessment associated with reduction in bleeding outcomes: the mAF-App II randomized trial. *Am J Med* 2020;**133**:1195–1202.e2. <https://doi.org/10.1016/j.amjmed.2020.03.019>
419. Lane DA, Lip GYH. Stroke and bleeding risk stratification in atrial fibrillation: a critical appraisal. *Eur Heart J Suppl* 2020;**22**:O14–27. <https://doi.org/10.1093/eurheartj/suaa178>
420. Lip GYH, Lane DA. Bleeding risk assessment in atrial fibrillation: observations on the use and misuse of bleeding risk scores. *J Thromb Haemost* 2016;**14**:1711–4. <https://doi.org/10.1111/jth.13386>
421. Gorog DA, Gue YX, Chao TF, Fauchier L, Ferreiro JL, Huber K, et al. Assessment and mitigation of bleeding risk in atrial fibrillation and venous thromboembolism: a position paper from the ESC working group on thrombosis, in collaboration with the European Heart Rhythm Association, the Association for Acute Cardiovascular Care and the Asia-Pacific Heart Rhythm Society. *Europace* 2022;**24**:1844–71. <https://doi.org/10.1093/europace/eauc020>
422. Nelson WW, Laliberté F, Patel AA, Germain G, Pilon D, McCormick N, et al. Stroke risk reduction outweighed bleeding risk increase from vitamin K antagonist treatment among nonvalvular atrial fibrillation patients with high stroke risk and low bleeding risk. *Curr Med Res Opin* 2017;**33**:631–8. <https://doi.org/10.1080/03007995.2016.1275936>
423. Hijazi Z, Lindbäck J, Oldgren J, Benz AP, Alexander JH, Connolly SJ, et al. Individual net clinical outcome with oral anticoagulation in atrial fibrillation using the ABC-AF risk scores. *Am Heart J* 2023;**261**:55–63. <https://doi.org/10.1016/j.ahj.2023.03.012>
424. Hijazi Z, Lindbäck J, Alexander JH, Hanna M, Held C, Hylek EM, et al. The ABC (age, biomarkers, clinical history) stroke risk score: a biomarker-based risk score for predicting stroke in atrial fibrillation. *Eur Heart J* 2016;**37**:1582–90. <https://doi.org/10.1093/eurheartj/ehw054>
425. Gao X, Cai X, Yang Y, Zhou Y, Zhu W. Diagnostic accuracy of the HAS-BLED bleeding score in VKA- or DOAC-treated patients with atrial fibrillation: a systematic review and meta-analysis. *Front Cardiovasc Med* 2021;**8**:757087. <https://doi.org/10.3389/fcvm.2021.757087>
426. Zhu W, He W, Guo L, Wang X, Hong K. The HAS-BLED score for predicting major bleeding risk in anticoagulated patients with atrial fibrillation: a systematic review and meta-analysis. *Clin Cardiol* 2015;**38**:555–61. <https://doi.org/10.1002/clc.22435>
427. Caldeira D, Costa J, Fernandes RM, Pinto FJ, Ferreira JJ. Performance of the HAS-BLED high bleeding-risk category, compared to ATRIA and HEMORR2HAGES in patients with atrial fibrillation: a systematic review and meta-analysis. *J Interv Card Electrophysiol* 2014;**40**:277–84. <https://doi.org/10.1007/s10840-014-9930-y>
428. Zeng J, Yu P, Cui W, Wang X, Ma J, Zeng C. Comparison of HAS-BLED with other risk models for predicting the bleeding risk in anticoagulated patients with atrial fibrillation: a PRISMA-compliant article. *Medicine (Baltimore)* 2020;**99**:e20782. <https://doi.org/10.1097/MD.00000000000020782>
429. Wang C, Yu Y, Zhu W, Yu J, Lip GYH, Hong K. Comparing the ORBIT and HAS-BLED bleeding risk scores in anticoagulated atrial fibrillation patients: a systematic review and meta-analysis. *Oncotarget* 2017;**8**:109703–11. <https://doi.org/10.18632/oncotarget.19858>
430. Loewen P, Dahri K. Risk of bleeding with oral anticoagulants: an updated systematic review and performance analysis of clinical prediction rules. *Ann Hematol* 2011;**90**:1191–200. <https://doi.org/10.1007/s00277-011-1267-3>
431. Hilken NA, Algra A, Greving JP. Predicting major bleeding in ischemic stroke patients with atrial fibrillation. *Stroke* 2017;**48**:3142–4. <https://doi.org/10.1161/STROKEAHA.117.019183>
432. Dalggaard F, Pieper K, Verheugt F, Camm AJ, Fox KA, Kakkar AK, et al. GARFIELD-AF model for prediction of stroke and major bleeding in atrial fibrillation: a Danish nationwide validation study. *BMJ Open* 2019;**9**:e033283. <https://doi.org/10.1136/bmjopen-2019-033283>
433. Mori N, Sotomi Y, Hirata A, Hirayama A, Sakata Y, Higuchi Y. External validation of the ORBIT bleeding score and the HAS-BLED score in nonvalvular atrial fibrillation patients using direct oral anticoagulants (Asian Data from the DIRECT Registry). *Am J Cardiol* 2019;**124**:1044–8. <https://doi.org/10.1016/j.amjcard.2019.07.005>
434. Yao X, Gersh BJ, Sangaralingham LR, Kent DM, Shah ND, Abraham NS, et al. Comparison of the CHA2DS2-VASc, CHADS2, HAS-BLED, ORBIT, and ATRIA risk scores in predicting non-vitamin K antagonist oral anticoagulants-associated bleeding in patients with atrial fibrillation. *Am J Cardiol* 2017;**120**:1549–56. <https://doi.org/10.1016/j.amjcard.2017.07.051>
435. Giustozzi M, Proietti G, Becattini C, Roila F, Agnelli G, Mandalà M. ICH in primary or metastatic brain cancer patients with or without anticoagulant treatment: a systematic review and meta-analysis. *Blood Adv* 2022;**6**:4873–83. <https://doi.org/10.1182/bloodadvances.2022008086>
436. Shoamaneh A. Anticoagulation in patients with cerebral amyloid angiopathy. *Lancet* 2023;**402**:1418–9. [https://doi.org/10.1016/S0140-6736\(23\)00205-1](https://doi.org/10.1016/S0140-6736(23)00205-1)
437. Kurlander JE, Barnes GD, Fisher A, Gonzalez JJ, Helmsinski D, Saini SD, et al. Association of antisecretory drugs with upper gastrointestinal bleeding in patients using oral anticoagulants: a systematic review and meta-analysis. *Am J Med* 2022;**135**:1231–1243.e8. <https://doi.org/10.1016/j.amjmed.2022.05.031>
438. Moayyedi P, Eikelboom JW, Bosch J, Connolly SJ, Dyal L, Shestakovska O, et al. Pantoprazole to prevent gastroduodenal events in patients receiving rivaroxaban and/or aspirin in a randomized, double-blind, placebo-controlled trial. *Gastroenterology* 2019;**157**:403–412.e5. <https://doi.org/10.1053/j.gastro.2019.04.041>
439. DiMarco JP, Flaker G, Waldo AL, Corley SD, Greene HL, Safford RE, et al. Factors affecting bleeding risk during anticoagulant therapy in patients with atrial fibrillation: observations from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. *Am Heart J* 2005;**149**:650–6. <https://doi.org/10.1016/j.ahj.2004.11.015>
440. Harskamp RE, Lucassen WAM, Lopes RD, Himmelreich JCL, Parati G, Weert H. Risk of stroke and bleeding in relation to hypertension in anticoagulated patients with atrial

- fibrillation: a meta-analysis of randomised controlled trials. *Acta Cardiol* 2022;**77**: 191–5. <https://doi.org/10.1080/00015385.2021.1882111>
441. Schulman S, Beyth RJ, Kearon C, Levine MN. Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians evidence-based clinical practice guidelines (8th Edition). *Chest* 2008;**133**:257s–98s. <https://doi.org/10.1378/chest.08-0674>
 442. Gallego P, Roldán V, Torregrosa JM, Gálvez J, Valdés M, Vicente V, et al. Relation of the HAS-BLED bleeding risk score to major bleeding, cardiovascular events, and mortality in anticoagulated patients with atrial fibrillation. *Circ Arrhythm Electrophysiol* 2012;**5**: 312–8. <https://doi.org/10.1161/CIRCEP.111.967000>
 443. Bouillon K, Bertrand M, Boudali L, Ducimetière P, Dray-Spira R, Zureik M. Short-term risk of bleeding during heparin bridging at initiation of vitamin K antagonist therapy in more than 90 000 patients with nonvalvular atrial fibrillation managed in outpatient care. *J Am Heart Assoc* 2016;**5**:e004065. <https://doi.org/10.1161/JAHA.116.004065>
 444. White HD, Gruber M, Feyzi J, Kaatz S, Tse HF, Husted S, et al. Comparison of outcomes among patients randomized to warfarin therapy according to anticoagulant control: results from SPORTIF III and V. *Arch Intern Med* 2007;**167**:239–45. <https://doi.org/10.1001/archinte.167.3.239>
 445. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Jr, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation* 2014;**130**:2071–104. <https://doi.org/10.1161/CIR.0000000000000040>
 446. Olesen JB, Lip GY, Lindhardsen J, Lane DA, Ahlehoj O, Hansen ML, et al. Risks of thromboembolism and bleeding with thromboprophylaxis in patients with atrial fibrillation: a net clinical benefit analysis using a 'real world' nationwide cohort study. *Thromb Haemostasis* 2011;**106**:739–49. <https://doi.org/10.1160/TH11-05-0364>
 447. Tomaselli GF, Mahaffey KW, Cuker A, Dobesh PP, Doherty JU, Eikelboom JW, et al. 2020 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol* 2020;**76**:594–622. <https://doi.org/10.1016/j.jacc.2020.04.053>
 448. Cuker A. Laboratory measurement of the non-vitamin K antagonist oral anticoagulants: selecting the optimal assay based on drug, assay availability, and clinical indication. *J Thromb Thrombolysis* 2016;**41**:241–7. <https://doi.org/10.1007/s11239-015-1282-7>
 449. Douxfils J, Ageno W, Samama CM, Lessire S, Ten Cate H, Verhamme P, et al. Laboratory testing in patients treated with direct oral anticoagulants: a practical guide for clinicians. *J Thromb Haemostasis* 2018;**16**:209–19. <https://doi.org/10.1111/jth.13912>
 450. Milling TJ, Jr, Refaai MA, Sarode R, Lewis B, Mangione A, Durr BL, et al. Safety of a four-factor prothrombin complex concentrate versus plasma for vitamin K antagonist reversal: an integrated analysis of two phase IIIb clinical trials. *Acad Emerg Med* 2016;**23**:466–75. <https://doi.org/10.1111/acem.12911>
 451. Pollack CV, Jr, Reilly PA, van Ryn J, Eikelboom JW, Glund S, Bernstein RA, et al. Idarucizumab for dabigatran reversal—full cohort analysis. *N Engl J Med* 2017;**377**: 431–41. <https://doi.org/10.1056/NEJMoa1707278>
 452. Connolly SJ, Sharma M, Cohen AT, Demchuk AM, Członkowska A, Lindgren AG, et al. ANNEXA-I investigators. Andexanet for factor Xa inhibitor-associated acute intracerebral hemorrhage. *N Engl J Med* 2024;**390**:1745–55. <https://doi.org/10.1056/NEJMoa2313040>
 453. Milioglu I, Farmakis I, Neudeker M, Hussain Z, Guha A, Giannakoulas G, et al. Prothrombin complex concentrate in major bleeding associated with DOACs: an updated systematic review and meta-analysis. *J Thromb Thrombolysis* 2021;**52**:1137–50. <https://doi.org/10.1007/s11239-021-02480-w>
 454. Meyre PB, Blum S, Hennings E, Aeschbacher S, Reichlin T, Rodondi N, et al. Bleeding and ischaemic events after first bleed in anticoagulated atrial fibrillation patients: risk and timing. *Eur Heart J* 2022;**43**:4899–908. <https://doi.org/10.1093/eurheartj/ehac587>
 455. Connolly SJ, Crowther M, Eikelboom JW, Gibson CM, Curnutte JT, Lawrence JH, et al. Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors. *N Engl J Med* 2019;**380**:1326–35. <https://doi.org/10.1056/NEJMoa1814051>
 456. Fanikos J, Murwin D, Gruenenfelder F, Tartakovsky I, França LR, Reilly PA, et al. Global use of idarucizumab in clinical practice: outcomes of the RE-VECTO surveillance program. *Thromb Haemostasis* 2020;**120**:27–35. <https://doi.org/10.1055/s-0039-1695771>
 457. Kotecha D, Calvert M, Deeks JJ, Griffith M, Kirchhof P, Lip GY, et al. A review of rate control in atrial fibrillation, and the rationale and protocol for the RATE-AF trial. *BMJ Open* 2017;**7**:e015099. <https://doi.org/10.1136/bmjopen-2016-015099>
 458. Hess PL, Sheng S, Matsouaka R, DeVore AD, Heidenreich PA, Yancy CW, et al. Strict versus lenient versus poor rate control among patients with atrial fibrillation and heart failure (from the get with the guidelines—heart failure program). *Am J Cardiol* 2020;**125**:894–900. <https://doi.org/10.1016/j.amjcard.2019.12.025>
 459. Van Gelder IC, Groenveld HF, Crijns HJ, Tuininga YS, Tijssen JG, Alings AM, et al. Lenient versus strict rate control in patients with atrial fibrillation. *N Engl J Med* 2010;**362**:1363–73. <https://doi.org/10.1056/NEJMoa1001337>
 460. Olshansky B, Rosenfeld LE, Warner AL, Solomon AJ, O'Neill G, Sharma A, et al. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study: approaches to control rate in atrial fibrillation. *J Am Coll Cardiol* 2004;**43**:1201–8. <https://doi.org/10.1016/j.jacc.2003.11.032>
 461. Ulimoen SR, Enger S, Carlson J, Platonov PG, Pripp AH, Abdelnoor M, et al. Comparison of four single-drug regimens on ventricular rate and arrhythmia-related symptoms in patients with permanent atrial fibrillation. *Am J Cardiol* 2013;**111**: 225–30. <https://doi.org/10.1016/j.amjcard.2012.09.020>
 462. Tisdale JE, Padhi ID, Goldberg AD, Silverman NA, Webb CR, Higgins RS, et al. A randomized, double-blind comparison of intravenous diltiazem and digoxin for atrial fibrillation after coronary artery bypass surgery. *Am Heart J* 1998;**135**:739–47. [https://doi.org/10.1016/S0002-8703\(98\)70031-6](https://doi.org/10.1016/S0002-8703(98)70031-6)
 463. Khand AU, Rankin AC, Martin W, Taylor J, Gemmell I, Cleland JG. Carvedilol alone or in combination with digoxin for the management of atrial fibrillation in patients with heart failure? *J Am Coll Cardiol* 2003;**42**:1944–51. <https://doi.org/10.1016/j.jacc.2003.07.020>
 464. Nikolaidou T, Channer KS. Chronic atrial fibrillation: a systematic review of medical heart rate control management. *Postgrad Med J* 2009;**85**:303–12. <https://doi.org/10.1136/pgmj.2008.068908>
 465. Figulla HR, Gietzen F, Zeymer U, Raiber M, Hegselmann J, Soballa R, et al. Diltiazem improves cardiac function and exercise capacity in patients with idiopathic dilated cardiomyopathy. Results of the Diltiazem in Dilated Cardiomyopathy Trial. *Circulation* 1996;**94**:346–52. <https://doi.org/10.1161/01.CIR.94.3.346>
 466. Andrade JG, Roy D, Wyse DG, Tardif JC, Talajic M, Leduc H, et al. Heart rate and adverse outcomes in patients with atrial fibrillation: a combined AFFIRM and AF-CHF substudy. *Heart Rhythm* 2016;**13**:54–61. <https://doi.org/10.1016/j.hrthm.2015.08.028>
 467. Weerasooriya R, Davis M, Powell A, Szili-Torok T, Shah C, Whalley D, et al. The Australian Intervention Randomized Control of Rate in Atrial Fibrillation Trial (AIRCRAFT). *J Am Coll Cardiol* 2003;**41**:1697–702. [https://doi.org/10.1016/S0735-1097\(03\)00338-3](https://doi.org/10.1016/S0735-1097(03)00338-3)
 468. Lim KT, Davis MJ, Powell A, Arnold L, Moulden K, Bulsara M, et al. Ablate and pace strategy for atrial fibrillation: long-term outcome of AIRCRAFT trial. *Europace* 2007;**9**: 498–505. <https://doi.org/10.1093/europace/eum091>
 469. Vijayaraman P, Subzposh FA, Napierkowski A. Atrioventricular node ablation and His bundle pacing. *Europace* 2017;**19**:iv10–6. <https://doi.org/10.1093/europace/eux263>
 470. Brignole M, Pokushalov E, Pentimalli F, Palmisano P, Chieffo E, Occhetta E, et al. A randomized controlled trial of atrioventricular junction ablation and cardiac resynchronization therapy in patients with permanent atrial fibrillation and narrow QRS. *Eur Heart J* 2018;**39**:3999–4008. <https://doi.org/10.1093/eurheartj/ehy555>
 471. Brignole M, Pentimalli F, Palmisano P, Landolina M, Quartieri F, Occhetta E, et al. AV junction ablation and cardiac resynchronization for patients with permanent atrial fibrillation and narrow QRS: the APAF-CRT mortality trial. *Eur Heart J* 2021;**42**:4731–9. <https://doi.org/10.1093/eurheartj/ehab569>
 472. Delle Karth G, Geppert A, Neunteufl T, Priglinger U, Haumer M, Gschwandtner M, et al. Amiodarone versus diltiazem for rate control in critically ill patients with atrial tachyarrhythmias. *Crit Care Med* 2001;**29**:1149–53. <https://doi.org/10.1097/00003246-200106000-00011>
 473. Hou ZY, Chang MS, Chen CY, Tu MS, Lin SL, Chiang HT, et al. Acute treatment of recent-onset atrial fibrillation and flutter with a tailored dosing regimen of intravenous amiodarone. A randomized, digoxin-controlled study. *Eur Heart J* 1995;**16**:521–8. <https://doi.org/10.1093/oxfordjournals.eurheartj.a060945>
 474. Van Gelder IC, Wyse DG, Chandler ML, Cooper HA, Olshansky B, Hagens VE, et al. Does intensity of rate-control influence outcome in atrial fibrillation? An analysis of pooled data from the RACE and AFFIRM studies. *Europace* 2006;**8**:935–42. <https://doi.org/10.1093/europace/eul106>
 475. Scheuermeyer FX, Grafstein E, Stenstrom R, Christenson J, Heslop C, Heilbron B, et al. Safety and efficiency of calcium channel blockers versus beta-blockers for rate control in patients with atrial fibrillation and no acute underlying medical illness. *Acad Emerg Med* 2013;**20**:222–30. <https://doi.org/10.1111/acem.12091>
 476. Siu CW, Lau CP, Lee WL, Lam KF, Tse HF. Intravenous diltiazem is superior to intravenous amiodarone or digoxin for achieving ventricular rate control in patients with acute uncomplicated atrial fibrillation. *Crit Care Med* 2009;**37**:2174–9, quiz 2180. <https://doi.org/10.1097/CCM.0b013e3181a02f56>
 477. Perrett M, Gohil N, Tica O, Bunting KV, Kotecha D. Efficacy and safety of intravenous beta-blockers in acute atrial fibrillation and flutter is dependent on beta-1 selectivity: a systematic review and meta-analysis of randomised trials. *Clin Res Cardiol* 2023;**113**:831–41. <https://doi.org/10.1007/s00392-023-02295-0>
 478. Darby AE, Dimarco JP. Management of atrial fibrillation in patients with structural heart disease. *Circulation* 2012;**125**:945–57. <https://doi.org/10.1161/CIRCULATIONAHA.111.019935>
 479. Imamura T, Kinugawa K. Novel rate control strategy with landiolol in patients with cardiac dysfunction and atrial fibrillation. *ESC Heart Fail* 2020;**7**:2208–13. <https://doi.org/10.1002/ehf2.12879>
 480. Ulimoen SR, Enger S, Pripp AH, Abdelnoor M, Arnesen H, Gjesdal K, et al. Calcium channel blockers improve exercise capacity and reduce N-terminal Pro-B-type natriuretic peptide levels compared with beta-blockers in patients with permanent atrial fibrillation. *Eur Heart J* 2014;**35**:517–24. <https://doi.org/10.1093/eurheartj/ehu429>
 481. Connolly SJ, Camm AJ, Halperin JL, Joyner C, Alings M, Amerena J, et al. Dronedronarone in high-risk permanent atrial fibrillation. *N Engl J Med* 2011;**365**:2268–76. <https://doi.org/10.1056/NEJMoa1109867>

482. Karwath A, Bunting KV, Gill SK, Tica O, Pendleton S, Aziz F, et al. Redefining beta-blocker response in heart failure patients with sinus rhythm and atrial fibrillation: a machine learning cluster analysis. *Lancet* 2021;**398**:1427–35. [https://doi.org/10.1016/S0140-6736\(21\)01638-X](https://doi.org/10.1016/S0140-6736(21)01638-X)
483. Koldenhof T, Wijtvet P, Pluymaekers N, Rienstra M, Folkeringa RJ, Bronzwaer P, et al. Rate control drugs differ in the prevention of progression of atrial fibrillation. *Europace* 2022;**24**:384–9. <https://doi.org/10.1093/europace/euab191>
484. Champs A, Mitchell C, Tica O, Ziff OJ, Bunting KV, Mobley AR, et al. Digoxin in patients with heart failure and/or atrial fibrillation: a systematic review and meta-analysis of 5.9 million patient years of follow-up. SSRN preprint. 2023. <https://doi.org/10.2139/ssrn.4544769>
485. Andrews P, Anseuw K, Kotecha D, Lapostolle F, Thanacoody R. Diagnosis and practical management of digoxin toxicity: a narrative review and consensus. *Eur J Emerg Med* 2023;**30**:395–401. <https://doi.org/10.1097/MEJ.0000000000001065>
486. Bavendiek U, Berliner D, Dávila LA, Schwab J, Maier L, Philipp SA, et al. Rationale and design of the DIGIT-HF trial (DIGitoxin to Improve ouTcomes in patients with advanced chronic Heart Failure): a randomized, double-blind, placebo-controlled study. *Eur J Heart Fail* 2019;**21**:676–84. <https://doi.org/10.1002/ehf.1452>
487. Clemons HF, Wood MA, Gilligan DM, Ellenbogen KA. Intravenous amiodarone for acute heart rate control in the critically ill patient with atrial tachyarrhythmias. *Am J Cardiol* 1998;**81**:594–8. [https://doi.org/10.1016/S0002-9149\(97\)00962-4](https://doi.org/10.1016/S0002-9149(97)00962-4)
488. Queiroga A, Marshall HJ, Clune M, Gammage MD. Ablate and pace revisited: long term survival and predictors of permanent atrial fibrillation. *Heart* 2003;**89**:1035–8. <https://doi.org/10.1136/heart.89.9.1035>
489. Geelen P, Brugada J, Andries E, Brugada P. Ventricular fibrillation and sudden death after radiofrequency catheter ablation of the atrioventricular junction. *Pacing Clin Electrophysiol* 1997;**20**:343–8. <https://doi.org/10.1111/j.1540-8159.1997.tb06179.x>
490. Wang RX, Lee HC, Hodge DO, Cha YM, Friedman PA, Rea RF, et al. Effect of pacing method on risk of sudden death after atrioventricular node ablation and pacemaker implantation in patients with atrial fibrillation. *Heart Rhythm* 2013;**10**:696–701. <https://doi.org/10.1016/j.hrthm.2013.01.021>
491. Chatterjee NA, Upadhyay GA, Ellenbogen KA, McAlister FA, Choudhry NK, Singh JP. Atrioventricular nodal ablation in atrial fibrillation: a meta-analysis and systematic review. *Circ Arrhythm Electrophysiol* 2012;**5**:68–76. <https://doi.org/10.1161/CIRCEP.111.967810>
492. Bradley DJ, Shen WK. Overview of management of atrial fibrillation in symptomatic elderly patients: pharmacologic therapy versus AV node ablation. *Clin Pharmacol Ther* 2007;**81**:284–7. <https://doi.org/10.1038/sj.clpt.6100062>
493. Ozcan C, Jahangir A, Friedman PA, Patel PJ, Munger TM, Rea RF, et al. Long-term survival after ablation of the atrioventricular node and implantation of a permanent pacemaker in patients with atrial fibrillation. *N Engl J Med* 2001;**344**:1043–51. <https://doi.org/10.1056/NEJM200104053441403>
494. Chatterjee NA, Upadhyay GA, Ellenbogen KA, Hayes DL, Singh JP. Atrioventricular nodal ablation in atrial fibrillation: a meta-analysis of biventricular vs. right ventricular pacing mode. *Eur J Heart Fail* 2012;**14**:661–7. <https://doi.org/10.1093/eurjhf/hfs036>
495. Huang W, Su L, Wu S. Pacing treatment of atrial fibrillation patients with heart failure: His bundle pacing combined with atrioventricular node ablation. *Card Electrophysiol Clin* 2018;**10**:519–35. <https://doi.org/10.1016/j.jcep.2018.05.016>
496. Huang W, Su L, Wu S, Xu L, Xiao F, Zhou X, et al. Benefits of permanent His bundle pacing combined with atrioventricular node ablation in atrial fibrillation patients with heart failure with both preserved and reduced left ventricular ejection fraction. *J Am Heart Assoc* 2017;**6**:e005309. <https://doi.org/10.1161/JAHA.116.005309>
497. Van Gelder IC, Hagens VE, Bosker HA, Kingma JH, Kamp O, Kingma T, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med* 2002;**347**:1834–40. <https://doi.org/10.1056/NEJMoa021375>
498. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002;**347**:1825–33. <https://doi.org/10.1056/NEJMoa021328>
499. Hohnloser SH, Kuck KH, Lilienthal J. Rhythm or rate control in atrial fibrillation—pharmacological intervention in atrial fibrillation (PIAF): a randomised trial. *Lancet* 2000;**356**:1789–94. [https://doi.org/10.1016/S0140-6736\(00\)03230-X](https://doi.org/10.1016/S0140-6736(00)03230-X)
500. Roy D, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med* 2008;**358**:2667–77. <https://doi.org/10.1056/NEJMoa0708789>
501. Blomström-Lundqvist C, Gizurarson S, Schwieler J, Jensen SM, Bergfeldt L, Kennebäck G, et al. Effect of catheter ablation vs antiarrhythmic medication on quality of life in patients with atrial fibrillation: the CAPTAF randomized clinical trial. *JAMA* 2019;**321**:1059–68. <https://doi.org/10.1001/jama.2019.0335>
502. Mark DB, Anstrom KJ, Sheng S, Piccini JP, Baloch KN, Monahan KH, et al. Effect of catheter ablation vs medical therapy on quality of life among patients with atrial fibrillation: the CABANA randomized clinical trial. *JAMA* 2019;**321**:1275–85. <https://doi.org/10.1001/jama.2019.0692>
503. Wilber DJ, Pappone C, Neuzil P, De Paola A, Marchlinski F, Natale A, et al. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. *JAMA* 2010;**303**:333–40. <https://doi.org/10.1001/jama.2009.2029>
504. Calkins H, Reynolds MR, Spector P, Sondhi M, Xu Y, Martin A, et al. Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation: two systematic literature reviews and meta-analyses. *Circ Arrhythm Electrophysiol* 2009;**2**:349–61. <https://doi.org/10.1161/CIRCEP.108.824789>
505. Jais P, Cauchemez B, Macle L, Daoud E, Khairy P, Subbiah R, et al. Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: the A4 study. *Circulation* 2008;**118**:2498–505. <https://doi.org/10.1161/CIRCULATIONAHA.108.772582>
506. Packer DL, Kowal RC, Wheelan KR, Irwin JM, Champagne J, Guerra PG, et al. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front (STOP AF) pivotal trial. *J Am Coll Cardiol* 2013;**61**:1713–23. <https://doi.org/10.1016/j.jacc.2012.11.064>
507. Poole JE, Bahnson TD, Monahan KH, Johnson G, Rostami H, Silverstein AP, et al. Recurrence of atrial fibrillation after catheter ablation or antiarrhythmic drug therapy in the CABANA trial. *J Am Coll Cardiol* 2020;**75**:3105–18. <https://doi.org/10.1016/j.jacc.2020.04.065>
508. Mont L, Bisbal F, Hernandez-Madrid A, Perez-Castellano N, Vinolas X, Arenal A, et al. Catheter ablation vs. antiarrhythmic drug treatment of persistent atrial fibrillation: a multicentre, randomized, controlled trial (SARA study). *Eur Heart J* 2014;**35**:501–7. <https://doi.org/10.1093/eurheartj/eh457>
509. Scherr D, Khairy P, Miyazaki S, Aurillac-Lavignolle V, Pascale P, Wilton SB, et al. Five-year outcome of catheter ablation of persistent atrial fibrillation using termination of atrial fibrillation as a procedural endpoint. *Circ Arrhythm Electrophysiol* 2015;**8**:18–24. <https://doi.org/10.1161/CIRCEP.114.001943>
510. Lau DH, Nattel S, Kalman JM, Sanders P. Modifiable risk factors and atrial fibrillation. *Circulation* 2017;**136**:583–96. <https://doi.org/10.1161/CIRCULATIONAHA.116.023163>
511. Sanders P, Elliott AD, Linz D. Upstream targets to treat atrial fibrillation. *J Am Coll Cardiol* 2017;**70**:2906–8. <https://doi.org/10.1016/j.jacc.2017.10.043>
512. Hohnloser SH, Crijns HJ, van Eickels M, Gaudin C, Page RL, Torp-Pedersen C, et al. Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med* 2009;**360**:668–78. <https://doi.org/10.1056/NEJMoa0803778>
513. Sohns C, Fox H, Marrouche NF, Crijns H, Costard-Jaeckle A, Bergau L, et al. Catheter ablation in end-stage heart failure with atrial fibrillation. *N Engl J Med* 2023;**389**:1380–9. <https://doi.org/10.1056/NEJMoa2306037>
514. Di Biase L, Mohanty P, Mohanty S, Santangeli P, Trivedi C, Lakkireddy D, et al. Ablation versus amiodarone for treatment of persistent atrial fibrillation in patients with congestive heart failure and an implanted device: results from the AATAC multicenter randomized trial. *Circulation* 2016;**133**:1637–44. <https://doi.org/10.1161/CIRCULATIONAHA.115.019406>
515. Nuotio I, Hartikainen JE, Gronberg T, Biancari F, Airaksinen KE. Time to cardioversion for acute atrial fibrillation and thromboembolic complications. *JAMA* 2014;**312**:647–9. <https://doi.org/10.1001/jama.2014.3824>
516. Garg A, Khunger M, Seicean S, Chung MK, Tchou PJ. Incidence of thromboembolic complications within 30 days of electrical cardioversion performed within 48 hours of atrial fibrillation onset. *JACC Clin Electrophysiol* 2016;**2**:487–94. <https://doi.org/10.1016/j.jacep.2016.01.018>
517. Tampieri A, Cipriano V, Mucci F, Rusconi AM, Lenzi T, Cenni P. Safety of cardioversion in atrial fibrillation lasting less than 48 h without post-procedural anticoagulation in patients at low cardioembolic risk. *Intern Emerg Med* 2018;**13**:87–93. <https://doi.org/10.1007/s11739-016-1589-1>
518. Airaksinen KE, Gronberg T, Nuotio I, Nikkinen M, Ylitalo A, Biancari F, et al. Thromboembolic complications after cardioversion of acute atrial fibrillation: the FinCV (Finnish CardioVersion) study. *J Am Coll Cardiol* 2013;**62**:1187–92. <https://doi.org/10.1016/j.jacc.2013.04.089>
519. Hansen ML, Jepsen RM, Olesen JB, Ruwald MH, Karasoy D, Gislason GH, et al. Thromboembolic risk in 16 274 atrial fibrillation patients undergoing direct current cardioversion with and without oral anticoagulant therapy. *Europace* 2015;**17**:18–23. <https://doi.org/10.1093/europace/euu189>
520. Bonfanti L, Annovi A, Sanchis-Gomar F, Saccenti C, Meschi T, Ticinesi A, et al. Effectiveness and safety of electrical cardioversion for acute-onset atrial fibrillation in the emergency department: a real-world 10-year single center experience. *Clin Exp Emerg Med* 2019;**6**:64–9. <https://doi.org/10.15441/ceem.17.286>
521. Telles-Garcia N, Dahal K, Kocherla C, Lip GYH, Reddy P, Dominic P. Non-vitamin K antagonists oral anticoagulants are as safe and effective as warfarin for cardioversion of atrial fibrillation: a systematic review and meta-analysis. *Int J Cardiol* 2018;**268**:143–8. <https://doi.org/10.1016/j.ijcard.2018.04.034>
522. Klein AL, Grimm RA, Murray RD, Apperson-Hansen C, Asinger RW, Black IW, et al. Use of transthoracic echocardiography to guide cardioversion in patients with atrial fibrillation. *N Engl J Med* 2001;**344**:1411–20. <https://doi.org/10.1056/NEJM200105103441901>
523. Brunetti ND, Tarantino N, De Gennaro L, Correale M, Santoro F, Di Biase M. Direct oral anti-coagulants compared to vitamin-K antagonists in cardioversion of atrial fibrillation: an updated meta-analysis. *J Thromb Thrombolysis* 2018;**45**:550–6. <https://doi.org/10.1007/s11239-018-1622-5>
524. Steinberg JS, Sadaniantz A, Kron J, Krahn A, Denny DM, Daubert J, et al. Analysis of cause-specific mortality in the Atrial Fibrillation Follow-up Investigation of Rhythm

- Management (AFFIRM) study. *Circulation* 2004;**109**:1973–80. <https://doi.org/10.1161/01.CIR.0000118472.77237.FA>
525. Crijns HJ, Weijs B, Fairley AM, Lewalter T, Maggioni AP, Martín A, et al. Contemporary real life cardioversion of atrial fibrillation: results from the multinational RHYTHM-AF study. *Int J Cardiol* 2014;**172**:588–94. <https://doi.org/10.1016/j.ijcard.2014.01.099>
 526. Kirchhof P, Andresen D, Bosch R, Borggrefe M, Meinertz T, Parade U, et al. Short-term versus long-term antiarrhythmic drug treatment after cardioversion of atrial fibrillation (Flec-SL): a prospective, randomised, open-label, blinded endpoint assessment trial. *Lancet* 2012;**380**:238–46. [https://doi.org/10.1016/S0140-6736\(12\)60570-4](https://doi.org/10.1016/S0140-6736(12)60570-4)
 527. Zhu W, Wu Z, Dong Y, Lip GYH, Liu C. Effectiveness of early rhythm control in improving clinical outcomes in patients with atrial fibrillation: a systematic review and meta-analysis. *BMC Med* 2022;**20**:340. <https://doi.org/10.1186/s12916-022-02545-4>
 528. Stellbrink C, Nixdorff U, Hofmann T, Lehman W, Daniel WG, Hanrath P, et al. Safety and efficacy of enoxaparin compared with unfractionated heparin and oral anticoagulants for prevention of thromboembolic complications in cardioversion of non-valvular atrial fibrillation: the Anticoagulation in Cardioversion using Enoxaparin (ACE) trial. *Circulation* 2004;**109**:997–1003. <https://doi.org/10.1161/01.CIR.0000120509.64740.DC>
 529. Lip GY, Hammerstingl C, Marin F, Cappato R, Meng IL, Kirsch B, et al. Left atrial thrombus resolution in atrial fibrillation or flutter: results of a prospective study with rivaroxaban (X-TRA) and a retrospective observational registry providing baseline data (CLOT-AF). *Am Heart J* 2016;**178**:126–34. <https://doi.org/10.1016/j.ahj.2016.05.007>
 530. Stiell IG, Eagles D, Nemnom MJ, Brown E, Taljaard M, Archambault PM, et al. Adverse events associated with electrical cardioversion in patients with acute atrial fibrillation and atrial flutter. *Can J Cardiol* 2021;**37**:1775–82. <https://doi.org/10.1016/j.cjca.2021.08.018>
 531. Stiell IG, Archambault PM, Morris J, Mercier E, Eagles D, Perry JJ, et al. RAFF-3 Trial: a stepped-wedge cluster randomised trial to improve care of acute atrial fibrillation and flutter in the emergency department. *Can J Cardiol* 2021;**37**:1569–77. <https://doi.org/10.1016/j.cjca.2021.06.016>
 532. Gurevitz OT, Ammash NM, Malouf JF, Chandrasekaran K, Rosales AG, Ballman KV, et al. Comparative efficacy of monophasic and biphasic waveforms for transthoracic cardioversion of atrial fibrillation and atrial flutter. *Am Heart J* 2005;**149**:316–21. <https://doi.org/10.1016/j.ahj.2004.07.007>
 533. Mortensen K, Risius T, Schwemer TF, Aydin MA, Köster R, Klemm HU, et al. Biphasic versus monophasic shock for external cardioversion of atrial flutter: a prospective, randomized trial. *Cardiology* 2008;**111**:57–62. <https://doi.org/10.1159/000113429>
 534. Inácio JF, da Rosa Mdos S, Shah J, Rosário J, Vissoci JR, Manica AL, et al. Monophasic and biphasic shock for transthoracic conversion of atrial fibrillation: systematic review and network meta-analysis. *Resuscitation* 2016;**100**:66–75. <https://doi.org/10.1016/j.resuscitation.2015.12.009>
 535. Eid M, Abu Jazar D, Medhekar A, Khalife W, Javaid A, Ahsan C, et al. Anterior-posterior versus anterior-lateral electrodes position for electrical cardioversion of atrial fibrillation: a meta-analysis of randomized controlled trials. *Int J Cardiol Heart Vasc* 2022;**43**:101129. <https://doi.org/10.1016/j.ijcha.2022.101129>
 536. Squara F, Elbaum C, Garret G, Liprandi L, Scarlatti D, Bun SS, et al. Active compression versus standard anterior-posterior defibrillation for external cardioversion of atrial fibrillation: a prospective randomized study. *Heart Rhythm* 2021;**18**:360–5. <https://doi.org/10.1016/j.hrthm.2020.11.005>
 537. Schmidt AS, Lauridsen KG, Torp P, Bach LF, Rickers H, Løfgren B. Maximum-fixed energy shocks for cardioverting atrial fibrillation. *Eur Heart J* 2020;**41**:626–31. <https://doi.org/10.1093/eurheartj/ehz585>
 538. Müssigbrodt A, John S, Kosiuk J, Richter S, Hindricks G, Bollmann A. Vernakalant-facilitated electrical cardioversion: comparison of intravenous vernakalant and amiodarone for drug-enhanced electrical cardioversion of atrial fibrillation after failed electrical cardioversion. *Europace* 2016;**18**:51–6. <https://doi.org/10.1093/europace/euv194>
 539. Climent VE, Marin F, Mainar L, Gomez-Aldaravi R, Martinez JG, Chorro FJ, et al. Effects of pretreatment with intravenous flecainide on efficacy of external cardioversion of persistent atrial fibrillation. *Pacing Clin Electrophysiol* 2004;**27**:368–72. <https://doi.org/10.1111/j.1540-8159.2004.00444.x>
 540. Tieleman RG, Van Gelder IC, Bosker HA, Kingma T, Wilde AA, Kirchhof CJ, et al. Does flecainide regain its antiarrhythmic activity after electrical cardioversion of persistent atrial fibrillation? *Heart Rhythm* 2005;**2**:223–30. <https://doi.org/10.1016/j.hrthm.2004.11.014>
 541. Oral H, Souza JJ, Michaud GF, Knight BP, Goyal R, Strickberger SA, et al. Facilitating transthoracic cardioversion of atrial fibrillation with ibutilide pretreatment. *N Engl J Med* 1999;**340**:1849–54. <https://doi.org/10.1056/NEJM199906173402401>
 542. Nair M, George LK, Koshy SK. Safety and efficacy of ibutilide in cardioversion of atrial flutter and fibrillation. *J Am Board Fam Med* 2011;**24**:86–92. <https://doi.org/10.3122/jabfm.2011.01.080096>
 543. Bianconi L, Mennuni M, Lukic V, Castro A, Chieffi M, Santini M. Effects of oral propafenone administration before electrical cardioversion of chronic atrial fibrillation: a placebo-controlled study. *J Am Coll Cardiol* 1996;**28**:700–6. [https://doi.org/10.1016/S0735-1097\(96\)00230-6](https://doi.org/10.1016/S0735-1097(96)00230-6)
 544. Channer KS, Birchall A, Steeds RP, Walters SJ, Yeo WW, West JN, et al. A randomized placebo-controlled trial of pre-treatment and short- or long-term maintenance therapy with amiodarone supporting DC cardioversion for persistent atrial fibrillation. *Eur Heart J* 2004;**25**:144–50. <https://doi.org/10.1016/j.ehj.2003.10.020>
 545. Capucci A, Villani GQ, Aschieri D, Rosi A, Piepoli MF. Oral amiodarone increases the efficacy of direct-current cardioversion in restoration of sinus rhythm in patients with chronic atrial fibrillation. *Eur Heart J* 2000;**21**:66–73. <https://doi.org/10.1053/ehj.1999.1734>
 546. Um KJ, McIntyre WF, Healey JS, Mendoza PA, Koziarz A, Amit G, et al. Pre- and post-treatment with amiodarone for elective electrical cardioversion of atrial fibrillation: a systematic review and meta-analysis. *Europace* 2019;**21**:856–63. <https://doi.org/10.1093/europace/euy310>
 547. Toso E, Iannaccone M, Caponi D, Rotondi F, Santoro A, Gallo C, et al. Does antiarrhythmic drugs premedication improve electrical cardioversion success in persistent atrial fibrillation? *J Electrocardiol* 2017;**50**:294–300. <https://doi.org/10.1016/j.jelectrocard.2016.12.004>
 548. Ganapathy AV, Monjazeb S, Ganapathy KS, Shanoon F, Razavi M. “Asymptomatic” persistent or permanent atrial fibrillation: a misnomer in selected patients. *Int J Cardiol* 2015;**185**:112–3. <https://doi.org/10.1016/j.ijcard.2015.03.122>
 549. Voskoboinik A, Kalman E, Plunkett G, Knott J, Moskovitch J, Sanders P, et al. A comparison of early versus delayed elective electrical cardioversion for recurrent episodes of persistent atrial fibrillation: a multi-center study. *Int J Cardiol* 2019;**284**:33–7. <https://doi.org/10.1016/j.ijcard.2018.10.068>
 550. Airaksinen KEJ. Early versus delayed cardioversion: why should we wait? *Expert Rev Cardiovasc Ther* 2020;**18**:149–54. <https://doi.org/10.1080/14779072.2020.1736563>
 551. Boriani G, Diemberger I, Biffi M, Martignani C, Branzi A. Pharmacological cardioversion of atrial fibrillation: current management and treatment options. *Drugs* 2004;**64**:2741–62. <https://doi.org/10.2165/00003495-200464240-00003>
 552. Dan GA, Martinez-Rubio A, Agewall S, Boriani G, Borggrefe M, Gaita F, et al. Antiarrhythmic drugs—clinical use and clinical decision making: a consensus document from the European Heart Rhythm Association (EHRA) and European Society of Cardiology (ESC) Working Group on Cardiovascular Pharmacology, endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS) and International Society of Cardiovascular Pharmacotherapy (ISCP). *Europace* 2018;**20**:731–732an. <https://doi.org/10.1093/europace/eux373>
 553. Gitt AK, Smolka W, Michailov G, Bernhardt A, Pittrow D, Lewalter T. Types and outcomes of cardioversion in patients admitted to hospital for atrial fibrillation: results of the German RHYTHM-AF study. *Clin Res Cardiol* 2013;**102**:713–23. <https://doi.org/10.1007/s00392-013-0586-x>
 554. Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation: executive summary. *Europace* 2018;**20**:157–208. <https://doi.org/10.1093/europace/eux275>
 555. Danias PG, Caulfield TA, Weigner MJ, Silverman DI, Manning WJ. Likelihood of spontaneous conversion of atrial fibrillation to sinus rhythm. *J Am Coll Cardiol* 1998;**31**:588–92. [https://doi.org/10.1016/S0735-1097\(97\)00534-2](https://doi.org/10.1016/S0735-1097(97)00534-2)
 556. Tsiachris D, Doundoulakis I, Pagkalidou E, Kordalis A, Deftereos S, Gatzoulis KA, et al. Pharmacologic cardioversion in patients with paroxysmal atrial fibrillation: a network meta-analysis. *Cardiovasc Drugs Ther* 2021;**35**:293–308. <https://doi.org/10.1007/s10557-020-07127-1>
 557. Grönberg T, Nuotio I, Nikkinen M, Ylitalo A, Vasankari T, Hartikainen JE, et al. Arrhythmic complications after electrical cardioversion of acute atrial fibrillation: the FinCV study. *Europace* 2013;**15**:1432–5. <https://doi.org/10.1093/europace/eut106>
 558. Brandes A, Crijns H, Rienstra M, Kirchhof P, Grove EL, Pedersen KB, et al. Cardioversion of atrial fibrillation and atrial flutter revisited: current evidence and practical guidance for a common procedure. *Europace* 2020;**22**:1149–61. <https://doi.org/10.1093/europace/euaa057>
 559. Stiell IG, Sivilotti MLA, Taljaard M, Bernie D, Vadeboncoeur A, Hohl CM, et al. Electrical versus pharmacological cardioversion for emergency department patients with acute atrial fibrillation (RAFF2): a partial factorial randomised trial. *Lancet* 2020;**395**:339–49. [https://doi.org/10.1016/S0140-6736\(19\)32994-0](https://doi.org/10.1016/S0140-6736(19)32994-0)
 560. Alboni P, Botto GL, Baldi N, Luzi M, Russo V, Gianfranchi L, et al. Outpatient treatment of recent-onset atrial fibrillation with the “pill-in-the-pocket” approach. *N Engl J Med* 2004;**351**:2384–91. <https://doi.org/10.1056/NEJMoa041233>
 561. Brembilla-Perrot B, Houriez P, Beurrier D, Claudon O, Terrier de la Chaise A, Louis P. Predictors of atrial flutter with 1:1 conduction in patients treated with class I antiarrhythmic drugs for atrial tachyarrhythmias. *Int J Cardiol* 2001;**80**:7–15. [https://doi.org/10.1016/S0167-5273\(01\)00459-4](https://doi.org/10.1016/S0167-5273(01)00459-4)
 562. Conde D, Costabel JP, Caro M, Ferro A, Lambardi F, Corrales Barboza A, et al. Flecainide versus vernakalant for conversion of recent-onset atrial fibrillation. *Int J Cardiol* 2013;**168**:2423–5. <https://doi.org/10.1016/j.ijcard.2013.02.006>
 563. Markey GC, Salter N, Ryan J. Intravenous flecainide for emergency department management of acute atrial fibrillation. *J Emerg Med* 2018;**54**:320–7. <https://doi.org/10.1016/j.jemermed.2017.11.016>
 564. Martinez-Marcos FJ, Garcia-Garmendia JL, Ortega-Carpio A, Fernandez-Gomez JM, Santos JM, Camacho C. Comparison of intravenous flecainide, propafenone, and

- amiodarone for conversion of acute atrial fibrillation to sinus rhythm. *Am J Cardiol* 2000;**86**:950–3. [https://doi.org/10.1016/S0002-9149\(00\)01128-0](https://doi.org/10.1016/S0002-9149(00)01128-0)
565. Reisinger J, Gatterer E, Lang W, Vanicek T, Eissner G, Bachleitner T, et al. Flecainide versus ibutilide for immediate cardioversion of atrial fibrillation of recent onset. *Eur Heart J* 2004;**25**:1318–24. <https://doi.org/10.1016/j.ehj.2004.04.030>
 566. Zhang N, Guo JH, Zhang H, Li XB, Zhang P, Xn Y. Comparison of intravenous ibutilide vs. propafenone for rapid termination of recent onset atrial fibrillation. *Int J Clin Pract* 2005;**59**:1395–400. <https://doi.org/10.1111/j.1368-5031.2005.00705.x>
 567. Camm AJ, Capucci A, Hohnloser SH, Torp-Pedersen C, Van Gelder IC, Mangal B, et al. A randomized active-controlled study comparing the efficacy and safety of vernakalant to amiodarone in recent-onset atrial fibrillation. *J Am Coll Cardiol* 2011;**57**:313–21. <https://doi.org/10.1016/j.jacc.2010.07.046>
 568. Roy D, Pratt CM, Torp-Pedersen C, Wyse DG, Toft E, Juul-Møller S, et al. Vernakalant hydrochloride for rapid conversion of atrial fibrillation: a phase 3, randomized, placebo-controlled trial. *Circulation* 2008;**117**:1518–25. <https://doi.org/10.1161/CIRCULATIONAHA.107.723866>
 569. Deedwania PC, Singh BN, Ellenbogen K, Fisher S, Fletcher R, Singh SN. Spontaneous conversion and maintenance of sinus rhythm by amiodarone in patients with heart failure and atrial fibrillation: observations from the veterans affairs congestive heart failure survival trial of antiarrhythmic therapy (CHF-STAT). The Department of Veterans Affairs CHF-STAT Investigators. *Circulation* 1998;**98**:2574–9. <https://doi.org/10.1161/01.cir.98.23.2574>
 570. Hofmann R, Steinwender C, Kammler J, Kypka A, Wimmer G, Leisch F. Intravenous amiodarone bolus for treatment of atrial fibrillation in patients with advanced congestive heart failure or cardiogenic shock. *Wien Klin Wochenschr* 2004;**116**:744–9. <https://doi.org/10.1007/s00508-004-0264-0>
 571. Alboni P, Botto GL, Boriani G, Russo G, Pacchioni F, Iori M, et al. Intravenous administration of flecainide or propafenone in patients with recent-onset atrial fibrillation does not predict adverse effects during 'pill-in-the-pocket' treatment. *Heart* 2010;**96**:546–9. <https://doi.org/10.1136/hrt.2009.187963>
 572. Khan IA. Single oral loading dose of propafenone for pharmacological cardioversion of recent-onset atrial fibrillation. *J Am Coll Cardiol* 2001;**37**:542–7. [https://doi.org/10.1016/S0735-1097\(00\)01116-5](https://doi.org/10.1016/S0735-1097(00)01116-5)
 573. Khan IA. Oral loading single dose flecainide for pharmacological cardioversion of recent-onset atrial fibrillation. *Int J Cardiol* 2003;**87**:121–8. [https://doi.org/10.1016/S0167-5273\(02\)00467-9](https://doi.org/10.1016/S0167-5273(02)00467-9)
 574. Al-Khatib SM, Allen LaPointe NM, Chatterjee R, Crowley MJ, Dupre ME, Kong DF, et al. Rate- and rhythm-control therapies in patients with atrial fibrillation: a systematic review. *Ann Intern Med* 2014;**160**:760–73. <https://doi.org/10.7326/M13-1467>
 575. Andrade JG, Aguilar M, Atzema C, Bell A, Cairns JA, Cheung CC, et al. The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society Comprehensive Guidelines for the Management of Atrial Fibrillation. *Can J Cardiol* 2020;**36**:1847–948. <https://doi.org/10.1016/j.cjca.2020.09.001>
 576. Lafuente-Lafuente C, Valembois L, Bergmann JF, Belmin J. Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation. *Cochrane Database Syst Rev* 2015;**3**:CD005049. <https://doi.org/10.1002/14651858.CD005049.pub4>
 577. Valembois L, Audureau E, Takeda A, Jarzebowski VV, Belmin J, Lafuente-Lafuente C. Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation. *Cochrane Database Syst Rev* 2019;**2019**:Cd005049. <https://doi.org/10.1002/14651858.CD005049.pub5>
 578. Crijns HJ, Van Gelder IC, Van Gilst WH, Hillege H, Gosselink AM, Lie KI. Serial antiarrhythmic drug treatment to maintain sinus rhythm after electrical cardioversion for chronic atrial fibrillation or atrial flutter. *Am J Cardiol* 1991;**68**:335–41. [https://doi.org/10.1016/0002-9149\(91\)90828-9](https://doi.org/10.1016/0002-9149(91)90828-9)
 579. Chatterjee S, Sardar P, Lichstein E, Mukherjee D, Aikat S. Pharmacologic rate versus rhythm-control strategies in atrial fibrillation: an updated comprehensive review and meta-analysis. *Pacing Clin Electrophysiol* 2013;**36**:122–33. <https://doi.org/10.1111/j.1540-8159.2012.03513.x>
 580. Kotecha D, Kirchhof P. Rate and rhythm control have comparable effects on mortality and stroke in atrial fibrillation but better data are needed. *Evid Based Med* 2014;**19**:222–3. <https://doi.org/10.1136/ebmed-2014-110062>
 581. Piccini JP, Hasselblad V, Peterson ED, Washam JB, Califf RM, Kong DF. Comparative efficacy of dronedarone and amiodarone for the maintenance of sinus rhythm in patients with atrial fibrillation. *J Am Coll Cardiol* 2009;**54**:1089–95. <https://doi.org/10.1016/j.jacc.2009.04.085>
 582. Eckardt L, Sehner S, Suling A, Borof K, Breithardt G, Crijns H, et al. Attaining sinus rhythm mediates improved outcome with early rhythm control therapy of atrial fibrillation: the EAST-AFNET 4 trial. *Eur Heart J* 2022;**43**:4127–44. <https://doi.org/10.1093/eurheartj/ehac471>
 583. Freemantle N, Lafuente-Lafuente C, Mitchell S, Eckert L, Reynolds M. Mixed treatment comparison of dronedarone, amiodarone, sotalol, flecainide, and propafenone, for the management of atrial fibrillation. *Europace* 2011;**13**:329–45. <https://doi.org/10.1093/europace/euq450>
 584. Frommeyer G, Eckardt L. Drug-induced proarrhythmia: risk factors and electrophysiological mechanisms. *Nat Rev Cardiol* 2016;**13**:36–47. <https://doi.org/10.1038/nrcardio.2015.110>
 585. Kochiadakis GE, Marketou ME, Igoumenidis NE, Chrysostomakis SI, Mavrikakis HE, Kaleboubas MD, et al. Amiodarone, sotalol, or propafenone in atrial fibrillation: which is preferred to maintain normal sinus rhythm? *Pacing Clin Electrophysiol* 2000;**23**:1883–7. <https://doi.org/10.1111/j.1540-8159.2000.tb07044.x>
 586. Roy D, Talajic M, Dorian P, Connolly S, Eisenberg MJ, Green M, et al. Amiodarone to prevent recurrence of atrial fibrillation. Canadian Trial of Atrial Fibrillation Investigators. *N Engl J Med* 2000;**342**:913–20. <https://doi.org/10.1056/NEJM200003303421302>
 587. Singh BN, Singh SN, Reda DJ, Tang XC, Lopez B, Harris CL, et al. Amiodarone versus sotalol for atrial fibrillation. *N Engl J Med* 2005;**352**:1861–72. <https://doi.org/10.1056/NEJMoa041705>
 588. Ehrlich JR, Look C, Kostev K, Israel CVW, Goette A. Impact of dronedarone on the risk of myocardial infarction and stroke in atrial fibrillation patients followed in general practices in Germany. *Int J Cardiol* 2019;**278**:126–32. <https://doi.org/10.1016/j.ijcard.2018.11.133>
 589. Singh BN, Connolly SJ, Crijns HJ, Roy D, Kowey PR, Capucci A, et al. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. *N Engl J Med* 2007;**357**:987–99. <https://doi.org/10.1056/NEJMoa054686>
 590. Stroobandt R, Stiebs B, Hoebrechts R. Propafenone for conversion and prophylaxis of atrial fibrillation. Propafenone Atrial Fibrillation Trial Investigators. *Am J Cardiol* 1997;**79**:418–23. [https://doi.org/10.1016/S0002-9149\(96\)00779-5](https://doi.org/10.1016/S0002-9149(96)00779-5)
 591. Wazni OM, Dandamudi G, Sood N, Hoyt R, Tyler J, Durrani S, et al. Cryoballoon ablation as initial therapy for atrial fibrillation. *N Engl J Med* 2021;**384**:316–24. <https://doi.org/10.1056/NEJMoa2029554>
 592. Cosedis Nielsen J, Johannessen A, Raatikainen P, Hindricks G, Walfridsson H, Kongstad O, et al. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. *N Engl J Med* 2012;**367**:1587–95. <https://doi.org/10.1056/NEJMoa1113566>
 593. Morillo CA, Verma A, Connolly SJ, Kuck KH, Nair GM, Champagne J, et al. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of paroxysmal atrial fibrillation (RAAFT-2): a randomized trial. *JAMA* 2014;**311**:692–700. <https://doi.org/10.1001/jama.2014.467>
 594. Kuniss M, Pavlovic N, Velagic V, Hermida JS, Healey S, Arena G, et al. Cryoballoon ablation vs. antiarrhythmic drugs: first-line therapy for patients with paroxysmal atrial fibrillation. *Europace* 2021;**23**:1033–41. <https://doi.org/10.1093/europace/euab029>
 595. Hocini M, Sanders P, Deisenhofer I, Jais P, Hsu LF, Scavee C, et al. Reverse remodeling of sinus node function after catheter ablation of atrial fibrillation in patients with prolonged sinus pauses. *Circulation* 2003;**108**:1172–5. <https://doi.org/10.1161/01.CIR.0000090685.13169.07>
 596. Inada K, Yamane T, Tokutake K, Yokoyama K, Mishima T, Hioki M, et al. The role of successful catheter ablation in patients with paroxysmal atrial fibrillation and prolonged sinus pauses: outcome during a 5-year follow-up. *Europace* 2014;**16**:208–13. <https://doi.org/10.1093/europace/eut159>
 597. Chen YW, Bai R, Lin T, Salim M, Sang CH, Long DY, et al. Pacing or ablation: which is better for paroxysmal atrial fibrillation-related tachycardia-bradycardia syndrome? *Pacing Clin Electrophysiol* 2014;**37**:403–11. <https://doi.org/10.1111/pace.12340>
 598. Zhang R, Wang Y, Yang M, Yang Y, Wang Z, Yin X, et al. Risk stratification for atrial fibrillation and outcomes in tachycardia-bradycardia syndrome: ablation vs. pacing. *Front Cardiovasc Med* 2021;**8**:674471. <https://doi.org/10.3389/fcvm.2021.674471>
 599. Oral H, Pappone C, Chugh A, Good E, Bogun F, Pelosi F, Jr, et al. Circumferential pulmonary-vein ablation for chronic atrial fibrillation. *N Engl J Med* 2006;**354**:934–41. <https://doi.org/10.1056/NEJMoa050955>
 600. Yan Huo TG, Schönbauer R, Wójcik M, Fiedler L, Roithinger FX, Martinek M, et al. Low-voltage myocardium-guided ablation trial of persistent atrial fibrillation. *NEJM Evid* 2022;**1**:EVID0a2200141. <https://doi.org/10.1056/EVID0a2200141>
 601. Reddy VY, Gerstenfeld EP, Natale A, Whang W, Cuoco FA, Patel C, et al. Pulsed field or conventional thermal ablation for paroxysmal atrial fibrillation. *N Engl J Med* 2023;**389**:1660–71. <https://doi.org/10.1056/NEJMoa2307291>
 602. Kalman JM, Al-Kaisey AM, Parameswaran R, Hawson J, Anderson RD, Lim M, et al. Impact of early vs. delayed atrial fibrillation catheter ablation on atrial arrhythmia recurrences. *Eur Heart J* 2023;**44**:2447–54. <https://doi.org/10.1093/eurheartj/ehad247>
 603. Kalman JM, Sanders P, Rosso R, Calkins H. Should we perform catheter ablation for asymptomatic atrial fibrillation? *Circulation* 2017;**136**:490–9. <https://doi.org/10.1161/CIRCULATIONAHA.116.024926>
 604. Hunter RJ, Berriman TJ, Diab I, Kamdar R, Richmond L, Baker V, et al. A randomized controlled trial of catheter ablation versus medical treatment of atrial fibrillation in heart failure (the CAMTAF trial). *Circ Arrhythm Electrophysiol* 2014;**7**:31–8. <https://doi.org/10.1161/CIRCEP.113.000806>
 605. Jones DG, Haldar SK, Hussain W, Sharma R, Francis DP, Rahman-Haley SL, et al. A randomized trial to assess catheter ablation versus rate control in the management of persistent atrial fibrillation in heart failure. *J Am Coll Cardiol* 2013;**61**:1894–903. <https://doi.org/10.1016/j.jacc.2013.01.069>
 606. Kuck KH, Merkely B, Zahn R, Arentz T, Seidl K, Schluter M, et al. Catheter ablation versus best medical therapy in patients with persistent atrial fibrillation and congestive heart failure: the randomized AMICA trial. *Circ Arrhythm Electrophysiol* 2019;**12**:e007731. <https://doi.org/10.1161/CIRCEP.119.007731>

607. MacDonald MR, Connelly DT, Hawkins NM, Steedman T, Payne J, Shaw M, et al. Radiofrequency ablation for persistent atrial fibrillation in patients with advanced heart failure and severe left ventricular systolic dysfunction: a randomised controlled trial. *Heart* 2011;**97**:740–7. <https://doi.org/10.1136/hrt.2010.207340>
608. Parkash R, Wells GA, Rouleau J, Talajic M, Essebag V, Skanes A, et al. Randomized ablation-based rhythm-control versus rate-control trial in patients with heart failure and atrial fibrillation: results from the RAFT-AF trial. *Circulation* 2022;**145**:1693–704. <https://doi.org/10.1161/CIRCULATIONAHA.121.057095>
609. Romero J, Gabr M, Alviz I, Briceño D, Díaz JC, Rodríguez D, et al. Improved survival in patients with atrial fibrillation and heart failure undergoing catheter ablation compared to medical treatment: a systematic review and meta-analysis of randomized controlled trials. *J Cardiovasc Electrophysiol* 2022;**33**:2356–66. <https://doi.org/10.1111/jce.15622>
610. Chen S, Purerfellner H, Meyer C, Acou VJ, Schratte A, Ling Z, et al. Rhythm control for patients with atrial fibrillation complicated with heart failure in the contemporary era of catheter ablation: a stratified pooled analysis of randomized data. *Eur Heart J* 2020;**41**:2863–73. <https://doi.org/10.1093/eurheartj/ehz443>
611. Prabhu S, Taylor AJ, Costello BT, Kaye DM, McLellan AJA, Voskoboinik A, et al. Catheter ablation versus medical rate control in atrial fibrillation and systolic dysfunction: the CAMERA-MRI study. *J Am Coll Cardiol* 2017;**70**:1949–61. <https://doi.org/10.1016/j.jacc.2017.08.041>
612. Packer DL, Piccini JP, Monahan KH, Al-Khalidi HR, Silverstein AP, Noseworthy PA, et al. Ablation versus drug therapy for atrial fibrillation in heart failure: results from the CABANA trial. *Circulation* 2021;**143**:1377–90. <https://doi.org/10.1161/CIRCULATIONAHA.120.050991>
613. Smit MD, Moes ML, Maass AH, Achekar ID, Van Geel PP, Hillege HL, et al. The importance of whether atrial fibrillation or heart failure develops first. *Eur J Heart Fail* 2012;**14**:1030–40. <https://doi.org/10.1093/eurjhf/hfs097>
614. Sohns C, Zintl K, Zhao Y, Dagher L, Andersen D, Siebels J, et al. Impact of left ventricular function and heart failure symptoms on outcomes post ablation of atrial fibrillation in heart failure: CASTLE-AF trial. *Circ Arrhythm Electrophysiol* 2020;**13**:e008461. <https://doi.org/10.1161/CIRCEP.120.008461>
615. Sugumar H, Prabhu S, Costello B, Chieng D, Azzopardi S, Voskoboinik A, et al. Catheter ablation versus medication in atrial fibrillation and systolic dysfunction: late outcomes of CAMERA-MRI study. *JACC Clin Electrophysiol* 2020;**6**:1721–31. <https://doi.org/10.1016/j.jacep.2020.08.019>
616. Kirstein B, Neudeck S, Gaspar T, Piorkowski J, Wechselberger S, Kronborg MB, et al. Left atrial fibrosis predicts left ventricular ejection fraction response after atrial fibrillation ablation in heart failure patients: the fibrosis-HF study. *Europace* 2020;**22**:1812–21. <https://doi.org/10.1093/europace/eaab179>
617. Ishiguchi H, Yoshiga Y, Shimizu A, Ueyama T, Fukuda M, Kato T, et al. Long-term events following catheter-ablation for atrial fibrillation in heart failure with preserved ejection fraction. *ESC Heart Fail* 2022;**9**:3505–18. <https://doi.org/10.1002/ehf2.14079>
618. Gu G, Wu J, Gao X, Liu M, Jin C, Xu Y. Catheter ablation of atrial fibrillation in patients with heart failure and preserved ejection fraction: a meta-analysis. *Clin Cardiol* 2022;**45**:786–93. <https://doi.org/10.1002/clc.23841>
619. Yamauchi R, Morishima I, Okumura K, Kanzaki Y, Morita Y, Takagi K, et al. Catheter ablation for non-paroxysmal atrial fibrillation accompanied by heart failure with preserved ejection fraction: feasibility and benefits in functions and B-type natriuretic peptide. *Europace* 2021;**23**:1252–61. <https://doi.org/10.1093/europace/eaab420>
620. Rordorf R, Scuzzoso F, Chun KRJ, Khelae SK, Kueffer FJ, Braegelmann KM, et al. Cryoballoon ablation for the treatment of atrial fibrillation in patients with concomitant heart failure and either reduced or preserved left ventricular ejection fraction: results from the Cryo AF global registry. *J Am Heart Assoc* 2021;**10**:e021323. <https://doi.org/10.1161/JAHA.121.021323>
621. Cha YM, Wokhlu A, Asirvatham SJ, Shen VK, Friedman PA, Munger TM, et al. Success of ablation for atrial fibrillation in isolated left ventricular diastolic dysfunction: a comparison to systolic dysfunction and normal ventricular function. *Circ Arrhythm Electrophysiol* 2011;**4**:724–32. <https://doi.org/10.1161/CIRCEP.110.960690>
622. Machino-Ohtsuka T, Seo Y, Ishizu T, Sugano A, Atsumi A, Yamamoto M, et al. Efficacy, safety, and outcomes of catheter ablation of atrial fibrillation in patients with heart failure with preserved ejection fraction. *J Am Coll Cardiol* 2013;**62**:1857–65. <https://doi.org/10.1016/j.jacc.2013.07.020>
623. Aldaas OM, Lupercio F, Darden D, Mylavarapu PS, Malladi CL, Han FT, et al. Meta-analysis of the usefulness of catheter ablation of atrial fibrillation in patients with heart failure with preserved ejection fraction. *Am J Cardiol* 2021;**142**:66–73. <https://doi.org/10.1016/j.amjcard.2020.11.039>
624. Black-Maier E, Ren X, Steinberg BA, Green CL, Barnett AS, Rosa NS, et al. Catheter ablation of atrial fibrillation in patients with heart failure and preserved ejection fraction. *Heart Rhythm* 2018;**15**:651–7. <https://doi.org/10.1016/j.hrthm.2017.12.001>
625. von Olshausen G, Benson L, Dahlström U, Lund LH, Savarese G, Braunschweig F. Catheter ablation for patients with atrial fibrillation and heart failure: insights from the Swedish Heart Failure Registry. *Eur J Heart Fail* 2022;**24**:1636–46. <https://doi.org/10.1002/ehf2.2604>
626. Shiraishi Y, Kohsaka S, Ikemura N, Kimura T, Katsumata Y, Tanimoto K, et al. Catheter ablation for patients with atrial fibrillation and heart failure with reduced and preserved ejection fraction: insights from the KiCS-AF multicentre cohort study. *Europace* 2023;**25**:83–91. <https://doi.org/10.1093/europace/eauc108>
627. Wu L, Narasimhan B, Ho KS, Zheng Y, Shah AN, Kantharia BK. Safety and complications of catheter ablation for atrial fibrillation: predictors of complications from an updated analysis of the national inpatient database. *J Cardiovasc Electrophysiol* 2021;**32**:1024–34. <https://doi.org/10.1111/jce.14979>
628. Tripathi B, Arora S, Kumar V, Abdelrahman M, Lahewala S, Dave M, et al. Temporal trends of in-hospital complications associated with catheter ablation of atrial fibrillation in the United States: an update from nationwide inpatient sample database (2011–2014). *J Cardiovasc Electrophysiol* 2018;**29**:715–24. <https://doi.org/10.1111/jce.13471>
629. Steinbeck G, Sinner MF, Lutz M, Müller-Nurasyid M, Kaab S, Reinecke H. Incidence of complications related to catheter ablation of atrial fibrillation and atrial flutter: a nationwide in-hospital analysis of administrative data for Germany in 2014. *Eur Heart J* 2018;**39**:4020–9. <https://doi.org/10.1093/eurheartj/ehy452>
630. Deshmukh A, Patel NJ, Pant S, Shah N, Chothani A, Mehta K, et al. In-hospital complications associated with catheter ablation of atrial fibrillation in the United States between 2000 and 2010: analysis of 93 801 procedures. *Circulation* 2013;**128**:2104–12. <https://doi.org/10.1161/CIRCULATIONAHA.113.003862>
631. Cheng EP, Liu CF, Yeo I, Markowitz SM, Thomas G, Ip JE, et al. Risk of mortality following catheter ablation of atrial fibrillation. *J Am Coll Cardiol* 2019;**74**:2254–64. <https://doi.org/10.1016/j.jacc.2019.08.1036>
632. Gawalko M, Duncker D, Manninger M, van der Velden RMJ, Hermans ANL, Verhaert DVM, et al. The European TeleCheck-AF project on remote app-based management of atrial fibrillation during the COVID-19 pandemic: centre and patient experiences. *Europace* 2021;**23**:1003–15. <https://doi.org/10.1093/europace/eaab050>
633. Rizas KD, Freyer L, Sappler N, von Stülpnagel L, Spielbichler P, Krasniqi A, et al. Smartphone-based screening for atrial fibrillation: a pragmatic randomized clinical trial. *Nat Med* 2022;**28**:1823–30. <https://doi.org/10.1038/s41591-022-01979-w>
634. Andrade JG, Champagne J, Dubuc M, Deyell MW, Verma A, Macle L, et al. Cryoballoon or radiofrequency ablation for atrial fibrillation assessed by continuous monitoring: a randomized clinical trial. *Circulation* 2019;**140**:1779–88. <https://doi.org/10.1161/CIRCULATIONAHA.119.042622>
635. Duytschaever M, Demolder A, Philips T, Sarkozy A, El Haddad M, Taghji P, et al. Pulmonary vein isolation with vs. without continued antiarrhythmic drug treatment in subjects with Recurrent Atrial Fibrillation (POWDER AF): results from a multicentre randomized trial. *Eur Heart J* 2018;**39**:1429–37. <https://doi.org/10.1093/eurheartj/ehx666>
636. Darkner S, Chen X, Hansen J, Pehrson S, Johannessen A, Nielsen JB, et al. Recurrence of arrhythmia following short-term oral AMIOdarone after Catheter ablation for atrial fibrillation: a double-blind, randomized, placebo-controlled study (AMIO-CAT trial). *Eur Heart J* 2014;**35**:3356–64. <https://doi.org/10.1093/eurheartj/ehu354>
637. Leong-Sit P, Roux JF, Zado E, Callans DJ, Garcia F, Lin D, et al. Antiarrhythmics after ablation of atrial fibrillation (SA study): six-month follow-up study. *Circ Arrhythm Electrophysiol* 2011;**4**:11–4. <https://doi.org/10.1161/CIRCEP.110.955393>
638. Kaitani K, Inoue K, Kobori A, Nakazawa Y, Ozawa T, Kurotobi T, et al. Efficacy of antiarrhythmic drugs short-term use after catheter ablation for atrial fibrillation (EAST-AF) trial. *Eur Heart J* 2016;**37**:610–8. <https://doi.org/10.1093/eurheartj/ehv501>
639. Noseworthy PA, Van Houten HK, Sangaralingham LR, Deshmukh AJ, Kapa S, Mulpuru SK, et al. Effect of antiarrhythmic drug initiation on readmission after catheter ablation for atrial fibrillation. *JACC Clin Electrophysiol* 2015;**1**:238–44. <https://doi.org/10.1016/j.jacep.2015.04.016>
640. Xu X, Alida CT, Yu B. Administration of antiarrhythmic drugs to maintain sinus rhythm after catheter ablation for atrial fibrillation: a meta-analysis. *Cardiovasc Ther* 2015;**33**:242–6. <https://doi.org/10.1111/1755-5922.12133>
641. Chen W, Liu H, Ling Z, Xu Y, Fan J, Du H, et al. Efficacy of short-term antiarrhythmic drugs use after catheter ablation of atrial fibrillation—a systematic review with meta-analyses and trial sequential analyses of randomized controlled trials. *PLoS One* 2016;**11**:e0156121. <https://doi.org/10.1371/journal.pone.0156121>
642. Schleberger R, Metzner A, Kuck KH, Andersen D, Willems S, Hoffmann E, et al. Antiarrhythmic drug therapy after catheter ablation for atrial fibrillation—insights from the German Ablation Registry. *Pharmacol Res Perspect* 2021;**9**:e00880. <https://doi.org/10.1002/prp2.880>
643. Zhang XD, Gu J, Jiang WF, Zhao L, Zhou L, Wang YL, et al. Optimal rhythm-control strategy for recurrent atrial tachycardia after catheter ablation of persistent atrial fibrillation: a randomized clinical trial. *Eur Heart J* 2014;**35**:1327–34. <https://doi.org/10.1093/eurheartj/ehu017>
644. Zhou L, He L, Wang W, Li C, Li S, Tang R, et al. Effect of repeat catheter ablation vs. antiarrhythmic drug therapy among patients with recurrent atrial tachycardia/atrial fibrillation after atrial fibrillation catheter ablation: data from CHINA-AF registry. *Europace* 2023;**25**:382–9. <https://doi.org/10.1093/europace/eauc169>
645. Fink T, Metzner A, Willems S, Eckardt L, Ince H, Brachmann J, et al. Procedural success, safety and patients satisfaction after second ablation of atrial fibrillation in the elderly: results from the German ablation registry. *Clin Res Cardiol* 2019;**108**:1354–63. <https://doi.org/10.1007/s00392-019-01471-5>

646. Winkle RA, Mead RH, Engel G, Kong MH, Fleming VW, Salcedo J, et al. Impact of obesity on atrial fibrillation ablation: patient characteristics, long-term outcomes, and complications. *Heart Rhythm* 2017;**14**:819–27. <https://doi.org/10.1016/j.hrthm.2017.02.023>
647. Sticherling C, Marin F, Birnie D, Boriani G, Calkins H, Dan G-A, et al. Antithrombotic management in patients undergoing electrophysiological procedures: a European Heart Rhythm Association (EHRA) position document endorsed by the ESC Working Group Thrombosis, Heart Rhythm Society (HRS), and Asia Pacific Heart Rhythm Society (APHRS). *EP Europace* 2015;**17**:1197–214. <https://doi.org/10.1093/eurpace/euv190>
648. Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA, et al. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. *J Interv Card Electrophysiol* 2012;**33**:171–257. <https://doi.org/10.1007/s10840-012-9672-7>
649. Noubiap JJ, Agbaedeng TA, Ndooudoungue AL, Nyaga UF, Kengne AP. Atrial thrombus detection on transoesophageal echocardiography in patients with atrial fibrillation undergoing cardioversion or catheter ablation: a pooled analysis of rates and predictors. *J Cardiovasc Electrophysiol* 2021;**32**:2179–88. <https://doi.org/10.1111/jce.15082>
650. Lurie A, Wang J, Hinnegan KJ, McIntyre WF, Belley-Côté EP, Amit G, et al. Prevalence of left atrial thrombus in anticoagulated patients with atrial fibrillation. *J Am Coll Cardiol* 2021;**77**:2875–86. <https://doi.org/10.1016/j.jacc.2021.04.036>
651. Efremidis M, Bazoukis G, Vlachos K, Prappa E, Megarisiotou A, Dragasis S, et al. Safety of catheter ablation of atrial fibrillation without pre- or peri-procedural imaging for the detection of left atrial thrombus in the era of uninterrupted anticoagulation. *J Arrhythm* 2021;**37**:28–32. <https://doi.org/10.1002/joa3.12466>
652. Diab M, Wazni OM, Saliba WJ, Tarakji KG, Ballout JA, Hutt E, et al. Ablation of atrial fibrillation without left atrial appendage imaging in patients treated with direct oral anticoagulants. *Circ Arrhythm Electrophysiol* 2020;**13**:e008301. <https://doi.org/10.1161/CIRCEP.119.008301>
653. Patel K, Natale A, Yang R, Trivedi C, Romero J, Briceno D, et al. Is transesophageal echocardiography necessary in patients undergoing ablation of atrial fibrillation on an uninterrupted direct oral anticoagulant regimen? Results from a prospective multicenter registry. *Heart Rhythm* 2020;**17**:2093–9. <https://doi.org/10.1016/j.hrthm.2020.07.017>
654. Mao YJ, Wang H, Huang PF. Meta-analysis of the safety and efficacy of using minimally interrupted novel oral anticoagulants in patients undergoing catheter ablation for atrial fibrillation. *J Interv Card Electrophysiol* 2021;**60**:407–17. <https://doi.org/10.1007/s10840-020-00754-6>
655. van Vugt SPG, Westra SW, Volleberg R, Hannink G, Nakamura R, de Asmundis C, et al. Meta-analysis of controlled studies on minimally interrupted vs. continuous use of non-vitamin K antagonist oral anticoagulants in catheter ablation for atrial fibrillation. *Europace* 2021;**23**:1961–9. <https://doi.org/10.1093/eurpace/euab175>
656. Ge Z, Faggioni M, Baber U, Sartori S, Sorrentino S, Farhan S, et al. Safety and efficacy of nonvitamin K antagonist oral anticoagulants during catheter ablation of atrial fibrillation: a systematic review and meta-analysis. *Cardiovasc Ther* 2018;**36**:e12457. <https://doi.org/10.1111/1755-5922.12457>
657. Asad ZUA, Akhtar KH, Jafry AH, Khan MH, Khan MS, Munir MB, et al. Uninterrupted versus interrupted direct oral anticoagulation for catheter ablation of atrial fibrillation: a systematic review and meta-analysis. *J Cardiovasc Electrophysiol* 2021;**32**:1995–2004. <https://doi.org/10.1111/jce.15043>
658. Mao YJ, Wang H, Huang PF. Peri-procedural novel oral anticoagulants dosing strategy during atrial fibrillation ablation: a meta-analysis. *Pacing Clin Electrophysiol* 2020;**43**:1104–14. <https://doi.org/10.1111/pace.14040>
659. Basu-Ray I, Khanra D, Kupó P, Bunch J, Theus SA, Mukherjee A, et al. Outcomes of uninterrupted vs interrupted periprocedural direct oral anticoagulants in atrial fibrillation ablation: a meta-analysis. *J Arrhythm* 2021;**37**:384–93. <https://doi.org/10.1002/joa3.12507>
660. Romero J, Cerrud-Rodriguez RC, Diaz JC, Rodriguez D, Arshad S, Alviz I, et al. Oral anticoagulation after catheter ablation of atrial fibrillation and the associated risk of thromboembolic events and intracranial hemorrhage: a systematic review and meta-analysis. *J Cardiovasc Electrophysiol* 2019;**30**:1250–7. <https://doi.org/10.1111/jce.14052>
661. Liu XH, Xu Q, Luo T, Zhang L, Liu HJ. Discontinuation of oral anticoagulation therapy after successful atrial fibrillation ablation: a systematic review and meta-analysis of prospective studies. *PLoS One* 2021;**16**:e0253709. <https://doi.org/10.1371/journal.pone.0253709>
662. Proietti R, AITurki A, Di Biase L, China P, Forleo G, Corrado A, et al. Anticoagulation after catheter ablation of atrial fibrillation: an unnecessary evil? A systematic review and meta-analysis. *J Cardiovasc Electrophysiol* 2019;**30**:468–78. <https://doi.org/10.1111/jce.13822>
663. Maduray K, Moneruzzaman M, Changwe GJ, Zhong J. Benefits and risks associated with long-term oral anticoagulation after successful atrial fibrillation catheter ablation: systematic review and meta-analysis. *Clin Appl Thromb Hemost* 2022;**28**:10760296221118480. <https://doi.org/10.1177/10760296221118480>
664. Brockmeyer M, Lin Y, Parco C, Karathanos A, Krieger T, Schulze V, et al. Uninterrupted anticoagulation during catheter ablation for atrial fibrillation: no difference in major bleeding and stroke between direct oral anticoagulants and vitamin K antagonists in an updated meta-analysis of randomised controlled trials. *Acta Cardiol* 2021;**76**:288–95. <https://doi.org/10.1080/00015385.2020.1724689>
665. Di Monaco A, Guida P, Vitulano N, Quadrini F, Troisi F, Langialonga T, et al. Catheter ablation of atrial fibrillation with uninterrupted anticoagulation: a meta-analysis of six randomized controlled trials. *J Cardiovasc Med (Hagerstown)* 2020;**21**:483–90. <https://doi.org/10.2459/JCM.0000000000000939>
666. Maesen B, Luermans J, Bidar E, Chaldoupi SM, Gelsomino S, Maessen JG, et al. A hybrid approach to complex arrhythmias. *Europace* 2021;**23**:ii28–33. <https://doi.org/10.1093/eurpace/eurab027>
667. van der Heijden CAJ, Vroomen M, Luermans JG, Vos R, Crijns H, Gelsomino S, et al. Hybrid versus catheter ablation in patients with persistent and longstanding persistent atrial fibrillation: a systematic review and meta-analysis. *Eur J Cardiothorac Surg* 2019;**56**:433–43. <https://doi.org/10.1093/ejcts/ezy475>
668. Boersma LV, Castella M, van Boven W, Berrueto A, Yilmaz A, Nadal M, et al. Atrial fibrillation catheter ablation versus surgical ablation treatment (FAST): a 2-center randomized clinical trial. *Circulation* 2012;**125**:23–30. <https://doi.org/10.1161/CIRCULATIONAHA.111.074047>
669. Castella M, Kotecha D, van Laar C, Wintgens L, Castillo Y, Kelder J, et al. Thoracoscopic vs. catheter ablation for atrial fibrillation: long-term follow-up of the FAST randomized trial. *Europace* 2019;**21**:746–53. <https://doi.org/10.1093/eurpace/euy325>
670. van der Heijden CAJ, Weberndörfer V, Vroomen M, Luermans JG, Chaldoupi SM, Bidar E, et al. Hybrid ablation versus repeated catheter ablation in persistent atrial fibrillation: a randomized controlled trial. *JACC Clin Electrophysiol* 2023;**9**:1013–23. <https://doi.org/10.1016/j.jacep.2022.12.011>
671. DeLurgio DB, Crossen KJ, Gill J, Blauth C, Oza SR, Magnano AR, et al. Hybrid convergent procedure for the treatment of persistent and long-standing persistent atrial fibrillation: results of CONVERGE clinical trial. *Circ Arrhythm Electrophysiol* 2020;**13**:e009288. <https://doi.org/10.1161/CIRCEP.120.009288>
672. Pokushalov E, Romanov A, Elesin D, Bogachev-Prokophiev A, Losik D, Bairamova S, et al. Catheter versus surgical ablation of atrial fibrillation after a failed initial pulmonary vein isolation procedure: a randomized controlled trial. *J Cardiovasc Electrophysiol* 2013;**24**:1338–43. <https://doi.org/10.1111/jce.12245>
673. Haldar S, Khan HR, Boyalla V, Kralj-Hans I, Jones S, Lord J, et al. Catheter ablation vs. thoracoscopic surgical ablation in long-standing persistent atrial fibrillation: CASA-AF randomized controlled trial. *Eur Heart J* 2020;**41**:4471–80. <https://doi.org/10.1093/eurheartj/ehaa658>
674. Doll N, Weimar T, Kosior DA, Bulava A, Mokracsek A, Mönnig G, et al. Efficacy and safety of hybrid epicardial and endocardial ablation versus endocardial ablation in patients with persistent and longstanding persistent atrial fibrillation: a randomised, controlled trial. *EClinicalMedicine* 2023;**61**:102052. <https://doi.org/10.1016/j.eclinm.2023.102052>
675. Malaisrie SC, McCarthy PM, Kruse J, Matsouka R, Andrei AC, Grau-Sepulveda MV, et al. Burden of preoperative atrial fibrillation in patients undergoing coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 2018;**155**:2358–2367 e1. <https://doi.org/10.1016/j.jtcvs.2018.01.069>
676. Saxena A, Dinh DT, Reid CM, Smith JA, Shardey GC, Newcomb AE. Does preoperative atrial fibrillation portend a poorer prognosis in patients undergoing isolated aortic valve replacement? A multicentre Australian study. *Can J Cardiol* 2013;**29**:697–703. <https://doi.org/10.1016/j.cjca.2012.08.016>
677. Quader MA, McCarthy PM, Gillinov AM, Alster JM, Cosgrove DM, 3rd, Lytle BW, et al. Does preoperative atrial fibrillation reduce survival after coronary artery bypass grafting? *Ann Thorac Surg* 2004;**77**:1514–22; discussion 1522–4. <https://doi.org/10.1016/j.athoracsur.2003.09.069>
678. Damiano RJ Jr, Schwartz FH, Bailey MS, Maniar HS, Munfakh NA, Moon MR, et al. The Cox Maze IV procedure: predictors of late recurrence. *J Thorac Cardiovasc Surg* 2011;**141**:113–21. <https://doi.org/10.1016/j.jtcvs.2010.08.067>
679. Cox JL, Schuessler RB, Boineau JP. The development of the Maze procedure for the treatment of atrial fibrillation. *Semin Thorac Cardiovasc Surg* 2000;**12**:2–14. [https://doi.org/10.1016/S1043-0679\(00\)70010-4](https://doi.org/10.1016/S1043-0679(00)70010-4)
680. Melby SJ, Zier A, Bailey MS, Cox JL, Lawton JS, Munfakh N, et al. A new era in the surgical treatment of atrial fibrillation: the impact of ablation technology and lesion set on procedural efficacy. *Ann Surg* 2006;**244**:583–92. <https://doi.org/10.1097/01.sla.0000237654.00841.26>
681. Badhwar V, Rankin JS, Damiano RJ Jr, Gillinov AM, Bakaeen FG, Edgerton JR, et al. The Society of Thoracic Surgeons 2017 clinical practice guidelines for the surgical treatment of atrial fibrillation. *Ann Thorac Surg* 2017;**103**:329–41. <https://doi.org/10.1016/j.athoracsur.2016.10.076>
682. Ad N, Henry L, Hunt S, Holmes SD. Impact of clinical presentation and surgeon experience on the decision to perform surgical ablation. *Ann Thorac Surg* 2013;**96**:763–8; discussion 768–9. <https://doi.org/10.1016/j.athoracsur.2013.03.066>
683. Cheng DC, Ad N, Martin J, Berglin EE, Chang BC, Doukas G, et al. Surgical ablation for atrial fibrillation in cardiac surgery: a meta-analysis and systematic review. *Innovations (Phila)* 2010;**5**:84–96. <https://doi.org/10.1177/155698451000500204>

684. McClure GR, Belley-Cote EP, Jaffer IH, Dvirnik N, An KR, Fortin G, et al. Surgical ablation of atrial fibrillation: a systematic review and meta-analysis of randomized controlled trials. *Europace* 2018;**20**:1442–50. <https://doi.org/10.1093/europace/eux336>
685. Phan K, Xie A, La Meir M, Black D, Yan TD. Surgical ablation for treatment of atrial fibrillation in cardiac surgery: a cumulative meta-analysis of randomised controlled trials. *Heart* 2014;**100**:722–30. <https://doi.org/10.1136/heartjnl-2013-305351>
686. Barnett SD, Ad N. Surgical ablation as treatment for the elimination of atrial fibrillation: a meta-analysis. *J Thorac Cardiovasc Surg* 2006;**131**:1029–35. <https://doi.org/10.1016/j.jtcvs.2005.10.020>
687. Gillinov AM, Gelijns AC, Parides MK, DeRose JJ, Jr, Moskowitz AJ, Voisine P, et al. Surgical ablation of atrial fibrillation during mitral-valve surgery. *N Engl J Med* 2015;**372**:1399–409. <https://doi.org/10.1056/NEJMoa1500528>
688. MacGregor RM, Bakir NH, Pedamallu H, Sinn LA, Maniar HS, Melby SJ, et al. Late results after stand-alone surgical ablation for atrial fibrillation. *J Thorac Cardiovasc Surg* 2022;**164**:1515–1528.e8. <https://doi.org/10.1016/j.jtcvs.2021.03.109>
689. Musharbash FN, Schill MR, Sinn LA, Schuessler RB, Maniar HS, Moon MR, et al. Performance of the Cox-Maze IV procedure is associated with improved long-term survival in patients with atrial fibrillation undergoing cardiac surgery. *J Thorac Cardiovasc Surg* 2018;**155**:159–70. <https://doi.org/10.1016/j.jtcvs.2017.09.095>
690. Rankin JS, Lerner DJ, Braid-Forbes MJ, McCrea MM, Badhwar V. Surgical ablation of atrial fibrillation concomitant to coronary-artery bypass grafting provides cost-effective mortality reduction. *J Thorac Cardiovasc Surg* 2020;**160**:675–686 e13. <https://doi.org/10.1016/j.jtcvs.2019.07.131>
691. Suwalski P, Kowalewski M, Jasinski M, Staromlynski J, Zembala M, Widenka K, et al. Survival after surgical ablation for atrial fibrillation in mitral valve surgery: analysis from the Polish National Registry of Cardiac Surgery Procedures (KROK). *J Thorac Cardiovasc Surg* 2019;**157**:1007–1018 e4. <https://doi.org/10.1016/j.jtcvs.2018.07.099>
692. Suwalski P, Kowalewski M, Jasinski M, Staromlynski J, Zembala M, Widenka K, et al. Surgical ablation for atrial fibrillation during isolated coronary artery bypass surgery. *Eur J Cardiothorac Surg* 2020;**57**:691–700. <https://doi.org/10.1093/ejcts/ezz298>
693. Wehbe M, Albert M, Lewalter T, Ouarrak T, Senges J, Hanke T, et al. The German cardiosurgery atrial fibrillation registry: 1-year follow-up outcomes. *Thorac Cardiovasc Surg* 2023;**71**:255–63. <https://doi.org/10.1055/s-0042-1750311>
694. Kim HJ, Kim YJ, Kim M, Yoo JS, Kim DH, Park DW, et al. Surgical ablation for atrial fibrillation during aortic and mitral valve surgery: a nationwide population-based cohort study. *J Thorac Cardiovasc Surg* 2024;**167**:981–93. <https://doi.org/10.1016/j.jtcvs.2022.08.038>
695. Ad N, Henry L, Hunt S, Holmes SD. Do we increase the operative risk by adding the Cox Maze III procedure to aortic valve replacement and coronary artery bypass surgery? *J Thorac Cardiovasc Surg* 2012;**143**:936–44. <https://doi.org/10.1016/j.jtcvs.2011.12.018>
696. Maesen B, van der Heijden CAJ, Bidar E, Vos R, Athanasios T, Maessen JG. Patient-reported quality of life after stand-alone and concomitant arrhythmia surgery: a systematic review and meta-analysis. *Interact Cardiovasc Thorac Surg* 2022;**34**:339–48. <https://doi.org/10.1093/icvts/ivab282>
697. Osmancik P, Budera P, Talavera D, Hlavicka J, Herman D, Holy J, et al. Five-year outcomes in cardiac surgery patients with atrial fibrillation undergoing concomitant surgical ablation versus no ablation. The long-term follow-up of the PRAGUE-12 study. *Heart Rhythm* 2019;**16**:1334–40. <https://doi.org/10.1016/j.hrthm.2019.05.001>
698. Lee R, Jivan A, Kruse J, McGee EC, Jr, Malaisrie SC, Bernstein R, et al. Late neurologic events after surgery for atrial fibrillation: rare but relevant. *Ann Thorac Surg* 2013;**95**:126–31; discussion 131–2. <https://doi.org/10.1016/j.athoracsurg.2012.08.048>
699. Kowalewski M, Pasierski M, Kolodziejczak M, Litwinowicz R, Kowalówka A, Wańha W, et al. Atrial fibrillation ablation improves late survival after concomitant cardiac surgery. *J Thorac Cardiovasc Surg* 2023;**166**:1656–1668.e8. <https://doi.org/10.1016/j.jtcvs.2022.04.035>
700. Cox JL, Ad N, Palazzo T. Impact of the maze procedure on the stroke rate in patients with atrial fibrillation. *J Thorac Cardiovasc Surg* 1999;**118**:833–40. [https://doi.org/10.1016/S0022-5223\(99\)70052-8](https://doi.org/10.1016/S0022-5223(99)70052-8)
701. Huffman MD, Karmali KN, Berendsen MA, Andrei AC, Kruse J, McCarthy PM, et al. Concomitant atrial fibrillation surgery for people undergoing cardiac surgery. *Cochrane Database Syst Rev* 2016;**8**:CD011814. <https://doi.org/10.1002/14651858.CD011814.pub2>
702. Kowalewski M, Pasierski M, Finke J, Kolodziejczak M, Staromlynski J, Litwinowicz R, et al. Permanent pacemaker implantation after valve and arrhythmia surgery in patients with preoperative atrial fibrillation. *Heart Rhythm* 2022;**19**:1442–9. <https://doi.org/10.1016/j.hrthm.2022.04.007>
703. Pokushalov E, Romanov A, Corbucci G, Cherniavsky A, Karaskov A. Benefit of ablation of first diagnosed paroxysmal atrial fibrillation during coronary artery bypass grafting: a pilot study. *Eur J Cardiothorac Surg* 2012;**41**:556–60. <https://doi.org/10.1093/ejcts/ezr101>
704. Yoo JS, Kim JB, Ro SK, Jung Y, Jung SH, Choo SJ, et al. Impact of concomitant surgical atrial fibrillation ablation in patients undergoing aortic valve replacement. *Circ J* 2014;**78**:1364–71. <https://doi.org/10.1253/circj.CJ-13-1533>
705. Malaisrie SC, Lee R, Kruse J, Lapin B, Wang EC, Bonow RO, et al. Atrial fibrillation ablation in patients undergoing aortic valve replacement. *J Heart Valve Dis* 2012;**21**:350–7.
706. Rankin JS, Lerner DJ, Braid-Forbes MJ, Ferguson MA, Badhwar V. One-year mortality and costs associated with surgical ablation for atrial fibrillation concomitant to coronary artery bypass grafting. *Eur J Cardiothorac Surg* 2017;**52**:471–7. <https://doi.org/10.1093/ejcts/ezx126>
707. Schill MR, Musharbash FN, Hansalia V, Greenberg JW, Melby SJ, Maniar HS, et al. Late results of the Cox-Maze IV procedure in patients undergoing coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 2017;**153**:1087–94. <https://doi.org/10.1016/j.jtcvs.2016.12.034>
708. Gupta D, Ding WY, Calvert P, Williams E, Das M, Tovmassian L, et al. Cryoballoon pulmonary vein isolation as first-line treatment for typical atrial flutter. *Heart* 2023;**109**:364–71. <https://doi.org/10.1136/heartjnl-2022-321729>
709. Steinberg C, Champagne J, Deyell MV, Dubuc M, Leong-Sit P, Calkins H, et al. Prevalence and outcome of early recurrence of atrial tachyarrhythmias in the cryoballoon vs irrigated radiofrequency catheter ablation (CIRCA-DOSE) study. *Heart Rhythm* 2021;**18**:1463–70. <https://doi.org/10.1016/j.hrthm.2021.06.1172>
710. Heijman J, Linz D, Schotten U. Dynamics of atrial fibrillation mechanisms and comorbidities. *Annu Rev Physiol* 2021;**83**:83–106. <https://doi.org/10.1146/annurev-physiol-031720-085307>
711. Fabritz L, Crijns H, Guasch E, Goette A, Hausler KG, Kotecha D, et al. Dynamic risk assessment to improve quality of care in patients with atrial fibrillation: the 7th AFNET/EHRA consensus conference. *Europace* 2021;**23**:329–44. <https://doi.org/10.1093/europace/eaab279>
712. Brandes A, Smit MD, Nguyen BO, Rienstra M, Van Gelder IC. Risk factor management in atrial fibrillation. *Arrhythm Electrophysiol Rev* 2018;**7**:118–27. <https://doi.org/10.15420/aer.2018.18.2>
713. Pokorney SD, Cocoros N, Al-Khalidi HR, Haynes K, Li S, Al-Khatib SM, et al. Effect of mailing educational material to patients with atrial fibrillation and their clinicians on use of oral anticoagulants: a randomized clinical trial. *JAMA Netw Open* 2022;**5**:e2214321. <https://doi.org/10.1001/jamanetworkopen.2022.14321>
714. Ritchie LA, Penson PE, Akpan A, Lip GYH, Lane DA. Integrated care for atrial fibrillation management: the role of the pharmacist. *Am J Med* 2022;**135**:1410–26. <https://doi.org/10.1016/j.amjmed.2022.07.014>
715. Guo Y, Guo J, Shi X, Yao Y, Sun Y, Xia Y, et al. Mobile health technology-supported atrial fibrillation screening and integrated care: a report from the mAFA-II trial long-term extension cohort. *Eur J Intern Med* 2020;**82**:105–11. <https://doi.org/10.1016/j.ejim.2020.09.024>
716. Yan H, Du YX, Wu FQ, Lu XY, Chen RM, Zhang Y. Effects of nurse-led multidisciplinary team management on cardiovascular hospitalization and quality of life in patients with atrial fibrillation: randomized controlled trial. *Int J Nurs Stud* 2022;**127**:104159. <https://doi.org/10.1016/j.ijnurstu.2021.104159>
717. Stewart S, Ball J, Horowitz JD, Marwick TH, Mahadevan G, Wong C, et al. Standard versus atrial fibrillation-specific management strategy (SAFETY) to reduce recurrent admission and prolong survival: pragmatic, multicentre, randomised controlled trial. *Lancet* 2015;**385**:775–84. [https://doi.org/10.1016/S0140-6736\(14\)61992-9](https://doi.org/10.1016/S0140-6736(14)61992-9)
718. Cox JL, Parkash R, Foster GA, Xie F, MacKillop JH, Ciaccia A, et al. Integrated management program advancing community treatment of atrial fibrillation (IMPACT-AF): a cluster randomized trial of a computerized clinical decision support tool. *Am Heart J* 2020;**224**:35–46. <https://doi.org/10.1016/j.ahj.2020.02.019>
719. Sposato LA, Stirling D, Saposnik G. Therapeutic decisions in atrial fibrillation for stroke prevention: the role of aversion to ambiguity and physicians' risk preferences. *J Stroke Cerebrovasc Dis* 2018;**27**:2088–95. <https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.03.005>
720. Noseworthy PA, Brito JP, Kunneman M, Hargraves IG, Zeballos-Palacios C, Montori VM, et al. Shared decision-making in atrial fibrillation: navigating complex issues in partnership with the patient. *J Interv Card Electrophysiol* 2019;**56**:159–63. <https://doi.org/10.1007/s10840-018-0465-5>
721. Poorcheraghi H, Negarandeh R, Pashaepoor S, Jorian J. Effect of using a mobile drug management application on medication adherence and hospital readmission among elderly patients with polypharmacy: a randomized controlled trial. *BMC Health Serv Res* 2023;**23**:1192. <https://doi.org/10.1186/s12913-023-10177-4>
722. Kotecha D, Chua WWL, Fabritz L, Hendriks J, Casadei B, Schotten U, et al. European Society of Cardiology (ESC) Atrial Fibrillation Guidelines Taskforce, the CATCH ME consortium, and the European Heart Rhythm Association (EHRA). European Society of Cardiology smartphone and tablet applications for patients with atrial fibrillation and their health care providers. *Europace* 2018;**20**:225–33. <https://doi.org/10.1093/europace/eux299>
723. Bunting KV, Gill SK, Sitch A, Mehta S, O'Connor K, Lip GY, et al. Improving the diagnosis of heart failure in patients with atrial fibrillation. *Heart* 2021;**107**:902–8. <https://doi.org/10.1136/heartjnl-2020-318557>
724. Donal E, Lip GY, Galderisi M, Goette A, Shah D, Marwan M, et al. EACVI/EHRA expert consensus document on the role of multi-modality imaging for the evaluation of patients with atrial fibrillation. *Eur Heart J Cardiovasc Imaging* 2016;**17**:355–83. <https://doi.org/10.1093/ehjci/jev354>

725. Bunting KV, O'Connor K, Steeds RP, Kotecha D. Cardiac imaging to assess left ventricular systolic function in atrial fibrillation. *Am J Cardiol* 2021;**139**:40–9. <https://doi.org/10.1016/j.amjcard.2020.10.012>
726. Timperley J, Mitchell AR, Becher H. Contrast echocardiography for left ventricular opacification. *Heart* 2003;**89**:1394–7. <https://doi.org/10.1136/heart.89.12.1394>
727. Kotecha D, Mohamed M, Shantsila E, Popescu BA, Steeds RP. Is echocardiography valid and reproducible in patients with atrial fibrillation? A systematic review. *Europace* 2017;**19**:1427–38. <https://doi.org/10.1093/europace/eux027>
728. Quintana RA, Dong T, Vajapey R, Reyalden R, Kwon DH, Harb S, et al. Preprocedural multimodality imaging in atrial fibrillation. *Circ Cardiovasc Imaging* 2022;**15**:e014386. <https://doi.org/10.1161/CIRCIMAGING.122.014386>
729. Laubrock K, von Loesch T, Steinmetz M, Lotz J, Frahm J, Uecker M, et al. Imaging of arrhythmia: real-time cardiac magnetic resonance imaging in atrial fibrillation. *Eur J Radiol Open* 2022;**9**:100404. <https://doi.org/10.1016/j.ejro.2022.100404>
730. Sciagrà R, Sotgia B, Boni N, Pupi A. Assessment of the influence of atrial fibrillation on gated SPECT perfusion data by comparison with simultaneously acquired nongated SPECT data. *J Nucl Med* 2008;**49**:1283–7. <https://doi.org/10.2967/jnumed.108.051797>
731. Clayton B, Roobottom C, Morgan-Hughes G. CT coronary angiography in atrial fibrillation: a comparison of radiation dose and diagnostic confidence with retrospective gating vs prospective gating with systolic acquisition. *Br J Radiol* 2015;**88**:20150533. <https://doi.org/10.1259/bjr.20150533>
732. Thrall G, Lane D, Carroll D, Lip GY. Quality of life in patients with atrial fibrillation: a systematic review. *Am J Med* 2006;**119**:448.e1–19. <https://doi.org/10.1016/j.amjmed.2005.10.057>
733. Steinberg BA, Dorian P, Anstrom KJ, Hess R, Mark DB, Noseworthy PA, et al. Patient-reported outcomes in atrial fibrillation research: results of a ClinicalTrials.gov analysis. *JACC Clin Electrophysiol* 2019;**5**:599–605. <https://doi.org/10.1016/j.jacep.2019.03.008>
734. Potpara TS, Mihajlovic M, Zec N, Marinkovic M, Kovacevic V, Simic J, et al. Self-reported treatment burden in patients with atrial fibrillation: quantification, major determinants, and implications for integrated holistic management of the arrhythmia. *Europace* 2020;**22**:1788–97. <https://doi.org/10.1093/europace/eaab210>
735. Moons P, Norekvål TM, Arbelo E, Borregaard B, Casadei B, Cosyns B, et al. Placing patient-reported outcomes at the centre of cardiovascular clinical practice: implications for quality of care and management. *Eur Heart J* 2023;**44**:3405–22. <https://doi.org/10.1093/eurheartj/ehad514>
736. Allan KS, Aves T, Henry S, Banfield L, Victor JC, Dorian P, et al. Health-related quality of life in patients with atrial fibrillation treated with catheter ablation or antiarrhythmic drug therapy: a systematic review and meta-analysis. *CJC Open* 2020;**2**:286–95. <https://doi.org/10.1016/j.cjco.2020.03.013>
737. Vanderhout S, Fergusson DA, Cook JA, Taljaard M. Patient-reported outcomes and target effect sizes in pragmatic randomized trials in ClinicalTrials.gov: a cross-sectional analysis. *PLoS Med* 2022;**19**:e1003896. <https://doi.org/10.1371/journal.pmed.1003896>
738. Steinberg BA, Piccini JP, Sr. Tackling patient-reported outcomes in atrial fibrillation and heart failure: identifying disease-specific symptoms? *Cardiol Clin* 2019;**37**:139–46. <https://doi.org/10.1016/j.ccl.2019.01.013>
739. Hårdén M, Nyström B, Bengtson A, Medin J, Frison L, Edvardsson N. Responsiveness of AF6, a new, short, validated, atrial fibrillation-specific questionnaire—symptomatic benefit of direct current cardioversion. *J Interv Card Electrophysiol* 2010;**28**:185–91. <https://doi.org/10.1007/s10840-010-9487-3>
740. Tailachidis P, Tsimtsiou Z, Galanis P, Theodorou M, Kouvelas D, Athanasakis K. The atrial fibrillation effect on Quality-of-Life (AFQTL) questionnaire: cultural adaptation and validation of the Greek version. *Hippokratia* 2016;**20**:264–7.
741. Moreira RS, Bassolli L, Coutinho E, Ferrer P, Bragança EO, Carvalho AC, et al. Reproducibility and reliability of the quality of life questionnaire in patients with atrial fibrillation. *Arq Bras Cardiol* 2016;**106**:171–81. <https://doi.org/10.5935/abc.20160026>
742. Arribas F, Ormaetxe JM, Peinado R, Perulero N, Ramírez P, Badia X. Validation of the AF-QoL, a disease-specific quality of life questionnaire for patients with atrial fibrillation. *Europace* 2010;**12**:364–70. <https://doi.org/10.1093/europace/eup421>
743. Bragança EO, Filho BL, Maria VH, Levy D, de Paola AA. Validating a new quality of life questionnaire for atrial fibrillation patients. *Int J Cardiol* 2010;**143**:391–8. <https://doi.org/10.1016/j.ijcard.2009.03.087>
744. International Consortium for Health Outcomes Measurement. *Atrial fibrillation data collection reference guide Version 5.0.1*. <https://connect.ichom.org/wp-content/uploads/2023/02/03-Atrial-Fibrillation-Reference-Guide-2023.5.0.1.pdf>
745. Dan GA, Dan AR, Ivanescu A, Buzea AC. Acute rate control in atrial fibrillation: an urgent need for the clinician. *Eur Heart J Suppl* 2022;**24**:D3–D10. <https://doi.org/10.1093/eurheartjsupp/suac022>
746. Shima N, Miyamoto K, Kato S, Yoshida T, Uchino S; AFTER-ICU study group. Primary success of electrical cardioversion for new-onset atrial fibrillation and its association with clinical course in non-cardiac critically ill patients: sub-analysis of a multicenter observational study. *J Intensive Care* 2021;**9**:46. <https://doi.org/10.1186/s40560-021-00562-8>
747. Betthausen KD, Gibson GA, Piche SL, Pope HE. Evaluation of amiodarone use for new-onset atrial fibrillation in critically ill patients with septic shock. *Hosp Pharm* 2021;**56**:116–23. <https://doi.org/10.1177/0018578719868405>
748. Drikite L, Bedford JP, O'Bryan L, Petrinic T, Rajappan K, Doidge J, et al. Treatment strategies for new onset atrial fibrillation in patients treated on an intensive care unit: a systematic scoping review. *Crit Care* 2021;**25**:257. <https://doi.org/10.1186/s13054-021-03684-5>
749. Bedford JP, Johnson A, Redfern O, Gerry S, Doidge J, Harrison D, et al. Comparative effectiveness of common treatments for new-onset atrial fibrillation within the ICU: accounting for physiological status. *J Crit Care* 2022;**67**:149–56. <https://doi.org/10.1016/j.jccr.2021.11.005>
750. Iwahashi N, Takahashi H, Abe T, Okada K, Akiyama E, Matsuzawa Y, et al. Urgent control of rapid atrial fibrillation by landiolol in patients with acute decompensated heart failure with severely reduced ejection fraction. *Circ Rep* 2019;**1**:422–30. <https://doi.org/10.1253/circrep.CR-19-0076>
751. Unger M, Morelli A, Singer M, Radermacher P, Rehberg S, Trimmel H, et al. Landiolol in patients with septic shock resident in an intensive care unit (LANDI-SEP): study protocol for a randomized controlled trial. *Trials* 2018;**19**:637. <https://doi.org/10.1186/s13063-018-3024-6>
752. Gonzalez-Pacheco H, Marquez MF, Arias-Mendoza A, Alvarez-Sangabriel A, Eid-Lidt G, Gonzalez-Hermosillo A, et al. Clinical features and in-hospital mortality associated with different types of atrial fibrillation in patients with acute coronary syndrome with and without ST elevation. *J Cardiol* 2015;**66**:148–54. <https://doi.org/10.1016/j.jicc.2014.11.001>
753. Krijthe BP, Leening MJ, Heeringa J, Kors JA, Hofman A, Franco OH, et al. Unrecognized myocardial infarction and risk of atrial fibrillation: the Rotterdam Study. *Int J Cardiol* 2013;**168**:1453–7. <https://doi.org/10.1016/j.ijcard.2012.12.057>
754. Soliman EZ, Safford MM, Muntner P, Khodnava Y, Dawood FZ, Zakai NA, et al. Atrial fibrillation and the risk of myocardial infarction. *JAMA Intern Med* 2014;**174**:107–14. <https://doi.org/10.1001/jamainternmed.2013.11912>
755. Kraleš S, Schneider K, Lang S, Suselbeck T, Borggreffe M. Incidence and severity of coronary artery disease in patients with atrial fibrillation undergoing first-time coronary angiography. *PLoS One* 2011;**6**:e24964. <https://doi.org/10.1371/journal.pone.0024964>
756. Coscia T, Nestelberger T, Boeddinghaus J, Lopez-Ayala P, Koehlin L, Miró Ò, et al. Characteristics and outcomes of type 2 myocardial infarction. *JAMA Cardiol* 2022;**7**:427–34. <https://doi.org/10.1001/jamacardio.2022.0043>
757. Guimaraes PO, Zakrotsky P, Goyal A, Lopes RD, Kaltenbach LA, Wang TY. Usefulness of antithrombotic therapy in patients with atrial fibrillation and acute myocardial infarction. *Am J Cardiol* 2019;**123**:12–8. <https://doi.org/10.1016/j.amjcard.2018.09.031>
758. Erez A, Goldenberg I, Sabbag A, Nof E, Zahger D, Atar S, et al. Temporal trends and outcomes associated with atrial fibrillation observed during acute coronary syndrome: real-world data from the Acute Coronary Syndrome Israeli Survey (ACSIS), 2000–2013. *Clin Cardiol* 2017;**40**:275–80. <https://doi.org/10.1002/clc.22654>
759. Vrints C, Andreotti F, Koskinas K, Rossell X, Adamo M, Ainslie J, et al. 2024 ESC Guidelines for the management of chronic coronary syndromes. *Eur Heart J* 2024. <https://doi.org/10.1093/eurheartj/ehae177>
760. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. *Eur Heart J* 2023;**44**:3720–826. <https://doi.org/10.1093/eurheartj/ehad191>
761. Park DY, Wang P, An S, Grimshaw AA, Frampton J, Ohman EM, et al. Shortening the duration of dual antiplatelet therapy after percutaneous coronary intervention for acute coronary syndrome: a systematic review and meta-analysis. *Am Heart J* 2022;**251**:101–14. <https://doi.org/10.1016/j.ahj.2022.05.019>
762. Gargiulo G, Goette A, Tijssen J, Eckardt L, Lewalter T, Vranckx P, et al. Safety and efficacy outcomes of double vs. triple antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary intervention: a systematic review and meta-analysis of non-vitamin K antagonist oral anticoagulant-based randomized clinical trials. *Eur Heart J* 2019;**40**:3757–67. <https://doi.org/10.1093/eurheartj/ehz732>
763. Dewilde WJ, Oirbans T, Verheugt FW, Kelder JC, De Smet BJ, Herrman JP, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet* 2013;**381**:1107–15. [https://doi.org/10.1016/S0140-6736\(12\)62177-1](https://doi.org/10.1016/S0140-6736(12)62177-1)
764. Lopes RD, Heizer G, Aronson R, Vora AN, Massaro T, Mehran R, et al. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. *N Engl J Med* 2019;**380**:1509–24. <https://doi.org/10.1056/NEJMoa1817083>
765. Gibson CM, Mehran R, Bode C, Halperin J, Verheugt FW, Wildgoose P, et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. *N Engl J Med* 2016;**375**:2423–34. <https://doi.org/10.1056/NEJMoa1611594>
766. Cannon CP, Bhatt DL, Oldgren J, Lip GYH, Ellis SG, Kimura T, et al. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. *N Engl J Med* 2017;**377**:1513–24. <https://doi.org/10.1056/NEJMoa1708454>
767. Vranckx P, Valgimigli M, Eckardt L, Tijssen J, Lewalter T, Gargiulo G, et al. Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, phase 3b trial. *Lancet* 2019;**394**:1335–43. [https://doi.org/10.1016/S0140-6736\(19\)31872-0](https://doi.org/10.1016/S0140-6736(19)31872-0)
768. Lopes RD, Hong H, Harskamp RE, Bhatt DL, Mehran R, Cannon CP, et al. Safety and efficacy of antithrombotic strategies in patients with atrial fibrillation undergoing

- percutaneous coronary intervention: a network meta-analysis of randomized controlled trials. *JAMA Cardiol* 2019;**4**:747–55. <https://doi.org/10.1001/jamacardio.2019.1880>
769. Oldgren J, Steg PG, Hohnloser SH, Lip GYH, Kimura T, Nordaby M, et al. Dabigatran dual therapy with ticagrelor or clopidogrel after percutaneous coronary intervention in atrial fibrillation patients with or without acute coronary syndrome: a subgroup analysis from the RE-DUAL PCI trial. *Eur Heart J* 2019;**40**:1553–62. <https://doi.org/10.1093/eurheartj/ehz059>
 770. Potpara TS, Mujovic N, Proietti M, Dagres N, Hindricks G, Collet JP, et al. Revisiting the effects of omitting aspirin in combined antithrombotic therapies for atrial fibrillation and acute coronary syndromes or percutaneous coronary interventions: meta-analysis of pooled data from the PIONEER AF-PCI, RE-DUAL PCI, and AUGUSTUS trials. *Europace* 2020;**22**:33–46. <https://doi.org/10.1093/eurpace/euz259>
 771. Haller PM, Sulzgruber P, Kaufmann C, Geelhoed B, Tamargo J, Wassmann S, et al. Bleeding and ischaemic outcomes in patients treated with dual or triple antithrombotic therapy: systematic review and meta-analysis. *Eur Heart J Cardiovasc Pharmacother* 2019;**5**:226–36. <https://doi.org/10.1093/ehjcvp/pvz021>
 772. Lopes RD, Hong H, Harskamp RE, Bhatt DL, Mehran R, Cannon CP, et al. Optimal antithrombotic regimens for patients with atrial fibrillation undergoing percutaneous coronary intervention: an updated network meta-analysis. *JAMA Cardiol* 2020;**5**:582–9. <https://doi.org/10.1001/jamacardio.2019.6175>
 773. Lopes RD, Vora AN, Liaw D, Granger CB, Darius H, Goodman SG, et al. An open-label, 2 × 2 factorial, randomized controlled trial to evaluate the safety of apixaban vs. vitamin K antagonist and aspirin vs. placebo in patients with atrial fibrillation and acute coronary syndrome and/or percutaneous coronary intervention: rationale and design of the AUGUSTUS trial. *Am Heart J* 2018;**200**:17–23. <https://doi.org/10.1016/j.jahj.2018.03.001>
 774. Windecker S, Lopes RD, Massaro T, Jones-Burton C, Granger CB, Aronson R, et al. Antithrombotic therapy in patients with atrial fibrillation and acute coronary syndrome treated medically or with percutaneous coronary intervention or undergoing elective percutaneous coronary intervention: insights from the AUGUSTUS trial. *Circulation* 2019;**140**:1921–32. <https://doi.org/10.1161/CIRCULATIONAHA.119.043308>
 775. Harskamp RE, Fanaroff AC, Lopes RD, Wojdyla DM, Goodman SG, Thomas LE, et al. Antithrombotic therapy in patients with atrial fibrillation after acute coronary syndromes or percutaneous intervention. *J Am Coll Cardiol* 2022;**79**:417–27. <https://doi.org/10.1016/j.jacc.2021.11.035>
 776. Alexander JH, Wojdyla D, Vora AN, Thomas L, Granger CB, Goodman SG, et al. Risk/benefit tradeoff of antithrombotic therapy in patients with atrial fibrillation early and late after an acute coronary syndrome or percutaneous coronary intervention: insights from AUGUSTUS. *Circulation* 2020;**141**:1618–27. <https://doi.org/10.1161/CIRCULATIONAHA.120.046534>
 777. Moayyedi P, Eikelboom JW, Bosch J, Connolly SJ, Dyal L, Shestakovska O, et al. Safety of proton pump inhibitors based on a large, multi-year, randomized trial of patients receiving rivaroxaban or aspirin. *Gastroenterology* 2019;**157**:682–691.e2. <https://doi.org/10.1053/j.gastro.2019.05.056>
 778. Jeridi D, Pellat A, Ginestet C, Assaf A, Hallit R, Corre F, et al. The safety of long-term proton pump inhibitor use on cardiovascular health: a meta-analysis. *J Clin Med* 2022;**11**:4096. <https://doi.org/10.3390/jcm11144096>
 779. Scally B, Emberson JR, Spata E, Reith C, Davies K, Halls H, et al. Effects of gastroprotectant drugs for the prevention and treatment of peptic ulcer disease and its complications: a meta-analysis of randomised trials. *Lancet Gastroenterol Hepatol* 2018;**3**:231–41. [https://doi.org/10.1016/S2468-1253\(18\)30037-2](https://doi.org/10.1016/S2468-1253(18)30037-2)
 780. Fiedler KA, Maeng M, Mehilli J, Schulz-Schupke S, Byrne RA, Sibbing D, et al. Duration of triple therapy in patients requiring oral anticoagulation after drug-eluting stent implantation: the ISAR-TRIPE trial. *J Am Coll Cardiol* 2015;**65**:1619–29. <https://doi.org/10.1016/j.jacc.2015.02.050>
 781. Matsumura-Nakano Y, Shizuta S, Komasa A, Morimoto T, Masuda H, Shiomi H, et al. Open-label randomized trial comparing oral anticoagulation with and without single antiplatelet therapy in patients with atrial fibrillation and stable coronary artery disease beyond 1 year after coronary stent implantation. *Circulation* 2019;**139**:604–16. <https://doi.org/10.1161/CIRCULATIONAHA.118.036768>
 782. Jensen T, Thrane PG, Olesen KKW, Würtz M, Mortensen MB, Glydenkerne C, et al. Antithrombotic treatment beyond 1 year after percutaneous coronary intervention in patients with atrial fibrillation. *Eur Heart J Cardiovasc Pharmacother* 2023;**9**:208–19. <https://doi.org/10.1093/ehjcvp/pvac058>
 783. Vitalis A, Shantsila A, Proietti M, Vohra RK, Kay M, Olshansky B, et al. Peripheral arterial disease in patients with atrial fibrillation: the AFFIRM study. *Am J Med* 2021;**134**:514–8. <https://doi.org/10.1016/j.amjmed.2020.08.026>
 784. Wasmer K, Unrath M, Köbe J, Malyar NM, Freisinger E, Meyborg M, et al. Atrial fibrillation is a risk marker for worse in-hospital and long-term outcome in patients with peripheral artery disease. *Int J Cardiol* 2015;**199**:223–8. <https://doi.org/10.1016/j.ijcard.2015.06.094>
 785. Griffin WF, Salahuddin T, O'Neal WT, Soliman EZ. Peripheral arterial disease is associated with an increased risk of atrial fibrillation in the elderly. *Europace* 2016;**18**:794–8. <https://doi.org/10.1093/eurpace/euv369>
 786. Lin LY, Lee CH, Yu CC, Tsai CT, Lai LP, Hwang JJ, et al. Risk factors and incidence of ischemic stroke in Taiwanese with nonvalvular atrial fibrillation—a nation wide database analysis. *Atherosclerosis* 2011;**217**:292–5. <https://doi.org/10.1016/j.atherosclerosis.2011.03.033>
 787. Su MI, Cheng YC, Huang YC, Liu CW. The impact of atrial fibrillation on one-year mortality in patients with severe lower extremity arterial disease. *J Clin Med* 2022;**11**:1936. <https://doi.org/10.3390/jcm11071936>
 788. Winkel TA, Hoeks SE, Schouten O, Zeymer U, Limbourg T, Baumgartner I, et al. Prognosis of atrial fibrillation in patients with symptomatic peripheral arterial disease: data from the REduction of Atherothrombosis for Continued Health (REACH) Registry. *Eur J Vasc Endovasc Surg* 2010;**40**:9–16. <https://doi.org/10.1016/j.ejvs.2010.03.003>
 789. Nejim B, Mathlouthi A, Weaver L, Faateh M, Arhuidese I, Malas MB. Safety of carotid artery revascularization procedures in patients with atrial fibrillation. *J Vasc Surg* 2020;**72**:2069–2078.e4. <https://doi.org/10.1016/j.jvs.2020.01.074>
 790. Jones WS, Hellkamp AS, Halperin J, Piccini JP, Breithardt G, Singer DE, et al. Efficacy and safety of rivaroxaban compared with warfarin in patients with peripheral artery disease and non-valvular atrial fibrillation: insights from ROCKET AF. *Eur Heart J* 2014;**35**:242–9. <https://doi.org/10.1093/eurheartj/ehz492>
 791. Aboyans V, Ricco JB, Bartelink MEL, Björck M, Brodmann M, Cohnert T, et al. 2017 ESC Guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European Society for Vascular Surgery (ESVS): document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries. Endorsed by: the European Stroke Organization (ESO) The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). *Eur Heart J* 2018;**39**:763–816. <https://doi.org/10.1093/eurheartj/ehx095>
 792. Schirmer CM, Bulsara KR, Al-Mufti F, Haranahalli N, Thibault L, Hettis SW. Antiplatelets and antithrombotics in neurointerventional procedures: guideline update. *J Neurointerv Surg* 2023;**15**:1155–62. <https://doi.org/10.1136/jnis-2022-019844>
 793. Berge E, Whiteley W, Audebert H, De Marchis GM, Fonseca AC, Padiglioni C, et al. European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. *Eur Stroke J* 2021;**6**:L–LXII. <https://doi.org/10.1177/2396987321989865>
 794. Caso V, Masuhr F. A narrative review of nonvitamin K antagonist oral anticoagulant use in secondary stroke prevention. *J Stroke Cerebrovasc Dis* 2019;**28**:2363–75. <https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.05.017>
 795. Fischer U, Koga M, Strbian D, Branca M, Abend S, Trelle S, et al. Early versus later anticoagulation for stroke with atrial fibrillation. *N Engl J Med* 2023;**388**:2411–21. <https://doi.org/10.1056/NEJMoa2303048>
 796. Oldgren J, Åsberg S, Hijazi Z, Wester P, Bertilsson M, Norrving B. Early versus delayed non-vitamin K antagonist oral anticoagulant therapy after acute ischemic stroke in atrial fibrillation (TIMING): a registry-based randomized controlled noninferiority study. *Circulation* 2022;**146**:1056–66. <https://doi.org/10.1161/CIRCULATIONAHA.122.060666>
 797. Schreuder F, van Nieuwenhuizen KM, Hofmeijer J, Vermeer SE, Kerkhoff H, Zock E, et al. Apixaban versus no anticoagulation after anticoagulation-associated intracerebral haemorrhage in patients with atrial fibrillation in The Netherlands (APACHE-AF): a randomised, open-label, phase 2 trial. *Lancet Neurol* 2021;**20**:907–16. [https://doi.org/10.1016/S1474-4422\(21\)00298-2](https://doi.org/10.1016/S1474-4422(21)00298-2)
 798. SoSTART Collaboration. Effects of oral anticoagulation for atrial fibrillation after spontaneous intracranial haemorrhage in the UK: a randomised, open-label, assessor-masked, pilot-phase, non-inferiority trial. *Lancet Neurol* 2021;**20**:842–53. [https://doi.org/10.1016/S1474-4422\(21\)00264-7](https://doi.org/10.1016/S1474-4422(21)00264-7)
 799. Klein Klouwenberg PM, Frencken JF, Kuipers S, Ong DS, Peelen LM, van Vught LA, et al. Incidence, predictors, and outcomes of new-onset atrial fibrillation in critically ill patients with sepsis. A cohort study. *Am J Respir Crit Care Med* 2017;**195**:205–11. <https://doi.org/10.1164/rccm.201603-0618OC>
 800. Gundlund A, Olesen JB, Butt JH, Christensen MA, Gislason GH, Torp-Pedersen C, et al. One-year outcomes in atrial fibrillation presenting during infections: a nationwide registry-based study. *Eur Heart J* 2020;**41**:1112–9. <https://doi.org/10.1093/eurheartj/ehz873>
 801. Induruwa I, Hennebry E, Hennebry J, Thakur M, Warburton EA, Khadjooi K. Sepsis-driven atrial fibrillation and ischaemic stroke. Is there enough evidence to recommend anticoagulation? *Eur J Intern Med* 2022;**98**:32–6. <https://doi.org/10.1016/j.ejim.2021.02.022>
 802. Ko D, Saleeba C, Sadiq H, Crawford S, Paul T, Shi Q, et al. Secondary precipitants of atrial fibrillation and anticoagulation therapy. *J Am Heart Assoc* 2021;**10**:e021746. <https://doi.org/10.1161/JAHA.121.021746>
 803. Li YG, Borgi M, Lip GY. Atrial fibrillation occurring initially during acute medical illness: the heterogeneous nature of disease, outcomes and management strategies. *Eur Heart J Acute Cardiovasc Care* 2018;**10**:2048872618801763. <https://doi.org/10.1177/2048872618801763>
 804. Lowres N, Hillis GS, Gladman MA, Kol M, Rogers J, Chow V, et al. Self-monitoring for recurrence of secondary atrial fibrillation following non-cardiac surgery or acute

- illness: a pilot study. *Int J Cardiol Heart Vasc* 2020;**29**:100566. <https://doi.org/10.1016/j.ijcha.2020.100566>
805. Søgaard M, Skjøth F, Nielsen PB, Smit J, Dalager-Pedersen M, Larsen TB, et al. Thromboembolic risk in patients with pneumonia and new-onset atrial fibrillation not receiving anticoagulation therapy. *JAMA Netw Open* 2022;**5**:e2213945. <https://doi.org/10.1001/jamanetworkopen.2022.13945>
 806. Walkey AJ, Hammill BG, Curtis LH, Benjamin EJ. Long-term outcomes following development of new-onset atrial fibrillation during sepsis. *Chest* 2014;**146**:1187–95. <https://doi.org/10.1378/chest.14-0003>
 807. McIntyre WF, Um KJ, Cheung CC, Belley-Côté EP, Dingwall O, Devereaux PJ, et al. Atrial fibrillation detected initially during acute medical illness: a systematic review. *Eur Heart J Acute Cardiovasc Care* 2019;**8**:130–41. <https://doi.org/10.1177/2048872618799748>
 808. Marcus GM, Vittinghoff E, Whitman IR, Joyce S, Yang V, Nah G, et al. Acute consumption of alcohol and discrete atrial fibrillation events. *Ann Intern Med* 2021;**174**:1503–9. <https://doi.org/10.7326/M21-0228>
 809. Marcus GM, Modrow MF, Schmid CH, Sigona K, Nah G, Yang J, et al. Individualized studies of triggers of paroxysmal atrial fibrillation: the I-STOP-AFib randomized clinical trial. *JAMA Cardiol* 2022;**7**:167–74. <https://doi.org/10.1001/jamacardio.2021.5010>
 810. Lin AL, Nah G, Tang JJ, Vittinghoff E, Dewland TA, Marcus GM. Cannabis, cocaine, methamphetamine, and opiates increase the risk of incident atrial fibrillation. *Eur Heart J* 2022;**43**:4933–42. <https://doi.org/10.1093/eurheartj/ehac558>
 811. Butt JH, Olesen JB, Havers-Borgersen E, Gundlund A, Andersson C, Gislason GH, et al. Risk of thromboembolism associated with atrial fibrillation following noncardiac surgery. *J Am Coll Cardiol* 2018;**72**:2027–36. <https://doi.org/10.1016/j.jacc.2018.07.088>
 812. Gundlund A, Kümler T, Bonde AN, Butt JH, Gislason GH, Torp-Pedersen C, et al. Comparative thromboembolic risk in atrial fibrillation with and without a secondary precipitant—Danish nationwide cohort study. *BMJ Open* 2019;**9**:e028468. <https://doi.org/10.1136/bmjopen-2018-028468>
 813. Walkey AJ, Quinn EK, Winter MR, McManus DD, Benjamin EJ. Practice patterns and outcomes associated with use of anticoagulation among patients with atrial fibrillation during sepsis. *JAMA Cardiol* 2016;**1**:682–90. <https://doi.org/10.1001/jamacardio.2016.2181>
 814. Darwish OS, Strube S, Nguyen HM, Tanios MA. Challenges of anticoagulation for atrial fibrillation in patients with severe sepsis. *Ann Pharmacother* 2013;**47**:1266–71. <https://doi.org/10.1177/1060028013500938>
 815. Quon MJ, Behloul H, Pilote L. Anticoagulant use and risk of ischemic stroke and bleeding in patients with secondary atrial fibrillation associated with acute coronary syndromes, acute pulmonary disease, or sepsis. *JACC Clin Electrophysiol* 2018;**4**:386–93. <https://doi.org/10.1016/j.jacep.2017.08.003>
 816. Echahidi N, Pibarot P, O'Hara G, Mathieu P. Mechanisms, prevention, and treatment of atrial fibrillation after cardiac surgery. *J Am Coll Cardiol* 2008;**51**:793–801. <https://doi.org/10.1016/j.jacc.2007.10.043>
 817. Gillinov AM, Bagiella E, Moskowitz AJ, Raiten JM, Groh MA, Bowdish ME, et al. Rate control versus rhythm control for atrial fibrillation after cardiac surgery. *N Engl J Med* 2016;**374**:1911–21. <https://doi.org/10.1056/NEJMoa1602002>
 818. Gaudino M, Di Franco A, Rong LQ, Piccini J, Mack M. Postoperative atrial fibrillation: from mechanisms to treatment. *Eur Heart J* 2023;**44**:1020–39. <https://doi.org/10.1093/eurheartj/ehad019>
 819. Kotecha D, Castella M. Is it time to treat post-operative atrial fibrillation just like regular atrial fibrillation? *Eur Heart J* 2020;**41**:652–654a. <https://doi.org/10.1093/eurheartj/ehz412>
 820. Konstantino Y, Zelnik Yovel D, Friger MD, Sahar G, Knyazer B, Amit G. Postoperative atrial fibrillation following coronary artery bypass graft surgery predicts long-term atrial fibrillation and stroke. *Isr Med Assoc J* 2016;**18**:744–8.
 821. Lee SH, Kang DR, Uhm JS, Shim J, Sung JH, Kim JY, et al. New-onset atrial fibrillation predicts long-term newly developed atrial fibrillation after coronary artery bypass graft. *Am Heart J* 2014;**167**:593–600.e1. <https://doi.org/10.1016/j.ahj.2013.12.010>
 822. Lin MH, Kamel H, Singer DE, Wu YL, Lee M, Ovbiagele B. Perioperative/postoperative atrial fibrillation and risk of subsequent stroke and/or mortality. *Stroke* 2019;**50**:1364–71. <https://doi.org/10.1161/STROKEAHA.118.023921>
 823. Alturki A, Marafi M, Proietti R, Cardinale D, Blackwell R, Dorian P, et al. Major adverse cardiovascular events associated with postoperative atrial fibrillation after noncardiac surgery: a systematic review and meta-analysis. *Circ Arrhythm Electrophysiol* 2020;**13**:e007437. <https://doi.org/10.1161/CIRCEP.119.007437>
 824. Goyal P, Kim M, Krishnan U, McCullough SA, Cheung JW, Kim LK, et al. Post-operative atrial fibrillation and risk of heart failure hospitalization. *Eur Heart J* 2022;**43**:2971–80. <https://doi.org/10.1093/eurheartj/ehac285>
 825. Eikelboom R, Sanjanwala R, Le ML, Yamashita MH, Arora RC. Postoperative atrial fibrillation after cardiac surgery: a systematic review and meta-analysis. *Ann Thorac Surg* 2021;**111**:544–54. <https://doi.org/10.1016/j.athoracsur.2020.05.104>
 826. Benedetto U, Gaudino MF, Dimagli A, Gerry S, Gray A, Lees B, et al. Postoperative atrial fibrillation and long-term risk of stroke after isolated coronary artery bypass graft surgery. *Circulation* 2020;**142**:1320–9. <https://doi.org/10.1161/CIRCULATIONAHA.120.046940>
 827. Taha A, Nielsen SJ, Bergfeldt L, Ahlsson A, Friberg L, Björck S, et al. New-onset atrial fibrillation after coronary artery bypass grafting and long-term outcome: a population-based nationwide study from the SWEDEHEART registry. *J Am Heart Assoc* 2021;**10**:e017966. <https://doi.org/10.1161/JAHA.120.017966>
 828. Dobrev D, Aguilar M, Heijman J, Guichard JB, Nattel S. Postoperative atrial fibrillation: mechanisms, manifestations and management. *Nat Rev Cardiol* 2019;**16**:417–36. <https://doi.org/10.1038/s41569-019-0166-5>
 829. Mathew JP, Fontes ML, Tudor IC, Ramsay J, Duke P, Mazer CD, et al. A multicenter risk index for atrial fibrillation after cardiac surgery. *JAMA* 2004;**291**:1720–9. <https://doi.org/10.1001/jama.291.14.1720>
 830. Villareal RP, Hariharan R, Liu BC, Kar B, Lee VV, Elayda M, et al. Postoperative atrial fibrillation and mortality after coronary artery bypass surgery. *J Am Coll Cardiol* 2004;**43**:742–8. <https://doi.org/10.1016/j.jacc.2003.11.023>
 831. Cardinale D, Sandri MT, Colombo A, Salvatici M, Tedeschi I, Bacchiani G, et al. Prevention of atrial fibrillation in high-risk patients undergoing lung cancer surgery: the PRESAGE trial. *Ann Surg* 2016;**264**:244–51. <https://doi.org/10.1097/SLA.0000000000001626>
 832. Ojima T, Nakamori M, Nakamura M, Katsuda M, Hayata K, Kato T, et al. Randomized clinical trial of lidoilol hydrochloride for the prevention of atrial fibrillation and post-operative complications after oesophagectomy for cancer. *Br J Surg* 2017;**104**:1003–9. <https://doi.org/10.1002/bjs.10548>
 833. Arsenault KA, Yusuf AM, Crystal E, Healey JS, Morillo CA, Nair GM, et al. Interventions for preventing post-operative atrial fibrillation in patients undergoing heart surgery. *Cochrane Database Syst Rev* 2013;**1**:CD003611. <https://doi.org/10.1002/14651858.CD003611.pub3>
 834. Ozyaydin M, Icli A, Yucel H, Akcay S, Peker O, Erdogan D, et al. Metoprolol vs. carvedilol or carvedilol plus N-acetyl cysteine on post-operative atrial fibrillation: a randomized, double-blind, placebo-controlled study. *Eur Heart J* 2013;**34**:597–604. <https://doi.org/10.1093/eurheartj/ehs423>
 835. O'Neal JB, Billings F, Liu X, Shotwell MS, Liang Y, Shah AS, et al. Effect of preoperative beta-blocker use on outcomes following cardiac surgery. *Am J Cardiol* 2017;**120**:1293–7. <https://doi.org/10.1016/j.amjcard.2017.07.012>
 836. Ziff OJ, Samra M, Howard JP, Bromage DI, Ruschitzka F, Francis DP, et al. Beta-blocker efficacy across different cardiovascular indications: an umbrella review and meta-analytic assessment. *BMC Med* 2020;**18**:103. <https://doi.org/10.1186/s12916-020-01564-3>
 837. Tisdale JE, Wroblewski HA, Wall DS, Rieger KM, Hammoud ZT, Young JV, et al. A randomized trial evaluating amiodarone for prevention of atrial fibrillation after pulmonary resection. *Ann Thorac Surg* 2009;**88**:886–93; discussion 894–5. <https://doi.org/10.1016/j.athoracsur.2009.04.074>
 838. Auer J, Weber T, Berent R, Puschmann R, Hartl P, Ng CK, et al. A comparison between oral antiarrhythmic drugs in the prevention of atrial fibrillation after cardiac surgery: the pilot Study of Prevention of Postoperative Atrial Fibrillation (SPPAF), a randomized, placebo-controlled trial. *Am Heart J* 2004;**147**:636–43. <https://doi.org/10.1016/j.ahj.2003.10.041>
 839. Buckley MS, Nolan PE, Jr, Slack MK, Tisdale JE, Hilleman DE, Copeland JG. Amiodarone prophylaxis for atrial fibrillation after cardiac surgery: meta-analysis of dose response and timing of initiation. *Pharmacotherapy* 2007;**27**:360–8. <https://doi.org/10.1592/phco.27.3.360>
 840. Riber LP, Christensen TD, Jensen HK, Højsgaard A, Pilegaard HK. Amiodarone significantly decreases atrial fibrillation in patients undergoing surgery for lung cancer. *Ann Thorac Surg* 2012;**94**:339–44; discussion 345–6. <https://doi.org/10.1016/j.athoracsur.2011.12.096>
 841. Couffignal C, Amour J, Ait-Hamou N, Cholley B, Fellahi JL, Duval X, et al. Timing of β -blocker reintroduction and the occurrence of postoperative atrial fibrillation after cardiac surgery: a prospective cohort study. *Anesthesiology* 2020;**132**:267–79. <https://doi.org/10.1097/ALN.0000000000003064>
 842. Piccini JP, Ahlsson A, Dorian P, Gillinov MA, Kowey PR, Mack MJ, et al. Design and rationale of a phase 2 study of NeurOtoxin (Botulinum Toxin Type A) for the PreVent of post-operative atrial fibrillation—the NOVA study. *Am Heart J* 2022;**245**:51–9. <https://doi.org/10.1016/j.ahj.2021.10.114>
 843. O'Brien B, Burrage PS, Ngai JY, Prutkin JM, Huang CC, Xu X, et al. Society of Cardiovascular Anesthesiologists/European Association of Cardiothoracic Anaesthetists Practice Advisory for the management of perioperative atrial fibrillation in patients undergoing cardiac surgery. *J Cardiothorac Vasc Anesth* 2019;**33**:12–26. <https://doi.org/10.1053/j.jvca.2018.09.039>
 844. Gaudino M, Sanna T, Ballman KV, Robinson NB, Hameed I, Audisio K, et al. Posterior left pericardiectomy for the prevention of atrial fibrillation after cardiac surgery: an adaptive, single-centre, single-blind, randomised, controlled trial. *Lancet* 2021;**398**:2075–83. [https://doi.org/10.1016/S0140-6736\(21\)02490-9](https://doi.org/10.1016/S0140-6736(21)02490-9)
 845. Abdelaziz A, Hafez AH, Elaraby A, Roshdy MR, Abdelaziz M, Eltohy MA, et al. Posterior pericardiectomy for the prevention of atrial fibrillation after cardiac surgery: a systematic review and meta-analysis of 25 randomised controlled trials. *EuroIntervention* 2023;**19**:e305–17. <https://doi.org/10.4244/EIJ-D-22-00948>
 846. Soletti GJ, Perezgrovas-Olaria R, Harik L, Rahouma M, Dimagli A, Alzhari T, et al. Effect of posterior pericardiectomy in cardiac surgery: a systematic review and

- meta-analysis of randomized controlled trials. *Front Cardiovasc Med* 2022;**9**:1090102. <https://doi.org/10.3389/fcvm.2022.1090102>
847. Conen D, Ke Wang M, Popova E, Chan MTV, Landoni G, Cata JP, et al. Effect of colchicine on perioperative atrial fibrillation and myocardial injury after non-cardiac surgery in patients undergoing major thoracic surgery (COP-AF): an international randomised trial. *Lancet* 2023;**402**:1627–35. [https://doi.org/10.1016/S0140-6736\(23\)01689-6](https://doi.org/10.1016/S0140-6736(23)01689-6)
 848. Fragão-Marques M, Teixeira F, Mancio J, Seixas N, Rocha-Neves J, Falcão-Pires I, et al. Impact of oral anticoagulation therapy on postoperative atrial fibrillation outcomes: a systematic review and meta-analysis. *Thromb J* 2021;**19**:89. <https://doi.org/10.1186/s12959-021-00342-2>
 849. Neves IA, Magalhães A, Lima da Silva G, Almeida AG, Borges M, Costa J, et al. Anticoagulation therapy in patients with post-operative atrial fibrillation: systematic review with meta-analysis. *Vascul Pharmacol* 2022;**142**:106929. <https://doi.org/10.1016/j.vph.2021.106929>
 850. Daoud EG, Strickberger SA, Man KC, Goyal R, Deeb GM, Bolling SF, et al. Preoperative amiodarone as prophylaxis against atrial fibrillation after heart surgery. *N Engl J Med* 1997;**337**:1785–91. <https://doi.org/10.1056/NEJM199712183372501>
 851. Yagdi T, Nalbantgil S, Ayik F, Apaydin A, Islamoglu F, Posacioglu H, et al. Amiodarone reduces the incidence of atrial fibrillation after coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 2003;**125**:1420–5. [https://doi.org/10.1016/S0022-5223\(02\)73292-3](https://doi.org/10.1016/S0022-5223(02)73292-3)
 852. Butt JH, Xian Y, Peterson ED, Olsen PS, Rorth R, Gundlund A, et al. Long-term thromboembolic risk in patients with postoperative atrial fibrillation after coronary artery bypass graft surgery and patients with nonvalvular atrial fibrillation. *JAMA Cardiol* 2018;**3**:417–24. <https://doi.org/10.1001/jamacardio.2018.0405>
 853. Gialdini G, Nearing K, Bhavé PD, Bonuccelli U, Iadecola C, Healey JS, et al. Perioperative atrial fibrillation and the long-term risk of ischemic stroke. *JAMA* 2014;**312**:616–22. <https://doi.org/10.1001/jama.2014.9143>
 854. Horwich P, Butth KJ, Legare JF. New onset postoperative atrial fibrillation is associated with a long-term risk for stroke and death following cardiac surgery. *J Card Surg* 2013;**28**:8–13. <https://doi.org/10.1111/jocs.12033>
 855. Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet* 2008;**371**:1839–47. [https://doi.org/10.1016/S0140-6736\(08\)60601-7](https://doi.org/10.1016/S0140-6736(08)60601-7)
 856. Hart RG, Diener HC, Coutts SB, Easton JD, Granger CB, O'Donnell MJ, et al. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol* 2014;**13**:429–38. [https://doi.org/10.1016/S1474-4422\(13\)70310-7](https://doi.org/10.1016/S1474-4422(13)70310-7)
 857. Sanna T, Diener HC, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA, et al. Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med* 2014;**370**:2478–86. <https://doi.org/10.1056/NEJMoa1313600>
 858. Rubiera M, Aires A, Antonenko K, Lémeret S, Nolte CH, Putaala J, et al. European Stroke Organisation (ESO) guideline on screening for subclinical atrial fibrillation after stroke or transient ischaemic attack of undetermined origin. *Eur Stroke J* 2022;**7**:VI. <https://doi.org/10.1177/23969873221099478>
 859. von Falkenhausen AS, Feil K, Sinner MF, Schönecker S, Müller J, Wischmann J, et al. Atrial fibrillation risk assessment after embolic stroke of undetermined source. *Ann Neurol* 2023;**93**:479–88. <https://doi.org/10.1002/ana.26545>
 860. Gladstone DJ, Spring M, Dorian P, Panzov V, Thorpe KE, Hall J, et al. Atrial fibrillation in patients with cryptogenic stroke. *N Engl J Med* 2014;**370**:2467–77. <https://doi.org/10.1056/NEJMoa1311376>
 861. Wächter R, Gröschel K, Gelbrich G, Hamann GF, Kermer P, Liman J, et al. Holter-electrocardiogram-monitoring in patients with acute ischaemic stroke (Find-AF(RANDOMISED)): an open-label randomised controlled trial. *Lancet Neurol* 2017;**16**:282–90. [https://doi.org/10.1016/S1474-4422\(17\)30002-9](https://doi.org/10.1016/S1474-4422(17)30002-9)
 862. Buck BH, Hill MD, Quinn FR, Butcher KS, Menon BK, Gulamhusein S, et al. Effect of implantable vs prolonged external electrocardiographic monitoring on atrial fibrillation detection in patients with ischemic stroke: the PER DIEM randomized clinical trial. *JAMA* 2021;**325**:2160–8. <https://doi.org/10.1001/jama.2021.6128>
 863. Bernstein RA, Kamel H, Granger CB, Piccini JP, Sethi PP, Katz JM, et al. Effect of long-term continuous cardiac monitoring vs usual care on detection of atrial fibrillation in patients with stroke attributed to large- or small-vessel disease: the STROKE-AF randomized clinical trial. *JAMA* 2021;**325**:2169–77. <https://doi.org/10.1001/jama.2021.6470>
 864. Tsigoulis G, Katsanos AH, Köhrmann M, Caso V, Perren F, Palaiodimos L, et al. Duration of implantable cardiac monitoring and detection of atrial fibrillation in ischemic stroke patients: a systematic review and meta-analysis. *J Stroke* 2019;**21**:302–11. <https://doi.org/10.5853/jos.2019.01067>
 865. Sagris D, Harrison SL, Buckley BJR, Ntaios G, Lip GYH. Long-term cardiac monitoring after embolic stroke of undetermined source: search longer, look harder. *Am J Med* 2022;**135**:e311–7. <https://doi.org/10.1016/j.amjmed.2022.04.030>
 866. Liantinioti C, Palaiodimos L, Tympas K, Parissis J, Theodorou A, Ikonomidis I, et al. Potential utility of neurosonology in paroxysmal atrial fibrillation detection in patients with cryptogenic stroke. *J Clin Med* 2019;**8**:2002. <https://doi.org/10.3390/jcm8112002>
 867. Tsigoulis G, Katsanos AH, Grory BM, Köhrmann M, Ricci BA, Tsioufis K, et al. Prolonged cardiac rhythm monitoring and secondary stroke prevention in patients with cryptogenic cerebral ischemia. *Stroke* 2019;**50**:2175–80. <https://doi.org/10.1161/STROKEAHA.119.025169>
 868. Favilla CG, Ingala E, Jara J, Fessler E, Cucchiara B, Messé SR, et al. Predictors of finding occult atrial fibrillation after cryptogenic stroke. *Stroke* 2015;**46**:1210–5. <https://doi.org/10.1161/STROKEAHA.114.007763>
 869. Lip GY, Nielsen PB. Should patients with atrial fibrillation and 1 stroke risk factor (CHA2DS2-VASc score 1 in men, 2 in women) be anticoagulated? Yes: even 1 stroke risk factor confers a real risk of stroke. *Circulation* 2016;**133**:1498–503; discussion 1503. <https://doi.org/10.1161/CIRCULATIONAHA.115.016713>
 870. Ricci B, Chang AD, Hemendinger M, Dakay K, Cutting S, Burton T, et al. A simple score that predicts paroxysmal atrial fibrillation on outpatient cardiac monitoring after embolic stroke of unknown source. *J Stroke Cerebrovasc Dis* 2018;**27**:1692–6. <https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.01.028>
 871. Kwong C, Ling AY, Crawford MH, Zhao SX, Shah NH. A clinical score for predicting atrial fibrillation in patients with cryptogenic stroke or transient ischemic attack. *Cardiology* 2017;**138**:133–40. <https://doi.org/10.1159/000476030>
 872. Li YG, Bisson A, Bodin A, Herbert J, Grammatico-Guillon L, Joung B, et al. C(2) HEST score and prediction of incident atrial fibrillation in poststroke patients: a French nationwide study. *J Am Heart Assoc* 2019;**8**:e012546. <https://doi.org/10.1161/JAHA.119.012546>
 873. Haeusler KG, Gröschel K, Köhrmann M, Anker SD, Brachmann J, Böhm M, et al. Expert opinion paper on atrial fibrillation detection after ischemic stroke. *Clin Res Cardiol* 2018;**107**:871–80. <https://doi.org/10.1007/s00392-018-1256-9>
 874. Dilaveris PE, Antoniou CK, Caiani EG, Casado-Arroyo R, Climent A, Cluitmans M, et al. ESC working group on e-cardiology position paper: accuracy and reliability of electrocardiogram monitoring in the detection of atrial fibrillation in cryptogenic stroke patients: in collaboration with the Council on Stroke, the European Heart Rhythm Association, and the Digital Health Committee. *Eur Heart J Digit Health* 2022;**3**:341–58. <https://doi.org/10.1093/ehjdh/ztac026>
 875. Diener HC, Sacco RL, Easton JD, Granger CB, Bernstein RA, Uchiyama S, et al. Dabigatran for prevention of stroke after embolic stroke of undetermined source. *N Engl J Med* 2019;**380**:1906–17. <https://doi.org/10.1056/NEJMoa1813959>
 876. Hart RG, Sharma M, Mundl H, Kasner SE, Bangdiwala SI, Berkowitz SD, et al. Rivaroxaban for stroke prevention after embolic stroke of undetermined source. *N Engl J Med* 2018;**378**:2191–201. <https://doi.org/10.1056/NEJMoa1802686>
 877. Poli S, Meissner C, Baezner HJ, Kraft A, Hillenbrand F, Hobohm C, et al. Apixaban for treatment of embolic stroke of undetermined source (ATTICUS) randomized trial—update of patient characteristics and study timeline after interim analysis. *Eur Heart J* 2021;**42**:ehab724.2070. <https://doi.org/10.1093/eurheartj/ehab724.2070>
 878. Vaidya VR, Arora S, Patel N, Badheka AO, Patel N, Agnihotri K, et al. Burden of arrhythmia in pregnancy. *Circulation* 2017;**135**:619–21. <https://doi.org/10.1161/CIRCULATIONAHA.116.026681>
 879. Lee MS, Chen W, Zhang Z, Duan L, Ng A, Spencer HT, et al. Atrial fibrillation and atrial flutter in pregnant women—a population-based study. *J Am Heart Assoc* 2016;**5**:e003182. <https://doi.org/10.1161/JAHA.115.003182>
 880. Tamirisa KP, Elkayam U, Briller JE, Mason PK, Pillarisetti J, Merchant FM, et al. Arrhythmias in pregnancy. *JACC Clin Electrophysiol* 2022;**8**:120–35. <https://doi.org/10.1016/j.jacep.2021.10.004>
 881. Salam AM, Ertekin E, van Hagen IM, Al Suwaidi J, Ruys TPE, Johnson MR, et al. Atrial fibrillation or flutter during pregnancy in patients with structural heart disease: data from the ROPAC (Registry on Pregnancy and Cardiac Disease). *JACC Clin Electrophysiol* 2015;**1**:284–92. <https://doi.org/10.1016/j.jacep.2015.04.013>
 882. Chokesuwattanasakul R, Thongprayoon C, Bathini T, O'Corragain OA, Sharma K, Prechawat S, et al. Incidence of atrial fibrillation in pregnancy and clinical significance: a meta-analysis. *Adv Med Sci* 2019;**64**:415–22. <https://doi.org/10.1016/j.advm.2019.07.003>
 883. Tamirisa KP, Dye C, Bond RM, Hollier LM, Marinescu K, Vaseghi M, et al. Arrhythmias and heart failure in pregnancy: a dialogue on multidisciplinary collaboration. *J Cardiovasc Dev Dis* 2022;**9**:199. <https://doi.org/10.3390/jcdd9070199>
 884. Al Bahawi T, Aqeeli A, Harrison SL, Lane DA, Skjøth F, Buchan I, et al. Pregnancy-related complications and incidence of atrial fibrillation: a systematic review. *J Clin Med* 2023;**12**:1316. <https://doi.org/10.3390/jcm12041316>
 885. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, Blomstrom-Lundqvist C, Cifkova R, De Bonis M, et al. 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy. *Eur Heart J* 2018;**39**:3165–241. <https://doi.org/10.1093/eurheartj/ehy340>
 886. Areia AL, Mota-Pinto A. Experience with direct oral anticoagulants in pregnancy—a systematic review. *J Perinat Med* 2022;**50**:457–61. <https://doi.org/10.1515/jpm-2021-0457>
 887. Ueberham L, Hindricks G. Anticoagulation in special patient populations with atrial fibrillation. *Herz* 2021;**46**:323–8. <https://doi.org/10.1007/s00059-021-05042-1>
 888. Bateman BT, Heide-Jørgensen U, Einarsdóttir K, Engeland A, Furu K, Gissler M, et al. β -Blocker use in pregnancy and the risk for congenital malformations: an international cohort study. *Ann Intern Med* 2018;**169**:665–73. <https://doi.org/10.7326/M18-0338>
 889. Butters L, Kennedy S, Rubin PC. Atenolol in essential hypertension during pregnancy. *BMJ* 1990;**301**:587–9. <https://doi.org/10.1136/bmj.301.6752.587>

890. Ramlakhan KP, Kauling RM, Schenkelaars N, Segers D, Yap SC, Post MC, et al. Supraventricular arrhythmia in pregnancy. *Heart* 2022;**108**:1674–81. <https://doi.org/10.1136/heartjnl-2021-320451>
891. Katritsis DG, Boriani G, Cosio FG, Hindricks G, Jais P, Josephson ME, et al. European Heart Rhythm Association (EHRA) consensus document on the management of supraventricular arrhythmias, endorsed by Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLAECE). *Eur Heart J* 2017;**19**:465–511. <https://doi.org/10.1093/eurheartj/ehw301>
892. Moore JS, Teefey P, Rao K, Berlowitz MS, Chae SH, Yankowitz J. Maternal arrhythmia: a case report and review of the literature. *Obstet Gynecol Surv* 2012;**67**:298–312. <https://doi.org/10.1097/OGX.0b013e318253a76e>
893. Wang YC, Chen CH, Su HY, Yu MH. The impact of maternal cardioversion on fetal haemodynamics. *Eur J Obstet Gynecol Reprod Biol* 2006;**126**:268–9. <https://doi.org/10.1016/j.ejogrb.2005.11.021>
894. European Heart Rhythm Association; European Association for Cardio-Thoracic Surgery; Camm AJ, Kirchhof P, Lip GY, Schotten U, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 2010;**31**:2369–429. <https://doi.org/10.1093/eurheartj/ehq278>
895. Kockova R, Kocka V, Kiernan T, Fahy GJ. Ibutilide-induced cardioversion of atrial fibrillation during pregnancy. *J Cardiovasc Electrophysiol* 2007;**18**:545–7. <https://doi.org/10.1111/j.1540-8167.2006.00752.x>
896. Georgiopoulos G, Tsiachris D, Kordalis A, Kontogiannis C, Spartalim M, Pietri P, et al. Pharmacotherapeutic strategies for atrial fibrillation in pregnancy. *Expert Opin Pharmacother* 2019;**20**:1625–36. <https://doi.org/10.1080/14656566.2019.1621290>
897. Jensen AS, Idorn L, Nørager B, Vejlsstrup N, Sondergaard L. Anticoagulation in adults with congenital heart disease: the who, the when and the how? *Heart* 2015;**101**:424–9. <https://doi.org/10.1136/heartjnl-2014-305576>
898. Pujol C, Niesert AC, Engelhardt A, Schoen P, Kusmenkov E, Pittrow D, et al. Usefulness of direct oral anticoagulants in adult congenital heart disease. *Am J Cardiol* 2016;**117**:450–5. <https://doi.org/10.1016/j.amjcard.2015.10.062>
899. Yang H, Bouma BJ, Dimopoulos K, Khairy P, Ladouceur M, Niwa K, et al. Non-vitamin K antagonist oral anticoagulants (NOACs) for thromboembolic prevention, are they safe in congenital heart disease? Results of a worldwide study. *Int J Cardiol* 2020;**299**:123–30. <https://doi.org/10.1016/j.ijcard.2019.06.014>
900. Renda G, Ricci F, Giugliano RP, De Caterina R. Non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation and valvular heart disease. *J Am Coll Cardiol* 2017;**69**:1363–71. <https://doi.org/10.1016/j.jacc.2016.12.038>
901. Caldeira D, David C, Costa J, Ferreira JJ, Pinto FJ. Non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation and valvular heart disease: systematic review and meta-analysis. *Eur Heart J Cardiovasc Pharmacother* 2018;**4**:111–8. <https://doi.org/10.1093/ehjcvp/pvx028>
902. Ammash NM, Phillips SD, Hodge DO, Connolly HM, Grogan MA, Friedman PA, et al. Outcome of direct current cardioversion for atrial arrhythmias in adults with congenital heart disease. *Int J Cardiol* 2012;**154**:270–4. <https://doi.org/10.1016/j.ijcard.2010.09.028>
903. Feltes TF, Friedman RA. Transesophageal echocardiographic detection of atrial thrombi in patients with nonfibrillation atrial tachyarrhythmias and congenital heart disease. *J Am Coll Cardiol* 1994;**24**:1365–70. [https://doi.org/10.1016/0735-1097\(94\)90121-X](https://doi.org/10.1016/0735-1097(94)90121-X)
904. Roos-Hesselink JW, Meijboom FJ, Spitaels SE, van Domburg R, van Rijen EH, Utens EM, et al. Excellent survival and low incidence of arrhythmias, stroke and heart failure long-term after surgical ASD closure at young age. A prospective follow-up study of 21–33 years. *Eur Heart J* 2003;**24**:190–7. [https://doi.org/10.1016/S0195-668X\(02\)00383-4](https://doi.org/10.1016/S0195-668X(02)00383-4)
905. Mas JL, Derumeaux G, Guillon B, Massardier E, Hosseini H, Mechtaouf L, et al. Patent foramen ovale closure or anticoagulation vs. antiplatelets after stroke. *N Engl J Med* 2017;**377**:1011–21. <https://doi.org/10.1056/NEJMoa1705915>
906. Gutierrez SD, Earing MG, Singh AK, Tweddell JS, Bartz PJ. Atrial tachyarrhythmias and the Cox-Maze procedure in congenital heart disease. *Congenit Heart Dis* 2013;**8**:434–9. <https://doi.org/10.1111/chd.12031>
907. Kobayashi J, Yamamoto F, Nakano K, Sasako Y, Kitamura S, Kosakai Y. Maze procedure for atrial fibrillation associated with atrial septal defect. *Circulation* 1998;**98**:I399–402.
908. Shim H, Yang JH, Park PW, Jeong DS, Jun TG. Efficacy of the Maze procedure for atrial fibrillation associated with atrial septal defect. *Korean J Thorac Cardiovasc Surg* 2013;**46**:98–103. <https://doi.org/10.5090/kjtc.2013.46.2.98>
909. Sherwin ED, Triedman JK, Walsh EP. Update on interventional electrophysiology in congenital heart disease: evolving solutions for complex hearts. *Circ Arrhythm Electrophysiol* 2013;**6**:1032–40. <https://doi.org/10.1161/CIRCEP.113.000313>
910. Chiha M, Samarasinghe S, Kabaker AS. Thyroid storm: an updated review. *J Intensive Care Med* 2015;**30**:131–40. <https://doi.org/10.1177/0885066613498053>
911. Y-Hassan S, Falhammar H. Cardiovascular manifestations and complications of pheochromocytomas and paragangliomas. *J Clin Med* 2020;**9**:2435. <https://doi.org/10.3390/jcm9082435>
912. Baumgartner C, da Costa BR, Collet TH, Feller M, Floriani C, Bauer DC, et al. Thyroid function within the normal range, subclinical hypothyroidism, and the risk of atrial fibrillation. *Circulation* 2017;**136**:2100–16. <https://doi.org/10.1161/CIRCULATIONAHA.117.028753>
913. Huang M, Yang S, Ge G, Zhi H, Wang L. Effects of thyroid dysfunction and the thyroid-stimulating hormone levels on the risk of atrial fibrillation: a systematic review and dose-response meta-analysis from cohort studies. *Endocr Pract* 2022;**28**:822–31. <https://doi.org/10.1016/j.eprac.2022.05.008>
914. Shin DG, Kang MK, Han D, Choi S, Cho JR, Lee N. Enlarged left atrium and decreased left atrial strain are associated with atrial fibrillation in patients with hyperthyroidism irrespective of conventional risk factors. *Int J Cardiovasc Imaging* 2022;**38**:613–20. <https://doi.org/10.1007/s10554-021-02450-6>
915. Sawin CT, Geller A, Wolf PA, Belanger AJ, Baker E, Bacharach P, et al. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. *N Engl J Med* 1994;**331**:1249–52. <https://doi.org/10.1056/NEJM199411103311901>
916. Lyon AR, López-Fernández T, Couch LS, Asteggiano R, Aznar MC, Bergler-Klein J, et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). *Eur Heart J* 2022;**43**:4229–361. <https://doi.org/10.1093/eurheartj/ehac244>
917. El Sabbagh R, Azar NS, Eid AA, Azar ST. Thyroid dysfunctions due to immune checkpoint inhibitors: a review. *Int J Gen Med* 2020;**13**:1003–9. <https://doi.org/10.2147/IJGM.S261433>
918. Gammage MD, Parle JV, Holder RL, Roberts LM, Hobbs FD, Wilson S, et al. Association between serum free thyroxine concentration and atrial fibrillation. *Arch Intern Med* 2007;**167**:928–34. <https://doi.org/10.1001/archinte.167.9.928>
919. Selmer C, Olesen JB, Hansen ML, Lindhardsen J, Olsen AM, Madsen JC, et al. The spectrum of thyroid disease and risk of new onset atrial fibrillation: a large population cohort study. *BMJ* 2012;**345**:e7895. <https://doi.org/10.1136/bmj.e7895>
920. Kim K, Yang PS, Jang E, Yu HT, Kim TH, Uhm JS, et al. Increased risk of ischemic stroke and systemic embolism in hyperthyroidism-related atrial fibrillation: a nationwide cohort study. *Am Heart J* 2021;**242**:123–31. <https://doi.org/10.1016/j.ahj.2021.08.018>
921. Zhang J, Bisson A, Fauchier G, Bodin A, Herbert J, Ducluzeau PH, et al. Yearly incidence of stroke and bleeding in atrial fibrillation with concomitant hyperthyroidism: a national discharge database study. *J Clin Med* 2022;**11**:1342. <https://doi.org/10.3390/jcm11051342>
922. Bartalena L, Bogazzi F, Chiovato L, Hubalewska-Dydejczyk A, Links TP, Vanderpump M. 2018 European Thyroid Association (ETA) guidelines for the management of amiodarone-associated thyroid dysfunction. *Eur Thyroid J* 2018;**7**:55–66. <https://doi.org/10.1159/000486957>
923. Cappellani D, Papini P, Di Certo AM, Morganti R, Urbani C, Manetti L, et al. Duration of exposure to thyrotoxicosis increases mortality of compromised AIT patients: the role of early thyroidectomy. *J Clin Endocrinol Metab* 2020;**105**:dgaa464. <https://doi.org/10.1210/clinem/dgaa464>
924. Trevisan C, Piovesan F, Lucato P, Zanforlini BM, De Rui M, Maggi S, et al. Parathormone, vitamin D and the risk of atrial fibrillation in older adults: a prospective study. *Nutr Metab Cardiovasc Dis* 2019;**29**:939–45. <https://doi.org/10.1016/j.numecd.2019.05.064>
925. Pepe J, Cipriani C, Curione M, Biamonte F, Colangelo L, Danese V, et al. Reduction of arrhythmias in primary hyperparathyroidism, by parathyroidectomy, evaluated with 24-h ECG monitoring. *Eur J Endocrinol* 2018;**179**:117–24. <https://doi.org/10.1530/EJE-17-0948>
926. Pepe J, Cipriani C, Sonato C, Raimo O, Biamonte F, Minisola S. Cardiovascular manifestations of primary hyperparathyroidism: a narrative review. *Eur J Endocrinol* 2017;**177**:R297–308. <https://doi.org/10.1530/EJE-17-0485>
927. Monticone S, D'Ascenzo F, Moretti C, Williams TA, Veglio F, Gaita F, et al. Cardiovascular events and target organ damage in primary aldosteronism compared with essential hypertension: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol* 2018;**6**:41–50. [https://doi.org/10.1016/S2213-8587\(17\)30319-4](https://doi.org/10.1016/S2213-8587(17)30319-4)
928. Bollati M, Lopez C, Bioletto F, Ponzetto F, Ghigo E, Maccario M, et al. Atrial fibrillation and aortic ectasia as complications of primary aldosteronism: focus on pathophysiological aspects. *Int J Mol Sci* 2022;**23**:2111. <https://doi.org/10.3390/ijms23042111>
929. Kim KJ, Hong N, Yu MH, Lee H, Lee S, Lim JS, et al. Time-dependent risk of atrial fibrillation in patients with primary aldosteronism after medical or surgical treatment initiation. *Hypertension* 2021;**77**:1964–73. <https://doi.org/10.1161/HYPERTENSIONAHA.120.16909>
930. Larsson SC, Lee WH, Burgess S, Allara E. Plasma cortisol and risk of atrial fibrillation: a Mendelian randomization study. *J Clin Endocrinol Metab* 2021;**106**:e2521–6. <https://doi.org/10.1210/clinem/dgab219>
931. Di Dalmazi G, Vicennati V, Pizzi C, Mosconi C, Tucci L, Balacchi C, et al. Prevalence and incidence of atrial fibrillation in a large cohort of adrenal incidentalomas: a long-term study. *J Clin Endocrinol Metab* 2020;**105**:dgaa270. <https://doi.org/10.1210/clinem/dgaa270>
932. Hong S, Kim KS, Han K, Park CY. Acromegaly and cardiovascular outcomes: a cohort study. *Eur Heart J* 2022;**43**:1491–9. <https://doi.org/10.1093/eurheartj/ehab822>
933. Polina I, Jansen HJ, Li T, Moghtadaei M, Bohne LJ, Liu Y, et al. Loss of insulin signaling may contribute to atrial fibrillation and atrial electrical remodeling in type 1 diabetes.

- Proc Natl Acad Sci USA* 2020;**117**:7990–8000. <https://doi.org/10.1073/pnas.1914853117>
934. Lee YB, Han K, Kim B, Lee SE, Jun JE, Ahn J, et al. Risk of early mortality and cardiovascular disease in type 1 diabetes: a comparison with type 2 diabetes, a nationwide study. *Cardiovasc Diabetol* 2019;**18**:157. <https://doi.org/10.1186/s12933-019-0953-7>
 935. Bisson A, Bodin A, Fauchier G, Herbert J, Angoulvant D, Ducluzeau PH, et al. Sex, age, type of diabetes and incidence of atrial fibrillation in patients with diabetes mellitus: a nationwide analysis. *Cardiovasc Diabetol* 2021;**20**:24. <https://doi.org/10.1186/s12933-021-01216-7>
 936. Dahlqvist S, Rosengren A, Gudbjörnsdóttir S, Pivodic A, Wedel H, Kosiborod M, et al. Risk of atrial fibrillation in people with type 1 diabetes compared with matched controls from the general population: a prospective case-control study. *Lancet Diabetes Endocrinol* 2017;**5**:799–807. [https://doi.org/10.1016/S2213-8587\(17\)30262-0](https://doi.org/10.1016/S2213-8587(17)30262-0)
 937. Cai X, Li J, Cai W, Chen C, Ma J, Xie Z, et al. Meta-analysis of type 1 diabetes mellitus and risk of cardiovascular disease. *J Diabetes Complications* 2021;**35**:107833. <https://doi.org/10.1016/j.jdiacomp.2020.107833>
 938. Zellerhoff S, Pistulli R, Monnig G, Hinterseer M, Beckmann BM, Kobe J, et al. Atrial arrhythmias in long-QT syndrome under daily life conditions: a nested case control study. *J Cardiovasc Electrophysiol* 2009;**20**:401–7. <https://doi.org/10.1111/j.1540-8167.2008.01339.x>
 939. Johnson JN, Tester DJ, Perry J, Salisbury BA, Reed CR, Ackerman MJ. Prevalence of early-onset atrial fibrillation in congenital long QT syndrome. *Heart Rhythm* 2008;**5**:704–9. <https://doi.org/10.1016/j.hrthm.2008.02.007>
 940. Gaita F, Giustetto C, Bianchi F, Wolpert C, Schimpf R, Riccardi R, et al. Short QT syndrome: a familial cause of sudden death. *Circulation* 2003;**108**:965–70. <https://doi.org/10.1161/01.CIR.0000085071.28695.C4>
 941. Borggrefe M, Wolpert C, Antzelevitch C, Veltmann C, Giustetto C, Gaita F, et al. Short QT syndrome genotype-phenotype correlations. *J Electrocardiol* 2005;**38**:75–80. <https://doi.org/10.1016/j.jelectrocard.2005.06.009>
 942. Giustetto C, Di Monte F, Wolpert C, Borggrefe M, Schimpf R, Sbragia P, et al. Short QT syndrome: clinical findings and diagnostic-therapeutic implications. *Eur Heart J* 2006;**27**:2440–7. <https://doi.org/10.1093/eurheartj/ehl185>
 943. Bordachar P, Reuter S, Garrigue S, Cai X, Hocini M, Jais P, et al. Incidence, clinical implications and prognosis of atrial arrhythmias in Brugada syndrome. *Eur Heart J* 2004;**25**:879–84. <https://doi.org/10.1016/j.ehj.2004.01.004>
 944. Francis J, Antzelevitch C. Atrial fibrillation and Brugada syndrome. *J Am Coll Cardiol* 2008;**51**:1149–53. <https://doi.org/10.1016/j.jacc.2007.10.062>
 945. Giustetto C, Schimpf R, Mazzanti A, Scrocco C, Maury P, Anttonen O, et al. Long-term follow-up of patients with short QT syndrome. *J Am Coll Cardiol* 2011;**58**:587–95. <https://doi.org/10.1016/j.jacc.2011.03.038>
 946. Gollob MH, Redpath CJ, Roberts JD. The short QT syndrome: proposed diagnostic criteria. *J Am Coll Cardiol* 2011;**57**:802–12. <https://doi.org/10.1016/j.jacc.2010.09.048>
 947. Kusano KF, Taniyama M, Nakamura K, Miura D, Banba K, Nagase S, et al. Atrial fibrillation in patients with Brugada syndrome relationships of gene mutation, electrophysiology, and clinical backgrounds. *J Am Coll Cardiol* 2008;**51**:1169–75. <https://doi.org/10.1016/j.jacc.2007.10.060>
 948. Rodríguez-Manero M, Namdar M, Sarkozy A, Casado-Arroyo R, Ricciardi D, de Asmundis C, et al. Prevalence, clinical characteristics and management of atrial fibrillation in patients with Brugada syndrome. *Am J Cardiol* 2013;**111**:362–7. <https://doi.org/10.1016/j.amjcard.2012.10.012>
 949. Choi YJ, Choi EK, Han KD, Jung JH, Park J, Lee E, et al. Temporal trends of the prevalence and incidence of atrial fibrillation and stroke among Asian patients with hypertrophic cardiomyopathy: a nationwide population-based study. *Int J Cardiol* 2018;**273**:130–5. <https://doi.org/10.1016/j.ijcard.2018.08.038>
 950. Hernandez-Ojeda J, Arbelo E, Borrás R, Berne P, Tolosana JM, Gomez-Juanatey A, et al. Patients with Brugada syndrome and implanted cardioverter-defibrillators: long-term follow-up. *J Am Coll Cardiol* 2017;**70**:1991–2002. <https://doi.org/10.1016/j.jacc.2017.08.029>
 951. Klopotoski M, Kwapiszewski A, Kukula K, Kamiolkowski J, Dabrowski M, Derejko P, et al. Clinical and echocardiographic parameters as risk factors for atrial fibrillation in patients with hypertrophic cardiomyopathy. *Clin Cardiol* 2018;**41**:1336–40. <https://doi.org/10.1002/clc.23050>
 952. Rowin EJ, Orfanos A, Estes NAM, Wang W, Link MS, Maron MS, et al. Occurrence and natural history of clinically silent episodes of atrial fibrillation in hypertrophic cardiomyopathy. *Am J Cardiol* 2017;**119**:1862–5. <https://doi.org/10.1016/j.amjcard.2017.02.040>
 953. Sacher F, Probst V, Maury P, Babuty D, Mansourati J, Komatsu Y, et al. Outcome after implantation of a cardioverter-defibrillator in patients with Brugada syndrome: a multi-center study-part 2. *Circulation* 2013;**128**:1739–47. <https://doi.org/10.1161/CIRCULATIONAHA.113.001941>
 954. Siontis KC, Geske JB, Ong K, Nishimura RA, Ommen SR, Gersh BJ. Atrial fibrillation in hypertrophic cardiomyopathy: prevalence, clinical correlations, and mortality in a large high-risk population. *J Am Heart Assoc* 2014;**3**:e001002. <https://doi.org/10.1161/JAHA.114.001002>
 955. Sumitomo N, Sakurada H, Taniguchi K, Matsumura M, Abe O, Miyashita M, et al. Association of atrial arrhythmia and sinus node dysfunction in patients with catecholaminergic polymorphic ventricular tachycardia. *Circ J* 2007;**71**:1606–9. <https://doi.org/10.1253/circj.71.1606>
 956. Sy RW, Gollob MH, Klein GJ, Yee R, Skanes AC, Gula LJ, et al. Arrhythmia characterization and long-term outcomes in catecholaminergic polymorphic ventricular tachycardia. *Heart Rhythm* 2011;**8**:864–71. <https://doi.org/10.1016/j.hrthm.2011.01.048>
 957. van Velzen HG, Theuns DA, Yap SC, Michels M, Schinkel AF. Incidence of device-detected atrial fibrillation and long-term outcomes in patients with hypertrophic cardiomyopathy. *Am J Cardiol* 2017;**119**:100–5. <https://doi.org/10.1016/j.amjcard.2016.08.092>
 958. Bourfiss M, Te Riele AS, Mast TP, Cramer MJ, Van Der Heijden J, Van Veen TAB, et al. Influence of genotype on structural atrial abnormalities and atrial fibrillation or flutter in arrhythmogenic right ventricular dysplasia/cardiomyopathy. *J Cardiovasc Electrophysiol* 2016;**27**:1420–8. <https://doi.org/10.1111/jce.13094>
 959. Camm CF, James CA, Tichnell C, Murray B, Bhonsale A, te Riele AS, et al. Prevalence of atrial arrhythmias in arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Heart Rhythm* 2013;**10**:1661–8. <https://doi.org/10.1016/j.hrthm.2013.08.032>
 960. Chu AF, Zado E, Marchlinski FE. Atrial arrhythmias in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia and ventricular tachycardia. *Am J Cardiol* 2010;**106**:720–2. <https://doi.org/10.1016/j.amjcard.2010.04.031>
 961. Hasselberg NE, Haland TF, Saberniak J, Brekke PH, Berge KE, Leren TP, et al. Lamin A/C cardiomyopathy: young onset, high penetrance, and frequent need for heart transplantation. *Eur Heart J* 2018;**39**:853–60. <https://doi.org/10.1093/eurheartj/ehx596>
 962. Kumar S, Baldinger SH, Gandjbakhch E, Maury P, Sellal JM, Androulakis AF, et al. Long-term arrhythmic and nonarrhythmic outcomes of lamin A/C mutation carriers. *J Am Coll Cardiol* 2016;**68**:2299–307. <https://doi.org/10.1016/j.jacc.2016.08.058>
 963. Mussigbrodt A, Knopp H, Efimova E, Weber A, Bertagnoli L, Hilbert S, et al. Supraventricular arrhythmias in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy associate with long-term outcome after catheter ablation of ventricular tachycardias. *Europace* 2018;**20**:1182–7. <https://doi.org/10.1093/europace/eux179>
 964. Pasotti M, Klersy C, Pilotto A, Marziliano N, Rapezzi C, Serio A, et al. Long-term outcome and risk stratification in dilated cardiomyopathies. *J Am Coll Cardiol* 2008;**52**:1250–60. <https://doi.org/10.1016/j.jacc.2008.06.044>
 965. Saguner AM, Ganahl S, Kraus A, Baldinger SH, Medeiros-Domingo A, Saguner AR, et al. Clinical role of atrial arrhythmias in patients with arrhythmogenic right ventricular dysplasia. *Circ J* 2014;**78**:2854–61. <https://doi.org/10.1253/circj.CJ-14-0474>
 966. Tonet JL, Castro-Miranda R, Iwa T, Poulain F, Frank R, Fontaine GH. Frequency of supraventricular tachyarrhythmias in arrhythmogenic right ventricular dysplasia. *Am J Cardiol* 1991;**67**:1153. [https://doi.org/10.1016/0002-9149\(91\)90886-P](https://doi.org/10.1016/0002-9149(91)90886-P)
 967. van Rijsingen IA, Nannenberg EA, Arbustini E, Elliott PM, Mogensen J, Hermans-van Ast JF, et al. Gender-specific differences in major cardiac events and mortality in lamin A/C mutation carriers. *Eur J Heart Fail* 2013;**15**:376–84. <https://doi.org/10.1093/eurjhf/hfs191>
 968. Aras D, Tufekcioglu O, Ergun K, Ozeke O, Yildiz A, Topaloglu S, et al. Clinical features of isolated ventricular noncompaction in adults long-term clinical course, echocardiographic properties, and predictors of left ventricular failure. *J Card Fail* 2006;**12**:726–33. <https://doi.org/10.1016/j.cardfail.2006.08.002>
 969. Li S, Zhang C, Liu N, Bai H, Hou C, Wang J, et al. Genotype-positive status is associated with poor prognosis in patients with left ventricular noncompaction cardiomyopathy. *J Am Heart Assoc* 2018;**7**:e009910. <https://doi.org/10.1161/JAHA.118.009910>
 970. Stollberger C, Blazek G, Winkler-Dworak M, Finsterer J. Atrial fibrillation in left ventricular noncompaction with and without neuromuscular disorders is associated with a poor prognosis. *Int J Cardiol* 2009;**133**:41–5. <https://doi.org/10.1016/j.ijcard.2007.11.099>
 971. Fatkin D, MacRae C, Sasaki T, Wolff MR, Porcu M, Frenneaux M, et al. Missense mutations in the rod domain of the lamin A/C gene as causes of dilated cardiomyopathy and conduction-system disease. *N Engl J Med* 1999;**341**:1715–24. <https://doi.org/10.1056/NEJM199912033412302>
 972. Hong K, Bjerregaard P, Gussak I, Brugada R. Short QT syndrome and atrial fibrillation caused by mutation in KCNH2. *J Cardiovasc Electrophysiol* 2005;**16**:394–6. <https://doi.org/10.1046/j.1540-8167.2005.40621.x>
 973. Olesen MS, Yuan L, Liang B, Holst AG, Nielsen N, Nielsen JB, et al. High prevalence of long QT syndrome-associated SCN5A variants in patients with early-onset lone atrial fibrillation. *Circ Cardiovasc Genet* 2012;**5**:450–9. <https://doi.org/10.1161/CIRCGENETICS.111.962597>
 974. Pappone C, Radinovic A, Manguso F, Vicedomini G, Sala S, Sacco FM, et al. New-onset atrial fibrillation as first clinical manifestation of latent Brugada syndrome: prevalence and clinical significance. *Eur Heart J* 2009;**30**:2985–92. <https://doi.org/10.1093/eurheartj/ehp326>
 975. Peters S. Atrial arrhythmias in arrhythmogenic cardiomyopathy: at the beginning or at the end of the disease story? *Circ J* 2015;**79**:446. <https://doi.org/10.1253/circj.CJ-14-1193>
 976. Rowin EJ, Hausvater A, Link MS, Abt P, Gionfriddo W, Wang W, et al. Clinical profile and consequences of atrial fibrillation in hypertrophic cardiomyopathy. *Circulation* 2017;**136**:2420–36. <https://doi.org/10.1161/CIRCULATIONAHA.117.029267>

977. Mazzanti A, Ng K, Faragli A, Maragna R, Chiodaroli E, Orphanou N, et al. Arrhythmic right ventricular cardiomyopathy: clinical course and predictors of arrhythmic risk. *J Am Coll Cardiol* 2016;**68**:2540–50. <https://doi.org/10.1016/j.jacc.2016.09.951>
978. Giustetto C, Cerrato N, Gribaudo E, Scrocco C, Castagno D, Richiardi E, et al. Atrial fibrillation in a large population with Brugada electrocardiographic pattern: prevalence, management, and correlation with prognosis. *Heart Rhythm* 2014;**11**:259–65. <https://doi.org/10.1016/j.hrthm.2013.10.043>
979. Beckmann BM, Holinski-Feder E, Walter MC, Haserück N, Reithmann C, Hinterseer M, et al. Laminopathy presenting as familial atrial fibrillation. *Int J Cardiol* 2010;**145**:394–6. <https://doi.org/10.1016/j.ijcard.2010.04.024>
980. Pizzale S, Gollob MH, Gow R, Birnie DH. Sudden death in a young man with catecholaminergic polymorphic ventricular tachycardia and paroxysmal atrial fibrillation. *J Cardiovasc Electrophysiol* 2008;**19**:1319–21. <https://doi.org/10.1111/j.1540-8167.2008.01211.x>
981. Sugiyasu A, Oginosawa Y, Nogami A, Hata Y. A case with catecholaminergic polymorphic ventricular tachycardia unmasked after successful ablation of atrial tachycardias from pulmonary veins. *Pacing Clin Electrophysiol* 2009;**32**:e21–4. <https://doi.org/10.1111/j.1540-8159.2009.02519.x>
982. Veltmann C, Kuschyk J, Schimpf R, Streitner F, Schoene N, Borggrefe M, et al. Prevention of inappropriate ICD shocks in patients with Brugada syndrome. *Clin Res Cardiol* 2010;**99**:37–44. <https://doi.org/10.1007/s00392-009-0075-4>
983. Brugada J, Katritsis DG, Arbelo E, Arribas F, Bax JJ, Blomstrom-Lundqvist C, et al. 2019 ESC Guidelines for the management of patients with supraventricular tachycardia. The Task Force for the management of patients with supraventricular tachycardia of the European Society of Cardiology (ESC). *Eur Heart J* 2020;**41**:655–720. <https://doi.org/10.1093/eurheartj/ehz467>
984. Klein GJ, Bashore TM, Sellers TD, Pritchett EL, Smith WM, Gallagher JJ. Ventricular fibrillation in the Wolff–Parkinson–White syndrome. *N Engl J Med* 1979;**301**:1080–5. <https://doi.org/10.1056/NEJM197911153012003>
985. Morady F, DiCarlo LA, Jr, Baerman JM, De Buitler M. Effect of propranolol on ventricular rate during atrial fibrillation in the Wolff–Parkinson–White syndrome. *Pacing Clin Electrophysiol* 1987;**10**:492–6. <https://doi.org/10.1111/j.1540-8159.1987.tb04511.x>
986. Sellers TD, Jr, Bashore TM, Gallagher JJ. Digitalis in the pre-excitation syndrome. Analysis during atrial fibrillation. *Circulation* 1977;**56**:260–7. <https://doi.org/10.1161/01.CIR.56.2.260>
987. Glatzer KA, Dorostkar PC, Yang Y, Lee RJ, Van Hare GF, Keung E, et al. Electrophysiological effects of ibutilide in patients with accessory pathways. *Circulation* 2001;**104**:1933–9. <https://doi.org/10.1161/hc4101.097538>
988. Ludmer PL, McGowan NE, Antman EM, Friedman PL. Efficacy of propafenone in Wolff–Parkinson–White syndrome: electrophysiologic findings and long-term follow-up. *J Am Coll Cardiol* 1987;**9**:1357–63. [https://doi.org/10.1016/S0735-1097\(87\)80478-3](https://doi.org/10.1016/S0735-1097(87)80478-3)
989. Simonian SM, Lotfipour S, Wall C, Langdorf MI. Challenging the superiority of amiodarone for rate control in Wolff–Parkinson–White and atrial fibrillation. *Intern Emerg Med* 2010;**5**:421–6. <https://doi.org/10.1007/s11739-010-0385-6>
990. Arbelo E, Protonotarios A, Gimeno JR, Arbustini E, Barriales-Villa R, Basso C, et al. 2023 ESC Guidelines for the management of cardiomyopathies. *Eur Heart J* 2023;**44**:3503–626. <https://doi.org/10.1093/eurheartj/ehad194>
991. Hu YF, Liu CJ, Chang PM, Tsao HM, Lin YJ, Chang SL, et al. Incident thromboembolism and heart failure associated with new-onset atrial fibrillation in cancer patients. *Int J Cardiol* 2013;**165**:355–7. <https://doi.org/10.1016/j.ijcard.2012.08.036>
992. Moslar RC, Vaduganathan M, Qamar A, Moslehi J, Piazza G, Giugliano RP. Anticoagulation strategies in patients with cancer: JACC review topic of the week. *J Am Coll Cardiol* 2019;**73**:1336–49. <https://doi.org/10.1016/j.jacc.2019.01.017>
993. Malavasi VL, Fantecchi E, Gianolio L, Pesce F, Longo G, Marietta M, et al. Atrial fibrillation in patients with active malignancy and use of anticoagulants: under-prescription but no adverse impact on all-cause mortality. *Eur J Intern Med* 2019;**59**:27–33. <https://doi.org/10.1016/j.ejim.2018.10.012>
994. Farmakis D, Parissis J, Filippatos G. Insights into onco-cardiology: atrial fibrillation in cancer. *J Am Coll Cardiol* 2014;**63**:945–53. <https://doi.org/10.1016/j.jacc.2013.11.026>
995. Yun JP, Choi EK, Han KD, Park SH, Jung JH, Ahn HJ, et al. Risk of atrial fibrillation according to cancer type: a nationwide population-based study. *JACC CardioOncol* 2021;**3**:221–32. <https://doi.org/10.1016/j.jacc.2021.03.006>
996. Alexandre J, Salem JE, Moslehi J, Sassier M, Ropert C, Cautela J, et al. Identification of anticancer drugs associated with atrial fibrillation: analysis of the WHO pharmacovigilance database. *Eur Heart J Cardiovasc Pharmacother* 2021;**7**:312–20. <https://doi.org/10.1093/ehjcvp/pvaa037>
997. Guha A, Fradley MG, Dent SF, Weintraub NL, Lustberg MB, Alonso A, et al. Incidence, risk factors, and mortality of atrial fibrillation in breast cancer: a SEER-medicare analysis. *Eur Heart J* 2022;**43**:300–12. <https://doi.org/10.1093/eurheartj/ehab745>
998. Pastori D, Marang A, Bisson A, Menichelli D, Herbert J, Lip GYH, et al. Thromboembolism, mortality, and bleeding in 2,435,541 atrial fibrillation patients with and without cancer: a nationwide cohort study. *Cancer* 2021;**127**:2122–9. <https://doi.org/10.1002/cncr.33470>
999. Aspberg S, Yu L, Gigante B, Smedby KE, Singer DE. Risk of ischemic stroke and major bleeding in patients with atrial fibrillation and cancer. *J Stroke Cerebrovasc Dis* 2020;**29**:104560. <https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.104560>
1000. D'Souza M, Carlson N, Fosbøl E, Lamberts M, Smedegaard L, Nielsen D, et al. CHA(2)DS(2)-VASc score and risk of thromboembolism and bleeding in patients with atrial fibrillation and recent cancer. *Eur J Prev Cardiol* 2018;**25**:651–8. <https://doi.org/10.1177/2047487318759858>
1001. Chen ST, Hellkamp AS, Becker RC, Berkowitz SD, Breithardt G, Fox KAA, et al. Efficacy and safety of rivaroxaban vs. warfarin in patients with non-valvular atrial fibrillation and a history of cancer: observations from ROCKET AF. *Eur Heart J Qual Care Clin Outcomes* 2019;**5**:145–52. <https://doi.org/10.1093/ehjqcco/qcy040>
1002. Melloni C, Dunning A, Granger CB, Thomas L, Khouri MG, Garcia DA, et al. Efficacy and safety of apixaban versus warfarin in patients with atrial fibrillation and a history of cancer: insights from the ARISTOTLE trial. *Am J Med* 2017;**130**:1440–8.e1. <https://doi.org/10.1016/j.amjmed.2017.06.026>
1003. Fanola CL, Ruff CT, Murphy SA, Jin J, Duggal A, Babilonia NA, et al. Efficacy and safety of edoxaban in patients with active malignancy and atrial fibrillation: analysis of the ENGAGE AF-TIMI 48 trial. *J Am Heart Assoc* 2018;**7**:e008987. <https://doi.org/10.1161/JAHA.118.008987>
1004. Sawant AC, Kumar A, McCray W, Tetewsky S, Parone L, Sridhara S, et al. Superior safety of direct oral anticoagulants compared to warfarin in patients with atrial fibrillation and underlying cancer: a national veterans affairs database study. *J Geriatr Cardiol* 2019;**16**:706–9. <https://doi.org/10.11909/j.issn.1671-5411.2019.09.006>
1005. Shah S, Norby FL, Datta YH, Lutsey PL, MacLehose RF, Chen LY, et al. Comparative effectiveness of direct oral anticoagulants and warfarin in patients with cancer and atrial fibrillation. *Blood Adv* 2018;**2**:200–9. <https://doi.org/10.1182/bloodadvances.2017010694>
1006. Mariani MV, Magnocavallo M, Straito M, Piro A, Severino P, Iannucci G, et al. Direct oral anticoagulants versus vitamin K antagonists in patients with atrial fibrillation and cancer: a meta-analysis. *J Thromb Thrombolysis* 2021;**51**:419–29. <https://doi.org/10.1007/s11239-020-02304-3>
1007. Deitelzweig S, Keshishian AV, Zhang Y, Kang A, Dhamane AD, Luo X, et al. Effectiveness and safety of oral anticoagulants among nonvalvular atrial fibrillation patients with active cancer. *JACC CardioOncol* 2021;**3**:411–24. <https://doi.org/10.1016/j.jacc.2021.06.004>
1008. Lin YS, Kuan FC, Chao TF, Wu M, Chen SW, Chen MC, et al. Mortality associated with the use of non-vitamin K antagonist oral anticoagulants in cancer patients: dabigatran versus rivaroxaban. *Cancer Med* 2021;**10**:7079–88. <https://doi.org/10.1002/cam4.4241>
1009. Atterman A, Asplund K, Friberg L, Engdahl J. Use of oral anticoagulants after ischaemic stroke in patients with atrial fibrillation and cancer. *J Intern Med* 2020;**288**:457–68. <https://doi.org/10.1111/joim.13092>
1010. Atterman A, Friberg L, Asplund K, Engdahl J. Net benefit of oral anticoagulants in patients with atrial fibrillation and active cancer: a nationwide cohort study. *Europace* 2020;**22**:58–65. <https://doi.org/10.1093/eurpace/euz306>
1011. Falanga A, Leader A, Ambaglio C, Bagoly Z, Castaman G, Elalamy I, et al. EHA guidelines on management of antithrombotic treatments in thrombocytopenic patients with cancer. *Hemasphere* 2022;**6**:e750. <https://doi.org/10.1097/HS9.0000000000000750>
1012. Lancellotti P, Suter TM, López-Fernández T, Galderisi M, Lyon AR, Van der Meer P, et al. Cardio-oncology services: rationale, organization, and implementation. *Eur Heart J* 2019;**40**:1756–63. <https://doi.org/10.1093/eurheartj/ehy453>
1013. Richter D, Guasti L, Walker D, Lambrinou E, Lionis C, Abreu A, et al. Frailty in cardiology: definition, assessment and clinical implications for general cardiology. A consensus document of the Council for Cardiology Practice (CCP), Association for Acute Cardio Vascular Care (ACVC), Association of Cardiovascular Nursing and Allied Professions (ACNAP), European Association of Preventive Cardiology (EAPC), European Heart Rhythm Association (EHRA), Council on Valvular Heart Diseases (VHD), Council on Hypertension (CHT), Council of Cardio-Oncology (CCO), Working Group (WG) aorta and peripheral vascular diseases, WG e-cardiology, WG thrombosis, of the European Society of Cardiology, European Primary Care Cardiology Society (EPPCCS). *Eur J Prev Cardiol* 2022;**29**:216–27. <https://doi.org/10.1093/eurjpc/zwaa167>
1014. Proietti M, Vitolo M, Harrison SL, Lane DA, Fauchier L, Marin F, et al. Impact of clinical phenotypes on management and outcomes in European atrial fibrillation patients: a report from the ESC-EHRA EURObservational Research Programme in AF (EORP-AF) general long-term registry. *BMC Med* 2021;**19**:256. <https://doi.org/10.1186/s12916-021-02120-3>
1015. Proietti M, Romiti GF, Vitolo M, Harrison SL, Lane DA, Fauchier L, et al. Epidemiology and impact of frailty in patients with atrial fibrillation in Europe. *Age Ageing* 2022;**51**:afac192. <https://doi.org/10.1093/ageing/afac192>
1016. Savelieva I, Fumagalli S, Kenny RA, Anker S, Benetos A, Boriani G, et al. EHRA expert consensus document on the management of arrhythmias in frailty syndrome, endorsed by the Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), Latin America Heart Rhythm Society (LAHRS), and Cardiac Arrhythmia

- Society of Southern Africa (CASSA). *Europace* 2023;**25**:1249–76. <https://doi.org/10.1093/europace/eaac123>
1017. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet* 2013;**381**:752–62. [https://doi.org/10.1016/S0140-6736\(12\)62167-9](https://doi.org/10.1016/S0140-6736(12)62167-9)
 1018. Villani ER, Tummolo AM, Palmer K, Gravina EM, Vetrano DL, Bernabei R, et al. Frailty and atrial fibrillation: a systematic review. *Eur J Intern Med* 2018;**56**:33–8. <https://doi.org/10.1016/j.ejim.2018.04.018>
 1019. Hang F, Chen J, Wang Z, Yan J, Wu Y. Association between the frailty and new-onset atrial fibrillation/flutter among elderly hypertensive patients. *Front Cardiovasc Med* 2022;**9**:881946. <https://doi.org/10.3389/fcvm.2022.881946>
 1020. Steinberg BA, Holmes DN, Ezekowitz MD, Fonarow GC, Kowey PR, Mahaffey KW, et al. Rate versus rhythm control for management of atrial fibrillation in clinical practice: results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry. *Am Heart J* 2013;**165**:622–9. <https://doi.org/10.1016/j.ahj.2012.12.019>
 1021. Ko D, Lin KJ, Bessette LG, Lee SB, Walkey AJ, Cheng S, et al. Trends in use of oral anticoagulants in older adults with newly diagnosed atrial fibrillation, 2010–2020. *JAMA Netw Open* 2022;**5**:e2242964. <https://doi.org/10.1001/jamanetworkopen.2022.42964>
 1022. Bul M, Shaikh F, McDonagh J, Ferguson C. Frailty and oral anticoagulant prescription in adults with atrial fibrillation: a systematic review. *Aging Med (Milton)* 2023;**6**:195–206. <https://doi.org/10.1002/agm2.12214>
 1023. Hu J, Zhou Y, Cai Z. Outcome of novel oral anticoagulant versus warfarin in frail elderly patients with atrial fibrillation: a systematic review and meta-analysis of retrospective studies. *Acta Clin Belg* 2023;**78**:367–77. <https://doi.org/10.1080/17843286.2023.2179908>
 1024. Zeng S, Zheng Y, Jiang J, Ma J, Zhu W, Cai X. Effectiveness and safety of DOACs vs. warfarin in patients with atrial fibrillation and frailty: a systematic review and meta-analysis. *Front Cardiovasc Med* 2022;**9**:907197. <https://doi.org/10.3389/fcvm.2022.907197>
 1025. Grymonprez M, Petrovic M, De Backer TL, Steurbaut S, Lahousse L. Impact of frailty on the effectiveness and safety of non-vitamin K antagonist oral anticoagulants (NOACs) in patients with atrial fibrillation: a nationwide cohort study. *Eur Heart J Qual Care Clin Outcomes* 2024;**10**:55–65. <https://doi.org/10.1093/ehjqqc/qcad019>
 1026. Kim D, Yang PS, Sung JH, Jang E, Yu HT, Kim TH, et al. Effectiveness and safety of anticoagulation therapy in frail patients with atrial fibrillation. *Stroke* 2022;**53**:1873–82. <https://doi.org/10.1161/STROKEAHA.121.036757>
 1027. Chao TF, Liu CJ, Lin YJ, Chang SL, Lo LW, Hu YF, et al. Oral anticoagulation in very elderly patients with atrial fibrillation: a nationwide cohort study. *Circulation* 2018;**138**:37–47. <https://doi.org/10.1161/CIRCULATIONAHA.117.031658>
 1028. Da Costa A, Thévenin J, Roche F, Romeyer-Bouchard C, Abdellaoui L, Messier M, et al. Results from the Loire-Ardèche-Drôme-Isère-Puy-de-Dôme (LADIP) trial on atrial flutter, a multicentric prospective randomized study comparing amiodarone and radiofrequency ablation after the first episode of symptomatic atrial flutter. *Circulation* 2006;**114**:1676–81. <https://doi.org/10.1161/CIRCULATIONAHA.106.638395>
 1029. Natale A, Newby KH, Pisano E, Leonelli F, Fanelli R, Potenza D, et al. Prospective randomized comparison of antiarrhythmic therapy versus first-line radiofrequency ablation in patients with atrial flutter. *J Am Coll Cardiol* 2000;**35**:1898–904. [https://doi.org/10.1016/S0735-1097\(00\)00635-5](https://doi.org/10.1016/S0735-1097(00)00635-5)
 1030. Chinitz JS, Gerstenfeld EP, Marchlinski FE, Callans DJ. Atrial fibrillation is common after ablation of isolated atrial flutter during long-term follow-up. *Heart Rhythm* 2007;**4**:1029–33. <https://doi.org/10.1016/j.hrthm.2007.04.002>
 1031. De Bortoli A, Shi LB, Ohm OJ, Hoff PI, Schuster P, Solheim E, et al. Incidence and clinical predictors of subsequent atrial fibrillation requiring additional ablation after cavotricuspid isthmus ablation for typical atrial flutter. *Scand Cardiovasc J* 2017;**51**:123–8. <https://doi.org/10.1080/14017431.2017.1304570>
 1032. Rahman F, Wang N, Yin X, Ellinor PT, Lubitz SA, LeLorier PA, et al. Atrial flutter: clinical risk factors and adverse outcomes in the Framingham Heart Study. *Heart Rhythm* 2016;**13**:233–40. <https://doi.org/10.1016/j.hrthm.2015.07.031>
 1033. Roth GA, Mensah GA, Johnson CO, Adolorato G, Ammirati E, Baddour LM, et al. Global burden of cardiovascular diseases and risk factors, 1990–2019: update from the GBD 2019 study. *J Am Coll Cardiol* 2020;**76**:2982–3021. <https://doi.org/10.1016/j.jacc.2020.11.010>
 1034. Lippi G, Sanchis-Gomar F, Cervellin G. Global epidemiology of atrial fibrillation: an increasing epidemic and public health challenge. *Int J Stroke* 2021;**16**:217–21. <https://doi.org/10.1177/1747493019897870>
 1035. Alonso A, Alam AB, Kamel H, Subbian V, Qian J, Boerwinkle E, et al. Epidemiology of atrial fibrillation in the all of US research program. *PLoS One* 2022;**17**:e0265498. <https://doi.org/10.1371/journal.pone.0265498>
 1036. Ghelani KP, Chen LY, Norby FL, Soliman EZ, Koton S, Alonso A. Thirty-year trends in the incidence of atrial fibrillation: the ARIC study. *J Am Heart Assoc* 2022;**11**:e023583. <https://doi.org/10.1161/JAHA.121.023583>
 1037. Williams BA, Chamberlain AM, Blankenship JC, Hylek EM, Voyce S. Trends in atrial fibrillation incidence rates within an integrated health care delivery system, 2006 to 2018. *JAMA Netw Open* 2020;**3**:e2014874. <https://doi.org/10.1001/jamanetworkopen.2020.14874>
 1038. Magnussen C, Niiranen TJ, Ojeda FM, Gianfagna F, Blankenberg S, Njølstad I, et al. Sex differences and similarities in atrial fibrillation epidemiology, risk factors, and mortality in community cohorts: results from the BiomarCaRE consortium (Biomarker for Cardiovascular Risk Assessment in Europe). *Circulation* 2017;**136**:1588–97. <https://doi.org/10.1161/CIRCULATIONAHA.117.028981>
 1039. Rodriguez CJ, Soliman EZ, Alonso A, Swett K, Okin PM, Goff DC, Jr, et al. Atrial fibrillation incidence and risk factors in relation to race-ethnicity and the population attributable fraction of atrial fibrillation risk factors: the multi-ethnic study of atherosclerosis. *Ann Epidemiol* 2015;**25**:71–6. <https://doi.org/10.1016/j.annepidem.2014.11.024>
 1040. Ugowe FE, Jackson LR, 2nd, Thomas KL. Racial and ethnic differences in the prevalence, management, and outcomes in patients with atrial fibrillation: a systematic review. *Heart Rhythm* 2018;**15**:1337–45. <https://doi.org/10.1016/j.hrthm.2018.05.019>
 1041. Volgman AS, Bairey Merz CN, Benjamin EJ, Curtis AB, Fang MC, Lindley KJ, et al. Sex and race/ethnicity differences in atrial fibrillation. *J Am Coll Cardiol* 2019;**74**:2812–5. <https://doi.org/10.1016/j.jacc.2019.09.045>
 1042. Chung SC, Sofat R, Acosta-Mena D, Taylor JA, Lambiasi PD, Casas JP, et al. Atrial fibrillation epidemiology, disparity and healthcare contacts: a population-wide study of 5.6 million individuals. *Lancet Reg Health Eur* 2021;**7**:100157. <https://doi.org/10.1016/j.lanepe.2021.100157>
 1043. Svennberg E, Tjong F, Goette A, Akoum N, Di Biase L, Bordachar P, et al. How to use digital devices to detect and manage arrhythmias: an EHRA practical guide. *Europace* 2022;**24**:979–1005. <https://doi.org/10.1093/europace/eaac038>
 1044. Spatz ES, Ginsburg GS, Rumsfeld JS, Turakhia MP. Wearable digital health technologies for monitoring in cardiovascular medicine. *N Engl J Med* 2024;**390**:346–56. <https://doi.org/10.1056/NEJMra2301903>
 1045. Cooke G, Doust J, Sanders S. Is pulse palpation helpful in detecting atrial fibrillation? A systematic review. *J Fam Pract* 2006;**55**:130–4.
 1046. Attia ZI, Noseworthy PA, Lopez-Jimenez F, Asirvatham SJ, Deshmukh AJ, Gersh BJ, et al. An artificial intelligence-enabled ECG algorithm for the identification of patients with atrial fibrillation during sinus rhythm: a retrospective analysis of outcome prediction. *Lancet* 2019;**394**:861–7. [https://doi.org/10.1016/S0140-6736\(19\)31721-0](https://doi.org/10.1016/S0140-6736(19)31721-0)
 1047. Hobbs FD, Fitzmaurice DA, Mant J, Murray E, Jowett S, Bryan S, et al. A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study. *Health Technol Assess* 2005;**9**:iii–iv, ix–x, 1–74. <https://doi.org/10.3310/hta9400>
 1048. Grond M, Jauss M, Hamann G, Stark E, Veltkamp R, Nabavi D, et al. Improved detection of silent atrial fibrillation using 72-hour Holter ECG in patients with ischemic stroke: a prospective multicenter cohort study. *Stroke* 2013;**44**:3357–64. <https://doi.org/10.1161/STROKEAHA.113.001884>
 1049. Rizos T, Guntner J, Jenetzky E, Marquardt L, Reichardt C, Becker R, et al. Continuous stroke unit electrocardiographic monitoring versus 24-hour Holter electrocardiography for detection of paroxysmal atrial fibrillation after stroke. *Stroke* 2012;**43**:2689–94. <https://doi.org/10.1161/STROKEAHA.112.654954>
 1050. Doliwa PS, Frykman V, Rosenqvist M. Short-term ECG for out of hospital detection of silent atrial fibrillation episodes. *Scand Cardiovasc J* 2009;**43**:163–8. <https://doi.org/10.1080/14017430802593435>
 1051. Tieleman RG, Plantinga Y, Rinkes D, Bartels GL, Posma JL, Cator R, et al. Validation and clinical use of a novel diagnostic device for screening of atrial fibrillation. *Europace* 2014;**16**:1291–5. <https://doi.org/10.1093/europace/eeu057>
 1052. Kearley K, Selwood M, Van den Bruel A, Thompson M, Mant D, Hobbs FR, et al. Triage tests for identifying atrial fibrillation in primary care: a diagnostic accuracy study comparing single-lead ECG and modified BP monitors. *BMJ Open* 2014;**4**:e004565. <https://doi.org/10.1136/bmjopen-2013-004565>
 1053. Barrett PM, Komatireddy R, Haaser S, Topol S, Sheard J, Encinas J, et al. Comparison of 24-hour Holter monitoring with 14-day novel adhesive patch electrocardiographic monitoring. *Am J Med* 2014;**127**:95.e11–7. <https://doi.org/10.1016/j.amjmed.2013.10.003>
 1054. Turakhia MP, Hoang DD, Zimetbaum P, Miller JD, Froelicher VF, Kumar UN, et al. Diagnostic utility of a novel leadless arrhythmia monitoring device. *Am J Cardiol* 2013;**112**:520–4. <https://doi.org/10.1016/j.amjcard.2013.04.017>
 1055. Rosenberg MA, Samuel M, Thosani A, Zimetbaum PJ. Use of a noninvasive continuous monitoring device in the management of atrial fibrillation: a pilot study. *Pacing Clin Electrophysiol* 2013;**36**:328–33. <https://doi.org/10.1111/pace.12053>
 1056. Turakhia MP, Ullal AJ, Hoang DD, Than CT, Miller JD, Friday KJ, et al. Feasibility of extended ambulatory electrocardiogram monitoring to identify silent atrial fibrillation in high-risk patients: the Screening Study for Undiagnosed Atrial Fibrillation (STUDY-AF). *Clin Cardiol* 2015;**38**:285–92. <https://doi.org/10.1002/clc.22387>
 1057. Rooney MR, Soliman EZ, Lutsey PL, Norby FL, Loehr LR, Mosley TH, et al. Prevalence and characteristics of subclinical atrial fibrillation in a community-dwelling elderly population: the ARIC study. *Circ Arrhythm Electrophysiol* 2019;**12**:e007390. <https://doi.org/10.1161/CIRCEP.119.007390>

1058. Stehlik J, Schmalfuss C, Bozkurt B, Nativi-Nicolau J, Wohlfahrt P, Wegerich S, et al. Continuous wearable monitoring analytics predict heart failure hospitalization: the LINK-HF multicenter study. *Circ Heart Fail* 2020;**13**:e006513. <https://doi.org/10.1161/CIRCHEARTFAILURE.119.006513>
1059. Ganne C, Talkad SN, Srinivas D, Somanna S. Ruptured blebs and racing hearts: autonomic cardiac changes in neurosurgeons during microsurgical clipping of aneurysms. *Br J Neurosurg* 2016;**30**:450–2. <https://doi.org/10.3109/02688697.2016.1159656>
1060. Smith WM, Riddell F, Madon M, Gleva MJ. Comparison of diagnostic value using a small, single channel, P-wave centric sternal ECG monitoring patch with a standard 3-lead Holter system over 24 hours. *Am Heart J* 2017;**185**:67–73. <https://doi.org/10.1016/j.ahj.2016.11.006>
1061. Olson JA, Fouts AM, Padanilam BJ, Prystowsky EN. Utility of mobile cardiac outpatient telemetry for the diagnosis of palpitations, presyncope, syncope, and the assessment of therapy efficacy. *J Cardiovasc Electrophysiol* 2007;**18**:473–7. <https://doi.org/10.1111/j.1540-8167.2007.00779.x>
1062. Derkac WM, Finkelmeier JR, Horgan DJ, Hutchinson MD. Diagnostic yield of asymptomatic arrhythmias detected by mobile cardiac outpatient telemetry and autotrigger looping event cardiac monitors. *J Cardiovasc Electrophysiol* 2017;**28**:1475–8. <https://doi.org/10.1111/jce.13342>
1063. Teplitzky BA, McRoberts M, Ghanbari H. Deep learning for comprehensive ECG annotation. *Heart Rhythm* 2020;**17**:881–8. <https://doi.org/10.1016/j.hrthm.2020.02.015>
1064. Jeon E, Oh K, Kwon S, Son H, Yun Y, Jung ES, et al. A lightweight deep learning model for fast electrocardiographic beats classification with a wearable cardiac monitor: development and validation study. *JMIR Med Inform* 2020;**8**:e17037. <https://doi.org/10.2196/17037>
1065. Breteler MJMM, Huizinga E, van Loon K, Leenen LPH, Dohmen DAJ, Kalkman CJ, et al. Reliability of wireless monitoring using a wearable patch sensor in high-risk surgical patients at a step-down unit in The Netherlands: a clinical validation study. *BMJ Open* 2018;**8**:e020162. <https://doi.org/10.1136/bmjopen-2017-020162>
1066. Hopkins L, Stacey B, Robinson DBT, James OP, Brown C, Egan RJ, et al. Consumer-grade biosensor validation for examining stress in healthcare professionals. *Physiol Rep* 2020;**8**:e14454. <https://doi.org/10.14814/phy2.14454>
1067. Steinhubl SR, Waalen J, Edwards AM, Ariniello LM, Mehta RR, Ebner GS, et al. Effect of a home-based wearable continuous ECG monitoring patch on detection of undiagnosed atrial fibrillation: the mSToPS randomized clinical trial. *JAMA* 2018;**320**:146–55. <https://doi.org/10.1001/jama.2018.8102>
1068. Elliot CA, Hamlin MJ, Lizamore CA. Validity and reliability of the hexoskin wearable biometric vest during maximal aerobic power testing in elite cyclists. *J Strength Cond Res* 2019;**33**:1437–44. <https://doi.org/10.1519/JSC.0000000000002005>
1069. Eysenck W, Freemantle N, Sulke N. A randomized trial evaluating the accuracy of AF detection by four external ambulatory ECG monitors compared to permanent pacemaker AF detection. *J Interv Card Electrophysiol* 2020;**57**:361–9. <https://doi.org/10.1007/s10840-019-00515-0>
1070. Fabregat-Andres O, Munoz-Macho A, Adell-Beltran G, Ibanez-Catala X, Macia A, Facila L. Evaluation of a new shirt-based electrocardiogram device for cardiac screening in soccer players: comparative study with treadmill ergospirometry. *Cardiol Res* 2014;**5**:101–7. <https://doi.org/10.14740/cr333w>
1071. Feito Y, Moriarty TA, Mangine G, Monahan J. The use of a smart-textile garment during high-intensity functional training: a pilot study. *J Sports Med Phys Fitness* 2019;**59**:947–54. <https://doi.org/10.23736/S0022-4707.18.08689-9>
1072. Pagola J, Juega J, Francisco-Pascual J, Moya A, Sanchis M, Bustamante A, et al. Yield of atrial fibrillation detection with textile wearable Holter from the acute phase of stroke: pilot study of crypto-AF registry. *Int J Cardiol* 2018;**251**:45–50. <https://doi.org/10.1016/j.ijcard.2017.10.063>
1073. Lau JK, Lowres N, Neubeck L, Brieger DB, Sy RW, Galloway CD, et al. iPhone ECG application for community screening to detect silent atrial fibrillation: a novel technology to prevent stroke. *Int J Cardiol* 2013;**165**:193–4. <https://doi.org/10.1016/j.ijcard.2013.01.220>
1074. Bumgarner JM, Lambert CT, Hussein AA, Cantillon DJ, Baranowski B, Wolski K, et al. Smartwatch algorithm for automated detection of atrial fibrillation. *J Am Coll Cardiol* 2018;**71**:2381–8. <https://doi.org/10.1016/j.jacc.2018.03.003>
1075. Lubitz SA, Faranesh AZ, Atlas SJ, McManus DD, Singer DE, Pagoto S, et al. Rationale and design of a large population study to validate software for the assessment of atrial fibrillation from data acquired by a consumer tracker or smartwatch: the Fitbit heart study. *Am Heart J* 2021;**238**:16–26. <https://doi.org/10.1016/j.ahj.2021.04.003>
1076. Perez MV, Mahaffey KW, Hedlin H, Rumsfeld JS, Garcia A, Ferris T, et al. Large-scale assessment of a smartwatch to identify atrial fibrillation. *N Engl J Med* 2019;**381**:1909–17. <https://doi.org/10.1056/NEJMoa1901183>
1077. Saghir N, Aggarwal A, Soneji N, Valencia V, Rodgers G, Kurian T. A comparison of manual electrocardiographic interval and waveform analysis in lead 1 of 12-lead ECG and apple watch ECG: a validation study. *Cardiovasc Digit Health J* 2020;**1**:30–6. <https://doi.org/10.1016/j.cvdhj.2020.07.002>
1078. Seshadri DR, Bittel B, Browsky D, Houghtaling P, Drummond CK, Desai MY, et al. Accuracy of apple watch for detection of atrial fibrillation. *Circulation* 2020;**141**:702–3. <https://doi.org/10.1161/CIRCULATIONAHA.119.044126>
1079. Zhang H, Zhang J, Li HB, Chen YX, Yang B, Guo YT, et al. Validation of single centre pre-mobile atrial fibrillation apps for continuous monitoring of atrial fibrillation in a real-world setting: pilot cohort study. *J Med Internet Res* 2019;**21**:e14909. <https://doi.org/10.2196/14909>
1080. Fan YY, Li YG, Li J, Cheng WK, Shan ZL, Wang YT, et al. Diagnostic performance of a smart device with photoplethysmography technology for atrial fibrillation detection: pilot study (Pre-mAFA II registry). *JMIR Mhealth Uhealth* 2019;**7**:e11437. <https://doi.org/10.2196/11437>
1081. Brito R, Mondouagne LP, Stettler C, Combescure C, Burri H. Automatic atrial fibrillation and flutter detection by a handheld ECG recorder, and utility of sequential finger and precordial recordings. *J Electrocardiol* 2018;**51**:1135–40. <https://doi.org/10.1016/j.jelectrocard.2018.10.093>
1082. Desteghe L, Raymaekers Z, Lutin M, Vijgen J, Dilling-Boer D, Koopman P, et al. Performance of handheld electrocardiogram devices to detect atrial fibrillation in a cardiology and geriatric ward setting. *Europace* 2017;**19**:29–39. <https://doi.org/10.1093/europace/euw025>
1083. Nigolian A, Dayal N, Nigolian H, Stettler C, Burri H. Diagnostic accuracy of multi-lead ECGs obtained using a pocket-sized bipolar handheld event recorder. *J Electrocardiol* 2018;**51**:278–81. <https://doi.org/10.1016/j.jelectrocard.2017.11.004>
1084. Magnusson P, Lyren A, Mattsson G. Diagnostic yield of chest and thumb ECG after cryptogenic stroke, Transient ECG Assessment in Stroke Evaluation (TEASE): an observational trial. *BMJ Open* 2020;**10**:e037573. <https://doi.org/10.1136/bmjopen-2020-037573>
1085. Carnlöf C, Schenck-Gustafsson K, Jensen-Urstad M, Insulander P. Instant electrocardiogram feedback with a new digital technique reduces symptoms caused by palpitations and increases health-related quality of life (the RedHeart study). *Eur J Cardiovasc Nurs* 2021;**20**:402–10. <https://doi.org/10.1093/eurcn/zvaa031>
1086. Haverkamp HT, Fosse SO, Schuster P. Accuracy and usability of single-lead ECG from smartphones—a clinical study. *Indian Pacing Electrophysiol J* 2019;**19**:145–9. <https://doi.org/10.1016/j.ipej.2019.02.006>
1087. Attia ZI, Kapa S, Lopez-Jimenez F, McKie PM, Ladewig DJ, Satam G, et al. Screening for cardiac contractile dysfunction using an artificial intelligence-enabled electrocardiogram. *Nat Med* 2019;**25**:70–4. <https://doi.org/10.1038/s41591-018-0240-2>
1088. Bekker CL, Noordergraaf F, Teerenstra S, Pop G, van den Bemt BJF. Diagnostic accuracy of a single-lead portable ECG device for measuring QTc prolongation. *Ann Noninvasive Electrocardiol* 2020;**25**:e12683. <https://doi.org/10.1111/anec.12683>
1089. Kaleschke G, Hoffmann B, Drewitz I, Steinbeck G, Naebauer M, Goette A, et al. Prospective, multicentre validation of a simple, patient-operated electrocardiographic system for the detection of arrhythmias and electrocardiographic changes. *Europace* 2009;**11**:1362–8. <https://doi.org/10.1093/europace/eup262>
1090. Guan J, Wang A, Song W, Obore N, He P, Fan S, et al. Screening for arrhythmia with the new portable single-lead electrocardiographic device (SnapECG): an application study in community-based elderly population in Nanjing, China. *Aging Clin Exp Res* 2021;**33**:133–40. <https://doi.org/10.1007/s40520-020-01512-4>
1091. Svennberg E, Stridh M, Engdahl J, Al-Khalili F, Friberg L, Frykman V, et al. Safe automatic one-lead electrocardiogram analysis in screening for atrial fibrillation. *Europace* 2017;**19**:1449–53. <https://doi.org/10.1093/europace/euw286>
1092. Musat DL, Milstein N, Mittal S. Implantable loop recorders for cryptogenic stroke (plus real-world atrial fibrillation detection rate with implantable loop recorders). *Card Electrophysiol Clin* 2018;**10**:111–8. <https://doi.org/10.1016/j.ccep.2017.11.011>
1093. Sakhi R, Theuns D, Szili-Torok T, Yap SC. Insertable cardiac monitors: current indications and devices. *Expert Rev Med Devices* 2019;**16**:45–55. <https://doi.org/10.1080/17434440.2018.1557046>
1094. Tomson TT, Passman R. The reveal LINQ insertable cardiac monitor. *Expert Rev Med Devices* 2015;**12**:7–18. <https://doi.org/10.1586/17434440.2014.953059>
1095. Ciconte G, Saviano M, Giannelli L, Calovic Z, Baldi M, Ciccio C, et al. Atrial fibrillation detection using a novel three-vector cardiac implantable monitor: the atrial fibrillation detect study. *Europace* 2017;**19**:1101–8. <https://doi.org/10.1093/europace/euw181>
1096. Hindricks G, Pokushalov E, Urban L, Taborsky M, Kuck KH, Lebedev D, et al. Performance of a new leadless implantable cardiac monitor in detecting and quantifying atrial fibrillation: results of the XPECT trial. *Circ Arrhythm Electrophysiol* 2010;**3**:141–7. <https://doi.org/10.1161/CIRCEP.109.877852>
1097. Mittal S, Rogers J, Sarkar S, Koehler J, Warman EN, Tomson TT, et al. Real-world performance of an enhanced atrial fibrillation detection algorithm in an insertable cardiac monitor. *Heart Rhythm* 2016;**13**:1624–30. <https://doi.org/10.1016/j.hrthm.2016.05.010>
1098. Nölker G, Mayer J, Boldt LH, Seidl K VVAND, Massa T, Kollum M, et al. Performance of an implantable cardiac monitor to detect atrial fibrillation: results of the DETECT AF study. *J Cardiovasc Electrophysiol* 2016;**27**:1403–10. <https://doi.org/10.1111/jce.13089>
1099. Sanders P, Püerferellner H, Pokushalov E, Sarkar S, Di Bacco M, Maus B, et al. Performance of a new atrial fibrillation detection algorithm in a miniaturized insertable cardiac monitor: results from the reveal LINQ usability study. *Heart Rhythm* 2016;**13**:1425–30. <https://doi.org/10.1016/j.hrthm.2016.03.005>

1100. Chan PH, Wong CK, Poh YC, Pun L, Leung WW, Wong YF, et al. Diagnostic performance of a smartphone-based photoplethysmographic application for atrial fibrillation screening in a primary care setting. *J Am Heart Assoc* 2016;**5**:e003428. <https://doi.org/10.1161/JAHA.116.003428>
1101. Mc MD, Chong JW, Soni A, Saczynski JS, Esa N, Napolitano C, et al. PULSE-SMART: pulse-based arrhythmia discrimination using a novel smartphone application. *J Cardiovasc Electrophysiol* 2016;**27**:51–7. <https://doi.org/10.1111/jce.12842>
1102. Proesmans T, Mortelmans C, Van Haelst R, Verbrugge F, Vandervoort P, Vaes B. Mobile phone-based use of the photoplethysmography technique to detect atrial fibrillation in primary care: diagnostic accuracy study of the FibriCheck app. *JMIR Mhealth Uhealth* 2019;**7**:e12284. <https://doi.org/10.2196/12284>
1103. Rozen G, Vaid J, Hosseini SM, Kaadan MI, Rafael A, Roka A, et al. Diagnostic accuracy of a novel mobile phone application for the detection and monitoring of atrial fibrillation. *Am J Cardiol* 2018;**121**:1187–91. <https://doi.org/10.1016/j.amjcard.2018.01.035>
1104. O'Sullivan JW, Grigg S, Crawford W, Turakhia MP, Perez M, Ingelsson E, et al. Accuracy of smartphone camera applications for detecting atrial fibrillation: a systematic review and meta-analysis. *JAMA Netw Open* 2020;**3**:e202064. <https://doi.org/10.1001/jamanetworkopen.2020.2064>
1105. Koenig N, Seeck A, Eckstein J, Mainka A, Huebner T, Voss A, et al. Validation of a new heart rate measurement algorithm for fingertip recording of video signals with smartphones. *Telemed J E Health* 2016;**22**:631–6. <https://doi.org/10.1089/tmj.2015.0212>
1106. Krivoshei L, Weber S, Burkard T, Maseli A, Brasier N, Kühne M, et al. Smart detection of atrial fibrillation†. *Europace* 2017;**19**:753–7. <https://doi.org/10.1093/eurpace/eww125>
1107. Wiesel J, Fitzg L, Herschman Y, Messineo FC. Detection of atrial fibrillation using a modified microlife blood pressure monitor. *Am J Hypertens* 2009;**22**:848–52. <https://doi.org/10.1038/ajh.2009.98>
1108. Chen Y, Lei L, Wang JG. Atrial fibrillation screening during automated blood pressure measurement—comment on “diagnostic accuracy of new algorithm to detect atrial fibrillation in a home blood pressure monitor”. *J Clin Hypertens (Greenwich)* 2017;**19**:1148–51. <https://doi.org/10.1111/jch.13081>
1109. Kane SA, Blake JR, McArdle FJ, Langley P, Sims AJ. Opportunistic detection of atrial fibrillation using blood pressure monitors: a systematic review. *Open Heart* 2016;**3**:e000362. <https://doi.org/10.1136/openhrt-2015-000362>
1110. Kario K. Evidence and perspectives on the 24-hour management of hypertension: hemodynamic biomarker-initiated ‘anticipation medicine’ for zero cardiovascular event. *Prog Cardiovasc Dis* 2016;**59**:262–81. <https://doi.org/10.1016/j.pcad.2016.04.001>
1111. Jaakkola J, Jaakkola S, Lahdenoja O, Hurnanen T, Koivisto T, Pänkälä M, et al. Mobile phone detection of atrial fibrillation with mechanocardiography: the MODE-AF study (mobile phone detection of atrial fibrillation). *Circulation* 2018;**137**:1524–7. <https://doi.org/10.1161/CIRCULATIONAHA.117.032804>
1112. Couderc JP, Kyal S, Mestha LK, Xu B, Peterson DR, Xia X, et al. Detection of atrial fibrillation using contactless facial video monitoring. *Heart Rhythm* 2015;**12**:195–201. <https://doi.org/10.1016/j.hrthm.2014.08.035>
1113. Yan BP, Lai WHS, Chan CKY, Au ACK, Freedman B, Poh YC, et al. High-throughput, contact-free detection of atrial fibrillation from video with deep learning. *JAMA Cardiol* 2020;**5**:105–7. <https://doi.org/10.1001/jamacardio.2019.4004>
1114. Yan BP, Lai WHS, Chan CKY, Chan SC, Chan LH, Lam KM, et al. Contact-free screening of atrial fibrillation by a smartphone using facial pulsatile photoplethysmographic signals. *J Am Heart Assoc* 2018;**7**:e008585. <https://doi.org/10.1161/JAHA.118.008585>
1115. Tsouri GR, Li Z. On the benefits of alternative color spaces for noncontact heart rate measurements using standard red-green-blue cameras. *J Biomed Opt* 2015;**20**:048002. <https://doi.org/10.1117/1.JBO.20.4.048002>
1116. Chan J, Rea T, Gollakota S, Sunshine JE. Contactless cardiac arrest detection using smart devices. *NPJ Digit Med* 2019;**2**:52. <https://doi.org/10.1038/s41746-019-0128-7>
1117. Guo Y, Wang H, Zhang H, Liu T, Liang Z, Xia Y, et al. Mobile photoplethysmographic technology to detect atrial fibrillation. *J Am Coll Cardiol* 2019;**74**:2365–75. <https://doi.org/10.1016/j.jacc.2019.08.019>
1118. Lubitz SA, Faranesh AZ, Selvaggi C, Atlas SJ, McManus DD, Singer DE, et al. Detection of atrial fibrillation in a large population using wearable devices: the Fitbit heart study. *Circulation* 2022;**146**:1415–24. <https://doi.org/10.1161/CIRCULATIONAHA.122.060291>
1119. Lopez Perales CR, Van Spall HGC, Maeda S, Jimenez A, Latcu DG, Milman A, et al. Mobile health applications for the detection of atrial fibrillation: a systematic review. *Europace* 2021;**23**:11–28. <https://doi.org/10.1093/eurpace/eaab139>
1120. Gill S, Bunting KV, Sartini C, Cardoso VR, Ghoreishi N, Uh HW, et al. Smartphone detection of atrial fibrillation using photoplethysmography: a systematic review and meta-analysis. *Heart* 2022;**108**:1600–7. <https://doi.org/10.1136/heartjnl-2021-320417>
1121. Mant J, Fitzmaurice DA, Hobbs FD, Jowett S, Murray ET, Holder R, et al. Accuracy of diagnosing atrial fibrillation on electrocardiogram by primary care practitioners and interpretative diagnostic software: analysis of data from screening for atrial fibrillation in the elderly (SAFE) trial. *BMJ* 2007;**335**:380. <https://doi.org/10.1136/bmj.39227.551713.AE>
1122. Halcox JPJ, Wareham K, Cardew A, Gilmore M, Barry JP, Phillips C, et al. Assessment of remote heart rhythm sampling using the AliveCor heart monitor to screen for atrial fibrillation: the REHEARSE-AF study. *Circulation* 2017;**136**:1784–94. <https://doi.org/10.1161/CIRCULATIONAHA.117.030583>
1123. Duarte R, Stainthorpe A, Greenhalgh J, Richardson M, Nevitt S, Mahon J, et al. Lead-I ECG for detecting atrial fibrillation in patients with an irregular pulse using single time point testing: a systematic review and economic evaluation. *Health Technol Assess* 2020;**24**:1–164. <https://doi.org/10.3310/hta24030>
1124. Mannhart D, Lischer M, Knecht S, du Fay de Lavallaz J, Strebel I, Serban T, et al. Clinical validation of 5 direct-to-consumer wearable smart devices to detect atrial fibrillation: BASEL wearable study. *JACC Clin Electrophysiol* 2023;**9**:232–42. <https://doi.org/10.1016/j.jacep.2022.09.011>
1125. Paul Nordin A, Carlöf C, Insulander P, Mohammad Ali A, Jensen-Urstad M, Saluveer O, et al. Validation of diagnostic accuracy of a handheld, smartphone-based rhythm recording device. *Expert Rev Med Devices* 2023;**20**:55–61. <https://doi.org/10.1080/17434440.2023.2171290>
1126. Gill SK, Barsky A, Guan X, Bunting KV, Karwath A, Tica O, et al. Consumer wearable devices to evaluate dynamic heart rate with digoxin versus beta-blockers: the RATE-AF randomised trial. *Nat Med* 2024;**30**:2030–2036. <https://doi.org/10.1038/s41591-024-03094-4>
1127. Kahwati LC, Asher GN, Kadro ZO, Keen S, Ali R, Coker-Schwimmer E, et al. Screening for atrial fibrillation: updated evidence report and systematic review for the US preventive services task force. *JAMA* 2022;**327**:368–83. <https://doi.org/10.1001/jama.2021.21811>
1128. Strong K, Wald N, Miller A, Alwan A. Current concepts in screening for noncommunicable disease: World Health Organization Consultation Group Report on methodology of noncommunicable disease screening. *J Med Screen* 2005;**12**:12–9. <https://doi.org/10.1258/0969141053279086>
1129. Whitfield R, Ascensão R, da Silva GL, Almeida AG, Pinto FJ, Caldeira D. Screening strategies for atrial fibrillation in the elderly population: a systematic review and network meta-analysis. *Clin Res Cardiol* 2023;**112**:705–15. <https://doi.org/10.1007/s00392-022-02117-9>
1130. Proietti M, Romiti GF, Vitolo M, Borgi M, Rocco AD, Farcomeni A, et al. Epidemiology of subclinical atrial fibrillation in patients with cardiac implantable electronic devices: a systematic review and meta-regression. *Eur J Intern Med* 2022;**103**:84–94. <https://doi.org/10.1016/j.ejim.2022.06.023>
1131. Healey JS, Alings M, Ha A, Leong-Sit P, Birnie DH, de Graaf JJ, et al. Subclinical atrial fibrillation in older patients. *Circulation* 2017;**136**:1276–83. <https://doi.org/10.1161/CIRCULATIONAHA.117.028845>
1132. Van Gelder IC, Healey JS, Crijns H, Wang J, Hohnloser SH, Gold MR, et al. Duration of device-detected subclinical atrial fibrillation and occurrence of stroke in ASSERT. *Eur Heart J* 2017;**38**:1339–44. <https://doi.org/10.1093/eurheartj/ehx042>
1133. Kemp Gudmundsdottir K, Fredriksson T, Svennberg E, Al-Khalili F, Friberg L, Frykman V, et al. Stepwise mass screening for atrial fibrillation using N-terminal B-type natriuretic peptide: the STROKESTOP II study. *Europace* 2020;**22**:24–32. <https://doi.org/10.1093/eurpace/euz255>
1134. Williams K, Modi RN, Dymond A, Hoare S, Powell A, Burt J, et al. Cluster randomised controlled trial of screening for atrial fibrillation in people aged 70 years and over to reduce stroke: protocol for the pilot study for the SAFER trial. *BMJ Open* 2022;**12**:e065066. <https://doi.org/10.1136/bmjopen-2022-065066>
1135. Elbadawi A, Sedhom R, Gad M, Hamed M, Elwagdy A, Barakat AF, et al. Screening for atrial fibrillation in the elderly: a network meta-analysis of randomized trials. *Eur J Intern Med* 2022;**105**:38–45. <https://doi.org/10.1016/j.ejim.2022.07.015>
1136. McIntyre WF, Diederichsen SZ, Freedman B, Schnabel RB, Svennberg E, Healey JS. Screening for atrial fibrillation to prevent stroke: a meta-analysis. *Eur Heart J Open* 2022;**2**:oeac044. <https://doi.org/10.1093/ehopen/oeac044>
1137. Lyth J, Svennberg E, Bernfort L, Aronsson M, Frykman V, Al-Khalili F, et al. Cost-effectiveness of population screening for atrial fibrillation: the STROKESTOP study. *Eur Heart J* 2023;**44**:196–204. <https://doi.org/10.1093/eurheartj/ehac547>
1138. Lubitz SA, Atlas SJ, Ashburner JM, Lipsanopoulos ATT, Borowski LH, Guan W, et al. Screening for atrial fibrillation in older adults at primary care visits: VITAL-AF randomized controlled trial. *Circulation* 2022;**145**:946–54. <https://doi.org/10.1161/CIRCULATIONAHA.121.057014>
1139. Uittenbogaart SB, Verbiest-van Gorp N, Lucassen WAM, Winkens B, Nielen M, Erkens PMG, et al. Opportunistic screening versus usual care for detection of atrial fibrillation in primary care: cluster randomised controlled trial. *BMJ* 2020;**370**:m3208. <https://doi.org/10.1136/bmj.m3208>
1140. Kaasenbrood F, Hollander M, de Bruijn SH, Dolmans CP, Tieleman RG, Hoes AW, et al. Opportunistic screening versus usual care for diagnosing atrial fibrillation in general practice: a cluster randomised controlled trial. *Br J Gen Pract* 2020;**70**:e427–33. <https://doi.org/10.3399/bjgp20X708161>
1141. Petryszyn P, Niewinski P, Staniak A, Piotrowski P, Well A, Well M, et al. Effectiveness of screening for atrial fibrillation and its determinants. A meta-analysis. *PLoS One* 2019;**14**:e0213198. <https://doi.org/10.1371/journal.pone.0213198>

1142. Wang Q, Richardson TG, Sanderson E, Tudball MJ, Ala-Korpela M, Davey Smith G, et al. A phenotype-wide bidirectional Mendelian randomization analysis of atrial fibrillation. *Int J Epidemiol* 2022;**51**:1153–66. <https://doi.org/10.1093/ije/dyac041>
1143. Siddiqi HK, Vinayagamoorthy M, Gencer B, Ng C, Pester J, Cook NR, et al. Sex differences in atrial fibrillation risk: the VITAL rhythm study. *JAMA Cardiol* 2022;**7**:1027–35. <https://doi.org/10.1001/jamacardio.2022.2825>
1144. Lu Z, Aribas E, Geurts S, Roeters van Lennep JE, Ikram MA, Bos MM, et al. Association between sex-specific risk factors and risk of new-onset atrial fibrillation among women. *JAMA Netw Open* 2022;**5**:e2229716. <https://doi.org/10.1001/jamanetworkopen.2022.29716>
1145. Wong GR, Nalliah CJ, Lee G, Voskoboinik A, Chieng D, Prabhu S, et al. Sex-related differences in atrial remodeling in patients with atrial fibrillation: relationship to ablation outcomes. *Circ Arrhythm Electrophysiol* 2022;**15**:e009925. <https://doi.org/10.1161/CIRCEP.121.009925>
1146. Mokgokong R, Schnabel R, Witt H, Miller R, Lee TC. Performance of an electronic health record-based predictive model to identify patients with atrial fibrillation across countries. *PLoS One* 2022;**17**:e0269867. <https://doi.org/10.1371/journal.pone.0269867>
1147. Schnabel RB, Witt H, Walker J, Ludwig M, Geelhoed B, Kossack N, et al. Machine learning-based identification of risk-factor signatures for undiagnosed atrial fibrillation in primary prevention and post-stroke in clinical practice. *Eur Heart J Qual Care Clin Outcomes* 2022;**9**:16–23. <https://doi.org/10.1093/ehjqqo/qcac013>
1148. Himmelreich JCL, Veelaers L, Lucassen WAM, Schnabel RB, Rienstra M, van Weert H, et al. Prediction models for atrial fibrillation applicable in the community: a systematic review and meta-analysis. *Europace* 2020;**22**:684–94. <https://doi.org/10.1093/europace/eaab005>
1149. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke statistics—2019 update: a report from the American Heart Association. *Circulation* 2019;**139**:e56–528. <https://doi.org/10.1161/CIR.00000000000000659>
1150. Allan V, Honarbakhsh S, Casas JP, Wallace J, Hunter R, Schilling R, et al. Are cardiovascular risk factors also associated with the incidence of atrial fibrillation? A systematic review and field synopsis of 23 factors in 32 population-based cohorts of 20 million participants. *Thromb Haemost* 2017;**117**:837–50. <https://doi.org/10.1160/TH16-11-0825>
1151. Kirchhof P, Lip GY, Van Gelder IC, Bax J, Hylek E, Kaab S, et al. Comprehensive risk reduction in patients with atrial fibrillation: emerging diagnostic and therapeutic options—a report from the 3rd Atrial Fibrillation Competence NETwork/European Heart Rhythm Association consensus conference. *Europace* 2012;**14**:8–27. <https://doi.org/10.1093/europace/eur241>
1152. Lu Z, Tilly MJ, Geurts S, Aribas E, Roeters van Lennep J, de Groot NMS, et al. Sex-specific anthropometric and blood pressure trajectories and risk of incident atrial fibrillation: the Rotterdam study. *Eur J Prev Cardiol* 2022;**29**:1744–55. <https://doi.org/10.1093/eurjpc/zwac083>
1153. Giacomantonio NB, Bredin SS, Foulds HJ, Warburton DE. A systematic review of the health benefits of exercise rehabilitation in persons living with atrial fibrillation. *Can J Cardiol* 2013;**29**:483–91. <https://doi.org/10.1016/j.cjca.2012.07.003>
1154. Andersen K, Farahmand B, Ahlborn A, Held C, Ljunghall S, Michaelsson K, et al. Risk of arrhythmias in 52 755 long-distance cross-country skiers: a cohort study. *Eur Heart J* 2013;**34**:3624–31. <https://doi.org/10.1093/eurheartj/ehs188>
1155. Qureshi WT, Alirhayim Z, Blaha MJ, Juraschek SP, Keteyian SJ, Brawner CA, et al. Cardiorespiratory fitness and risk of incident atrial fibrillation: results from the Henry Ford exercise testing (FIT) project. *Circulation* 2015;**131**:1827–34. <https://doi.org/10.1161/CIRCULATIONAHA.114.014833>
1156. Kwok CS, Anderson SG, Myint PK, Mamas MA, Loke YK. Physical activity and incidence of atrial fibrillation: a systematic review and meta-analysis. *Int J Cardiol* 2014;**177**:467–76. <https://doi.org/10.1016/j.ijcard.2014.09.104>
1157. Abdulla J, Nielsen JR. Is the risk of atrial fibrillation higher in athletes than in the general population? A systematic review and meta-analysis. *Europace* 2009;**11**:1156–9. <https://doi.org/10.1093/europace/eup197>
1158. Cheng M, Hu Z, Lu X, Huang J, Gu D. Caffeine intake and atrial fibrillation incidence: dose response meta-analysis of prospective cohort studies. *Can J Cardiol* 2014;**30**:448–54. <https://doi.org/10.1016/j.cjca.2013.12.026>
1159. Conen D, Chiuvè SE, Everett BM, Zhang SM, Buring JE, Albert CM. Caffeine consumption and incident atrial fibrillation in women. *Am J Clin Nutr* 2010;**92**:509–14. <https://doi.org/10.3945/ajcn.2010.29627>
1160. Shen J, Johnson VM, Sullivan LM, Jacques PF, Magnani JW, Lubitz SA, et al. Dietary factors and incident atrial fibrillation: the Framingham heart study. *Am J Clin Nutr* 2011;**93**:261–6. <https://doi.org/10.3945/ajcn.110.001305>
1161. Schnabel RB, Yin X, Gona P, Larson MG, Beiser AS, McManus DD, et al. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham heart study: a cohort study. *Lancet* 2015;**386**:154–62. [https://doi.org/10.1016/S0140-6736\(14\)61774-8](https://doi.org/10.1016/S0140-6736(14)61774-8)
1162. Furberg CD, Psaty BM, Manolio TA, Gardin JM, Smith VE, Rautaharju PM. Prevalence of atrial fibrillation in elderly subjects (the cardiovascular health study). *Am J Cardiol* 1994;**74**:236–41. [https://doi.org/10.1016/0002-9149\(94\)90363-8](https://doi.org/10.1016/0002-9149(94)90363-8)
1163. Lip GYH, Collet JP, de Caterina R, Fauchier L, Lane DA, Larsen TB, et al. Antithrombotic therapy in atrial fibrillation associated with valvular heart disease: executive summary of a joint consensus document from the European Heart Rhythm Association (EHRA) and European Society of Cardiology Working Group on Thrombosis, Endorsed by the ESC Working Group on Valvular Heart Disease, Cardiac Arrhythmia Society of Southern Africa (CASSA), Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), South African Heart (SA Heart) Association and Sociedad Latinoamericana de Estimulacion Cardiaca y Electrofisiologia (SOLEACE). *Thromb Haemost* 2017;**117**:2215–36. <https://doi.org/10.1160/TH-17-10-0709>
1164. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham heart study. *JAMA* 1994;**271**:840–4. <https://doi.org/10.1001/jama.1994.03510350050036>
1165. Michniewicz E, Młodawska E, Łopatowska P, Tomaszuk-Kazberuk A, Malyszko J. Patients with atrial fibrillation and coronary artery disease—double trouble. *Adv Med Sci* 2018;**63**:30–5. <https://doi.org/10.1016/j.advm.2017.06.005>
1166. Loomba RS, Buelow MW, Aggarwal S, Arora RR, Kovach J, Ginde S. Arrhythmias in adults with congenital heart disease: what are risk factors for specific arrhythmias? *Pacing Clin Electrophysiol* 2017;**40**:353–61. <https://doi.org/10.1111/pace.12983>
1167. Siland JE, Geelhoed B, Roselli C, Wang B, Lin HJ, Weiss S, et al. Resting heart rate and incident atrial fibrillation: a stratified Mendelian randomization in the AFGen consortium. *PLoS One* 2022;**17**:e0268768. <https://doi.org/10.1371/journal.pone.0268768>
1168. Geurts S, Tilly MJ, Arshi B, Stricker BHC, Kors JA, Deckers JW, et al. Heart rate variability and atrial fibrillation in the general population: a longitudinal and Mendelian randomization study. *Clin Res Cardiol* 2023;**112**:747–58. <https://doi.org/10.1007/s00392-022-02072-5>
1169. Aune D, Feng T, Schlesinger S, Janszky I, Norat T, Riboli E. Diabetes mellitus, blood glucose and the risk of atrial fibrillation: a systematic review and meta-analysis of cohort studies. *J Diabetes Complications* 2018;**32**:501–11. <https://doi.org/10.1016/j.jdiacomp.2018.02.004>
1170. Nakanishi K, Daimon M, Fujii K, Iwama K, Yoshida Y, Hirose K, et al. Prevalence of glucose metabolism disorders and its association with left atrial remodelling before and after catheter ablation in patients with atrial fibrillation. *Europace* 2023;**25**:eua4119. <https://doi.org/10.1093/europace/eurad119>
1171. Kim J, Kim D, Jang E, Kim D, You SC, Yu HT, et al. Associations of high-normal blood pressure and impaired fasting glucose with atrial fibrillation. *Heart* 2023;**109**:929–35. <https://doi.org/10.1136/heartjnl-2022-322094>
1172. Lee SS, Ae Kong K, Kim D, Lim YM, Yang PS, Yi JE, et al. Clinical implication of an impaired fasting glucose and prehypertension related to new onset atrial fibrillation in a healthy Asian population without underlying disease: a nationwide cohort study in Korea. *Eur Heart J* 2017;**38**:2599–607. <https://doi.org/10.1093/eurheartj/ehx316>
1173. Alonso A, Lopez FL, Matsushita K, Loehr LR, Agarwal SK, Chen LY, et al. Chronic kidney disease is associated with the incidence of atrial fibrillation: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation* 2011;**123**:2946–53. <https://doi.org/10.1161/CIRCULATIONAHA.111.020982>
1174. Bansal N, Zelnick LR, Alonso A, Benjamin EJ, de Boer IH, Deo R, et al. eGFR and albuminuria in relation to risk of incident atrial fibrillation: a meta-analysis of the Jackson heart study, the multi-ethnic study of atherosclerosis, and the cardiovascular health study. *Clin J Am Soc Nephrol* 2017;**12**:1386–98. <https://doi.org/10.2215/CJN.01860217>
1175. Asad Z, Abbas M, Javed I, Korantzopoulos P, Stavarakis S. Obesity is associated with incident atrial fibrillation independent of gender: a meta-analysis. *J Cardiovasc Electrophysiol* 2018;**29**:725–32. <https://doi.org/10.1111/jce.13458>
1176. Aune D, Sen A, Schlesinger S, Norat T, Janszky I, Romundstad P, et al. Body mass index, abdominal fatness, fat mass and the risk of atrial fibrillation: a systematic review and dose-response meta-analysis of prospective studies. *Eur J Epidemiol* 2017;**32**:181–92. <https://doi.org/10.1007/s10654-017-0232-4>
1177. May AM, Blackwell T, Stone PH, Stone KL, Cawthon PM, Sauer WH, et al. Central sleep-disordered breathing predicts incident atrial fibrillation in older men. *Am J Respir Crit Care Med* 2016;**193**:783–91. <https://doi.org/10.1164/rccm.201508-1523OC>
1178. Tung P, Levitzky YS, Wang R, Weng J, Quan SF, Gottlieb DJ, et al. Obstructive and central sleep apnea and the risk of incident atrial fibrillation in a community cohort of men and women. *J Am Heart Assoc* 2017;**6**:e004500. <https://doi.org/10.1161/JAHA.116.004500>
1179. Desai R, Patel U, Singh S, Bhuvra R, Fong HK, Nunna P, et al. The burden and impact of arrhythmia in chronic obstructive pulmonary disease: insights from the national inpatient sample. *Int J Cardiol* 2019;**281**:49–55. <https://doi.org/10.1016/j.ijcard.2019.01.074>
1180. O'Neal WT, Efrid JT, Qureshi WT, Yeboah J, Alonso A, Heckbert SR, et al. Coronary artery calcium progression and atrial fibrillation: the multi-ethnic study of atherosclerosis. *Circ Cardiovasc Imaging* 2015;**8**:e003786. <https://doi.org/10.1161/CIRCIMAGING.115.003786>
1181. Chen LY, Leening MJ, Norby FL, Roetker NS, Hofman A, Franco OH, et al. Carotid intima-media thickness and arterial stiffness and the risk of atrial fibrillation: the Atherosclerosis Risk in Communities (ARIC) study, Multi-Ethnic Study of

- Atherosclerosis (MESA), and the Rotterdam study. *J Am Heart Assoc* 2016;**5**:e002907. <https://doi.org/10.1161/JAHA.115.002907>
1182. Geurts S, Brunborg C, Papageorgiou G, Ikram MA, Kavousi M. Subclinical measures of peripheral atherosclerosis and the risk of new-onset atrial fibrillation in the general population: the Rotterdam study. *J Am Heart Assoc* 2022;**11**:e023967. <https://doi.org/10.1161/JAHA.121.023967>
 1183. Cheng S, Keyes MJ, Larson MG, McCabe EL, Newton-Cheh C, Levy D, et al. Long-term outcomes in individuals with prolonged PR interval or first-degree atrio-ventricular block. *JAMA* 2009;**301**:2571–7. <https://doi.org/10.1001/jama.2009.888>
 1184. Alonso A, Jensen PN, Lopez FL, Chen LY, Psaty BM, Folsom AR, et al. Association of sick sinus syndrome with incident cardiovascular disease and mortality: the atherosclerosis risk in communities study and cardiovascular health study. *PLoS One* 2014;**9**:e109662. <https://doi.org/10.1371/journal.pone.0109662>
 1185. Bodin A, Bisson A, Gaborit C, Herbert J, Clementy N, Babuty D, et al. Ischemic stroke in patients with sinus node disease, atrial fibrillation, and other cardiac conditions. *Stroke* 2020;**51**:1674–81. <https://doi.org/10.1161/STROKEAHA.120.029048>
 1186. Bunch TJ, May HT, Bair TL, Anderson JL, Crandall BG, Cutler MJ, et al. Long-term natural history of adult Wolff–Parkinson–White syndrome patients treated with and without catheter ablation. *Circ Arrhythm Electrophysiol* 2015;**8**:1465–71. <https://doi.org/10.1161/CIRCEP.115.003013>
 1187. Chang SH, Kuo CF, Chou IJ, See LC, Yu KH, Luo SF, et al. Association of a family history of atrial fibrillation with incidence and outcomes of atrial fibrillation: a population-based family cohort study. *JAMA Cardiol* 2017;**2**:863–70. <https://doi.org/10.1001/jamacardio.2017.1855>
 1188. Fox CS, Parise H, D'Agostino RB, Sr, Lloyd-Jones DM, Vasan RS, Wang TJ, et al. Parental atrial fibrillation as a risk factor for atrial fibrillation in offspring. *JAMA* 2004;**291**:2851–5. <https://doi.org/10.1001/jama.291.23.2851>
 1189. Lubitz SA, Yin X, Fontes JD, Magnani JW, Rienstra M, Pai M, et al. Association between familial atrial fibrillation and risk of new-onset atrial fibrillation. *JAMA* 2010;**304**:2263–9. <https://doi.org/10.1001/jama.2010.1690>
 1190. Zoller B, Ohlsson H, Sundquist J, Sundquist K. High familial risk of atrial fibrillation/atrial flutter in multiplex families: a nationwide family study in Sweden. *J Am Heart Assoc* 2013;**2**:e003384. <https://doi.org/10.1161/JAHA.112.003384>
 1191. Ko D, Benson MD, Ngo D, Yang Q, Larson MG, Wang TJ, et al. Proteomics profiling and risk of new-onset atrial fibrillation: Framingham heart study. *J Am Heart Assoc* 2019;**8**:e010976. <https://doi.org/10.1161/JAHA.118.010976>
 1192. Khera AV, Chaffin M, Aragam KG, Haas ME, Roselli C, Choi SH, et al. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. *Nat Genet* 2018;**50**:1219–24. <https://doi.org/10.1038/s41588-018-0183-z>
 1193. Buckley BJR, Harrison SL, Gupta D, Fazio-Eynullayeva E, Underhill P, Lip GYH. Atrial fibrillation in patients with cardiomyopathy: prevalence and clinical outcomes from real-world data. *J Am Heart Assoc* 2021;**10**:e021970. <https://doi.org/10.1161/JAHA.121.021970>
 1194. Chen M, Ding N, Mok Y, Mathews L, Hoogveen RC, Ballantyne CM, et al. Growth differentiation factor 15 and the subsequent risk of atrial fibrillation: the atherosclerosis risk in communities study. *Clin Chem* 2022;**68**:1084–93. <https://doi.org/10.1093/clinchem/hvac096>
 1195. Chua W, Purmah Y, Cardoso VR, Gkoutos GV, Tull SP, Neculau G, et al. Data-driven discovery and validation of circulating blood-based biomarkers associated with prevalent atrial fibrillation. *Eur Heart J* 2019;**40**:1268–76. <https://doi.org/10.1093/eurheartj/ehy815>
 1196. Brady PF, Chua W, Nehaj F, Connolly DL, Khashaba A, Purmah YJV, et al. Interactions between atrial fibrillation and natriuretic peptide in predicting heart failure hospitalization or cardiovascular death. *J Am Heart Assoc* 2022;**11**:e022833. <https://doi.org/10.1161/JAHA.121.022833>
 1197. Werhahn SM, Becker C, Mende M, Haarmann H, Nolte K, Laufs U, et al. NT-proBNP as a marker for atrial fibrillation and heart failure in four observational outpatient trials. *ESC Heart Fail* 2022;**9**:100–9. <https://doi.org/10.1002/ehf2.13703>
 1198. Geelhoed B, Börschel CS, Niiranen T, Palosaari T, Havulinna AS, Fouodo CJK, et al. Assessment of causality of natriuretic peptides and atrial fibrillation and heart failure: a Mendelian randomization study in the FINRISK cohort. *Europace* 2020;**22**:1463–9. <https://doi.org/10.1093/eurpace/euaa158>
 1199. Toprak B, Brandt S, Brederecke J, Gianfagna F, Vishram-Nielsen JKK, Ojeda FM, et al. Exploring the incremental utility of circulating biomarkers for robust risk prediction of incident atrial fibrillation in European cohorts using regressions and modern machine learning methods. *Europace* 2023;**25**:812–9. <https://doi.org/10.1093/eurpace/ueac260>
 1200. Benz AP, Hijazi Z, Lindbäck J, Connolly SJ, Eikelboom JW, Oldgren J, et al. Biomarker-based risk prediction with the ABC-AF scores in patients with atrial fibrillation not receiving oral anticoagulation. *Circulation* 2021;**143**:1863–73. <https://doi.org/10.1161/CIRCULATIONAHA.120.053100>
 1201. Monrad M, Sajadieh A, Christensen JS, Kettel M, Raaschou-Nielsen O, Tjønneland A, et al. Long-term exposure to traffic-related air pollution and risk of incident atrial fibrillation: a cohort study. *Environ Health Perspect* 2017;**125**:422–7. <https://doi.org/10.1289/EHP392>
 1202. Walkey AJ, Greiner MA, Heckbert SR, Jensen PN, Piccini JP, Sinner MF, et al. Atrial fibrillation among medicare beneficiaries hospitalized with sepsis: incidence and risk factors. *Am Heart J* 2013;**165**:949–955.e3. <https://doi.org/10.1016/j.ahj.2013.03.020>
 1203. Svensson T, Kitlinski M, Engstrom G, Melander O. Psychological stress and risk of incident atrial fibrillation in men and women with known atrial fibrillation genetic risk scores. *Sci Rep* 2017;**7**:42613. <https://doi.org/10.1038/srep42613>
 1204. Eaker ED, Sullivan LM, Kelly-Hayes M, D'Agostino RB, Sr, Benjamin EJ. Anger and hostility predict the development of atrial fibrillation in men in the Framingham offspring study. *Circulation* 2004;**109**:1267–71. <https://doi.org/10.1161/01.CIR.0000118535.15205.8F>
 1205. Chen LY, Bigger JT, Hickey KT, Chen H, Lopez-Jimenez C, Banerji MA, et al. Effect of intensive blood pressure lowering on the risk of atrial fibrillation and P-wave indices in the ACCORD blood pressure trial. *Am J Hypertens* 2016;**29**:1276–82. <https://doi.org/10.1093/ajh/hpv172>
 1206. Soliman EZ, Rahman AF, Zhang ZM, Rodriguez CJ, Chang TI, Bates JT, et al. Effect of intensive blood pressure lowering on the risk of atrial fibrillation. *Hypertension* 2020;**75**:1491–6. <https://doi.org/10.1161/HYPERTENSIONAHA.120.14766>
 1207. Larstorp ACK, Stokke IM, Kjeldsen SE, Hecht Olsen M, Okin PM, Devereux RB, et al. Antihypertensive therapy prevents new-onset atrial fibrillation in patients with isolated systolic hypertension: the LIFE study. *Blood Press* 2019;**28**:317–26. <https://doi.org/10.1080/08037051.2019.1633905>
 1208. Healey JS, Baranchuk A, Crystal E, Morillo CA, Garfinkle M, Yusuf S, et al. Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a meta-analysis. *J Am Coll Cardiol* 2005;**45**:1832–9. <https://doi.org/10.1016/j.jacc.2004.11.070>
 1209. Swedberg K, Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Shi H, et al. Eplerenone and atrial fibrillation in mild systolic heart failure: results from the EMPHASIS-HF (eplerenone in mild patients hospitalization and survival study in heart failure) study. *J Am Coll Cardiol* 2012;**59**:1598–603. <https://doi.org/10.1016/j.jacc.2011.11.063>
 1210. Wang M, Zhang Y, Wang Z, Liu D, Mao S, Liang B. The effectiveness of SGLT2 inhibitor in the incidence of atrial fibrillation/atrial flutter in patients with type 2 diabetes mellitus/heart failure: a systematic review and meta-analysis. *J Thorac Dis* 2022;**14**:1620–37. <https://doi.org/10.21037/jtd-22-550>
 1211. Yin Z, Zheng H, Guo Z. Effect of sodium-glucose co-transporter protein 2 inhibitors on arrhythmia in heart failure patients with or without type 2 diabetes: a meta-analysis of randomized controlled trials. *Front Cardiovasc Med* 2022;**9**:902923. <https://doi.org/10.3389/fcvm.2022.902923>
 1212. Tedrow UB, Conen D, Ridker PM, Cook NR, Koplan BA, Manson JE, et al. The long- and short-term impact of elevated body mass index on the risk of new atrial fibrillation the WHS (Women's Health Study). *J Am Coll Cardiol* 2010;**55**:2319–27. <https://doi.org/10.1016/j.jacc.2010.02.029>
 1213. Chan YH, Chen SW, Chao TF, Kao YW, Huang CY, Chu PH. The impact of weight loss related to risk of new-onset atrial fibrillation in patients with type 2 diabetes mellitus treated with sodium-glucose cotransporter 2 inhibitor. *Cardiovasc Diabetol* 2021;**20**:93. <https://doi.org/10.1186/s12933-021-01285-8>
 1214. Mishima RS, Verdichio CV, Noubiap JJ, Ariyaratnam JP, Gallagher C, Jones D, et al. Self-reported physical activity and atrial fibrillation risk: a systematic review and meta-analysis. *Heart Rhythm* 2021;**18**:520–8. <https://doi.org/10.1016/j.hrthm.2020.12.017>
 1215. Elliott AD, Linz D, Mishima R, Kadhim K, Gallagher C, Middeldorp ME, et al. Association between physical activity and risk of incident arrhythmias in 402 406 individuals: evidence from the UK Biobank cohort. *Eur Heart J* 2020;**41**:1479–86. <https://doi.org/10.1093/eurheartj/ehz897>
 1216. Jin MN, Yang PS, Song C, Yu HT, Kim TH, Uhm JS, et al. Physical activity and risk of atrial fibrillation: a nationwide cohort study in general population. *Sci Rep* 2019;**9**:13270. <https://doi.org/10.1038/s41598-019-49686-w>
 1217. Khurshid S, Weng LC, Al-Alusi MA, Halford JL, Haimovich JS, Benjamin EJ, et al. Accelerometer-derived physical activity and risk of atrial fibrillation. *Eur Heart J* 2021;**42**:2472–83. <https://doi.org/10.1093/eurheartj/ehab250>
 1218. Tikkanen E, Gustafsson S, Ingelsson E. Associations of fitness, physical activity, strength, and genetic risk with cardiovascular disease: longitudinal analyses in the UK biobank study. *Circulation* 2018;**137**:2583–91. <https://doi.org/10.1161/CIRCULATIONAHA.117.032432>
 1219. Morseth B, Graff-Iversen S, Jacobsen BK, Jørgensen L, Nyrnes A, Thelle DS, et al. Physical activity, resting heart rate, and atrial fibrillation: the Tromsø study. *Eur Heart J* 2016;**37**:2307–13. <https://doi.org/10.1093/eurheartj/ehw059>
 1220. Csengeri D, Sprünker NA, Di Castelnuovo A, Niiranen T, Vishram-Nielsen JK, Costanzo S, et al. Alcohol consumption, cardiac biomarkers, and risk of atrial fibrillation and adverse outcomes. *Eur Heart J* 2021;**42**:1170–7. <https://doi.org/10.1093/eurheartj/ehaa953>
 1221. Gallagher C, Hendriks JML, Elliott AD, Wong CX, Rangnekar G, Middeldorp ME, et al. Alcohol and incident atrial fibrillation – a systematic review and meta-analysis. *Int J Cardiol* 2017;**246**:46–52. <https://doi.org/10.1016/j.ijcard.2017.05.133>

1222. Tu SJ, Gallagher C, Elliott AD, Linz D, Pitman BM, Hendriks JML, et al. Risk thresholds for total and beverage-specific alcohol consumption and incident atrial fibrillation. *JACC Clin Electrophysiol* 2021;**7**:1561–9. <https://doi.org/10.1016/j.jacep.2021.05.013>
1223. Lee JW, Roh SY, Yoon WS, Kim J, Jo E, Bae DH, et al. Changes in alcohol consumption habits and risk of atrial fibrillation: a nationwide population-based study. *Eur J Prev Cardiol* 2024;**31**:49–58. <https://doi.org/10.1093/eurjpc/zwad270>
1224. Chang SH, Wu LS, Chiou MJ, Liu JR, Yu KH, Kuo CF, et al. Association of metformin with lower atrial fibrillation risk among patients with type 2 diabetes mellitus: a population-based dynamic cohort and *in vitro* studies. *Cardiovasc Diabetol* 2014;**13**: 123. <https://doi.org/10.1186/s12933-014-0123-x>
1225. Tseng CH. Metformin use is associated with a lower incidence of hospitalization for atrial fibrillation in patients with type 2 diabetes mellitus. *Front Med (Lausanne)* 2021; **7**:592901. <https://doi.org/10.3389/fmed.2020.592901>
1226. Li WJ, Chen XQ, Xu LL, Li YQ, Luo BH. SGLT2 inhibitors and atrial fibrillation in type 2 diabetes: a systematic review with meta-analysis of 16 randomized controlled trials. *Cardiovasc Diabetol* 2020;**19**:130. <https://doi.org/10.1186/s12933-020-01105-5>
1227. Srivatsa UN, Malhotra P, Zhang XJ, Beri N, Xing G, Brunson A, et al. Bariatric surgery to alleviate occurrence of atrial fibrillation hospitalization—BLOC-AF. *Heart Rhythm* 2020;**17**:96–102. <https://doi.org/10.1016/j.hrthm.2020.04.004>
1228. Hoskuldottir G, Sattar N, Miftaraj M, Naslund I, Ottosson J, Franzen S, et al. Potential effects of bariatric surgery on the incidence of heart failure and atrial fibrillation in patients with type 2 diabetes mellitus and obesity and on mortality in patients with preexisting heart failure: a nationwide, matched, observational cohort study. *J Am Heart Assoc* 2021;**10**:e019323. <https://doi.org/10.1161/JAHA.120.019323>
1229. Chokesuwattanasakul R, Thongprayoon C, Bathini T, Sharma K, Watthanasuntorn K, Lertjitbanjong P, et al. Incident atrial fibrillation in patients undergoing bariatric surgery: a systematic review and meta-analysis. *Intern Med J* 2020;**50**:810–7. <https://doi.org/10.1111/imj.14436>
1230. Lynch KT, Mehaffey JH, Hawkins RB, Hassinger TE, Hallowell PT, Kirby JL. Bariatric surgery reduces incidence of atrial fibrillation: a propensity score-matched analysis. *Surg Obes Relat Dis* 2019;**15**:279–85. <https://doi.org/10.1016/j.soard.2018.11.021>
1231. Jamaly S, Carlsson L, Peltonen M, Jacobson P, Sjöström L, Karason K. Bariatric surgery and the risk of new-onset atrial fibrillation in Swedish obese subjects. *J Am Coll Cardiol* 2016;**68**:2497–504. <https://doi.org/10.1016/j.jacc.2016.09.940>
1232. Okin PM, Hille DA, Larstorp AC, Wachtell K, Kjeldsen SE, Dahlöf B, et al. Effect of lower on-treatment systolic blood pressure on the risk of atrial fibrillation in hypertensive patients. *Hypertension* 2015;**66**:368–73. <https://doi.org/10.1161/HYPERTENSIONAHA.115.05728>
1233. Wachtell K, Lehto M, Gerds E, Olsen MH, Hornestam B, Dahlöf B, et al. Angiotensin II receptor blockade reduces new-onset atrial fibrillation and subsequent stroke compared to atenolol: the Losartan Intervention for End point reduction in hypertension (LIFE) study. *J Am Coll Cardiol* 2005;**45**:712–9. <https://doi.org/10.1016/j.jacc.2004.10.068>
1234. Schmieder RE, Kjeldsen SE, Julius S, McInnes GT, Zanchetti A, Hua TA, et al. Reduced incidence of new-onset atrial fibrillation with angiotensin II receptor blockade: the VALUE trial. *J Hypertens* 2008;**26**:403–11. <https://doi.org/10.1097/HJH.0b013e3282f35c67>
1235. Schaer BA, Schneider C, Jick SS, Conen D, Osswald S, Meier CR. Risk for incident atrial fibrillation in patients who receive antihypertensive drugs: a nested case-control study. *Ann Intern Med* 2010;**152**:78–84. <https://doi.org/10.7326/0003-4819-152-2-201001190-00005>
1236. Dewland TA, Soliman EZ, Yamal JM, Davis BR, Alonso A, Albert CM, et al. Pharmacologic prevention of incident atrial fibrillation: long-term results from the ALLHAT (antihypertensive and lipid-lowering treatment to prevent heart attack trial). *Circ Arrhythm Electrophysiol* 2017;**10**:e005463. <https://doi.org/10.1161/CIRCEP.117.005463>
1237. Butt JH, Docherty KF, Jhund PS, de Boer RA, Böhm M, Desai AS, et al. Dapagliflozin and atrial fibrillation in heart failure with reduced ejection fraction: insights from DAPA-HF. *Eur J Heart Fail* 2022;**24**:513–25. <https://doi.org/10.1002/ejhf.2381>
1238. Liu X, Liu H, Wang L, Zhang L, Xu Q. Role of sacubitril-valsartan in the prevention of atrial fibrillation occurrence in patients with heart failure: a systematic review and meta-analysis of randomized controlled trials. *PLOS ONE* 2022;**17**:e0263131. <https://doi.org/10.1371/journal.pone.0263131>
1239. Hess PL, Jackson KP, Hasselblad V, Al-Khatib SM. Is cardiac resynchronization therapy an antiarrhythmic therapy for atrial fibrillation? A systematic review and meta-analysis. *Curr Cardiol Rep* 2013;**15**:330. <https://doi.org/10.1007/s11886-012-0330-6>
1240. Fatemi O, Yuriditsky E, Tsioufis C, Tsachris D, Morgan T, Basile J, et al. Impact of intensive glycemic control on the incidence of atrial fibrillation and associated cardiovascular outcomes in patients with type 2 diabetes mellitus (from the action to control cardiovascular risk in diabetes study). *Am J Cardiol* 2014;**114**:1217–22. <https://doi.org/10.1016/j.amjcard.2014.07.045>
1241. Nantsupawat T, Wongcharoen W, Chattipakorn SC, Chattipakorn N. Effects of metformin on atrial and ventricular arrhythmias: evidence from cell to patient. *Cardiovasc Diabetol* 2020;**19**:198. <https://doi.org/10.1186/s12933-020-01176-4>
1242. Chang CY, Yeh YH, Chan YH, Liu JR, Chang SH, Lee HF, et al. Dipeptidyl peptidase-4 inhibitor decreases the risk of atrial fibrillation in patients with type 2 diabetes: a nationwide cohort study in Taiwan. *Cardiovasc Diabetol* 2017;**16**:159. <https://doi.org/10.1186/s12933-017-0640-5>
1243. Ostropelets A, Elias PA, Reyes MV, Wan EY, Pajvani UB, Hripcsak G, et al. Metformin is associated with a lower risk of atrial fibrillation and ventricular arrhythmias compared with sulfonylureas: an observational study. *Circ Arrhythm Electrophysiol* 2021; **14**:e009115. <https://doi.org/10.1161/CIRCEP.120.009115>
1244. Proietti R, Lip GYH. Sodium-glucose cotransporter 2 inhibitors: an additional management option for patients with atrial fibrillation? *Diabetes Obes Metab* 2022;**24**: 1897–900. <https://doi.org/10.1111/dom.14818>
1245. Karamichalakis N, Kolovos V, Paraskevaidis I, Tsougos E. A new hope: sodium-glucose cotransporter-2 inhibition to prevent atrial fibrillation. *J Cardiovasc Dev Dis* 2022;**9**:236. <https://doi.org/10.3390/jcdd9080236>
1246. Lee S, Zhou J, Leung KSK, Wai AKC, Jeevaratnam K, King E, et al. Comparison of sodium-glucose cotransporter-2 inhibitor and dipeptidyl peptidase-4 inhibitor on the risks of new-onset atrial fibrillation, stroke and mortality in diabetic patients: a propensity score-matched study in Hong Kong. *Cardiovasc Drugs Ther* 2023;**37**: 561–9. <https://doi.org/10.1007/s10557-022-07319-x>
1247. Elliott AD, Maatman B, Emery MS, Sanders P. The role of exercise in atrial fibrillation prevention and promotion: finding optimal ranges for health. *Heart Rhythm* 2017;**14**: 1713–20. <https://doi.org/10.1016/j.hrthm.2017.07.001>
1248. Newman W, Parry-Williams G, Wiles J, Edwards J, Hulbert S, Kipourou K, et al. Risk of atrial fibrillation in athletes: a systematic review and meta-analysis. *Br J Sports Med* 2021;**55**:1233–8. <https://doi.org/10.1136/bjsports-2021-103994>

2024 ESC Guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS)

Supplementary data

Developed by the task force for the management of atrial fibrillation of the European Society of Cardiology (ESC), with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC.

Endorsed by the European Stroke Organisation (ESO)

Authors/Task Force Members: Isabelle C. Van Gelder  ^{*†}, (Chairperson) (Netherlands), Michiel Rienstra  [±], (Task Force Co-ordinator) (Netherlands), Karina V. Bunting  [±], (Task Force Co-ordinator) (United Kingdom), Ruben Casado-Arroyo  (Belgium), Valeria Caso  ¹ (Italy), Harry J.G.M. Crijns  (Netherlands), Tom J.R. De Potter  (Belgium), Jeremy Dwight (United Kingdom), Luigina Guasti  (Italy), Thorsten Hanke  ² (Germany), Tiny Jaarsma  (Sweden), Maddalena Lettino  (Italy), Maja-Lisa Løchen  (Norway), R. Thomas Lumbers  (United Kingdom), Bart Maesen  ² (Netherlands), Inge Mølgaard (Denmark), Giuseppe M.C. Rosano (United Kingdom), Prashanthan Sanders  (Australia), Renate B. Schnabel  (Germany), Piotr Suwalski  ² (Poland), Emma Svennberg  (Sweden), Juan Tamargo  (Spain), Otilia Tica  (Romania), Vassil Traykov  (Bulgaria), Stylianos Tzeis (Greece), Dipak Kotecha  ^{*†}, (Chairperson) (United Kingdom), and ESC Scientific Document Group

* Corresponding authors: Isabelle C. Van Gelder, Department of Cardiology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands. Tel: +31 50 3611327, Email: i.c.van.gelder@umcg.nl; and Dipak Kotecha, Institute of Cardiovascular Sciences, University of Birmingham, United Kingdom & NIHR Birmingham Biomedical Research Centre, University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom. Tel: +44 121 3718124, Email: d.kotecha@bham.ac.uk.

[†] The two Chairpersons contributed equally to the document and are joint corresponding authors.

[±] The two Task Force Co-ordinators contributed equally to the document.

Author/Task Force Member affiliations are listed in author information in the full text.

¹ Representing European Stroke Organisation (ESO)

² Representing European Association for Cardio-Thoracic Surgery (EACTS)

ESC Clinical Practice Guidelines (CPG) Committee: listed in the Appendix of the full text.

ESC subspecialty communities having participated in the development of this document:

Associations: Association of Cardiovascular Nursing & Allied Professions (ACNAP), Association for Acute CardioVascular Care (ACVC), European Association of Cardiovascular Imaging (EACVI), European Association of Preventive Cardiology (EAPC), European Association of Percutaneous Cardiovascular Interventions (EAPCI), European Heart Rhythm Association (EHRA), Heart Failure Association (HFA).

Councils: Council for Cardiology Practice, Council of Cardio-Oncology, Council on Cardiovascular Genomics, Council on Stroke.

Working Groups: Cardiac Cellular Electrophysiology, Cardiovascular Pharmacotherapy, E-Cardiology, Thrombosis.

Patient Forum

© The European Society of Cardiology 2024. All rights reserved. For permissions, please email: journals.permissions@oup.com.

Document Reviewers: Nikolaos Dagres, (CPG Review Co-ordinator) (Germany), Bianca Rocca, (CPG Review Co-ordinator) (Italy), Syed Ahsan (United Kingdom)², Pietro Ameri (Italy), Elena Arbelo (Spain), Axel Bauer (Austria), Michael A. Borger (Germany), Sergio Buccheri (Sweden), Barbara Casadei (United Kingdom), Ovidiu Chioncel (Romania), Dobromir Dobrev (Germany), Laurent Fauchier (France), Bruna Gigante (Sweden), Michael Glikson (Israel), Ziad Hijazi (Sweden), Gerhard Hindricks (Germany), Daniela Husser (Germany), Borja Ibanez (Spain), Stefan James (Sweden), Stefan Kaab (Germany), Paulus Kirchhof (Germany), Lars Køber (Denmark), Konstantinos C. Koskinas (Switzerland), Thomas Kumler (Denmark), Gregory Y.H. Lip (United Kingdom), John Mandrolia (United States of America), Nikolaus Marx (Germany), John William Mcevoy (Ireland), Borislava Mihaylova (United Kingdom), Richard Mindham (United Kingdom), Denisa Muraru (Italy), Lis Neubeck (United Kingdom), Jens Cosedis Nielsen (Denmark), Jonas Oldgren (Sweden), Maurizio Paciaroni (Italy)¹, Agnes A. Pasquet (Belgium), Eva Prescott (Denmark), Filip Rega² (Belgium), Francisco Javier Rossello (Spain), Marcin Rucinski (Poland), Sacha P. Salzberg² (Switzerland), Sam Schulman (Canada), Philipp Sommer (Germany), Jesper Hastrup Svendsen (Denmark), Jurrien M. ten Berg (Netherlands), Hugo Ten Cate (Netherlands), Ilonca Vaartjes (Netherlands), Christiaan Jm. Vrints (Belgium), Adam Witkowski (Poland), and Katja Zeppenfeld (Netherlands)

All experts involved in the development of these Guidelines have submitted declarations of interest which are reported in a supplementary document to the Guidelines. See the *European Heart Journal* online or www.escardio.org/Guidelines for submitted declarations of interest and evidence tables.

Disclaimer. The ESC Guidelines represent the views of the ESC and were produced after careful consideration of the scientific and medical knowledge and the evidence available at the time of their publication. The ESC is not responsible in the event of any contradiction, discrepancy and/or ambiguity between the ESC Guidelines and any other official recommendations or guidelines issued by the relevant public health authorities, in particular in relation to good use of healthcare or therapeutic strategies. Health professionals are encouraged to take the ESC Guidelines fully into account when exercising their clinical judgment, as well as in the determination and the implementation of preventive, diagnostic or therapeutic medical strategies; however, the ESC Guidelines do not override, in any way whatsoever, the individual responsibility of health professionals to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient and, where appropriate and/or necessary, the patient's caregiver. Nor do the ESC Guidelines exempt health professionals from taking into full and careful consideration the relevant official updated recommendations or guidelines issued by the competent public health authorities, in order to manage each patient's case in light of the scientifically accepted data pursuant to their respective ethical and professional obligations. It is also the health professional's responsibility to verify the applicable rules and regulations relating to drugs and medical devices at the time of prescription. The ESC warns readers that the technical language may be misinterpreted and declines any responsibility in this respect.

Permissions. The content of these European Society of Cardiology (ESC) Guidelines has been published for personal and educational use only. No commercial use is authorized. No part of the ESC Guidelines may be translated or reproduced in any form without written permission from the ESC. Permissions can be obtained upon submission of a written request to Oxford University Press, the publisher of the *European Heart Journal* and the party authorized to handle such permissions on behalf of the ESC (journals.permissions@oup.com).

Keywords

Guidelines • Atrial fibrillation • AF-CARE • Comorbidity • Risk factors • Anticoagulation • Rate control • Rhythm control • Cardioversion • Antiarrhythmic drugs • Catheter ablation • AF surgery • Evaluation • Stroke • Thromboembolism

Table of contents

1. Introduction	3	4.2. AF in inherited cardiomyopathies and primary arrhythmia syndromes	12
2. Definition and clinical impact of AF	4	5. Screening and prevention of AF	12
2.1. Pathophysiology of AF	4	5.1. Benefit and cost-effectiveness of screening for AF	12
2.2. Diagnostic evaluation of new AF	4	5.2. Factors associated with incident AF	13
3. Patient-centred, multidisciplinary AF management	5	5.3. Genomics and AF risk	14
3.1. Institution of anticoagulation	7	5.4. Primary prevention of AF	14
3.2. Percutaneous left atrial appendage occlusion	8	5.4.1. Hypertension—attributable risk for AF	14
3.3. Assessment of bleeding risk due to anticoagulation	9	5.4.2. Heart failure—attributable risk for AF	14
4. The AF-CARE pathway in specific clinical settings	11	5.4.3. Diabetes mellitus—attributable risk for AF	14
4.1. Amiodarone-induced thyroid disorders	11	5.4.4. Obesity—attributable risk for AF	14
		5.4.5. Sleep apnoea syndrome—attributable risk for AF	14

5.4.6. Physical activity—attributable risk for AF	15
5.4.7. Alcohol intake—attributable risk for AF	15
6. References	15

List of tables

Table S1 Design of services to enable better AF-CARE	5
Table S2 Education and resources	6
Table S3 Risk scores for stroke and thromboembolism in atrial fibrillation	7
Table S4 Ongoing registered trials of percutaneous left atrial appendage occlusion devices vs. pharmacological treatment	9
Table S5 Published bleeding risk scores	9
Table S6 AF treatment considerations for inherited cardiac diseases	12
Table S7 Risk scores for prediction of atrial fibrillation	13

List of figures

Figure S1 Multimodality imaging in atrial fibrillation	4
Figure S2 Suggested antithrombotic regimen post left atrial appendage occlusion device implantation	8

Abbreviations and acronyms

AAD	Antiarrhythmic drugs
ABC Pathway	'A' Avoid stroke (with anticoagulants), 'B' Better symptom management, with patient-centred decisions on rate or rhythm control, 'C' Cardiovascular and comorbidity risk optimization
ACP	Amplatzer Cardiac Plug
AF	Atrial fibrillation
AF-CARE	[C] Comorbidity and risk factor management, [A] Avoid stroke and thromboembolism, [R] Reduce symptoms by rate and rhythm control, [E] Evaluation and dynamic reassessment
AHI	Apnoea–hypopnoea index
AI	Artificial intelligence
AIH	Amiodarone-induced hypothyroidism
AIT	Amiodarone-induced hyperthyroidism
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AP	Anterior-posterior
ARIC	Atherosclerosis Risk in Communities Study
AST	Aspartate aminotransferase
BMI	Body mass index
b.p.m.	Beats per minute
BP	Blood pressure
BW	Body weight
C ₂ HES	C ₂ : CAD/COPD, H: hypertension; E: elderly (age ≥75 years); S: systolic HF; and T: thyroid disease (hyperthyroidism)
CAD	Coronary artery disease
CHS	Cardiovascular Health Study
CI	Confidence interval
CKD	Chronic kidney disease
CMR	Cardiac magnetic resonance
COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
CYID	Chinese Yunnan Insurance Database
DOAC	Direct oral anticoagulant
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate

ESC	European Society of Cardiology
FHS	Framingham Health Study
GFR	Glomerular filtration rate
GI	Gastrointestinal
GP	General practitioner
HbA1c	Haemoglobin A1c (glycated or glycosylated haemoglobin)
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
i.v.	Intravenous
I _{Ca,L}	L-type Ca ²⁺ -current
I _{K1}	Inward-rectifier K ⁺ -current
INR	International normalized ratio
IQR	Interquartile range
JMC	Japanese Medical Check
LA	Left atrial
LAA	Left atrial appendage
LAAO	Left atrial appendage occlusion
LGE	Late gadolinium enhancement
LoE	Level of evidence
LQTS	Long QT syndrome
LV	Left ventricle
LVEF	Left ventricular ejection fraction
MHS	Maccabi Healthcare Services
MI	Myocardial infarction
NSAID	Non-steroidal anti-inflammatory drug
NT-proBNP	N-terminal pro B-type natriuretic peptides
OAC	Oral anticoagulant
PAD	Peripheral arterial disease
QRS	Q wave, R wave, and S wave, the 'QRS complex' represents ventricular depolarization
RCT	Randomized controlled trial
SBP	Systolic blood pressure
TEE	Transoesophageal echo
TIA	Transient ischaemic attack
TOE	Transoesophageal echocardiography
TSH	Thyroid-stimulating hormone
TTE	Transthoracic echocardiography
VKA	Vitamin K antagonist
VT	Ventricular tachycardia
WHS	Women's Health Study

1. Introduction

This supplementary file accompanies the main document for the 2024 *ESC Guidelines for the management of atrial fibrillation*. It includes additional text and figures that are limited to specific areas where the task force felt that further discussion would aid clinical interpretation and implementation. In-depth detail on pathophysiology, mechanisms, and therapies has been avoided to keep the guidelines focused on the practical management of atrial fibrillation (AF).

An additional supplementary file is available that contains:

- (i) **Evidence Tables:** references that support recommendations with a level of evidence (LoE) A or B are presented, along with a brief summary of the studies and their outcomes, plus key findings and biases relevant to the stipulated recommendations. The Evidence Tables are not an exhaustive review of the evidence, but include important studies that supported the task force decision on the class and LoE. Where possible, according to the evidence base available, the task force have prioritized the studies according to the hierarchy of evidence: meta-analyses of multiple randomized control trials

(RCTs) within a systematic review (highest LoE); large RCTs; smaller but pertinent RCTs, other systematic reviews and meta-analyses; and observational cohort data (lowest LoE).

- (ii) **Additional Evidence Tables:** references are presented that supported discussions within the task force in challenging areas. The Additional Evidence Tables are not an exhaustive review of the evidence, but provide a brief summary of each study, its outcomes, key findings, and biases relevant to the section in the guidelines.

2. Definition and clinical impact of AF

2.1. Pathophysiology of AF

Ectopic activity, particularly occurring in the pulmonary veins, is critically involved in AF onset.¹ Several factors predispose the pulmonary veins to

generate ectopic activity, including cardiovascular risk factors, and both ion-channel and structural abnormalities.^{2–4} Atrial fibrillation is defined by altered atrial structure and function,⁴ including electrical and fibrotic remodelling in the atria, which promotes AF progression. Important pathways pertinent to AF arrhythmogenesis are still unidentified.⁵ Compared with atrial cells, pulmonary veins have smaller L-type Ca^{2+} -current ($I_{\text{Ca,L}}$) and inward-rectifier K^{+} -current (I_{K1}), as well as larger delayed-rectifier K^{+} -currents.² These characteristics reduce action potential duration, increasing the likelihood of re-entry and spontaneous ectopy due to delayed afterdepolarizations. The pulmonary veins are also located adjacent to major cardiac autonomic ganglia, which modulate the electric properties of the atrium and consequently contribute to AF vulnerability.^{6,7} Fibrous tissue content in the atria is more extensive in patients with AF than without, and correlates with adverse clinical outcomes.⁸ Spontaneous atrial ectopic activity also appears to be a significant trigger for re-entry.^{8–10}

2.2. Diagnostic evaluation of new AF

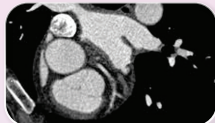
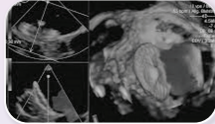
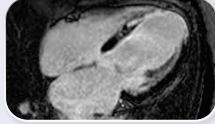
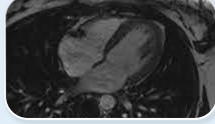
AF-CARE pathway	Objective for imaging	Assessment	Example of pathology
 Comorbidity and risk factor management	To assess for coronary artery disease or underlying ischaemia To determine aetiology of heart failure	Coronary CT angiogram or other ischaemic imaging CMR to determine tissue characterization	
 Avoid stroke and thromboembolism	To rule out thrombus and ensure safety of rhythm control strategy To guide left atrial appendage occlusion procedure	CT, CMR, or TOE for left atrial appendage anatomy	
 Reduce symptoms by rate and rhythm control	To determine potential to maintain sinus rhythm To determine potential to improve LV systolic function To assist in planning rhythm control	CMR for assessment of left atrial fibrosis CMR for assessment of left ventricular fibrosis and scar CT to determine pulmonary vein anatomy	
 Evaluation and dynamic reassessment	To detect changes in the heart's structure and function which may affect the patient's management plan	Where TTE is insufficient, use of CMR or TOE to assess change in valve disease or ventricular function	



Figure S1 Multimodality imaging in atrial fibrillation. AF-CARE, Atrial fibrillation—[C] Comorbidity and risk factor management, [A] Avoid stroke and thromboembolism, [R] Reduce symptoms by rate and rhythm control, [E] Evaluation and dynamic reassessment; CMR, cardiac magnetic resonance; CT, computed tomography; LGE, late gadolinium enhancement; LV, left ventricle; TTE, transthoracic echocardiography; TOE, transoesophageal echocardiography. Images from open-source databases with creative commons licences (<https://images.app.goo.gl/qVrmYsg3U8crw9TQ7>; <https://images.app.goo.gl/dLZKj3PXfcviUrvj8>; <https://images.app.goo.gl/MRwN9BtoV6caNDBD7>; <https://images.app.goo.gl/s12vyoFbqZ6gQLB1A>)

3. Patient-centred, multidisciplinary AF management

Table S1 Design of services to enable better AF-CARE

Components of the patient pathway	Pre-diagnosis	Initial presentation	Specialist review and treatment	Follow-up and ongoing management in the community	
Objectives	• Awareness • Prevention		• Diagnostic confirmation • Baseline investigation • Risk factor and comorbidity modification • Prevention of stroke and thromboembolism • Reduction of symptoms from AF • Early patient engagement • Family history	• Optimizing access to AF-CARE • Accurate and comprehensive diagnostic evaluation as needed • Patient and family engagement in decision-making • Individualized patient-centred treatment plan	• Improved patient quality of life • Ongoing risk factor and comorbidity evaluation and management • Patient empowerment and self-management • Ongoing adherence to holistic healthcare plan
Organizational requirements	• Risk factor and comorbidity assessment tools • Awareness of AF and risk factors		• Protocols for baseline assessment by primary care physicians, acute general physicians, neurologists, stroke physicians • Educational programmes for patients, carers, and healthcare professionals	• Dedicated AF service as needed • Referral processes to reach services needed for AF patients • Local protocol development and dissemination where needed • Educational programmes • Measurement of quality indicators (including patient-reported outcome measures to detect areas for improvement)	• Protocols for primary care follow-up and ongoing assessment • Assessment of outcomes • Individualized advance care plans for re-referral/hospital admission devised in conjunction with patients
Resources	• Community nurses • Primary care physicians/general practitioners • Dieticians • Exercise physiologists • Pharmacists • Government media programmes • Clinical psychologists • Patient organizations		• ECG, echocardiography, continuous ECG monitoring • Online educational resources, e.g. https://www.afibmatters.org/ • Anticoagulation clinics where needed for patients on vitamin K antagonists • Scoring systems for risk of thromboembolism • Taking steps to address modifiable bleeding risk factors • Tailored protocols for healthcare professionals, patients, and carers	• General practitioner co-ordination • Service co-ordinators/administrators • Specialist nurses • ESC Guidelines • Echocardiography, transoesophageal echocardiography, other cardiac imaging, ablation	• Patient-reported outcome measures • Agreed key performance indicators • Patient advocates • Clinical decision-support systems • Telehealth

AF, atrial fibrillation; AF-CARE, Atrial fibrillation—[C] Comorbidity and risk factor management, [A] Avoid stroke and thromboembolism, [R] Reduce symptoms by rate and rhythm control, [E] Evaluation and dynamic reassessment; ECG, electrocardiogram; ESC, European Society of Cardiology.

Table S2 Education and resources

Educational topics for patient and carer	Professional and educational resources and strategies (tailored to each patient taking into account socioeconomic, ethnic, age-related factors)
The condition • What it is (what happens in the heart) • Causes—including risk factors, comorbidities, family history, and lifestyle contributors • Symptoms that may be attributable to AF • Patterns of presentation • Potential complications and prognostic implications Purpose of investigations and the implications of the results • Blood tests • Rhythm analysis and monitoring • Structural and functional tests Basic principles of management • Risk factor and comorbidity management—understanding the role of diet, alcohol, obesity, smoking, recreational drug use, and the role of exercise and physical activity • Purpose, benefits and complications of: ◦ anticoagulation ◦ rate vs. rhythm control • Understanding the role, dosing, benefits, and side effects of medications	Personnel • Primary care and community physicians, hospital specialists, pharmacists, specialist nurses, patient organizations Information delivery tools • Paper-based—leaflets, posters, patient-held care plans • Web-based—patient and professional websites, e.g. https://www.afibmatters.org, https://esc365.escardio.org, videos, etc.
Shared management decision-making • Understanding the role of shared decision-making, the basic principles of management including drug, catheter, and device-based interventions; their benefits, complications, and prognostic implications at all stages in the patient pathway	• Encouraging a culture of shared decision-making through education of all healthcare professionals in the team • Design educational videos in conjunction with patient representatives • Provision of time and opportunity to discuss concerns arising at all stages of management both in and outside the outpatient setting using specialist nurses, telephone, and Email services
Living with, and self-management of, AF in the community • Understanding of the potential impact upon psychological health, work, leisure, travel, and sexual function • Self-management strategies—e.g. pill-in-the-pocket • Awareness of features indicating deterioration of condition and their relative urgency; provision of education to prevent anxiety • Understanding of when, and from which healthcare professionals and departments, to seek advice, including strategies for managing AF recurrences • Understanding treatment side effects and when to seek help	• Identify members of the team trained to discuss and evaluate the potential psychological and lifestyle impact of the diagnosis in a dedicated, confidential, and supportive environment • Clear plan provided for patient/carers following consultation with key healthcare professionals • Discuss practical issues and possible barriers to taking medication, such as work schedules (e.g. night shifts), and what to do in case of a missed dose, etc. • Inform and discuss a personalized approach to increasing the level of physical activity • Inform and discuss that sexual activity is safe for AF patients who are stable (optimally managed). Provide advice on addressing factors predisposing to sexual problems. Discuss and provide available pharmacological treatment for sexual problems and refer to specialist for sexual counselling when necessary

AF, atrial fibrillation.

3.1. Institution of anticoagulation

Table S3 Risk scores for stroke and thromboembolism in atrial fibrillation

Score	Parameters	References
CHADS ₂	Congestive heart failure history (+1) Hypertension history (+1) Age $\geq$ 75 years (+1) Diabetes mellitus history (+1) Stroke or TIA symptoms previously (+2)	11,12
CHA ₂ DS ₂ -VASc	Congestive heart failure history (+1) Hypertension history (+1) Age $\geq$ 75 years (+2) Diabetes mellitus history (+1) Stroke, TIA, and thromboembolism (+2) Vascular disease history (prior MI, peripheral artery disease, or aortic plaque) (+1) Age 65–74 years (+1) Female sex (+1)	11,12
GARFIELD-AF	Age (score) Weight (score) Pulse b.p.m. (score) Diastolic blood pressure (score) Ethnicity Sex (f/m) History of bleeding (yes/no) History of heart failure or LVEF <40% (yes/no) History of stroke (yes/no) Diabetes type 1 or type 2 (yes/no) Current smoker (yes/no) Dementia (yes/no) Current use of antiplatelet drugs (yes/no) Carotid occlusive disease (yes/no) Moderate to severe chronic kidney disease (yes/no) History of coronary artery disease (yes/no)	13,14
ATRIA	Previous stroke (yes/no) Age (<65 years: 8 points if previous stroke, 0 points if no history of stroke; 65–74 years: 7 points if previous stroke, 3 points if no history of stroke; 75–84 years: 7 points if previous stroke, 5 points if no history of stroke; >85 years: 9 points if previous stroke, 6 points if no history of stroke) Woman (yes: 1 point; no: 0 point) Diabetes mellitus (yes: 1 point; no: 0 point) Chronic heart failure (yes: 1 point; no: 0 point) Hypertension (yes: 1 point; no: 0 point) Proteinuria (yes: 1 point; no: 0 point) eGFR <45 mL/min or end-stage renal disease (yes: 1 point; no: 0 point)	15,16
ABC stroke	Prior stroke/transient ischaemic attack (yes/no) Age NT-pro-BNP (ng/L) High sensitivity troponin-T or I (ng/L)	17,18

ABC, age, biomarker, clinical history; AF, atrial fibrillation; ATRIA, anticoagulation and risk factors in atrial fibrillation; b.p.m., beats per minute; CHADS₂, congestive heart failure, hypertension, age > 75 years, diabetes; previous stroke (2 points); CHA₂DS₂-VASc, congestive heart failure, hypertension, age $\geq$ 75 years (2 points), diabetes mellitus, prior stroke or TIA or thromboembolism (2 points), vascular disease, age 65–74 years, sex category; eGFR, estimated glomerular filtration rate; f, female; GARFIELD-AF, Global Anticoagulant Registry in the FIELD-Atrial fibrillation; LVEF, left ventricular ejection fraction; m, male; MI, myocardial infarction; NT-proBNP, N-terminal pro B-type natriuretic peptides; TIA, transient ischaemic attack. See Table 10 in the main guideline for the CHA₂DS₂-VA score.

3.2. Percutaneous left atrial appendage occlusion

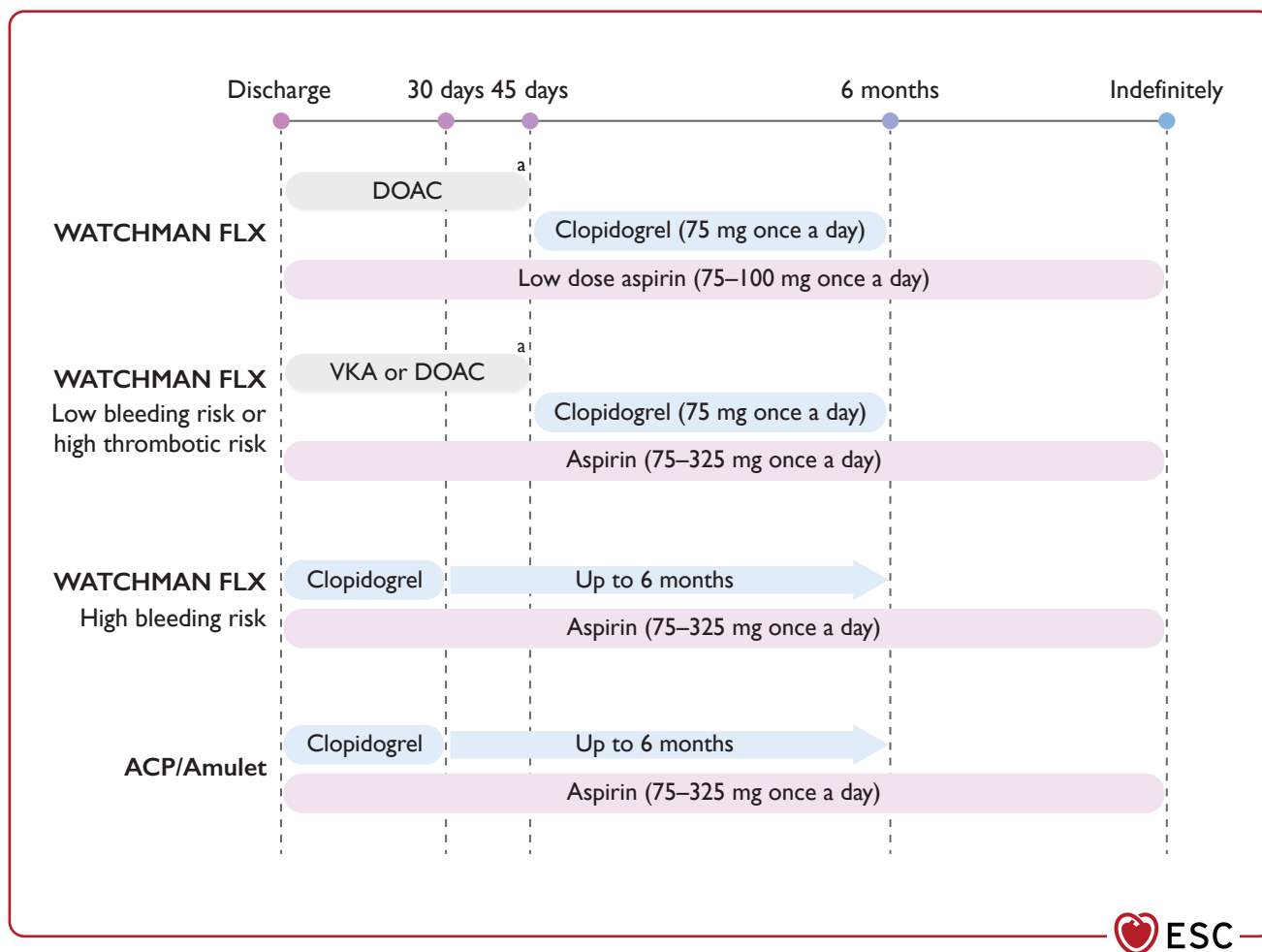


Figure S2 Suggested antithrombotic regimen post left atrial appendage occlusion device implantation. ACP, Amplatzer Cardiac Plug; DOAC, direct oral anticoagulant; LAA, left atrial appendage; OAC, oral anticoagulants; TEE, transoesophageal echo; VKA, vitamin K antagonist. ^aIf a leak >5 mm is TEE-documented at the 45 day follow-up, continuation of OAC plus aspirin is continued until adequate LAA sealing is confirmed

Table S4 Ongoing registered trials of percutaneous left atrial appendage occlusion devices vs. pharmacological treatment

Clinical trial	Number	Compared groups	Patient population	Sample size	Follow-up	Estimated completion
OPTION	NCT03795298	WATCHMAN FLX vs. OAC	AF patients with prior catheter ablation 90–180 days prior to randomization	1600	3 years	November 2024
CLOSURE-AF	NCT03463317	LAAO devices vs. (N) OAC	AF patients at high risk of stroke and high bleeding risk	1512	2 years	March 2025
CLEARANCE	NCT04298723	Watchman/Watchman FLX vs. standard of care	AF patients' status post-intracranial bleeding >6 weeks	550	2 years	June 2025
ASAP-TOO	NCT02928497	WATCHMAN vs. antiplatelet or no treatment	AF patients not deemed to be suitable for OAC	481	5 years	December 2025
COMPARE LAAO ¹⁹	NCT04676880	LAAO devices vs. antiplatelet or no treatment	High stroke risk contraindication for OAC	609	3 years	November 2026
CHAMPION-AF	NCT04394546	WATCHMAN FLX vs. DOACs	AF patients recommended for long-term OAC therapy	3000	3 years	December 2027
CATALYST	NCT04226547	Amulet LAAO vs. DOACs	AF patients recommended for long-term OAC therapy	2650	2 years	April 2029
STROKECLOSE	NCT02830152	Amulet LAAO vs. OAC or antiplatelet or no therapy	AF patients with high stroke risk and intracranial haemorrhage within 6 months	750	5 years	May 2030
OCCLUSION-AF ²⁰	NCT03642509	LAAO devices vs. DOACs	AF patients with prior ischaemic stroke or TIA	750	5 years	October 2030

© ESC 2024

AF, atrial fibrillation; DOAC, direct oral anticoagulant; LAAO, left atrial appendage occlusion; OAC, oral anticoagulants; TIA, transient ischaemic attack.

3.3. Assessment of bleeding risk due to anticoagulation

Table S5 Published bleeding risk scores

Score	Criteria	Point	Low risk	Intermediate risk (if applicable)	High risk
ABC-bleeding ¹⁷	Age	Risk model to calculate continuous risk score of bleeding event within 1 year	<1% risk for bleeding within 1 year	1–2% risk for bleeding within 1 year	>2% risk for bleeding within 1 year
	Growth differentiation factor-15				
	High-sensitivity cardiac troponin T				
	Haemoglobin				
	History of bleeding				
ATRIA ²¹	Anaemia (haemoglobin <13 g/dL [male], <12 g/dL [female])	+3	≤3	4	5–10
	Severe renal disease (glomerular filtration rate <30 mL/min or dialysis dependent)	+3			
	Age ≥75 years	+2			
	Any prior haemorrhage diagnosis (e.g. GI bleed, intracranial haemorrhage)	+1			
	Hypertension history	+1			

Continued

DOAC ²²	Age 60–69 years	+2	Very low risk (0–3 points) ($<1.00\%$ major bleeding per year)	Low risk (4–5 points) (1.00– 1.99% per year)	Moderate risk (6–7 points) (2.00–4.99% per year)	High risk (8–9 points) (5.00– 9.99% per year)	Very high risk (10 points) ($\geq 10.00\%$ per year)
	Age 70–74 years	+3					
	Age 75–79 years	+4					
	Age ≥ 80 years	+5					
	Creatinine clearance/ estimated GFR 30–60 mL/ min	+1					
	Creatinine clearance/ estimated GFR <30 mL/ min	+2					
	Underweight (body mass index <18.5 kg/m ²)	+1					
	Stroke/transient ischaemic attack/embolism history	+1					
	Diabetes	+1					
	Hypertension	+1					
	Antiplatelet use (aspirin)	+2					
	Dual antiplatelet	+3					
	Non-steroidal anti-inflammatory use	+1					
	Bleeding history	+3					
	Liver disease (defined as AST, ALT, ALP $\geq 3 \times$ upper limit of normal, ALP $\geq 2 \times$ ULN, or cirrhosis)	+2					
GARFIELD-AF ¹³	Age	Risk model to calculate risk of bleeding event within 1 year	Calculates risk of major bleeding including haemorrhagic stroke within 1 year according to: no OAC treatment/VKA treatment/OAC treatment				
	Pulse						
	History of bleeding						
	Moderate to severe kidney disease (CKD III–V)						
	History of coronary artery disease or peripheral vascular disease						
	Diabetes (type 1 or 2)						
	Current use of antiplatelet drugs (e.g. aspirin, clopidogrel)						
	Carotid occlusive disease						
HAS-BLED ²³	Hypertension (uncontrolled hypertension; systolic BP >160 mmHg)	+1	0	1–2	≥ 3		
	Abnormal renal or liver function	+1 +1					
	Renal: chronic dialysis, renal transplant, serum creatinine ≥ 2.3 mg/dL (200 μ mol/L) Liver: cirrhosis, bilirubin $>2 \times$ ULN with AST/ALT/ AP $>3 \times$ ULN						
	Stroke	+1					
	Bleeding (Bleeding history or predisposition [anaemia])	+1					
	Labile INR (therapeutic time in range $<60\%$)	+1					
	Elderly (age >65 years)	+1					
	Drugs or alcohol	+1					
	Drugs—other antiplatelet agents or NSAIDs Alcohol—more than 8 drinks/week	+1					

Continued

HEMORR ₂ HAGES ²⁴	Hepatic or renal disease	+1	0 or 1	2 or 3	≥4
	Ethanol (alcohol) abuse	+1			
	Malignancy history	+1			
	Older (age >75 years)	+1			
	Reduced platelet count or function (includes aspirin use, any thrombocytopaenia or blood dyscrasia, such as haemophilia)	+1			
	Rebleeding risk (history of past bleeding)	+2			
	Hypertension (uncontrolled)	+1			
	Anaemia (Hb <13 g/dL for men; Hb <12 g/dL for women)	+1			
	Genetic factors (CYP 2C9 single-nucleotide polymorphisms)	+1			
ORBIT ²⁵	Age >74 years	+1	0–2	3	≥4
	Bleeding history (any history of GI bleeding, intracranial bleeding, or haemorrhagic stroke)	+2			
	GFR <60 mL/min/1.73 m ²	+1			
	Treatment with antiplatelet agents	+1			

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; AP, anterior-posterior; BP, blood pressure; CKD, chronic kidney disease; DOAC, direct oral anticoagulant; GFR, glomerular filtration rate; GI, gastrointestinal; Hb, haemoglobin; INR, international normalized ratio; NSAID, non-steroidal anti-inflammatory drug; OAC, oral anticoagulants; ULN, upper limit of normal; VKA, vitamin K antagonist.

4. The AF-CARE pathway in specific clinical settings

4.1. Amiodarone-induced thyroid disorders

Amiodarone-induced thyroid disorders, both hypo- and hyperthyroidism, affect about 20% of patients, depending on the characteristics of the thyroid (normal or pathological) and environment (iodine-sufficient/-deficient areas).

All patients who are candidates for amiodarone treatment should be screened for thyroid function (thyroid-stimulating hormone [TSH] levels and possibly thyroid ultrasound). Thyroid function should be monitored frequently (at least every 3 months).²⁶ If the patient has pre-existing hypothyroidism, amiodarone can be initiated considering the need of increasing substitutive doses of T4. In the case of nodular goitre or reduced TSH, amiodarone treatment should be carefully discussed in a multidisciplinary setting. In the case of hyperthyroidism, amiodarone is contraindicated, and other antiarrhythmic drugs, or eventually a prophylactic thyroidectomy, can be considered.²⁷

There are some expected changes to thyroid hormones during amiodarone treatment. In the early phases of amiodarone treatment, this includes mild TSH increase and mild T3 reduction. In chronic amiodarone treatment, mild/moderate FT4 elevation and normal TSH are expected (due to amiodarone's ability to inhibit thyroid deiodinase).

These conditions do not usually require any treatment.²⁸ During amiodarone treatment, the overload of iodine and/or cytotoxic effect of the drug may produce thyroid dysfunction, including amiodarone-induced hypothyroidism (AIH) or amiodarone-induced hyperthyroidism (AIT).

Amiodarone-induced hypothyroidism presents as an elevated TSH (according to age) or rapid TSH rising from baseline values associated with normal or low FT4 (often associated with thyroid autoimmunity —anti-thyroglobulin antibodies and/or anti-thyroid peroxidase antibodies increase). In AIH patients, appropriate doses of levo-thyroxine (LT4) are initiated, with a low starting dose that is progressively increased to reach TSH values appropriate for the patient. Patients older than 65 years, who are taking other medications in addition to LT4 for a variety of comorbidities, require lower weight-based doses of LT4 to normalize their serum TSH.^{28,29}

Amiodarone-induced hyperthyroidism presents as a suppressed or low TSH with high FT4, or both high FT4 and FT3. There are two distinct types, AIT1 (overproduction: hyperthyroidism) and AIT2 (excess thyroid hormone release: thyrotoxicosis) with or without underlying thyroid disease, respectively. In a few cases, the two forms may coexist. A diagnostic framework is mandatory in AIT to initiate therapy early, which is mainly based on anti-thyroid drugs in AIT1 and on corticosteroids in AIT2. In all cases of low or suppressed TSH values, particularly during amiodarone treatment, patients should be promptly referred to an expert endocrinologist.²⁸

4.2. AF in inherited cardiomyopathies and primary arrhythmia syndromes

Table S6 AF treatment considerations for inherited cardiac diseases

Condition	Prevalence of AF	Contraindicated drugs	Special consideration for treatment			
			Anticoagulation	Rate control	Rhythm control AAD	Ablation
Long QT syndrome	2–29% ^{30,31}	QT-prolonging drugs (amiodarone, sotalol)	According to cardioembolic risk	Beta-blockers	LQTS1: mexiletine ³² LQT-3: flecainide ³³	No data
Short QT syndrome	18–70% ^{34–38}		According to cardioembolic risk		Propafenone ³⁹ Quinidine ^{40,41}	No data
Brugada syndrome	6–53% ^{42–47}	Class IC drugs	According to cardioembolic risk		Quinidine Bepridil	^{48–51}
Catecholaminergic polymorphic VT	11–37% ^{52,53}		According to cardioembolic risk	Beta-blockers ^{54–56}	Flecainide ^{56–60} Propafenone ⁶¹	^{52,62}
Hypertrophic cardiomyopathy	17–30% ^{63–68}	Class I drugs	Always ^{69,70} (if no contraindication)	Beta-blockers	Rhythm control is preferred. Amiodarone ^{69,71} Sotalol	^{65,72–79}
Arrhythmogenic right ventricular cardiomyopathy	9–30% ^{80–85}		According to cardioembolic risk	Beta-blockers ⁸⁶		No data
Familial dilated cardiomyopathy	25–49% ^{87,88} LMNA related ^{89–91}		According to cardioembolic risk			
Wolf–Parkinson–White syndrome	Variable (7–50%, as presenting arrhythmia in 20%) ^{92,93}	Digoxin, verapamil, diltiazem, beta-blockers, amiodarone	According to cardioembolic risk	Procainamide, propafenone, or flecainide for acute rate control	Accessory pathway(s) catheter ablation first, then AAD for AF as needed	As needed

© ESC 2024

AAD, antiarrhythmic drugs; AF, atrial fibrillation; i.v., intravenous; LMNA, LMNA gene; LQTS, long QT syndrome; VT, ventricular tachycardia.

5. Screening and prevention of AF

5.1. Benefit and cost-effectiveness of screening for AF

Early detection of AF enables early treatment that can prevent AF-related mortality and morbidity. In healthcare-based screening studies, most participants had an indication for OAC, should AF be detected.^{94,95} This is in contrast with studies performed using consumer-based wearables, where most individuals did not have an indication for OAC, even if AF was detected.^{96–98} But screening for AF need not be focused only on oral anticoagulants; it could also provide an important opportunity to treat associated risk factors, which might further reduce AF burden and prevent downstream events.⁹⁹

There are potential harms in screening for AF. A false positive AF diagnosis could lead to additional diagnostic burdens on the healthcare services, and could lead to overtreatment with OAC with an associated increased bleeding risk.¹⁰⁰ Thus far, no increased bleeding risks have been seen in outcome studies.⁹⁴ Patients participating in screening might feel increased anxiety, but in the SAFE study there was no increased anxiety of those randomized to screening.¹⁰¹ The burden of AF required to initiate OAC therapy is not known.

During electrocardiogram (ECG) screening other arrhythmias can be detected, but the benefits or risks of this remains to be investigated further.¹⁰²

There have been several studies investigating the cost-effectiveness of screening for AF. In one RCT, clinical outcome data were used¹⁰³ instead of assumptions on outcome. A screening study^{94,104} performed in 75-year-olds showed that screening was associated with lower costs and gained quality-adjusted life years compared with no screening. Similar results have been seen in studies using computer-simulated outcomes,^{105–111} and have shown cost-effectiveness using ambulatory devices in the pharmacy/general practitioner (GP) setting,^{106,108} during influenza vaccination,¹⁰⁷ and in rural communities.¹⁰⁵ Notably, local differences in healthcare systems, demographics, cost structures, as well as willingness to pay, exist, and might impede the generalizability of results.¹¹² Screening for AF in patients with prior stroke has also shown cost-effectiveness using intermittent ECG recordings¹¹³ or for cryptogenic stroke cases with implantable loop recorders compared with standard of care.¹¹⁴

Some models have compared the cost-effectiveness of several screening modalities. Intermittent ECG recordings repeated for 2 weeks were more cost-effective in 75-year-olds in the United States of America compared with a single time point 12-lead ECG.¹¹⁵ In GP

practices, pulse check was the most cost-effective, followed by single-lead ECG screening, blood pressure monitoring with AF detection algorithm, and lastly, no screening.¹¹⁶ For wearables, wrist-worn devices provided a greater benefit compared with screening with 12-lead ECG or pulse palpation, and a stepwise screening approach using a wrist-worn photoplethysmography-device first, confirmed by

patch ECG, was the most cost-effective.¹¹¹ In the future, using artificial intelligence (AI) models to identify individuals at risk of AF and screen these might prove cost-effective.¹¹⁷

Overall, screening for AF in an elderly population seems to be a cost-effective use of healthcare resources, although more studies are required to address the most beneficial modality.

5.2. Factors associated with incident AF

Table S7 Risk scores for prediction of atrial fibrillation

Score	Database/cohort	Individuals (n)	C Index (95% CI)	Variables
FHS score (10-year risk) ¹¹⁸	FHS 100% white, 55% female, 61 years (45–95 years)	4764 (457 cases)	0.78 (0.76–0.80)	Age, sex, significant murmur, HF, SBP, hypertension treatment, body mass index, PR interval
CHARGE-AF score (5-year risk) ¹¹⁹	ARIC, CHS, FHS 81% white, 19% black, 57% female, 65 years (46–94 years)	18 556 (1771 cases)	0.77 (0.75–0.78)	Age, ethnicity, height, weight, SBP/diastolic blood pressure, current smoking, hypertension treatment, diabetes, history of myocardial infarction, HF
ARIC score (10-year risk) ¹²⁰	ARIC 73% white, 27% black, 55% female, 45–64 years	14 546 (515 cases)	0.78 (N/A)	Age, ethnicity, height, smoking status, SBP, hypertension treatment, precordial murmur, left ventricular hypertrophy, left atrial enlargement, diabetes, CAD, HF
WHS score (10-year risk) ¹²¹	100% white, 100% female, median 53 years (IQR 49–59)	19 940 (616 cases)	0.72 (0.68–0.75)	Age, weight, height, SBP, alcohol use, smoking
MHS (10-year risk) ¹²²	MHS (Israeli) 54% female, 63 years	145 182 (2791 cases)	0.75 (0.74–0.76)	Age, sex, body mass index, history of myocardial infarction, history of PAD, hypertension treatment, SBP, COPD, autoimmune/inflammatory disease (female), age to HF
JMC score (7-year risk) ¹²³	JMC 100% Japanese, 35% female, 52 years	65 984 (349 cases)	0.77 (SE 0.02)	Age, waist circumference, diastolic blood pressure, alcohol consumption, heart rate, cardiac murmur
C ₂ HES _T score ¹²⁴	CYID 100% Asian, 43% female, 47 years	471 446 (921 cases)	0.75 (0.73–0.77)	CAD/COPD, hypertension, elderly, systolic HF, thyroid disease
C ₂ HES _T score (1-year risk)	French nationwide cohort	240 459 (14 095 cases)	0.734 (0.73–0.74)	CAD/COPD, hypertension, elderly, systolic HF, thyroid disease
Shandong score ¹²⁵	Shandong 100% Chinese, 33% female, 57 years (45–85 years)	33 186 (134 cases)	0.77 (N/A)	Age, sex, CAD, hypertension
PREVEND score ¹²⁶	Prevention of Renal and Vascular End-stage Disease (PREVEND) study, white 50% women 49 ± 13 years (range ≤35 to ≥62 years)	8265 (250 cases)	0.83 (0.81–0.85)	Advancing age, male sex, BMI, antihypertensive drug use, previous myocardial infarction, and previous stroke

Continued

Seirei score ¹²³	Seirei, Asian, 52.4 (40–79 years) 34.9% women	65 984 (349 cases)	0.77 (0.75–0.79)	Age, waist circumference, diastolic blood pressure, alcohol consumption, heart rate, and cardiac murmur, ECG variables: left ventricular hypertrophy, atrial enlargement, atrial premature contraction, and ventricular premature contraction
Suita score ¹²⁷	Suita Study, Asian, 55.7% women, mean age 55.7, 30–79 years	6898 (311 cases)	0.75 (0.72–0.77)	Age, sex, systolic hypertension, overweight, excessive drinking, coronary artery disease; current smoking; non-high-density lipoprotein-cholesterol; arrhythmia other than AF; cardiac murmur

© ESC 2024

AF, atrial fibrillation; ARIC, Atherosclerosis Risk in Communities Study; C₂HES score, C2:CAD/COPD (1 point each); H, hypertension (1 point); E, elderly (age ≥75 years, 2 points); S, systolic HF (2 points); and T, thyroid disease (hyperthyroidism, 1 point); CAD, coronary artery disease; CHARGE-AF, Cohorts for Aging and Research in Genomic Epidemiology-Atrial Fibrillation; CHS, Cardiovascular Health Study; COPD, chronic obstructive pulmonary disease; CYID, Chinese Yunnan Insurance Database; ECG, electrocardiogram; FHS, Framingham Heart Study; HF, heart failure; IQR, interquartile range; JMC, Japanese Medical Check; MHS, Maccabi Healthcare Services; MI, myocardial infarction; N/A, not available; PAD, peripheral artery disease; SBP, systolic blood pressure; SE, standard error; WHS, Women's Health Study.

5.3. Genomics and AF risk

Increasing numbers of common genetic polymorphisms and variation identified by genetic sequencing analyses have been related to AF.¹²⁸ Genetic information can be combined in genetic instruments.¹²⁹ The combination of information achieves risks greater than monogenic AF with AF mutations.¹³⁰ The discriminatory ability of polygenic risk scores improves prediction of AF, providing information on top of classical risk factors,¹³¹ and will be further optimized, including additional variants related to AF. Polygenic and genome-wide risk scores could be used to identify individuals at highest risk for refined AF screening.¹³² Since genetic information is not broadly available yet, the clinical applicability and cost-effectiveness have to be demonstrated.

5.4. Primary prevention of AF

5.4.1. Hypertension—attributable risk for AF

Hypertension is the most common modifiable risk factor associated with AF.¹³³ It is increasingly recognized that earlier stages of hypertension are also associated with an increased risk of developing AF, including pre-hypertension (systolic blood pressures >120 mmHg but less than 140 mmHg, or diastolic blood pressures greater than 80 mmHg but less than 90 mmHg) and increased aortic stiffness.^{134–136} The presence and also the duration and pattern of hypertension may have an influence on incident AF, with a differential gender impact (hypertension may contribute to a greater extent in women compared with men).^{137,138}

5.4.2. Heart failure—attributable risk for AF

Heart failure is an important risk factor for the development of AF, including both heart failure with reduced ejection fraction and heart failure with preserved ejection fraction (HFpEF). In the long-term Framingham cohort, the incident rate of AF in patients with prevalent HF was 47.8 per 1000 patient-years (95% CI, 24.1–71.6), compared with 7.9 per 1000 patient-years (95% CI, 7.3–8.4) in those without HF, with an adjusted two-fold risk of AF associated with having HF.¹³⁹ Patients with HFpEF have particularly high rates of incident AF,¹²⁶ although there are many confounders to consider.¹⁴⁰

5.4.3. Diabetes mellitus—attributable risk for AF

Diabetes is an independent risk factor for AF, and HbA1c (glycated or glycosylated haemoglobin) levels correlate with incident AF in patients with and without diabetes.^{141,142} In addition, prediabetes and diabetes increase the risk of AF by 20% and 28%, respectively, with a dose-response relationship between increasing blood glucose and AF, with a 12% increase in the relative risk per 20 mg/dL increase in blood glucose.^{143,144} A higher burden of AF is present in patients with diabetes who present more frequently with permanent AF, greater severity of symptoms, and lower quality of life.^{145–147} Obesity, dysmetabolic substrates, including oxidative stress, inflammation, epicardial adipose tissue, imbalance in gut microbiota, and autonomic dysfunctions, lead to functional, electrical, and structural cardiac remodelling favouring AF.^{148–150}

5.4.4. Obesity—attributable risk for AF

Obesity is associated with the development and progression of AF.¹⁵¹ Obesity frequently coexists with several other risk factors that have been independently associated with the development of AF.^{152,153} In a large European individual patient-level registry, which followed subjects for up to 10 years, 30–40% of incident AF risk was attributed to body mass index (BMI), hypertension, and a history of stroke or myocardial infarction, with a higher risk attributed to BMI in the younger population.¹⁵⁴ Although the association between BMI and AF is recognized for both sexes, there is evidence of a stronger link in men.¹⁵⁵ Emerging evidence observes that obesity may have a greater impact on incident AF in younger patient populations.¹⁵⁶ Indeed, even childhood obesity may heighten the risk of AF during adult life.¹⁵⁷ Obesity is associated with a greater risk of post-operative atrial fibrillation with every 5 kg/m² increase in BMI being associated with a 10% greater risk.¹⁵¹

5.4.5. Sleep apnoea syndrome—attributable risk for AF

Sleep apnoea has been associated with the development of AF. In a retrospective study of individuals with sleep apnoea identified by a sleep study, during a mean 4.7 year follow-up, the cumulative probability of incident AF was 14%.¹⁵⁸ Genetic evidence of the causal effect of obstructive sleep apnoea on increased risk of AF was reported in Mendelian randomization studies.^{159,160} Hypoxia, oxidative stress, inflammation, electrical and structural atrial remodelling, changes in

intrathoracic pressure, and autonomic imbalance can contribute to patients' susceptibility towards AF.^{161–163} The risk of AF has been best correlated with an increasing apnoea–hypopnoea index (AHI).¹⁶² However, there is emerging evidence that this may not be without its limitations. Indeed, nightly variation is documented in AHI, suggesting that if the index of suspicion is high, repeated testing may be warranted.^{164,165} Several studies have proposed the need to include increased nocturnal hypoxaemia and not just AHI in the determination of sleep apnoea.^{166–169} Mapping studies have identified significant atrial changes in individuals with sleep apnoea with reduced atrial voltages, conduction slowing, fractionated electrograms, and a greater propensity for non-pulmonary vein triggers of AF.^{170–172}

5.4.6. Physical activity—attributable risk for AF

There is increasing evidence that inactivity represents an independent AF risk factor.^{173–176} The incidence of AF also appears to be increased among elite athletes. A meta-analysis of six studies showed that athletes had a five-fold increased risk of AF compared with age-matched controls.¹⁷⁷ Endurance training, particularly in men, has been associated with a higher risk of AF in some studies.^{178–182} Therefore, clinicians should be aware of the heightened risk of AF in endurance athletes and should provide adequate education on the impact of participating in high-volume endurance training.

5.4.7. Alcohol intake—attributable risk for AF

Alcohol excess is a risk factor for incident AF, seemingly in a dose-dependent manner. Even modest habitual alcohol intake of 1.2 drinks/day was associated with an increased risk of AF in a long-term cohort study.¹⁸³ The mechanism may be that acute exposure to alcohol reduces atrial effective refractory periods, particularly in the pulmonary veins.¹⁸⁴ In a population cohort study in the United Kingdom, low levels of alcohol consumption (<7 standard drinks per week) were associated with the lowest risk of incident AF, but this was dependent on the type of alcohol. Any consumption of beer or cider was associated with increased AF risk.¹⁸⁵ In heavy drinkers (World Health Organization criteria: >60 g/day for men and >40 g/day for women), a Korean national population study found lower rates of incident AF in those who abstained from drinking compared with individuals who maintained heavy alcohol consumption (weighted HR, 0.38; 95% CI, 0.17–0.85).¹⁸⁶ A systematic review of observational studies identified gender differences between alcohol intake and incident AF, with greater risk at moderate alcohol consumption in men than women.¹⁸⁷

6. References

- Haïssaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med* 1998;**339**:659–66. <https://doi.org/10.1056/NEJM199809033391003>
- Ehrlich JR, Cha TJ, Zhang L, Chartier D, Melynk P, Hohnloser SH, et al. Cellular electrophysiology of canine pulmonary vein cardiomyocytes: action potential and ionic current properties. *J Physiol* 2003;**551**:801–13. <https://doi.org/10.1113/jphysiol.2003.046417>
- Hocini M, Ho SY, Kawara T, Linnenbank AC, Potse M, Shah D, et al. Electrical conduction in canine pulmonary veins: electrophysiological and anatomic correlation. *Circulation* 2002;**105**:2442–8. <https://doi.org/10.1161/01.CIR.0000016062.80020.11>
- Schnabel RB, Marinelli EA, Arbelo E, Boriani G, Boveda S, Buckley CM, et al. Early diagnosis and better rhythm management to improve outcomes in patients with atrial fibrillation: the 8th AFNET/EHRA consensus conference. *Europace* 2023;**25**:6–27. <https://doi.org/10.1093/europace/euac062>
- Nattel S, Heijman J, Zhou L, Dobrev D. Molecular basis of atrial fibrillation pathophysiology and therapy: a translational perspective. *Circ Res* 2020;**127**:51–72. <https://doi.org/10.1161/CIRCRESAHA.120.316363>
- Lemola K, Chartier D, Yeh YH, Dubuc M, Cartier R, Armour A, et al. Pulmonary vein region ablation in experimental vagal atrial fibrillation: role of pulmonary veins versus autonomic ganglia. *Circulation* 2008;**117**:470–7. <https://doi.org/10.1161/CIRCULATIONAHA.107.737023>
- Saburkina I, Rysevaite K, Pauziene N, Mischke K, Schauerte P, Jalife J, et al. Epicardial neural ganglionated plexus of ovine heart: anatomic basis for experimental cardiac electrophysiology and nerve protective cardiac surgery. *Heart Rhythm* 2010;**7**:942–50. <https://doi.org/10.1016/j.hrthm.2010.02.036>
- Malcolm-Lawes LC, Juli C, Karim R, Bai W, Quest R, Lim PB, et al. Automated analysis of atrial late gadolinium enhancement imaging that correlates with endocardial voltage and clinical outcomes: a 2-center study. *Heart Rhythm* 2013;**10**:1184–91. <https://doi.org/10.1016/j.hrthm.2013.04.030>
- Vincenti A, Brambilla R, Fumagalli MG, Merola R, Pedretti S. Onset mechanism of paroxysmal atrial fibrillation detected by ambulatory Holter monitoring. *Europace* 2006;**8**:204–10. <https://doi.org/10.1093/europace/euj043>
- Li D, Fareh S, Leung TK, Nattel S. Promotion of atrial fibrillation by heart failure in dogs: atrial remodeling of a different sort. *Circulation* 1999;**100**:87–95. <https://doi.org/10.1161/01.CIR.100.1.87>
- Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish atrial fibrillation cohort study. *Eur Heart J* 2012;**33**:1500–10. <https://doi.org/10.1093/eurheartj/ehr488>
- Chen JY, Zhang AD, Lu HY, Guo J, Wang FF, Li ZC. CHADS2 versus CHA2DS2-VASc score in assessing the stroke and thromboembolism risk stratification in patients with atrial fibrillation: a systematic review and meta-analysis. *J Geriatr Cardiol* 2013;**10**:258–66. <https://doi.org/10.3969/j.issn.1671-5411.2013.03.004>
- Fox KAA, Lucas JE, Pieper KS, Bassand JP, Camm AJ, Fitzmaurice DA, et al. Improved risk stratification of patients with atrial fibrillation: an integrated GARFIELD-AF tool for the prediction of mortality, stroke and bleed in patients with and without anticoagulation. *BMJ Open* 2017;**7**:e017157. <https://doi.org/10.1136/bmjopen-2017-017157>
- Dalgaard F, Pieper K, Verheugt F, Camm AJ, Fox KA, Kakkar AK, et al. GARFIELD-AF model for prediction of stroke and major bleeding in atrial fibrillation: a Danish nationwide validation study. *BMJ Open* 2019;**9**:e033283. <https://doi.org/10.1136/bmjopen-2019-033283>
- Singer DE, Chang Y, Borowsky LH, Fang MC, Pomernacki NK, Udaltsova N, et al. A new risk scheme to predict ischemic stroke and other thromboembolism in atrial fibrillation: the ATRIA study stroke risk score. *J Am Heart Assoc* 2013;**2**:e000250. <https://doi.org/10.1161/JAHA.113.000250>
- Zhu W, Fu L, Ding Y, Huang L, Xu Z, Hu J, et al. Meta-analysis of ATRIA versus CHA2DS2-VASc for predicting stroke and thromboembolism in patients with atrial fibrillation. *Int J Cardiol* 2017;**227**:436–42. <https://doi.org/10.1016/j.ijcard.2016.11.015>
- Hijazi Z, Lindback J, Alexander JH, Hanna M, Held C, Hylek EM, et al. The ABC (age, biomarkers, clinical history) stroke risk score: a biomarker-based risk score for predicting stroke in atrial fibrillation. *Eur Heart J* 2016;**37**:1582–90. <https://doi.org/10.1093/eurheartj/ehw054>
- Hijazi Z, Lindback J, Oldgren J, Benz AP, Alexander JH, Connolly SJ, et al. Individual net clinical outcome with oral anticoagulation in atrial fibrillation using the ABC-AF risk scores. *Am Heart J* 2023;**261**:55–63. <https://doi.org/10.1016/j.ahj.2023.03.012>
- Huijboom M, Maarse M, Aarnink E, van Dijk V, Swaans M, van der Heijden J, et al. COMPARE LAO: rationale and design of the randomized controlled trial “COMPARing effectiveness and safety of left atrial appendage occlusion to standard of care for atrial fibrillation patients at high stroke risk and ineligible to use oral anticoagulation therapy”. *Am Heart J* 2022;**250**:45–56. <https://doi.org/10.1016/j.ahj.2022.05.001>
- Korsholm K, Damgaard D, Valentin JB, Packer EJS, Odenstedt J, Sinisalo J, et al. Left atrial appendage occlusion vs novel oral anticoagulation for stroke prevention in atrial fibrillation: rationale and design of the multicenter randomized occlusion-AF trial. *Am Heart J* 2022;**243**:28–38. <https://doi.org/10.1016/j.ahj.2021.08.020>
- Fang MC, Go AS, Chang Y, Borowsky LH, Pomernacki NK, Udaltsova N, et al. A new risk scheme to predict warfarin-associated hemorrhage: the ATRIA (anticoagulation and risk factors in atrial fibrillation) study. *J Am Coll Cardiol* 2011;**58**:395–401. <https://doi.org/10.1016/j.jacc.2011.03.031>
- Aggarwal R, Ruff CT, Virdone S, Perreault S, Kakkar AK, Palazzolo MG, et al. Development and validation of the DOAC score: a novel bleeding risk prediction tool for patients with atrial fibrillation on direct-acting oral anticoagulants. *Circulation* 2023;**148**:936–46. <https://doi.org/10.1161/CIRCULATIONAHA.123.064556>
- Pisters R, Lane DA, Nieuwlaar R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the euro heart survey. *Chest* 2010;**138**:1093–100. <https://doi.org/10.1378/chest.10-0134>
- Gage BF, Yan Y, Milligan PE, Waterman AD, Culverhouse R, Rich MW, et al. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). *Am Heart J* 2006;**151**:713–9. <https://doi.org/10.1016/j.ahj.2005.04.017>

25. O'Brien EC, Simon DN, Thomas LE, Hylek EM, Gersh BJ, Ansell JE, et al. The ORBIT bleeding score: a simple bedside score to assess bleeding risk in atrial fibrillation. *Eur Heart J* 2015;**36**:3258–64. <https://doi.org/10.1093/eurheartj/ehv476>
26. Ross DS, Burch HB, Cooper DS, Greenlee MC, Lauberg P, Maia AL, et al. 2016 American thyroid association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. *Thyroid* 2016;**26**:1343–421. <https://doi.org/10.1089/thy.2016.0229>
27. Cappellani D, Papini P, Di Certo AM, Morganti R, Urbani C, Manetti L, et al. Duration of exposure to thyrotoxicosis increases mortality of compromised AIT patients: the role of early thyroidectomy. *J Clin Endocrinol Metab* 2020;**105**:e3427–36. <https://doi.org/10.1210/clinem/dgaa686>
28. Ylli D, Wartofsky L, Burman KD. Evaluation and treatment of amiodarone-induced thyroid disorders. *J Clin Endocrinol Metab* 2021;**106**:226–36. <https://doi.org/10.1210/clinem/dgaa686>
29. Jonklaas J, Bianco AC, Bauer AJ, Burman KD, Cappola AR, Celi FS, et al. Guidelines for the treatment of hypothyroidism: prepared by the American thyroid association task force on thyroid hormone replacement. *Thyroid* 2014;**24**:1670–751. <https://doi.org/10.1089/thy.2014.0028>
30. Johnson JN, Tester DJ, Perry J, Salisbury BA, Reed CR, Ackerman MJ. Prevalence of early-onset atrial fibrillation in congenital long QT syndrome. *Heart Rhythm* 2008;**5**:704–9. <https://doi.org/10.1016/j.hrthm.2008.02.007>
31. Zellerhoff S, Pistulli R, Monnig G, Hinterseer M, Beckmann BM, Kobe J, et al. Atrial arrhythmias in long-QT syndrome under daily life conditions: a nested case control study. *J Cardiovasc Electrophysiol* 2009;**20**:401–7. <https://doi.org/10.1111/j.1540-8167.2008.01339.x>
32. El Yaman M, Perry J, Makielski JC, Ackerman MJ. Suppression of atrial fibrillation with mexiletine pharmacotherapy in a young woman with type 1 long QT syndrome. *Heart Rhythm* 2008;**5**:472–4. <https://doi.org/10.1016/j.hrthm.2007.10.029>
33. Benito B, Brugada R, Perich RM, Lizotte E, Cinca J, Mont L, et al. A mutation in the sodium channel is responsible for the association of long QT syndrome and familial atrial fibrillation. *Heart Rhythm* 2008;**5**:1434–40. <https://doi.org/10.1016/j.hrthm.2008.07.013>
34. Gaita F, Giustetto C, Bianchi F, Wolpert C, Schimpf R, Riccardi R, et al. Short QT syndrome: a familial cause of sudden death. *Circulation* 2003;**108**:965–70. <https://doi.org/10.1161/01.CIR.0000085071.28695.C4>
35. Borggrefe M, Wolpert C, Antzelevitch C, Veltmann C, Giustetto C, Gaita F, et al. Short QT syndrome. Genotype-phenotype correlations. *J Electrocardiol* 2005;**38**:75–80. <https://doi.org/10.1016/j.jelectrocard.2005.06.009>
36. Giustetto C, Di Monte F, Wolpert C, Borggrefe M, Schimpf R, Sbragia P, et al. Short QT syndrome: clinical findings and diagnostic-therapeutic implications. *Eur Heart J* 2006;**27**:2440–7. <https://doi.org/10.1093/eurheartj/ehl185>
37. Giustetto C, Schimpf R, Mazzanti A, Scrocco C, Maury P, Anttonen O, et al. Long-term follow-up of patients with short QT syndrome. *J Am Coll Cardiol* 2011;**58**:587–95. <https://doi.org/10.1016/j.jacc.2011.03.038>
38. Gollob MH, Redpath CJ, Roberts JD. The short QT syndrome: proposed diagnostic criteria. *J Am Coll Cardiol* 2011;**57**:802–12. <https://doi.org/10.1016/j.jacc.2010.09.048>
39. Hong K, Bjerregaard P, Gussak I, Brugada R. Short QT syndrome and atrial fibrillation caused by mutation in KCNH2. *J Cardiovasc Electrophysiol* 2005;**16**:394–6. <https://doi.org/10.1046/j.1540-8167.2005.40621.x>
40. Patel C, Antzelevitch C. Cellular basis for arrhythmogenesis in an experimental model of the SQT1 form of the short QT syndrome. *Heart Rhythm* 2008;**5**:585–90. <https://doi.org/10.1016/j.hrthm.2008.01.022>
41. Nof E, Burashnikov A, Antzelevitch C. Cellular basis for atrial fibrillation in an experimental model of short QT1: implications for a pharmacological approach to therapy. *Heart Rhythm* 2010;**7**:251–7. <https://doi.org/10.1016/j.hrthm.2009.10.017>
42. Bordachar P, Reuter S, Garrigue S, Cai X, Hocini M, Jais P, et al. Incidence, clinical implications and prognosis of atrial arrhythmias in Brugada syndrome. *Eur Heart J* 2004;**25**:879–84. <https://doi.org/10.1016/j.ehj.2004.01.004>
43. Kusano KF, Taniyama M, Nakamura K, Miura D, Banba K, Nagase S, et al. Atrial fibrillation in patients with Brugada syndrome relationships of gene mutation, electrophysiology, and clinical backgrounds. *J Am Coll Cardiol* 2008;**51**:1169–75. <https://doi.org/10.1016/j.jacc.2007.10.060>
44. Francis J, Antzelevitch C. Atrial fibrillation and Brugada syndrome. *J Am Coll Cardiol* 2008;**51**:1149–53. <https://doi.org/10.1016/j.jacc.2007.10.062>
45. Rodriguez-Manero M, Namdar M, Sarkozy A, Casado-Arroyo R, Ricciardi D, de Asmundis C, et al. Prevalence, clinical characteristics and management of atrial fibrillation in patients with Brugada syndrome. *Am J Cardiol* 2013;**111**:362–7. <https://doi.org/10.1016/j.amjcard.2012.10.012>
46. Sacher F, Probst V, Maury P, Babuty D, Mansourati J, Komatsu Y, et al. Outcome after implantation of a cardioverter-defibrillator in patients with Brugada syndrome: a multicenter study-part 2. *Circulation* 2013;**128**:1739–47. <https://doi.org/10.1161/CIRCULATIONAHA.113.001941>
47. Hernandez-Ojeda J, Arbelo E, Borrás R, Berne P, Tolosana JM, Gomez-Juanatey A, et al. Patients with Brugada syndrome and implanted cardioverter-defibrillators: long-term follow-up. *J Am Coll Cardiol* 2017;**70**:1991–2002. <https://doi.org/10.1016/j.jacc.2017.08.029>
48. Yamada T, Yoshida Y, Tsuboi N, Murakami Y, Okada T, McElderry HT, et al. Efficacy of pulmonary vein isolation in paroxysmal atrial fibrillation patients with a Brugada electrocardiogram. *Circ J* 2008;**72**:281–6. <https://doi.org/10.1253/circj.72.281>
49. Sairaku A, Yoshida Y, Nakano Y, Kihara Y. Ablation of atrial fibrillation in Brugada syndrome patients with an implantable cardioverter defibrillator to prevent inappropriate shocks resulting from rapid atrial fibrillation. *Int J Cardiol* 2013;**168**:5273–6. <https://doi.org/10.1016/j.ijcard.2013.08.016>
50. Kitamura T, Fukamizu S, Kawamura I, Hojo R, Aoyama Y, Komiya K, et al. Long-term efficacy of catheter ablation for paroxysmal atrial fibrillation in patients with Brugada syndrome and an implantable cardioverter-defibrillator to prevent inappropriate shock therapy. *Heart Rhythm* 2016;**13**:1455–9. <https://doi.org/10.1016/j.hrthm.2016.03.006>
51. Mugnai G, Hünük B, Ströcker E, Ruggiero D, Coutino-Moreno HE, Takarada K, et al. Long-term outcome of pulmonary vein isolation in patients with paroxysmal atrial fibrillation and Brugada syndrome. *Europace* 2018;**20**:548–54. <https://doi.org/10.1093/europace/euw428>
52. Sumitomo N, Sakurada H, Taniguchi K, Matsumura M, Abe O, Miyashita M, et al. Association of atrial arrhythmia and sinus node dysfunction in patients with catecholaminergic polymorphic ventricular tachycardia. *Circ J* 2007;**71**:1606–9. <https://doi.org/10.1253/circj.71.1606>
53. Sy RW, Gollob MH, Klein GJ, Yee R, Skanes AC, Gula LJ, et al. Arrhythmia characterization and long-term outcomes in catecholaminergic polymorphic ventricular tachycardia. *Heart Rhythm* 2011;**8**:864–71. <https://doi.org/10.1016/j.hrthm.2011.01.048>
54. Kazemian P, Gollob MH, Pantano A, Oudit GY. A novel mutation in the RYR2 gene leading to catecholaminergic polymorphic ventricular tachycardia and paroxysmal atrial fibrillation: dose-dependent arrhythmia-event suppression by β -blocker therapy. *Can J Cardiol* 2011;**27**:870.e7–10. <https://doi.org/10.1016/j.cjca.2011.02.003>
55. van der Werf C, Lieve KV, Bos JM, Lane CM, Denjoy I, Roses-Noguer F, et al. Implantable cardioverter-defibrillators in previously undiagnosed patients with catecholaminergic polymorphic ventricular tachycardia resuscitated from sudden cardiac arrest. *Eur Heart J* 2019;**40**:2953–61. <https://doi.org/10.1093/eurheartj/ehz309>
56. Di Pino A, Caruso E, Costanzo L, Guccione P. A novel RyR2 mutation in a 2-year-old baby presenting with atrial fibrillation, atrial flutter, and atrial ectopic tachycardia. *Heart Rhythm* 2014;**11**:1480–3. <https://doi.org/10.1016/j.hrthm.2014.04.037>
57. Watanabe H, Chopra N, Laver D, Hwang HS, Davies SS, Roach DE, et al. Flecainide prevents catecholaminergic polymorphic ventricular tachycardia in mice and humans. *Nat Med* 2009;**15**:380–3. <https://doi.org/10.1038/nm.1942>
58. van der Werf C, Kannankeril PJ, Sacher F, Krahn AD, Viskin S, Leenhardt A, et al. Flecainide therapy reduces exercise-induced ventricular arrhythmias in patients with catecholaminergic polymorphic ventricular tachycardia. *J Am Coll Cardiol* 2011;**57**:2244–54. <https://doi.org/10.1016/j.jacc.2011.01.026>
59. Watanabe H, Steele DS, Knollmann BC. Mechanism of antiarrhythmic effects of flecainide in catecholaminergic polymorphic ventricular tachycardia. *Circ Res* 2011;**109**:712–3. <https://doi.org/10.1161/CIRCRESAHA.111.251322>
60. Sikkil MB, Collins TP, Rowlands C, Shah M, O'Gara P, Williams AJ, et al. Flecainide reduces Ca(2+) spark and wave frequency via inhibition of the sarcolemmal sodium current. *Cardiovasc Res* 2013;**98**:286–96. <https://doi.org/10.1093/cvr/cvt012>
61. Faggioni M, Savio-Galimberti E, Venkataraman R, Hwang HS, Kannankeril PJ, Darbar D, et al. Suppression of spontaneous Ca elevations prevents atrial fibrillation in caldesmon 2-null hearts. *Circ Arrhythm Electrophysiol* 2014;**7**:313–20. <https://doi.org/10.1161/CIRCEP.113.000994>
62. Sugiyasu A, Oginosawa Y, Nogami A, Hata Y. A case with catecholaminergic polymorphic ventricular tachycardia unmasked after successful ablation of atrial tachycardias from pulmonary veins. *Pacing Clin Electrophysiol* 2009;**32**:e21–4. <https://doi.org/10.1111/j.1540-8159.2009.02519.x>
63. Siontis KC, Geske JB, Ong K, Nishimura RA, Ommen SR, Gersh BJ. Atrial fibrillation in hypertrophic cardiomyopathy: prevalence, clinical correlations, and mortality in a large high-risk population. *J Am Heart Assoc* 2014;**3**:e001002. <https://doi.org/10.1161/JAHA.114.001002>
64. Guttmann OP, Rahman MS, O'Mahony C, Anastakis A, Elliott PM. Atrial fibrillation and thromboembolism in patients with hypertrophic cardiomyopathy: systematic review. *Heart* 2014;**100**:465–72. <https://doi.org/10.1136/heartjnl-2013-304276>
65. Rowin EJ, Hausvater A, Link MS, Abt P, Gionfriddo W, Wang W, et al. Clinical profile and consequences of atrial fibrillation in hypertrophic cardiomyopathy. *Circulation* 2017;**136**:2420–36. <https://doi.org/10.1161/CIRCULATIONAHA.117.029267>
66. van Velzen HG, Theuns DA, Yap SC, Michels M, Schinkel AF. Incidence of device-detected atrial fibrillation and long-term outcomes in patients with hypertrophic cardiomyopathy. *Am J Cardiol* 2017;**119**:100–5. <https://doi.org/10.1016/j.amjcard.2016.08.092>
67. Klopotoski M, Kwapiszewska A, Kukula K, Jamiolkowski J, Dabrowski M, Derejko P, et al. Clinical and echocardiographic parameters as risk factors for atrial fibrillation in patients with hypertrophic cardiomyopathy. *Clin Cardiol* 2018;**41**:1336–40. <https://doi.org/10.1002/clc.23050>
68. Choi YJ, Choi EK, Han KD, Jung JH, Park J, Lee E, et al. Temporal trends of the prevalence and incidence of atrial fibrillation and stroke among Asian patients with

- hypertrophic cardiomyopathy: a nationwide population-based study. *Int J Cardiol* 2018; **273**:130–5. <https://doi.org/10.1016/j.ijcard.2018.08.038>
69. Elliott PM, Anastasakis A, Borgers MA, Borggrefe M, Cecchi F, Charron P, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the task force for the diagnosis and management of hypertrophic cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J* 2014; **35**:2733–79. <https://doi.org/10.1093/eurheartj/ehu284>
 70. Jung H, Yang PS, Jang E, Yu HT, Kim TH, Uhm JS, et al. Effectiveness and safety of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation with hypertrophic cardiomyopathy: a nationwide cohort study. *Chest* 2019; **155**:354–63. <https://doi.org/10.1016/j.chest.2018.11.009>
 71. Robinson K, Frenneaux MP, Stockins B, Karatasakis G, Poloniecki JD, McKenna WJ. Atrial fibrillation in hypertrophic cardiomyopathy: a longitudinal study. *J Am Coll Cardiol* 1990; **15**:1279–85. [https://doi.org/10.1016/S0735-1097\(10\)80014-2](https://doi.org/10.1016/S0735-1097(10)80014-2)
 72. Bunch TJ, Munger TM, Friedman PA, Asirvatham SJ, Brady PA, Cha YM, et al. Substrate and procedural predictors of outcomes after catheter ablation for atrial fibrillation in patients with hypertrophic cardiomyopathy. *J Cardiovasc Electrophysiol* 2008; **19**:1009–14. <https://doi.org/10.1111/j.1540-8167.2008.01192.x>
 73. Di Donna P, Olivetto I, Delcré SD, Caponi D, Scaglione M, Nault I, et al. Efficacy of catheter ablation for atrial fibrillation in hypertrophic cardiomyopathy: impact of age, atrial remodelling, and disease progression. *Europace* 2010; **12**:347–55. <https://doi.org/10.1093/europace/euq013>
 74. Bassiouny M, Lindsay BD, Lever H, Saliba W, Klein A, Banna M, et al. Outcomes of non-pharmacologic treatment of atrial fibrillation in patients with hypertrophic cardiomyopathy. *Heart Rhythm* 2015; **12**:1438–47. <https://doi.org/10.1016/j.hrthm.2015.03.042>
 75. Ha HS, Wang N, Wong S, Phan S, Liao J, Kumar N, et al. Catheter ablation for atrial fibrillation in hypertrophic cardiomyopathy patients: a systematic review. *J Interv Card Electrophysiol* 2015; **44**:161–70. <https://doi.org/10.1007/s10840-015-0047-8>
 76. Zhao DS, Shen Y, Zhang Q, Lin G, Lu YH, Chen BT, et al. Outcomes of catheter ablation of atrial fibrillation in patients with hypertrophic cardiomyopathy: a systematic review and meta-analysis. *Europace* 2016; **18**:508–20. <https://doi.org/10.1093/europace/euv339>
 77. Providencia R, Elliott P, Patel K, McCready J, Babu G, Srinivasan N, et al. Catheter ablation for atrial fibrillation in hypertrophic cardiomyopathy: a systematic review and meta-analysis. *Heart* 2016; **102**:1533–43. <https://doi.org/10.1136/heartjnl-2016-309406>
 78. Chen X, Dong JZ, Du X, Wu JH, Yu RH, Long DY, et al. Long-term outcome of catheter ablation for atrial fibrillation in patients with apical hypertrophic cardiomyopathy. *J Cardiovasc Electrophysiol* 2018; **29**:951–7. <https://doi.org/10.1111/jce.13645>
 79. Lapenna E, Pozzoli A, De Bonis M, La Canna G, Nisi T, Nascimbene S, et al. Mid-term outcomes of concomitant surgical ablation of atrial fibrillation in patients undergoing cardiac surgery for hypertrophic cardiomyopathy. *Eur J Cardiothorac Surg* 2017; **51**:1112–8. <https://doi.org/10.1093/ejcts/ezx017>
 80. Chu AF, Zado E, Marchlinski FE. Atrial arrhythmias in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia and ventricular tachycardia. *Am J Cardiol* 2010; **106**:720–2. <https://doi.org/10.1016/j.amjcard.2010.04.031>
 81. Camm CF, James CA, Tichnell C, Murray B, Bhonsale A, te Riele AS, et al. Prevalence of atrial arrhythmias in arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Heart Rhythm* 2013; **10**:1661–8. <https://doi.org/10.1016/j.hrthm.2013.08.032>
 82. Saguner AM, Ganahl S, Kraus A, Baldinger SH, Medeiros-Domingo A, Saguner AR, et al. Clinical role of atrial arrhythmias in patients with arrhythmogenic right ventricular dysplasia. *Circ J* 2014; **78**:2854–61. <https://doi.org/10.1253/circj.CJ-14-0474>
 83. Boufiss M, Te Riele AS, Mast TP, Cramer MJ, Van Der Heijden J, Van Veen TAB, et al. Influence of genotype on structural atrial abnormalities and atrial fibrillation or flutter in arrhythmogenic right ventricular dysplasia/cardiomyopathy. *J Cardiovasc Electrophysiol* 2016; **27**:1420–8. <https://doi.org/10.1111/jce.13094>
 84. Mussigbrodt A, Knopp H, Efimova E, Weber A, Bertagnolli L, Hilbert S, et al. Supraventricular arrhythmias in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy associate with long-term outcome after catheter ablation of ventricular tachycardias. *Europace* 2018; **20**:1182–7. <https://doi.org/10.1093/europace/eux179>
 85. Tonet JL, Castro-Miranda R, Iwa T, Poulain F, Frank R, Fontaine GH. Frequency of supraventricular tachyarrhythmias in arrhythmogenic right ventricular dysplasia. *Am J Cardiol* 1991; **67**:1153. [https://doi.org/10.1016/0002-9149\(91\)90886-P](https://doi.org/10.1016/0002-9149(91)90886-P)
 86. Corrado D, Wichter T, Link MS, Hauer R, Marchlinski F, Anastasakis A, et al. Treatment of arrhythmogenic right ventricular cardiomyopathy/dysplasia: an international task force consensus statement. *Eur Heart J* 2015; **36**:3227–37. <https://doi.org/10.1093/eurheartj/ehv162>
 87. Yeung C, Enriquez A, Suarez-Fuster L, Baranchuk A. Atrial fibrillation in patients with inherited cardiomyopathies. *Europace* 2019; **21**:22–32. <https://doi.org/10.1093/europace/euy064>
 88. van Rijsingen IA, Nannenberg EA, Arbustini E, Elliott PM, Mogensen J, Hermans-van Ast JF, et al. Gender-specific differences in major cardiac events and mortality in lamin A/C mutation carriers. *Eur J Heart Fail* 2013; **15**:376–84. <https://doi.org/10.1093/eurjhf/hfs191>
 89. Hasselberg NE, Haland TF, Saberniak J, Brekke PH, Berge KE, Leren TP, et al. Lamin A/C cardiomyopathy: young onset, high penetrance, and frequent need for heart transplantation. *Eur Heart J* 2018; **39**:853–60. <https://doi.org/10.1093/eurheartj/ehx596>
 90. Kumar S, Baldinger SH, Gandjbakhch E, Maury P, Sellal JM, Androulakis AF, et al. Long-term arrhythmic and nonarrhythmic outcomes of lamin A/C mutation carriers. *J Am Coll Cardiol* 2016; **68**:2299–307. <https://doi.org/10.1016/j.jacc.2016.08.058>
 91. Pasotti M, Klersy C, Pilotto A, Marziliano N, Rapezzi C, Serio A, et al. Long-term outcome and risk stratification in dilated cardiomyopathies. *J Am Coll Cardiol* 2008; **52**:1250–60. <https://doi.org/10.1016/j.jacc.2008.06.044>
 92. Krijthe BP, Kunst A, Benjamin EJ, Lip GY, Franco OH, Hofman A, et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *Eur Heart J* 2013; **34**:2746–51. <https://doi.org/10.1093/eurheartj/ehs280>
 93. Etheridge SP, Escudero CA, Blaufox AD, Law IH, Dechert-Crooks BE, Stephenson EA, et al. Life-threatening event risk in children with Wolff-Parkinson-White syndrome: a multicenter international study. *JACC Clin Electrophysiol* 2018; **4**:433–44. <https://doi.org/10.1016/j.jacep.2017.10.009>
 94. Svennberg E, Friberg L, Frykman V, Al-Khalili F, Engdahl J, Rosenqvist M. Clinical outcomes in systematic screening for atrial fibrillation (STROKESTOP): a multicentre, parallel group, unmasked, randomised controlled trial. *Lancet* 2021; **398**:1498–506. [https://doi.org/10.1016/S0140-6736\(21\)01637-8](https://doi.org/10.1016/S0140-6736(21)01637-8)
 95. Svendsen JH, Diederichsen SZ, Højberg S, Krieger DW, Graff C, Kronborg C, et al. Implantable loop recorder detection of atrial fibrillation to prevent stroke (the LOOP study): a randomised controlled trial. *Lancet* 2021; **398**:1507–16. [https://doi.org/10.1016/S0140-6736\(21\)01698-6](https://doi.org/10.1016/S0140-6736(21)01698-6)
 96. Guo Y, Wang H, Zhang H, Liu T, Liang Z, Xia Y, et al. Mobile photoplethysmographic technology to detect atrial fibrillation. *J Am Coll Cardiol* 2019; **74**:2365–75. <https://doi.org/10.1016/j.jacc.2019.08.019>
 97. Perez MV, Mahaffey KW, Hedlin H, Rumsfeld JS, Garcia A, Ferris T, et al. Large-scale assessment of a smartwatch to identify atrial fibrillation. *N Engl J Med* 2019; **381**:1909–17. <https://doi.org/10.1056/NEJMoa1901183>
 98. Lubitz SA, Atlas SJ, Ashburner JM, Lipsanopoulos ATT, Borowsky LH, Guan W, et al. Screening for atrial fibrillation in older adults at primary care visits: VITAL-AF randomized controlled trial. *Circulation* 2022; **145**:946–54. <https://doi.org/10.1161/CIRCULATIONAHA.121.057014>
 99. Kirchhof P, Camm AJ, Goette A, Brandes A, Eckardt L, Elvan A, et al. Early rhythm-control therapy in patients with atrial fibrillation. *N Engl J Med* 2020; **383**:1305–16. <https://doi.org/10.1056/NEJMoa2019422>
 100. Welton NJ, McAleenan A, Thom HH, Davies P, Hollingworth W, Higgins JP, et al. Screening strategies for atrial fibrillation: a systematic review and cost-effectiveness analysis. *Health Technol Assess* 2017; **21**:1–236. <https://doi.org/10.3310/hta21290>
 101. Hobbs FD, Fitzmaurice DA, Mant J, Murray E, Jowett S, Bryan S, et al. A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study. *Health Technol Assess* 2005; **9**:iii–iv, ix–x, 1–74. <https://doi.org/10.3310/hta9400>
 102. Steinhilb SR, Waalen J, Edwards AM, Ariniello LM, Mehta RR, Ebner GS, et al. Effect of a home-based wearable continuous ECG monitoring patch on detection of undiagnosed atrial fibrillation: the mSToPS randomized clinical trial. *JAMA* 2018; **320**:146–55. <https://doi.org/10.1001/jama.2018.8102>
 103. Lyth J, Svennberg E, Bernfort L, Aronsson M, Frykman V, Al-Khalili F, et al. Cost-effectiveness of population screening for atrial fibrillation: the STROKESTOP study. *Eur Heart J* 2023; **44**:196–204. <https://doi.org/10.1093/eurheartj/ehac547>
 104. Svennberg E, Engdahl J, Al-Khalili F, Friberg L, Frykman V, Rosenqvist M. Mass screening for untreated atrial fibrillation: the STROKESTOP study. *Circulation* 2015; **131**:2176–84. <https://doi.org/10.1161/CIRCULATIONAHA.114.014343>
 105. Orchard J, Li J, Freedman B, Webster R, Salkeld G, Hespe C, et al. Atrial fibrillation screen, management, and guideline-recommended therapy in the rural primary care setting: a cross-sectional study and cost-effectiveness analysis of eHealth tools to support all stages of screening. *J Am Heart Assoc* 2020; **9**:e017080. <https://doi.org/10.1161/JAHA.120.017080>
 106. Lowres N, Neubeck L, Salkeld G, Krass I, McLachlan AJ, Redfern J, et al. Feasibility and cost-effectiveness of stroke prevention through community screening for atrial fibrillation using iPhone ECG in pharmacies. The SEARCH-AF study. *Thromb Haemost* 2014; **111**:1167–76. <https://doi.org/10.1160/TH14-03-0231>
 107. Jacobs MS, Kaasenbrood F, Postma MJ, van Hulst M, Tieleman RG. Cost-effectiveness of screening for atrial fibrillation in primary care with a handheld, single-lead electrocardiogram device in The Netherlands. *Europace* 2018; **20**:12–8. <https://doi.org/10.1093/europace/euw285>
 108. Ghazal F, Aronsson M, Al-Khalili F, Rosenqvist M, Levin L. Cost-effectiveness of screening for atrial fibrillation in a single primary care center at a 3-year follow-up. *Scand Cardiovasc J* 2022; **56**:35–41. <https://doi.org/10.1080/14017431.2022.2060523>
 109. Aronsson M, Svennberg E, Rosenqvist M, Engdahl J, Al-Khalili F, Friberg L, et al. Cost-effectiveness of mass screening for untreated atrial fibrillation using intermittent ECG recording. *Europace* 2015; **17**:1023–9. <https://doi.org/10.1093/europace/euv083>

110. Moran PS, Teljeur C, Ryan M, Smith SM. Systematic screening for the detection of atrial fibrillation. *Cochrane Database Syst Rev* 2016;**6**:CD009586. <https://doi.org/10.1002/14651858.CD009586.pub3>
111. Chen W, Khurshid S, Singer DE, Atlas SJ, Ashburner JM, Ellnor PT, et al. Cost-effectiveness of screening for atrial fibrillation using wearable devices. *JAMA Health Forum* 2022;**3**:e222419. <https://doi.org/10.1001/jamahealthforum.2022.2419>
112. Chu Y, Dai L, Qi S, Smith ML, Huang H, Li Y, et al. Challenges from variation across regions in cost effectiveness analysis in multi-regional clinical trials. *Front Pharmacol* 2016;**7**:371. <https://doi.org/10.3389/fphar.2016.00371>
113. Levin LA, Husberg M, Sobocinski PD, Kull VF, Friberg L, Rosenqvist M, et al. A cost-effectiveness analysis of screening for silent atrial fibrillation after ischaemic stroke. *Europace* 2015;**17**:207–14. <https://doi.org/10.1093/eurpace/euu213>
114. Sawyer LM, Witte KK, Reynolds MR, Mittal S, Grimsey Jones FW, Rosemas SC, et al. Cost-effectiveness of an insertable cardiac monitor to detect atrial fibrillation in patients with cryptogenic stroke. *J Comp Eff Res* 2021;**10**:127–41. <https://doi.org/10.2217/ceer-2020-0224>
115. Oguz M, Lanitis T, Li X, Wygant G, Singer DE, Friend K, et al. Cost-effectiveness of extended and one-time screening versus no screening for non-valvular atrial fibrillation in the USA. *Appl Health Econ Health Policy* 2020;**18**:533–45. <https://doi.org/10.1007/s40258-019-00542-y>
116. Tarride JE, Quinn FR, Blackhouse G, Sandhu RK, Burke N, Gladstone DJ, et al. Is screening for atrial fibrillation in Canadian family practices cost-effective in patients 65 years and older? *Can J Cardiol* 2018;**34**:1522–5. <https://doi.org/10.1016/j.cjca.2018.05.016>
117. Hill NR, Groves L, Dickerson C, Boyce R, Lawton S, Hurst M, et al. Identification of undiagnosed atrial fibrillation using a machine learning risk prediction algorithm and diagnostic testing (PULSe-AI) in primary care: cost-effectiveness of a screening strategy evaluated in a randomized controlled trial in England. *J Med Econ* 2022;**25**:974–83. <https://doi.org/10.1080/13696998.2022.2102355>
118. Schnabel RB, Sullivan LM, Levy D, Pencina MJ, Massaro JM, D'Agostino RB, Sr, et al. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. *Lancet* 2009;**373**:739–45. [https://doi.org/10.1016/S0140-6736\(09\)60443-8](https://doi.org/10.1016/S0140-6736(09)60443-8)
119. Alonso A, Krijthe BP, Aspelund T, Stepan KA, Pencina MJ, Moser CB, et al. Simple risk model predicts incidence of atrial fibrillation in a racially and geographically diverse population: the CHARGE-AF consortium. *J Am Heart Assoc* 2013;**2**:e000102. <https://doi.org/10.1161/JAHA.112.000102>
120. Chamberlain AM, Agarwal SK, Folsom AR, Soliman EZ, Chambless LE, Crow R, et al. A clinical risk score for atrial fibrillation in a biracial prospective cohort (from the Atherosclerosis Risk in Communities [ARIC] study). *Am J Cardiol* 2011;**107**:85–91. <https://doi.org/10.1016/j.amjcard.2010.08.049>
121. Everett BM, Cook NR, Conen D, Chasman DI, Ridker PM, Albert CM. Novel genetic markers improve measures of atrial fibrillation risk prediction. *Eur Heart J* 2013;**34**:2243–51. <https://doi.org/10.1093/eurheartj/ehs033>
122. Aronson D, Shalev V, Katz R, Chodick G, Mutlak D. Risk score for prediction of 10-year atrial fibrillation: a community-based study. *Thromb Haemost* 2018;**118**:1556–63. <https://doi.org/10.1055/s-0038-1668522>
123. Hamada R, Muto S. Simple risk model and score for predicting of incident atrial fibrillation in Japanese. *J Cardiol* 2019;**73**:65–72. <https://doi.org/10.1016/j.jcc.2018.06.005>
124. Li YG, Pastori D, Farcomeni A, Yang PS, Jang E, Joung B, et al. A simple clinical risk score (C(2)HEST) for predicting incident atrial fibrillation in Asian subjects: derivation in 471,446 Chinese subjects, with internal validation and external application in 451,199 Korean subjects. *Chest* 2019;**155**:510–8. <https://doi.org/10.1016/j.chest.2018.09.011>
125. Ding L, Li J, Wang C, Li X, Su Q, Zhang G, et al. Incidence of atrial fibrillation and its risk prediction model based on a prospective urban Han Chinese cohort. *J Hum Hypertens* 2017;**31**:574–9. <https://doi.org/10.1038/jhh.2017.23>
126. Vermond RA, Geelhoed B, Verweij N, Tieleman RG, Van der Harst P, Hillege HL, et al. Incidence of atrial fibrillation and relationship with cardiovascular events, heart failure, and mortality: a community-based study from the Netherlands. *J Am Coll Cardiol* 2015;**66**:1000–7. <https://doi.org/10.1016/j.jacc.2015.06.1314>
127. Kokubo Y, Watanabe M, Higashiyama A, Nakao YM, Kusano K, Miyamoto Y. Development of a basic risk score for incident atrial fibrillation in a Japanese general population—the Suita study. *Circ J* 2017;**81**:1580–8. <https://doi.org/10.1253/circj.CJ-17-0277>
128. Roselli C, Chaffin MD, Weng LC, Aeschbacher S, Ahlberg G, Albert CM, et al. Multi-ethnic genome-wide association study for atrial fibrillation. *Nat Genet* 2018;**50**:1225–33. <https://doi.org/10.1038/s41588-018-0133-9>
129. Khera AV, Chaffin M, Aragam KG, Haas ME, Roselli C, Choi SH, et al. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. *Nat Genet* 2018;**50**:1219–24. <https://doi.org/10.1038/s41588-018-0183-z>
130. Choi SH, Jurgens SJ, Weng LC, Pirruccello JP, Roselli C, Chaffin M, et al. Monogenic and polygenic contributions to atrial fibrillation risk: results from a national biobank. *Circ Res* 2020;**126**:200–9. <https://doi.org/10.1161/CIRCRESAHA.119.315686>
131. Börschel CS, Ohlrogge AH, Geelhoed B, Niiranen T, Havulinna AS, Palosaari T, et al. Risk prediction of atrial fibrillation in the community combining biomarkers and genetics. *Europace* 2021;**23**:674–81. <https://doi.org/10.1093/eurpace/euraa334>
132. Muse ED, Wineinger NE, Spencer EG, Peters M, Henderson R, Zhang Y, et al. Validation of a genetic risk score for atrial fibrillation: a prospective multicenter cohort study. *PLoS Med* 2018;**15**:e1002525. <https://doi.org/10.1371/journal.pmed.1002525>
133. Huxley RR, Lopez FL, Folsom AR, Agarwal SK, Loehr LR, Soliman EZ, et al. Absolute and attributable risks of atrial fibrillation in relation to optimal and borderline risk factors: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation* 2011;**123**:1501–8. <https://doi.org/10.1161/CIRCULATIONAHA.110.009035>
134. O'Neal WT, Soliman EZ, Qureshi W, Alonso A, Heckbert SR, Herrington D. Sustained pre-hypertensive blood pressure and incident atrial fibrillation: the multi-ethnic study of atherosclerosis. *J Am Soc Hypertens* 2015;**9**:191–6. <https://doi.org/10.1016/j.jash.2015.01.001>
135. Cremer A, Lainé M, Papaioannou G, Yeim S, Gosse P. Increased arterial stiffness is an independent predictor of atrial fibrillation in hypertensive patients. *J Hypertens* 2015;**33**:2150–5. <https://doi.org/10.1097/HJH.0000000000000652>
136. Conen D, Tedrow UB, Koplan BA, Glynn RJ, Buring JE, Albert CM. Influence of systolic and diastolic blood pressure on the risk of incident atrial fibrillation in women. *Circulation* 2009;**119**:2146–52. <https://doi.org/10.1161/CIRCULATIONAHA.108.830042>
137. Sharashova E, Wilsaard T, Ball J, Morseth B, Gerds E, Hopstock LA, et al. Long-term blood pressure trajectories and incident atrial fibrillation in women and men: the Tromsø study. *Eur Heart J* 2020;**41**:1554–62. <https://doi.org/10.1093/eurheartj/ehz234>
138. Espnes H, Ball J, Lochen ML, Wilsaard T, Njølstad I, Mathiesen EB, et al. Sex-specific associations between blood pressure and risk of atrial fibrillation subtypes in the Tromsø study. *J Clin Med* 2021;**10**:1514. <https://doi.org/10.3390/jcm10071514>
139. Santhanakrishnan R, Wang N, Larson MG, Magnani JW, McManus DD, Lubitz SA, et al. Atrial fibrillation begets heart failure and vice versa: temporal associations and differences in preserved versus reduced ejection fraction. *Circulation* 2016;**133**:484–92. <https://doi.org/10.1161/CIRCULATIONAHA.115.018614>
140. Tica O, Khambo W, Kotecha D. Breaking the cycle of heart failure with preserved ejection fraction and atrial fibrillation. *Card Fail Rev* 2022;**8**:e32. <https://doi.org/10.15420/cfr.2022.03>
141. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham heart study. *JAMA* 1994;**271**:840–4. <https://doi.org/10.1001/jama.1994.03510350050036>
142. Huxley RR, Alonso A, Lopez FL, Filion KB, Agarwal SK, Loehr LR, et al. Type 2 diabetes, glucose homeostasis and incident atrial fibrillation: the Atherosclerosis Risk in Communities study. *Heart* 2012;**98**:133–8. <https://doi.org/10.1136/heartjnl-2011-300503>
143. Aune D, Feng T, Schlesinger S, Janszky I, Norat T, Riboli E. Diabetes mellitus, blood glucose and the risk of atrial fibrillation: a systematic review and meta-analysis of cohort studies. *J Diabetes Complications* 2018;**32**:501–11. <https://doi.org/10.1016/j.jdiacomp.2018.02.004>
144. Seyed Ahmadi S, Svensson AM, Pivodic A, Rosengren A, Lind M. Risk of atrial fibrillation in persons with type 2 diabetes and the excess risk in relation to glycaemic control and renal function: a Swedish cohort study. *Cardiovasc Diabetol* 2020;**19**:9. doi:10.1186/s12933-019-0983-1
145. Ding WY, Kotalczyk A, Boriani G, Marin F, Blomstrom-Lundqvist C, Potpara TS, et al. Impact of diabetes on the management and outcomes in atrial fibrillation: an analysis from the ESC-EHRA EORP-AF long-term general registry. *Eur J Intern Med* 2022;**103**:41–9. <https://doi.org/10.1016/j.ejim.2022.04.026>
146. Echouffo-Tcheugui JB, Shrader P, Thomas L, Gersh BJ, Kowey PR, Mahaffey KW, et al. Care patterns and outcomes in atrial fibrillation patients with and without diabetes: ORBIT-AF registry. *J Am Coll Cardiol* 2017;**70**:1325–35. <https://doi.org/10.1016/j.jacc.2017.07.755>
147. Boriani G, Vitolo M, Diemberger I, Proietti M, Valenti AC, Malavasi VL, et al. Optimizing indices of atrial fibrillation susceptibility and burden to evaluate atrial fibrillation severity, risk and outcomes. *Cardiovasc Res* 2021;**117**:1–21. <https://doi.org/10.1093/cvr/cvab147>
148. Wang A, Green JB, Halperin JL, Piccini JP, Sr. Atrial fibrillation and diabetes mellitus: JACC review topic of the week. *J Am Coll Cardiol* 2019;**74**:1107–15. <https://doi.org/10.1016/j.jacc.2019.07.020>
149. Gawalko M, Agbaedeng TA, Saljic A, Muller DN, Wilck N, Schnabel R, et al. Gut microbiota, dysbiosis and atrial fibrillation: Arrhythmogenic mechanisms and potential clinical implications. *Cardiovasc Res* 2022;**118**:2415–27. <https://doi.org/10.1093/cvr/cvab292>
150. Packer M. Disease-treatment interactions in the management of patients with obesity and diabetes who have atrial fibrillation: the potential mediating influence of epicardial adipose tissue. *Cardiovasc Diabetol* 2019;**18**:121. <https://doi.org/10.1186/s12933-019-0927-9>
151. Wong CX, Sullivan T, Sun MT, Mahajan R, Pathak RK, Middeldorp M, et al. Obesity and the risk of incident, post-operative, and post-ablation atrial fibrillation: a meta-analysis of 626,603 individuals in 51 studies. *JACC Clin Electrophysiol* 2015;**1**:139–52. <https://doi.org/10.1016/j.jacep.2015.04.004>

152. Di Benedetto L, Michels G, Luben R, Khaw KT, Pfister R. Individual and combined impact of lifestyle factors on atrial fibrillation in apparently healthy men and women: the EPIC-Norfolk prospective population study. *Eur J Prev Cardiol* 2018;**25**:1374–83. <https://doi.org/10.1177/2047487318782379>
153. Grundvold I, Bodegard J, Nilsson PM, Svenblad B, Johansson G, Ostgren CJ, et al. Body weight and risk of atrial fibrillation in 7,169 patients with newly diagnosed type 2 diabetes; an observational study. *Cardiovasc Diabetol* 2015;**14**:5. <https://doi.org/10.1186/s12933-014-0170-3>
154. Morseth B, Geelhoed B, Linneberg A, Johansson L, Kuulasmaa K, Salomaa V, et al. Age-specific atrial fibrillation incidence, attributable risk factors and risk of stroke and mortality: results from the MORGAM consortium. *Open Heart* 2021;**8**:e001624. <https://doi.org/10.1136/openhrt-2021-001624>
155. Ball J, Lochen ML, Wilsaard T, Schirmer H, Hopstock LA, Morseth B, et al. Sex differences in the impact of body mass index on the risk of future atrial fibrillation: insights from the longitudinal population-based Tromsø study. *J Am Heart Assoc* 2018;**7**:e008414. <https://doi.org/10.1161/JAHA.117.008414>
156. Kim IS, Choi YJ, Choi EY, Min PK, Yoon YW, Lee BK, et al. Comparison of risk profiles for new-onset atrial fibrillation between patients aged <60 and ≥60 years. *PLoS One* 2021;**16**:e0258770. <https://doi.org/10.1371/journal.pone.0258770>. eCollection 2021
157. Chen W, Yao D, Yan H, Wang M, Pan Y. Genetically predicted childhood obesity and adult atrial fibrillation: a Mendelian randomization study. *Nutr Metab Cardiovasc Dis* 2022;**32**:1019–26. <https://doi.org/10.1016/j.numecd.2021.12.001>
158. Gami AS, Hodge DO, Herges RM, Olson EJ, Nykodym J, Kara T, et al. Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation. *J Am Coll Cardiol* 2007;**49**:565–71. <https://doi.org/10.1016/j.jacc.2006.08.060>
159. Chen W, Cai X, Yan H, Pan Y. Causal effect of obstructive sleep apnea on atrial fibrillation: a Mendelian randomization study. *J Am Heart Assoc* 2021;**10**:e022560. <https://doi.org/10.1161/JAHA.121.022560>
160. Li Y, Leng Y, Tang H, Deng P, Wang J, Yuan H, et al. Assessment of the causal effects of obstructive sleep apnea on atrial fibrillation: a Mendelian randomization study. *Front Cardiovasc Med* 2022;**9**:843681. <https://doi.org/10.3389/fcvm.2022.843681>
161. Linz D, McEvoy RD, Cowie MR, Somers VK, Nattel S, Levy P, et al. Associations of obstructive sleep apnea with atrial fibrillation and continuous positive airway pressure treatment: a review. *JAMA Cardiol* 2018;**3**:532–40. <https://doi.org/10.1001/jamacardio.2018.0095>
162. Gami AS, Pressman G, Caples SM, Kanagala R, Gard JJ, Davison DE, et al. Association of atrial fibrillation and obstructive sleep apnea. *Circulation* 2004;**110**:364–7. <https://doi.org/10.1161/01.CIR.0000136587.68725.8E>
163. Youssef I, Kamran H, Yacoub M, Patel N, Goulbourne C, Kumar S, et al. Obstructive sleep apnea as a risk factor for atrial fibrillation: a meta-analysis. *J Sleep Disord Ther* 2018;**7**:282. <https://doi.org/10.4172/2167-0277.1000282>
164. Linz D, Brooks AG, Elliott AD, Kalman JM, McEvoy RD, Lau DH, et al. Nightly variation in sleep apnea severity as atrial fibrillation risk. *J Am Coll Cardiol* 2018;**72**:2406–7. <https://doi.org/10.1016/j.jacc.2018.08.2159>
165. Linz D, Brooks AG, Elliott AD, Nalliah CJ, Hendriks JML, Middeldorp ME, et al. Variability of sleep apnea severity and risk of atrial fibrillation: the VARIOS-AF study. *JACC Clin Electrophysiol* 2019;**5**:692–701. <https://doi.org/10.1016/j.jacep.2019.03.005>
166. Zhang D, Ma Y, Xu J, Yi F. Association between obstructive sleep apnea (OSA) and atrial fibrillation (AF): a dose-response meta-analysis. *Medicine (Baltimore)* 2022;**101**:e29443. <https://doi.org/10.1097/MD.00000000000029443>
167. Cadby G, McArdle N, Briffa T, Hillman DR, Simpson L, Knuijan M, et al. Severity of OSA is an independent predictor of incident atrial fibrillation hospitalization in a large sleep-clinic cohort. *Chest* 2015;**148**:945–52. <https://doi.org/10.1378/chest.15-0229>
168. Kendzerska T, Gershon AS, Atzema C, Dorian P, Mangat I, Hawker G, et al. Sleep apnea increases the risk of new hospitalized atrial fibrillation: a historical cohort study. *Chest* 2018;**154**:1330–9. <https://doi.org/10.1016/j.chest.2018.08.1075>
169. Linz D, Malferteiner MV, Werner N, Lerzer C, Gfulner F, Linz B, et al. Nocturnal hypoxemic burden during positive airway pressure treatment across different central sleep apnea etiologies. *Sleep Med* 2021;**79**:62–70. <https://doi.org/10.1016/j.sleep.2021.01.007>
170. Dimitri H, Ng M, Brooks AG, Kuklik P, Stiles MK, Lau DH, et al. Atrial remodeling in obstructive sleep apnea: implications for atrial fibrillation. *Heart Rhythm* 2012;**9**:321–7. <https://doi.org/10.1016/j.hrthm.2011.10.017>
171. Anter E, Di Biase L, Contreras-Valdes FM, Gianni C, Mohanty S, Tschabrunn CM, et al. Atrial substrate and triggers of paroxysmal atrial fibrillation in patients with obstructive sleep apnea. *Circ Arrhythm Electrophysiol* 2017;**10**:e005407. <https://doi.org/10.1161/CIRCEP.117.005407>
172. Nalliah CJ, Wong GR, Lee G, Voskoboinik A, Kee K, Goldin J, et al. Sleep apnoea has a dose-dependent effect on atrial remodelling in paroxysmal but not persistent atrial fibrillation: a high-density mapping study. *Europace* 2021;**23**:691–700. <https://doi.org/10.1093/europace/eaab275>
173. Mozaffarian D, Furberg CD, Psaty BM, Siscovick D. Physical activity and incidence of atrial fibrillation in older adults: the cardiovascular health study. *Circulation* 2008;**118**:800–7. <https://doi.org/10.1161/CIRCULATIONAHA.108.785626>
174. Drca N, Wolk A, Jensen-Ustad M, Larsson SC. Physical activity is associated with a reduced risk of atrial fibrillation in middle-aged and elderly women. *Heart* 2015;**101**:1627–30. <https://doi.org/10.1136/heartjnl-2014-307145>
175. Everett BM, Conen D, Buring JE, Moorthy MV, Lee IM, Albert CM. Physical activity and the risk of incident atrial fibrillation in women. *Circ Cardiovasc Qual Outcomes* 2011;**4**:321–7. <https://doi.org/10.1161/CIRCOUTCOMES.110.951442>
176. Huxley RR, Misialek JR, Agarwal SK, Loehr LR, Soliman EZ, Chen LY, et al. Physical activity, obesity, weight change, and risk of atrial fibrillation: the Atherosclerosis Risk in Communities study. *Circ Arrhythm Electrophysiol* 2014;**7**:620–5. <https://doi.org/10.1161/CIRCEP.113.001244>
177. Abdulla J, Nielsen JR. Is the risk of atrial fibrillation higher in athletes than in the general population? A systematic review and meta-analysis. *Europace* 2009;**11**:1156–9. <https://doi.org/10.1093/europace/eup197>
178. Newman VW, Parry-Williams G, Wiles J, Edwards J, Hulbert S, Kipourou K, et al. Risk of atrial fibrillation in athletes: a systematic review and meta-analysis. *Br J Sports Med* 2021;**55**:1233–8. <https://doi.org/10.1136/bjsports-2021-103994>
179. Andersen K, Farahmand B, Ahlbom A, Held C, Ljunghall S, Michaelsson K, et al. Risk of arrhythmias in 52 755 long-distance cross-country skiers: a cohort study. *Eur Heart J* 2013;**34**:3624–31. <https://doi.org/10.1093/eurheartj/ehs188>
180. Baldesberger S, Bauersfeld U, Candinas R, Seifert B, Zuber M, Ritter M, et al. Sinus node disease and arrhythmias in the long-term follow-up of former professional cyclists. *Eur Heart J* 2008;**29**:71–8. <https://doi.org/10.1093/eurheartj/ehm555>
181. Elosua R, Arquer A, Mont L, Sambola A, Molina L, García-Morán E, et al. Sport practice and the risk of lone atrial fibrillation: a case-control study. *Int J Cardiol* 2006;**108**:332–7. <https://doi.org/10.1016/j.ijcard.2005.05.020>
182. Molina L, Mont L, Marrugat J, Berrueto A, Brugada J, Bruguera J, et al. Long-term endurance sport practice increases the incidence of lone atrial fibrillation in men: a follow-up study. *Europace* 2008;**10**:618–23. <https://doi.org/10.1093/europace/eun071>
183. Csengeri D, Sprünker NA, Di Castelnuovo A, Niiranen T, Vishram-Nielsen JK, Costanzo S, et al. Alcohol consumption, cardiac biomarkers, and risk of atrial fibrillation and adverse outcomes. *Eur Heart J* 2021;**42**:1170–7. <https://doi.org/10.1093/eurheartj/ehaa953>
184. Marcus GM, Vittinghoff E, Whitman IR, Joyce S, Yang V, Nah G, et al. Acute consumption of alcohol and discrete atrial fibrillation events. *Ann Intern Med* 2021;**174**:1503–9. <https://doi.org/10.7326/M21-0228>
185. Tu SJ, Gallagher C, Elliott AD, Linz D, Pitman BM, Hendriks JML, et al. Risk thresholds for total and beverage-specific alcohol consumption and incident atrial fibrillation. *JACC Clin Electrophysiol* 2021;**7**:1561–9. <https://doi.org/10.1016/j.jacep.2021.05.013>
186. Lee JW, Roh SY, Yoon WS, Kim J, Jo E, Bae DH, et al. Changes in alcohol consumption habits and risk of atrial fibrillation: a nationwide population-based study. *Eur J Prev Cardiol* 2024;**31**:49–58. <https://doi.org/10.1093/eurjpc/zwad270>
187. Gallagher C, Hendriks JML, Elliott AD, Wong CX, Rangnekar G, Middeldorp ME, et al. Alcohol and incident atrial fibrillation—a systematic review and meta-analysis. *Int J Cardiol* 2017;**246**:46–52. <https://doi.org/10.1016/j.ijcard.2017.05.133>

2024 ESC Guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS)

Evidence tables

Developed by the task force for the management of atrial fibrillation of the European Society of Cardiology (ESC)

Table of Contents

Tables of Evidence for Recommendations 3

Additional Evidence Tables **Error! Bookmark not defined.**

Abbreviations and acronyms 8

References 874

Tables of Evidence for Recommendations

Evidence Table 1 for Recommendation Table 1 (Sec. 3) — Recommendations for the diagnosis of atrial fibrillation	21
Evidence Table 2 for Recommendation Table 2 (Sec. 3) — Recommendations for symptom evaluation in patients with atrial fibrillation.....	30
Evidence Table 3 for Recommendation Table 3 (Sec. 3) — Recommendation for diagnostic evaluation in patients with new atrial fibrillation	43
Evidence Table 4 for Recommendation Table 4 (Sec. 4) — Recommendations for patient-centred care and education	55
Evidence Table 5 for Recommendation Table 5 (Sec. 5) — Recommendations for comorbidity and risk factor management in atrial fibrillation	68
Evidence Table 6 for Recommendation Table 6 (Sec. 6) — Recommendations to assess and manage thromboembolic risk in atrial fibrillation	172
Evidence Table 7 for Recommendation Table 7 (Sec. 6) — Recommendations for oral anticoagulation in atrial fibrillation.....	206
Evidence Table 8 for Recommendation Table 8 (Sec. 6) — Recommendations for combining antiplatelet drugs with anticoagulants for stroke prevention on oral anticoagulation in atrial fibrillation	245
Evidence Table 9 for Recommendation Table 9 (Sec. 6) — Recommendation on thromboembolism despite anticoagulation	257
Evidence Table 10 for Recommendation Table 10 (Sec. 6) — Recommendations for percutaneous left atrial appendage occlusion	263
Evidence Table 11 for Recommendation Table 11 (Sec. 6) — Recommendations for surgical left atrial appendage occlusion	276
Evidence Table 12 for Recommendation Table 12 (Sec. 6) — Recommendations for assessment of bleeding risk factors.....	291
Evidence Table 13 for Recommendation Table 13 (Sec. 6) — Recommendations for management of bleeding in anticoagulated patients	330
Evidence Table 14 for Recommendation Table 14 (Sec. 7) — Recommendations for heart rate control in patients with atrial fibrillation	340

Evidence Table 15 for Recommendation Table 15 (Sec. 7) — Recommendations for general concepts in rhythm control.....	398
Evidence Table 16 for Recommendation Table 16 (Sec. 7) — Recommendations for electrical cardioversion of atrial fibrillation	437
Evidence Table 17 for Recommendation Table 17 (Sec. 7) — Recommendations for pharmacological cardioversion of atrial fibrillation	463
Evidence Table 18 for Recommendation Table 18 (Sec. 7) — Recommendations for antiarrhythmic drugs for long-term maintenance of sinus rhythm	489
Evidence Table 19 for Recommendation Table 19 (Sec. 7) — Recommendations for catheter ablation of atrial fibrillation	517
Evidence Table 20 for Recommendation Table 20 (Sec. 7) — Recommendations for anticoagulation in patients undergoing catheter ablation.....	552
Evidence Table 21 for Recommendation Table 21 (Sec. 7) — Recommendations for endoscopic and hybrid atrial fibrillation ablation	589
Evidence Table 22 for Recommendation Table 22 (Sec. 7) — Recommendations for atrial fibrillation ablation during cardiac surgery	612
Evidence Table 23 for Recommendation Table 23 (Sec. 8) — Recommendations to measure and improve patient quality of life	639
Evidence Table 24 for Recommendation Table 24 (Sec. 9) — Recommendations for patients with an acute coronary syndromes or undergoing percutaneous intervention.....	648
Evidence Table 25 for Recommendation Table 25 (Sec. 9) — Recommendations for triggered atrial fibrillation.....	681
Evidence Table 26 for Recommendation Table 26 (Sec. 9) — Recommendations for prevention of postoperative atrial fibrillation	691
Evidence Table 27 for Recommendation Table 27 (Sec. 9) — Recommendations for patients with embolic stroke of unknown source	711
Evidence Table 28 for Recommendation Table 28 (Sec. 9) — Recommendations for patients with atrial fibrillation during pregnancy.....	724
Evidence Table 29 for Recommendation Table 29 (Sec. 9) — Recommendations for patients with AF and congenital heart disease	732

Evidence Table 30 for Recommendation Table 30 (Sec. 9) — Recommendations for prevention of thromboembolism in AF	746
Evidence Table 31 for Recommendation Table 31 (Sec. 10) — Recommendations for screening for atrial fibrillation	748
Evidence Table 32 for Recommendation Table 32 (Sec. 10) — Recommendations for prevention of atrial fibrillation	781

Additional Evidence Tables

Additional Evidence Table S1 — Diagnostic criteria for atrial fibrillation.....	26
Additional Evidence Table S2 — Adverse events associated with atrial fibrillation	46
Additional Evidence Table S3 — Patient-centred care and education.....	63
Additional Evidence Table S4 — Comorbidity and risk factor management.....	127
Additional Evidence Table S5 — Institution of anticoagulation.....	197
Additional Evidence Table S6 — Direct oral anticoagulants.....	237
Additional Evidence Table S7 — Vitamin K antagonists.....	239
Additional Evidence Table S8 — Anticoagulation in the context of chronic kidney disease	241
Additional Evidence Table S9 — Antiplatelet drugs and combinations with anticoagulants	252
Additional Evidence Table S10 — Percutaneous left atrial appendage occlusion	269
Additional Evidence Table S11 — Surgical left appendage occlusion.....	285
Additional Evidence Table S12 — Bleeding risk factors	300
Additional Evidence Table S13 — Bleeding risk scores	313
Additional Evidence Table S14 — Management of bleeding.....	337
Additional Evidence Table S15 — Rate control: Drugs	363
Additional Evidence Table S16 — Rate control: Role of pacing	383
Additional Evidence Table S17 — General principles and anticoagulation in rhythm control	423
Additional Evidence Table S18 — Electrical cardioversion	444
Additional Evidence Table S19 — Recommendations for antiarrhythmic drugs for long-term maintenance of sinus rhythm.....	503
Additional Evidence Table S20 — Catheter ablation.....	548
Additional Evidence Table S21 — Left atrial appendage thrombus peri-ablation	557
Additional Evidence Table S22 — Studies on minimally interrupted vs. interrupted oral anticoagulation	562
Additional Evidence Table S23 — Discontinuing oral anticoagulation post-ablation	578

Additional Evidence Table S24 — Rhythm control: Endoscopic and hybrid atrial fibrillation ablation.....	602
Additional Evidence Table S25 — Atrial fibrillation ablation during cardiac surgery	623
Additional Evidence Table S26 — Recommendations to measure and improve patient quality of life.....	647
Additional Evidence Table S27 — Acute and chronic coronary syndromes in patients with atrial fibrillation	668
Additional Evidence Table S28 — Acute stroke or intracranial haemorrhage in patients with atrial fibrillation.....	675
Additional Evidence Table S29 — Patients with embolic stroke of unknown source (ESUS)	719
Additional Evidence Table S30 — Congenital heart diseases and AF	733
Additional Evidence Table S31 — AF in inherited cardiomyopathies and primary arrhythmia syndromes.....	738
Additional Evidence Table S32 — Screening strategies for atrial fibrillation.....	761
Additional Evidence Table S33 — Prediction of incident atrial fibrillation	766
Additional Evidence Table S34 — Hypertension	827
Additional Evidence Table S35 — Heart failure.....	831
Additional Evidence Table S36 — Diabetes mellitus.....	835
Additional Evidence Table S37 — Obesity	843
Additional Evidence Table S38 — Sleep apnoea syndrome	849
Additional Evidence Table S39 — Physical activity.....	867

Abbreviations and acronyms

AA	Atrial arrhythmia
AAD	Antiarrhythmic drugs
ABC Pathway	‘A’ Avoid stroke (with anticoagulants), ‘B’ Better symptom management, with patient-centred decisions on rate or rhythm control, ‘C’ Cardiovascular and comorbidity risk optimization
AC	Anticoagulation
ACC	American College of Cardiology
ACD	All-cause death
ACE	Angiotensin-converting enzyme
ACEi	Angiotensin-converting enzyme inhibitor
ACS	Acute coronary syndromes
ACT	Activated clotting time
ADT	Antiarrhythmic drug therapy
AF	Atrial fibrillation
AFEQT	Atrial Fibrillation Effect on QualiTy-of-Life (questionnaire)
AFF	Atrial fibrillation or flutter
AFL	Atrial flutter
AFQLQ	Atrial Fibrillation Quality of Life Questionnaire
AF-QoL	Atrial Fibrillation Quality of Life (questionnaire)
AFSS	Atrial Fibrillation Severity Scale
AHA	American Heart Association
AHI	Apnoea–hypopnoea index
AI	Artificial intelligence
AIS	Acute ischemic stroke
AIT	Amiodarone-induced hyperthyroidism

AL	Anterior-lateral
ARB	Angiotensin receptor blocker
ALT	Alanine aminotransferase
AP	Anterior-posterior
APT	Antiplatelet therapy
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor neprilysin inhibitor
ASA	Aspirin
ASD	Atrial septal defect
AST	Aspartate aminotransferase
AT	Atrial tachycardia
ATA	Atrial tachyarrhythmia
ATTR	Transthyretin amyloid cardiomyopathy
AUC	Area under curve
AV	Atrioventricular
AVN	Atrioventricular node
AVR	Aortic valve replacement
b.p.m.	Beats per minute
BAS	Bariatric surgery
BID	<i>Bis in die</i>
BMI	Body mass index
BMT	Best medical therapy
BNP	B-type natriuretic peptide
BP	Blood pressure
BQ	Berlin Questionnaire
BRI	Bleeding Risk Index
BS	Bariatric surgery

BTE	Biphasic truncated exponential
BTE-HE	Biphasic truncated exponential-high energy
BW	Body weight
CA	Catheter ablation
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CAEP	Canadian Association of Emergency Physicians
CARTO	An electroanatomic navigation system
CCB	Calcium channel blocker
CDS	Clinical decision support
CDSS	A decision-support tool
CFE	Complex fractionated electrogram
CG	Control group
CHD	Congenital heart disease
CHF	Congestive heart failure
CHS	Cardiovascular Health Study
CIED	Cardiovascular implantable electronic device
CKD	Chronic kidney disease
CMIV	Cox-maze IV
CMR	Cardiac magnetic resonance
CMS	Centres for Medicare & Medicaid Services
COA	Catheter left atrial appendage occlusion combined with ablation
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CPR	Clinical prediction rules
CPVA	Circumferential pulmonary vein ablation
CrCl	Creatinine clearance

CRF	Cardiorespiratory fitness
CRNM	Clinically relevant nonmajor
CRT	Cardiac resynchronization therapy
CT	Computed tomography
CV	Cardiovascular
CVA	Cerebrovascular accident
CVD	Cardiovascular disease
CVE	Cardiovascular events
CVS	Cardioversion
DALYs	Disability-adjusted life years
DAPT	Dual antiplatelet therapy
DAs	Decision aids
DAT	Dual therapy
DBP	Diastolic blood pressure
DC	Direct current
DCCV	Direct current cardioversion
DM	Diabetes mellitus
DOAC	Direct oral anticoagulant
DOR	Diagnostic odds ratio
EAT	Ectopic atrial tachycardia
ECA	External carotid artery
ECG	Electrocardiogram
ECV	Electrical cardioversion
ED	Emergency department
EF	Ejection fraction
eGFR	estimated glomerular filtration rate
EHR	Electronic health records

EHRA	European Heart Rhythm Association
EP	Electrophysiology
EPPY	Events per patient year
EQ-5D	EuroQOL five dimensions questionnaire
ER	Emergency room
ESC	European Society of Cardiology
ESS	Epworth Sleepiness Scale
ESUS	Embolic stroke of undetermined source
ETP	Exercise training programme
FU	Follow-up
GCS	Glasgow coma scale
GFI	Groningen Frailty Indicator
GFR	Glomerular filtration rate
GI	Gastrointestinal
GLP	Glucagon-like peptide
GP	General practitioner
GPRD	General Practice Research Database
GRS	Genetic risk score
GWAS	Genome-wide association studies
HAS-BLED	Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalised ratio, Elderly (>65 years), Drugs/alcohol concomitantly (score)
HBP	His bundle pacing
HC	Hip circumference
HCA	Hybrid convergent ablation
HCM	Hypertrophic cardiomyopathy
HCP	Healthcare professional

HF	Heart failure
HFmrEF	Heart failure with mildly reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HR	Hazard ratio
HRQoL	Health-related quality of life
HRV	Heart rate variability
HRw	Weight hazard ratio
hsTnI	High sensitivity troponin I
HTN	Hypertension
IA	Intra-arterial
IV	Intravenous
ICB	Intracranial bleeding
ICD	Implantable cardioverter-defibrillator
ICE	Intracardiac echocardiography
ICH	Intracranial haemorrhage
ICM	Insertable cardiac monitor
ICU	Intensive care unit
IDC	Idiopathic dilated cardiomyopathy
IG	Immunoglobulin
IHD	Ischemic heart disease
ILI	Intensive lifestyle Intervention
ILR	Implantable loop recorder
INR	International normalized ratio
IPT	Inverse probability of treatment
IPW	Inverse probability weighting
IQR	Interquartile range

IR	Incidence rates
IRR	Incidence risk ratio
ISH	Isolated systolic hypertension
ISTH	International Society on Thrombosis and Haemostasis
IVT	Intravenous thrombolysis
JMC	Japanese Medical Check
JSTOR	Journal storage
LA	Left atrial
LAA	Left atrial appendage
LAAC	Left atrial appendage closure
LAACE	Left atrial appendage clip exclusion
LAAE	Left atrial appendage exclusion
LAAO	Left atrial appendage occlusion
LAAT	Left atrial appendage thrombus
LAd	Left atrial diameter
LAF	Lone atrial fibrillation
LAT	Left atrial thrombi
LMWH	Low molecular weight heparin
LSM	Lifestyle modifications
LSPAF	Long-standing persistent atrial fibrillation
LV	Left ventricle
LVAD	Left ventricular assist device
LVED	Left ventricle end diastolic
LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy
MACCE	Major adverse cardiac and cerebrovascular events
MACE	Major adverse cardiovascular event

MAE	Major adverse events
MB	Major bleeding
MCS	Mental health component score
MD	Mean difference
MDT	Multidisciplinary team
MED	Medical
mEHRA	Modified European Heart Association score
MET	Metabolic equivalent
mEVAL	Utah My Evaluation program
MI	Myocardial infarction
MIRs	Mortality-to-incidence ratio
mITT	Modified intention-to-treat
MLHF-Q	Minnesota Living With Heart Failure Questionnaire
MLWHF	Minnesota Living with Heart Failure
mOBRI	Modified outpatient bleeding risk index
MRA	Mineralocorticoid receptor antagonist
MRC	Medical rate control
MRI	Magnetic resonance imaging
MS	Metabolic syndrome
NACE	Net adverse clinical events
NHB	Non-Hispanic blacks
NHW	Non-Hispanic white
NIHSS	National Institutes of Health Stroke Scale
NNT	Number needed to treat
NNTH	Number need to treat for an additional harmful outcome
NPAF	Nonparoxysmal atrial fibrillation
NPV	Negative predictive value

NRI	Net reclassification improvement
NSAID	Non-steroidal anti-inflammatory drug
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NVAF	Non-valvular atrial fibrillation
NYHA	New York Heart Association
OAC	Oral anticoagulant
OAT	Oral anticoagulant therapy
OR	Odds ratio
OSA	Obstructive sleep apnoea
PA	Physical activity
PAF	Paroxysmal AF
PB	Pulsed biphasic
PCC	Prothrombin complex concentrate
PCI	Percutaneous intervention
PCS	Physical component summary score
PCV	Pharmacological cardioversion
PFO	Patent foramen ovale
POAF	Post-operative atrial fibrillation
PP	Posterior pericardiotomy
PPI	Proton pump inhibitor
PPM	Permanent pacemaker
PPV	Positive predictive value
PRO	Patient reported outcomes
PRS	Polygenic risk score
PSG	Polysomnography
PSM	Propensity score matching
PV	Pulmonary vein

PVAI	Pulmonary vein antrum isolation
PVI	Pulmonary vein isolation
PWI	Pulse wave index
QALYs	Quality-Adjusted Life-Years
QI	Quality indicator
QLAF	Quality of Life in Atrial Fibrillation
QoL	Quality of life
QRS	Q wave, R wave, and S wave, the 'QRS complex' represents ventricular depolarization
QTc	Corrected QT interval
RA	Right atrial
RAS	Renin-angiotensin-system acting agent
RCT	Randomized controlled trial
RD	Risk difference
RDN	Renal denervation
RF	Radiofrequency
RFA	Radiofrequency ablation
RFCA	Radiofrequency catheter ablation
RFM	Risk factor modification/risk factor management
RHR	Resting heart rate
RR	Relative risk
SA	Sleep apnoea
SAE	Serious adverse event
SBP	Systolic blood pressure
SCD	Sudden cardiac death
SCE	Silent cerebral embolism
SCI	Silent cerebral infarction

SCL	Symptom checklist
SD	Standard deviation
SDB	Sleep disordered breathing
SE	Standard error
SEC	Seconds
SEE	Systemic embolism event
SF-12	Short-form 12
SFS	Short-Form score
SGLT2	sodium-glucose cotransporter-2
SIP	Sickness Impact Profile
SMD	Standardized mean difference
SOE	Strength of evidence
SR	Sinus rhythm
SS	Silent stroke
STEMI	ST-segment elevation myocardial infarction
T2DM	Type 2 diabetes mellitus
TAT	Triple antithrombotic therapy
TCA	Thoracoscopic surgical left atrial appendage clipping combined with ablation
TE	Thromboembolism
TIA	Transient ischaemic attack
TID	Three times a day
TOE	Transoesophageal echocardiography
TTE	Transthoracic echocardiogram
TTN	Titin gene
TTR	Time in therapeutic range
TVR	Target vessel revascularization

UFH	Unfractionated heparin
UI	Uncertainty interval
UK	United Kingdom
US	United States
VKA	Vitamin K antagonist
VT	Ventricular tachycardia
WC	Waist circumference
WHO	World Health Organization
WHS	Women's Health Study
WPW	Wolff–Parkinson–White syndrome

Evidence Table 1 for Recommendation Table 1 (Sec. 3) — Recommendations for the diagnosis of atrial fibrillation

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
SPAF, 1991	¹	RCT	1330	Intervention: warfarin (dose-adjusted) or aspirin Control: placebo	Inclusion: adults with AF documented on 1 ECG if constant AF or 2 ECGs if intermittent AF in the preceding 12 months with or without history of stroke or TIA	Stroke/Systemic embolism; Death	Reduces the risk of: Stroke/systemic embolism (by 67%; 95% CI 28–75%; $P=0.01$). Death by 58% (95% CI 20–78%; $P=0.01$)	Clinical AF confirmed by an ECG led to treatment with impact on patient outcomes

Connolly, 2009 (RE-LY)	²	RCT	18 113	Intervention: dabigatran (in two dosing regimens) Control: open label warfarin	Inclusion: AF documented on 1–2 ECGs at screening or within 6 months beforehand and other specified risk characteristics	Primary outcome: stroke or systemic embolism Secondary outcomes: stroke, systemic embolism, and death	Primary outcome: 1.69% per year for warfarin, 1.53% for dabigatran 110 mg (relative risk [RR] =0.91; 95% CI 0.74–1.11; <i>P</i> <0.001 for non-inferiority) and 1.11% per year for dabigatran 150 mg (RR=0.66; 95% CI 0.53–0.82; <i>P</i> <0.001 for superiority)	Clinical AF confirmed by an ECG led to treatment with impact on patient outcomes

Patel, 2011 (ROCKET-AF)	³	RCT	14 264	Intervention: rivaroxaban Control: warfarin	Inclusion: AF documented on 2 occasions, on 1–2 ECGs and a moderate to high risk of stroke (CHADS ₂ ≥ 2)	Primary efficacy outcome: composite of stroke, systemic embolism, or CV death	Primary endpoint (HR=0.79; 95% CI 0.66–0.96; <i>P</i> <0.001 for non-inferiority)	Clinical AF confirmed by an ECG led to treatment with impact on patient outcomes

Granger, 2011 (ARISTOTLE)	⁴	RCT	18 201	Intervention: apixaban Control: warfarin	Inclusion: High stroke risk patient with persistent AF or AFL documented on ECG at enrolment or paroxysmal AF documented on 2 ECGs at least 2 weeks apart in the 12 months before enrolment	Primary efficacy outcome: stroke and systemic embolism Primary safety endpoint: major bleeding as per ISTH criteria. Key secondary outcome: death from any cause	Primary outcome (HR=0.79; 95% CI 0.66–0.95; $P<0.001$ for non-inferiority, $P=0.001$ for superiority). All-cause mortality (HR=0.89; 95% CI 0.80–0.99; $P=0.047$)	Clinical AF confirmed by an ECG led to treatment with impact on patient outcomes

Giugliano, 2013 (ENGAGE-TIMI 48)	⁵	RCT	21 105	Intervention: edoxaban (2 dosing regimens) Control: warfarin	Inclusion: Patients >21 years with high stroke risk (CHADS2 ≥ 2) and AF documented on electrical tracing within 12 months before randomization	Primary efficacy endpoint: time to first adjudicated stroke or systemic embolic event	Primary endpoint for high dose edoxaban (HR=0.79; 95% CI 0.63–0.99; $P<0.001$ for non-inferiority). Low dose edoxaban (HR=1.07; 95% CI 0.87–1.31; $P=0.005$ for non-inferiority)	Clinical AF confirmed by an ECG led to treatment with impact on patient outcomes

Additional Evidence Table S1 — Diagnostic criteria for atrial fibrillation

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Svennberg, 2021 (STROKESTOP)	⁶	RCT	7165	Intervention: invited to screening for AF Control: no screening	Inclusion: Residents aged 75 or 76 years in the regions of Halland and Stockholm in Sweden. Exclusion: none criteria	Combined primary endpoint of ischaemic or haemorrhagic stroke, systemic embolism, bleeding leading to hospitalisation and all-cause mortality	Fewer primary endpoint events occurred in the intervention group HR= 0.96 [95% CI 0.92–1.00]; <i>P</i> =0.045. Limitations: study was underpowered; the endpoint events were not adjudicated but were obtained from routine	Screening for AF using a single-lead ECG showed a small net benefit compared with standard of care

							clinical data	
Hohnloser, 2009 (ATHENA)	⁷	RCT	4628	Intervention: dronedarone Control: placebo	Inclusion: patients with AF and additional risk factors for death	The primary outcome: first hospitalization due to CV events or death. Secondary outcomes: death from any cause, death from CV causes, and hospitalization due to CV events	The primary outcome occurred in 734 patients (31.9%) in the dronedarone group and in 917 patients (39.4%) in the placebo group (for dronedarone HR=0.76;95% I CI 0.69–0.84; P<0.001)	Persistent or paroxysmal AF confirmed by two 12-lead ECGs, one of which had to show sinus rhythm, demonstrated improvement in cardiovascular outcomes with dronedarone treatment
Yusuf, 2011 (ACTIVE-I)	⁸	RCT	9016	Intervention: irbesartan Control: placebo	Inclusion: patients with AF and a history of risk factors for	Coprimary outcome: stroke, myocardial infarction, or	Coprimary outcome: 5.4% per 100 person- years in both groups (with	A 12 lead ECG or a series of transtelephonic monitoring transmissions

					stroke	death from vascular causes; secondary outcome: composite of primary outcome plus hospitalization for heart failure	irbesartan, HR=0.99; $P=0.85$). Second coprimary outcome: 7.3% per 100 person-years with irbesartan and 7.7% per 100 person-years with placebo (HR=0.94; $P=0.12$)	were used to confirm AF and to demonstrate that irbesartan did not reduce cardiovascular events in these patients
Svennberg, 2015	⁹	Prospective cohort study	7173	Intervention: screening for AF Control: no screening	Inclusion: Individuals born in 1936 to 1937 living in Stockholm County or in Halland region at the end of 2011	AF detection OAC initiation	New AF was detected in 218 patients (3.0%; 95% confidence interval [CI], 2.7–3.5). 149 patients with known AF were	Mass screening for AF in a 75- to 76-year-old population identifies a significant proportion of participants with untreated

					were identified by their unique civic registration numbers Exclusion: none criteria		not using OACs, constituting 2.1% (95% CI, 1.8–2.4) of the screened population. Prevalence of untreated AF was 5.1% (95% CI, 4.6–5.7). Initiation of OAC treatment was made in 3.7% (95% CI, 3.3–4.2) of the screened population. Limitations: short detection period; largely Caucasian population	AF. Initiation of stroke prophylactic treatment was highly successful in individuals with newly diagnosed AF

Evidence Table 2 for Recommendation Table 2 (Sec. 3) — Recommendations for symptom evaluation in patients with atrial fibrillation

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Kirchhof, 2020 (EAST-AFNET4)	¹⁰	RCT	2789	Intervention: early rhythm control Control: care as usual	Inclusion: early AF (diagnosed ≤1 year before enrolment) and cardiovascular conditions	Secondary outcomes: Quality of life (QoL) using EQ-5D and SF-12 scores. Symptom evaluation with European Heart Rhythm Association (EHRA) classification	Improvement in QoL and symptoms from baseline to 2 years in both arms of the trial, with no difference between groups: ED-5D -1.0 early, -2.7 control; treatment effect 1.1 (-0.7 to 2.8)	Early or delayed rhythm control improves QoL and symptoms at 2 years
Kotecha, 2020	¹¹	RCT	160	Group 1: digoxin,	Inclusion: aged ≥60 years; permanent	Primary outcome: SF36 QoL	No significant between-	MEHRA class and QoL

(RATE-AF)				Group 2: bisoprolol, or alternative β -blocker treatment	AF in need for heart rate control from a clinician's perspective; breathlessness (NYHA class $\geq$ II)	physical component summary score (SF-36 PCS) at 6 months. Secondary outcomes: modified (m)EHRA symptom classification; SF-36, EQ-5D and AFEQT QoL at 6 and 12 months	group difference in SF-36 PCS (adjusted mean difference=1.4; 95% CI -1.1 to 3.8; $P=0.28$). mEHRA class at 6 months; digoxin 53% reported a 2-class improvement vs. 9% for beta-blockers (adjusted OR 10.3, 95% CI, 4.0 to 26.6; $P<0.001$); maintained at 12-months	measures used as an outcome to demonstrate beneficial treatment effects of rate control therapy

							($P<0.001$). 4 domains of SF-36 and EQ-5D significantly better with digoxin at 12-months	
Mantovan , 2013 (STAR-AF)	¹²	RCT	100 AF patients	The Substrate and Trigger Ablation for Reduction of AF (STAR AF) trial compared 3 strategies for ablation of high-burden paroxysmal/persistent AF: complex fractionated electrogram ablation (CFE),	The STAR AF study found 88%, 68%, and 38% freedom from AF >30 seconds at 12 months for PVI with CFE, PVI, and CFE approaches, respectively ($P=0.001$)	There was a significant improvement in physical health (24%) and mental health (19%) component scores from baseline to 12 months after ablation ($P<0.05$ for both). Significant QOL improvements were seen for all	QOL was measured before ablation and at 12 months after ablation using the Short-Form Health Survey (SF-36) scale. Transformed scores were calculated for each of the 8	QOL after AF ablation improves regardless of procedural outcome. QOL scores were only negatively affected in patients with a high symptomatic burden of arrhythmia recurrence

				pulmonary vein isolation (PVI), or a combined approach (PVI with CFE). This sub-analysis aimed to identify the effect on quality of life (QOL) conferred by ablation strategy, AF recurrence, and type of AF		3 ablation strategies despite differences in outcome. QOL measurements also improved regardless of AF recurrence, except in patients with an AF burden in the highest quartile (median 27.2 hours per month). AF recurrence independently predicted aggregate QOL score	subscales of the SF-36, and also converted to physical health and mental health component scores	suggesting that significant reduction in AF burden can improve QOL without total elimination of AF
Samuel, 2021 (CIRCA-DOSE)	¹³	RCT	346 patients (>18 years were	A secondary analysis of a prospective, parallel-group,	The exposure in the present analysis is the absolute difference in AF	At 12 months, a 1-point improvement in AFEQT score	To determine the association between	In patients with primarily low-burden paroxysmal AF,

			randomized 1:1:1 to contact force-guided radiofrequency ablation, 4-minute cryoballoon ablation, or 2-minute cryoballoon ablation)	multicenter, single-masked randomized clinical trial (Cryoballoon vs. Irrigated Radiofrequency Catheter Ablation: Double Short vs. Standard Exposure Duration [CIRCA-DOSE] study)	burden prior to ablation and 12 months following ablation, as evaluated by the AFEQT Score	was observed for every absolute reduction in daily AF burden of 15.8 minutes (95% CI 7.2–24.4; $P<0.001$), or every 0.63% (95% CI 0.30–0.95; $P<0.001$) reduction in relative AF burden from baseline	change in AF burden and quality of life in the year following ablation	the reduction in AF burden following ablation may be associated with a clinically meaningful improvement in quality of life
Terricabras, 2020 (STAR-AF II)	¹⁴	RCT	549 patients who underwent ablation. Patients underwent AF	A prespecified secondary analysis of the Substrate and Trigger Ablation for Reduction of Atrial	Inclusion: patients to have had symptomatic persistent AF (<3 years) refractory to at least 1 antiarrhythmic agent and no previous	Significant improvements in mean (SD) PCS (68.3 [20.7] to 82.5 [18.6]) and MCS (35.3 [8.6] to 37.5 [7.6]) occurred 18	To evaluate whether the procedural outcome of ablation for AF is associated with quality of	In this secondary analysis, decreases in AF burden after ablation for AF were significantly

			ablation with 1 of 3 ablation strategies: (1) pulmonary vein isolation (PVI), (2) PVI plus complex fractionated electrograms, or (3) PVI plus linear lesions	Fibrillation-Part II (STAR AF II) prospective randomized clinical trial, which compared 3 strategies for ablation of persistent AF	ablations	months after ablation ($P<.05$ for both). Significant QOL improvement occurred in all 3 study arms and regardless of AF recurrence, defined as AF episodes lasting more than 30 seconds: for no recurrence, mean (SD) PCS increased from 66.5 (20.9) to 79.1 (19.4) and MCS from 35.3 (8.7) to 37.7 (7.7)	life (QOL) measures	associated with improvements in QOL. Quality of life changes were significantly associated with the percentage of AF burden reduction after ablation
Jones, 2020 (RATE-	¹⁵	RCT	160 patients	Focus groups of patients with symptomatic	The RATE-AF trial randomised 160 patients aged ≥ 60	Substantial impairment of health-related	There was marked variability in	The impact of comorbidities is poorly

AF)				permanent AF in a trial of heart rate control	years with permanent AF and at least NYHA class II dyspnoea to either digoxin or beta-blockers	QoL was noted in 160 trial patients, with impact on all domains apart from mental health	symptoms in individual patients, with some describing severe impact on activities of daily living, and profound interaction with comorbidities such as arthritis	appreciated in the context of AF, with considerable variability in QoL that requires both generic and AF-specific assessment
Kotecha, 2016	¹⁶	Systematic review and meta-analysis of RCT and observational studies	Screened 2216 articles, of which eight articles describing five	A systematic review of the measurement properties of AF -specific health-related quality of life questionnaires	Inclusion: Articles describing: Atrial Fibrillation 6 (AF6), AFEQT, Atrial Fibrillation Quality of Life Questionnaire (AFQLQ), Atrial Fibrillation Quality of	Good reliability (internal consistency and test-retest reliability) was demonstrated for AF6, AFEQT, AFQLQ and	Responsiveness was positively rated only in AFEQT, but with limited evidence. Overall,	Given the low ratings for many measurement properties, no single questionnaire can be

			questionnaires were eligible for inclusion		Life (AFQoL), and Quality of Life in Atrial Fibrillation (QLAF)	AFQoL. Content, construct and criterion validity were positively rated only in AFEQT	AFEQT showed strong positive evidence for 2 of 9 measurement properties, compared to one for AFQoL and none for the remaining questionnaires	recommended, although AFEQT performed strongest
Schnabel, 2018	¹⁷	Prospective cohort study	6196	Consecutive patients with AF were enrolled at 461 centres. Interventions: pharmacological or ECV as	Inclusion: ≥18 years; with AF	Outcomes: presence of sinus rhythm on the follow-up ECG; adequate heart rate control. Disease outcomes:	EHRA score presented in a dichotomized manner was associated with: cardioversion	Higher symptom burden as assessed by the EHRA score predicts rhythm control interventions

				well as catheter ablation upon follow-up		ischemic stroke/transient ischemic attack/arterial embolism, coronary events, heart failure, and major bleeding	s (OR=1.21; 95% CI 1.01–1.45) catheter ablation (OR=1.97; 95% CI 1.44–2.69) and HF incidence (OR=1.65; 95% CI 1.16–2.34)	
Sandhu, 2017	¹⁸	Prospective cohort study	100 patients underwent electrical cardioversion and completed follow-up	A prospective cohort study of consecutive patients with AF referred for outpatient electrical cardioversion at 2 hospitals in Edmonton from 2013–2014	The overall mean AFEQT score was 55.6 ± 24.4 , and the domain-specific scores were as follows: symptoms, 66.2 ± 26.6 ; daily activities, 48.5 ± 29.5 ; treatment concerns, 57.6 ± 25.8 ; and treatment satisfaction, $56.7 \pm$	There were significant improvements in the vast majority of the SF-36 and AFEQT domains for the 51 patients who maintained sinus rhythm at 3 months	Patients who were in AF by 3 months demonstrated improvements in the AFEQT treatment concern score ($P=0.02$) and SF-36	There are significant QoL benefits for patients who maintain sinus rhythm after electrical cardioversion

					26.1		emotional role value ($P<0.01$) compared with baseline values, which may be the result of treatment expectations related to cardioversion	
Zenger, 2020	¹⁹	Prospective cohort study	1338 patients completed the AF Symptom Severity Scale (AFSS) symptom score	The Utah My Evaluation (mEVAL) program collects the Toronto AFSS in AF outpatients at the University of Utah	Inclusion: a clinical diagnosis of AF, an outpatient visit with a University of Utah adult electrophysiology clinician from October 2016 to January 2020; and completed the entire seven-item	At 6-months, worse baseline symptom score was associated with the use of rhythm control (37.1% vs. 24.5%; $P<0.001$). Younger age (mean difference 2.92 for <65 vs.	Compared subsequent clinical management at 6 months between patients with better versus worse AF HRQoL	AF Patient-reported outcomes (PROs) in clinical practice identify highly-symptomatic patients, corroborating findings in more

					symptom score domain of at least one AFSS PRO assessment	≥75; $P<.001$), female sex (mean difference 2.57; $P<.001$), pulmonary disease (mean difference 1.88; $P<.001$), and depression (mean difference 2.46; $P<.001$) were associated with higher scores		controlled, clinical trials. Increased AFSS score correlates with more aggressive clinical management, supporting the utility of disease-specific PROs guiding clinical practice
Wynn, 2014	²⁰	Prospective cohort study	362 patients attending the heart rhythm clinics during 2012	EHRA classification versus quality of life (QoL) measures	Inclusion: consecutive patients with a diagnosis of AF attending designated heart rhythm/electrophysiology clinics at a single specialist	A step-wise, negative association was seen between the EHRA class and both the AFEQT and EQ-5D scores. Health-	The mEHRA score separates Class 2 (symptomatic AF not limiting daily activities) into	MEHRA class 2b may be an appropriate treatment threshold

					cardiac hospital in England	related utility was only significantly different between Classes 2 and 3 ($P<0.001$)	whether the patients were 'troubled by their AF' (Class 2b) or not (Class 2a), with observable differences in QoL and health utility ($P=0.01$)	
Arbelo, 2021	²¹	Guideline	Patients with AF	The construction of candidate QIs (including a systematic review of the literature) and the selection of the final set of QIs (using a modified	N/a	Quality indicator development	Six domains of AF care (patient assessment, anticoagulation, rate control, rhythm control, risk factor management,	It is anticipated that implementation of these Quality Indicators will improve the quality of AF care

				Delphi method)			and outcomes), and provides 17 main and 17 secondary QIs for the diagnosis and management of AF	

Evidence Table 3 for Recommendation Table 3 (Sec. 3) — Recommendation for diagnostic evaluation in patients with new atrial fibrillation

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Tops, 2010	²²	Review	The role of multimodality imaging in the evaluation and treatment of AF is discussed	Imaging outpatients presenting with AF	First, an overview of the initial assessment of an AF patient is provided, including the role of different imaging techniques. Secondly, the role of imaging in the invasive treatment of AF with catheter ablation is reviewed	An overview of the initial assessment of an AF patient and conditions that are associated with AF	Left atrial size assessment and the screening for thrombus formation are addressed. Issues that should be considered before the procedure including contraindications and pulmonary veins are discussed	Multimodality imaging plays an important role in the initial assessment of AF patients, and during subsequent invasive treatment with catheter ablation
Roney, 2021	²³	Review	Not applicable	Review the use of multimodality	Several imaging modalities which	How imaging modalities are	Describes how advanced	Imaging combined with

				imaging for left atrial ablation procedures	for atrial arrhythmia catheter ablation guide: patient selection, pre-procedural planning, intra-procedural guidance, and post-procedural assessment	routinely used in the peri-ablation period	imaging techniques may inform patient selection for ablation and ablation targets them	advanced analyses for personalization of ablation targets can improve catheter ablation outcomes
Troughton, 2003	²⁴	Review	Not applicable	Review of different echocardiographic modalities	Transoesophageal, intracardiac and transthoracic echocardiography use in AF are discussed	Highlight the echocardiographic modalities that are available and their role in the evaluation and management of AF	Describes how echocardiographic imaging techniques may inform on cardiac structure and function, aetiology of AF, role in stroke risk assessment pre-cardioversion, and guidance	Echocardiography provides vital information about cardiac function, complications, and prognosis in patients with AF

							during ablation procedures	

Additional Evidence Table S2 — Adverse events associated with atrial fibrillation

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Odutayo, 2016	²⁵	Systematic review and meta-analysis of RCTs and observational studies	104 eligible cohort studies involving 9 686 513 participants (587 867 with AF)	AF vs. no AF	Cohort studies examining the association between AF and outcomes	Mortality, stroke, heart disease	All-cause mortality (RR=1.46; 95% CI 1.39–1.54); cardiovascular mortality (RR=2.03; 95% CI 1.79–2.30); sudden cardiac death (SCD) (RR=1.88; 95% CI 1.36–2.60); stroke (RR=2.42; 95% CI 2.17–2.71); heart failure (RR=4.99; 3.04–8.22)	AF associated with increased risk of most cardiovascular outcomes
Rattanawong, 2018	²⁶	Systematic review and meta-analysis of RCTs and	27 studies, 8401 AF patients and 67 608 non-AF	AF vs. no AF	Cohort studies examining the association between AF and SCD	SCD	AF patients were associated with a higher risk of SCD (pooled RR=2.04; 95% CI 1.77–2.35;	AF was associated with increased risk of SCD

		observational studies	controls				$P < 0.01$ $I^2 = 42.66$;))	
Ruddox, 2017	²⁷	Systematic review and meta-analysis of RCTs and observational studies	15 cohort studies (8 prospective) Of 220 928 participants , of whom 17.5% were exposed to AF	AF vs. no-AF	Studies with follow-up of at least 500 stable patients for either cardiac endpoints or all-cause mortality for >12 months	Risk of myocardial infarction (MI); cardiac events and all-cause mortality	AF was associated with an increased risk of MI (RR=1.54; 95% CI 1.26–1.85); all-cause mortality (RR=1.95; 95% CI 1.50–2.54); and heart failure (RR=4.62; 95% CI 3.13–6.83)	AF was associated with an increased risk of MI in patients without coronary heart disease and an increased risk of all-cause mortality and heart failure in patients with and without coronary heart disease
Zuin, 2021	²⁸	Systematic review and meta-analysis of RCTs and observational studies	18 studies 3 559 349 subjects, of which 902 741 (25.3%)	AF vs. individuals without this arrhythmia	The association between AF and dementia and the relative impact	Primary outcome: development of any kind of dementia in AF	HR=1.40; 95% CI 1.27–1.54; $P < 0.001$; $I^2 = 93.5\%$) for dementia in subjects with AF	AF was associated with an increased risk of developing dementia and

		nal studies	developed dementia		of follow-up period	patients		Alzheimer disease
Lin, 2021	²⁹	Systematic review and meta-analysis of RCTs and observational studies	613 920 patients (9 studies included: 2 prospective and 7 retrospective)	DOAC vs. no-treatment	Inclusion: AF patients ≥ 18 years; investigating the effects of OACs on the incidence of dementia; RCTs or observational studies. Exclusion: history of dementia or moderate-to-severe cognitive dysfunction	Primary outcome: incidence of dementia during the follow-up in AF patients with and without DOAC use	DOAC therapy was associated with a reduced risk of dementia compared with no treatment (RR= 0.72; 95% CI 0.60–0.86; $P= 0.000$). Limitations: high heterogeneity, inconsistent direction of effect in subgroup analysis with an observational window	DOAC therapy was associated with a protective effect for dementia in patients with AF
Giannone, 2022	³⁰	Systematic review and meta-	4 cohort studies and 2 case	AF vs. no-AF	Association between AF and dementia	Dementia	Individuals with AF were associated with increased risk of	AF was associated with dementia in

		analysis of RCTs and observational studies	studies: 1.6 million participants with a mean age at recruitment ranging from 42 to 85 years		in adults aged <70 years		developing dementia: RR=1.50; 95% CI 1.00–2.26 in patients aged <70 years; and RR=1.06; 95% CI 0.55–2.06 in those aged <65 years	observational cohorts
Papanastasiou, 2021	³¹	Systematic review and meta-analysis of RCTs and observational studies	The number of enrolled patients ranged from 57 to 1 627 631 among the included studies	AF vs. no-AF	Inclusion: studies investigating the association between AF and cognitive impairment (or dementia) cross-sectionally and longitudinally. Exclusion: studies	Cognitive impairment, all-cause dementia, vascular dementia, and Alzheimer's disease	AF was associated with dementia (OR=1.6; 95% CI 1.3–2.1; I ² = 31%) and the combined outcome of cognitive impairment or dementia (OR=1.5; 95% CI 1.4–1.8; I ² = 34%). The results were similar even when studies including only stroke-free patients were pooled	AF was associated with an increased risk of cognitive impairment, all-cause dementia, vascular dementia, and Alzheimer's disease

					encompassing and analysing exclusively patients with stroke history		together (OR 2.2; 95% CI 1.4–3.5; I ² = 96%), but the heterogeneity was high. AF was associated with increased risk of both vascular (OR=1.7; 95% CI 1.2–2.3; I ² =43%) and Alzheimer's dementia (HR=1.4; 95% CI 1.2–1.6; I ² =42%)	
Proietti, 2020	³²	Systematic review and meta-analysis of RCTs and observational studies	56 370 patients were included	AF vs. non-AF	Inclusion: studies that identified patients with and without AF as well as patients with and without Alzheimer's disease and reported	New onset of Alzheimer's disease	The random-effect pooled analysis showed a HR=1.30; 95% CI 1.01–1.59 and the heterogeneity was not high, I ² =48.1%	Patients with AF had an increased risk of developing new onset of Alzheimer's disease

					results of at least one relevant outcome			
Mongkhon, 2019	³³	Systematic review and meta-analysis of RCTs and observational studies	452 878 patients	DOAC vs. non-DOAC	Inclusion: RCTs or observational studies in patients with AF patients ≥ 18 years and had no history of dementia; DOACs' effects on the incidence of dementia/cognitive decline	Primary outcome: incidence of dementia or cognitive impairment among AF patients with and without OACs	DOAC use was associated with a protective effect in reducing dementia risk (RR=0.79; 95% CI 0.67–0.93; I ² =59.7%; $P=0.005$). Further, high percentage of time in therapeutic range (TTR) was associated with a decreased risk of dementia (RR=0.38; 95% CI 0.22–0.64; I ² =81.8%; $P<0.001$). Limitations: lack of adjusted effect ratios and heterogeneity of included studies	Oral anticoagulant therapy was associated with a reduced risk of dementia/cognitive impairment in patients with AF

Bassand, 2018 (GARFIELD-AF)	³⁴	Prospective registry	28 628 prospective patients with AF	Non-valvular AF	Inclusion: ≥18 years with non-valvular AF diagnosed within the previous 6 weeks, and with at least one non-prespecified risk factor for stroke as judged by the investigator	Primary objective: to identify the variables associated with the risks of all three major outcome measures, namely death, stroke/SE and bleeding, particularly those linked to modifiable risk factors	During 2-year follow-up, the rates of all-cause mortality were 3.84 (95% CI 3.68–4.02); stroke/SE 1.27 (95% CI 1.18–1.38), and major bleeding (first occurrences) 0.71 (95% 0.64–0.79) per 100 person-years. Factors associated with a higher risk of death: age, 'other race' (Caucasian/Hispanic/Latino), smoking, diabetes mellitus, history of stroke/TIA/SE, history of bleeding, cardiac failure, VascD, moderate-to severe renal disease, and	Newly diagnosed AF was associated with death as the most frequent adverse event, occurring at threefold the rate of stroke/SE and fivefold the rate of major bleeding

							non-paroxysmal forms of AF	
Boriani, 2019 (EORP)	³⁵	Prospective registry	9663 AF patients 86% on DOAC	DOAC vs. VKA	Inclusion: AF documented within 12 months before enrolment based on objective ECG evaluation. All patients were ≥18 years old	The relationship between baseline antithrombotic therapy use and the occurrence of major clinical adverse events	A lower risk for any TE/ACS/CV death was associated with patients treated only with VKA (HR=0.44; 95% CI 0.31–0.63) and DOACs (HR=0.37; 95% CI 0.26–0.54), compared with those not treated with any antithrombotic therapy	The 1-year follow-up of EORP-AF General Long-Term Registry reported a low occurrence of thromboembolic and haemorrhagic events, although mortality was high
Dai, 2021 (Global Burden of Diseases, Injuries, and Risk Factors Study)	³⁶	Prospective registry	In 2017, 37.57 million (95% UI 32.55–42.59) prevalent	AF (including AFL) vs. no-AF	Data for the burden of AF extracted through a query tool from the website of the Institute for	Mortality rate	AF contributed to 287 241 (95% UI 276 355–304 759) deaths globally in 2017. The age-standardized mortality rate of AF was 4.0 (95% UI 3.9–	In countries with lower socio-demographic index from 1990 to 2017 were associated with

(GBD))			cases and 3.05 million (95% UI 2.61–3.51) incident cases of AF globally		Health Metrics and Evaluation systematically and globally assessed the temporal trends of AF		4.2) per 100 000 people	an increased AF-related mortality rates

Evidence Table 4 for Recommendation Table 4 (Sec. 4) — Recommendations for patient-centred care and education

Study	Ref	Details and quality of evidence				Summary of key findings		
		Population and study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Van den Dries, 2020 (ALL-IN)	37	RCT	1657	Intervention: integrated care (IG) Control Group (CG): usual care	Inclusion: known and newly diagnosed AF	All-cause mortality, CV mortality, Non CV mortality, Hospitalization, Bleeding, use of OAC, Quality of life	In IG vs. CG: All-cause mortality= 3.5 vs. 6.7 per 100 patient-years (HR=0.55; 95% CI 0.37–0.82). CV mortality: NS Non cv mortality (HR=0.47; 95% CI 0.27–0.82). Hospitalization: NS (adjusted IRR 0.84; 95% CI 0.69–1.03) Bleeding: NS, RR= 1.6 (95%	IG had no impact on use of anticoagulation, quality of life and hospitalization. However IG reduced the risk of death

							CI 0.70–2.62) No impact on use of OAC which was high in both groups. Quality of life not different. s: possible selection bias	
Vinereanu, 2017, (IMPACT-AF)	³⁸	RCT	2281	Team: not a team intervention. Components : patient and HCP education; regular monitoring and feedback to HCPs. Control group: care	Inclusion: patients with AF and an indication for oral anticoagulation	Change in proportion of patients on OAC at 1-year: intervention 68– 80% vs. usual care 64–67%; (OR=3.28; 95% CI 1.67–6.44) for OAC use between groups	Key findings: significant increase in the proportion of patients treated with oral anticoagulants. Bias: no obvious biases	Not a disease management intervention but a quality improvement educational intervention. Positive impact on anticoagulation, and stroke rate, negative impact on minor bleeds. All-cause death

				as usual				and composite of stroke, systemic embolism, or major bleeding not different
Wijtvliet, 2019 (RACE 4)	³⁹	RCT	1375	Intervention: nurse-led integrated care Control group: care as usual	Inclusion: newly Diagnosed AF	Composite of CV death and CV hospital admissions; received anticoagulation in full accordance with the guidelines;	Composite of CV death and CV hospital admissions nurse-led=9.7% per year vs. usual care=11.6% per year (HR=0.85; 95% CI 0.69–1.04; <i>P</i> =0.12). 81% nurse-led care patients vs. 82% usual-care patients, received anticoagulation	Nurse-led integrated care Improved adherence to guideline recommendations, but no impact on anticoagulation, hospitalization rates, death rates, quality of life, knowledge scale and patient self-management. Nurse-led treatment was

							in full accordance with the guidelines Biases: heterogeneity in results due to difference in site experience	marginally more costly without a significant difference in QALYs
Hendriks 2012, 2014	40 41	RCT	712	Team: nurse-led AF care including decision support software based on clinical guidelines, supervised by a cardiologist. Control	Inclusion: newly diagnosed AF	CV hospitalization or CV death; Quality of life	CV hospitalization or CV death IG=14.3% vs. CG=20.8% (HR=0.65; 95% CI 0.45–0.93; <i>P</i> =0.017). CV death occurred in 1.1% in the nurse-led care vs. 3.9% in the cardiologist	Nurse-led integrated care decreases the rates of hospitalization, and death. No difference on the effect on quality of life

				group: care as usual (cardiologist only)			group (HR=0.28; 95% CI 0.09–0.85; <i>P</i> =0.025). Cardiovascular hospitalization amounted 13.5% vs. 19.1% (HR=0.66; 95% CI 0.46–0.96; <i>P</i> =0.029). Quality of life significantly improved in both groups with no significant differences between the two groups. Bias: single center study	

Qvist, 2016	⁴²	Prospective cohort study	596 patients from the real world and 356 patients from a clinical trial	Real-world AF clinics cohort vs. nurse-led AF care in the clinical trial cohort	Inclusion: ≥18 years of age with AF documented by ECG and/or Holter monitoring	Primary outcome: a composite of CV-related hospitalisation and death	The composite primary end point occurred with an incidence rate of 8.0 (95% CI 6.1–10.4) per 100 person-years in the real-world population and 8.3 (95% CI 6.3-10.9) per 100 person-years in the clinical trial, with a crude HR=0.83; 95% CI 0.56–1.23) in trial settings. Biases: residual confounding;	Structured, nurse-led, hospital-based AF care in routine clinical settings were associated with at least as good patient outcomes as the results achieved in clinical trial settings

							occurred; relatively short follow-up period; modest statistical precision	
Carter, 2016	⁴³	Prospective cohort study	433 patients (185 patients enrolled into the usual- care group, and 228 patients enrolled in the AF clinic group) with newly	Usual-care vs. subsequentl y the AF clinic. Any patient referred from 1 of the 3 EDs for new-onset AF were eligible for inclusion into the intervention phase	Inclusion: ≥18 years who presented to 1 of the 3 EDs with a new diagnosis of AF confirmed electrocardiographi cally and who were referred and evaluated by a specialist. Exclusion: patients' primary residence was outside the jurisdiction of the EDs; valvular AF; a prior diagnosis of	Primary outcome: composite of death, cardiovascular hospitalization, and AF-related emergency department visits	Primary outcome occurred in 44 (26.2%) patients in the usual-care group and 29 (17.3%) patients in the AF clinic group (OR=0.71; 95% CI 0.59–1; <i>P</i> =0.05) at 12 months Bias: patients in the usual- care group	An integrated approach to AF management as compared to usual specialist care was associated with a reduction in important cardiovascular outcomes and improvement in AF guideline adherence

			diagnosed AF in the 3 emergency departments		AF; life expectancy <6 months at the time of the AF diagnosis		were identified retrospectively; study conducted in a universal healthcare provider system, and the resource restraints of the system affected the wait times for specialty assessment	

Additional Evidence Table S3 — Patient-centred care and education

Study	Ref	Details and quality of evidence				Summary of key findings		
		Population and study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Yan, 2022	⁴⁴	RCT	235	Intervention: a nurse-led multidisciplinary team using a educational support; psychological support; social media tools (Apps); coordinating and linking patients to multidisciplinary team Control group: care as usual	Inclusion: diagnosed with AF	Anticoagulation use; cardiovascular hospitalization; death; quality of life	Intervention arm had fewer cardiovascular (CV) hospitalization (17 vs. 35, $P=0.006$) and a greater improvement in quality of life (QoL) than those receiving usual care (scores, 588.0 ± 106.0 vs. 519.1 ± 120.7 at 6 months and 674.4 ± 53.4 vs. 584.1 ± 105.9 at 12 months; both $P<0.001$). No difference between	Integrated care as applied decreases the rates of CV hospitalization, improves QoL, does not affect use of OAC, nor mortality

							OAC use and cardiovascular death between the two groups. Bias: small study, single centre study tertiary referral centre	
Guo, 2020, (mAFA II)	⁴⁵	RCT	3324	Team: doctor managed mobile App team that takes an ABC approach. Components: personal health record; clinical decision support; symptom reporting and advice; patient educational	Inclusion: newly diagnosed AF	Composite of ischemic stroke/systemic thromboembolism, all-cause death and rehospitalisation	Lower risk of, death, and rehospitalisation with intervention: (1.9% vs. 8.0%; HR=0.39). Rates of rehospitalisation alone were lower in the intervention: (1.2% vs. 4.5%; HR=0.32). No significant effect on adherence to OAC. Bias: possible flawed cluster	Integrate care using a mobile application, decreases the rates of adverse events. No effect on OAC use

				program; patient involvement in self-care. Control group: care as usual			improvement (baseline differences in age and use of oral anticoagulation); possible selection bias due to mobile phone use	
Cox, 2020 (IMPACT-AF)	⁴⁶	RCT	1145	Team: no specific team; primary care providers were using a clinical decision support (CDS) tool (family physicians, nurse practitioners, nurses). Components: CDS tool; guideline-based	Inclusion: known and newly diagnosed AF	Primary efficacy outcome was a composite of unplanned CV hospitalizations and AF-related ED visits; the primary safety outcome was major bleeding, both over 1 year	Key findings: No significant effects on the primary efficacy (130 control vs. 118 CDS, HR=0.98; 95% CI 0.71–1.37; <i>P</i> =0.92) or safety (<i>n</i> = 7 usual care vs. <i>n</i> = 8 CDS, 1.3% total, <i>P</i> =0.93) at 12 months. Bias: issues with fidelity to CDS tool and short follow up	Study evaluated one single structure parameter rather than integrated care. No significant no impact on outcomes using a CDS tool. Quality of life not reported

				physician monitoring system; patient self-monitoring system. Control group: care as usual			might explain the lack of effects	
Stewart, 2015, (SAFETY)	⁴⁷	RCT	335	Team: Mix of home-based visits and nurse-led clinic. Components: home visit, Holter monitoring (7 ± 14 days post-discharge) by cardiac nurse, prolonged follow-up, MDT support as needed. Followed by a	Inclusion: recurrent paroxysmal, persistent, or permanent AF	Death or unplanned readmission IG=76% vs. UC=82% (HR=0.97; 95% CI 0.7f.23; <i>P</i> =0.85), Fewer days of recurrent unplanned hospital stays in patients assigned to IG. No difference for AF readmissions, bleeding events,	The intervention lead to more days alive and out of hospital. Bias: issues with power and blinding	Positive impact on days alive and out of hospital, but not prolonged event-free survival

				combination of repeat home visits, scheduled clinic reviews, and telephone follow-up. Control group: care as usual		ACS and cerebrovascular events. Slight improvement in quality-of-life		
Vanharen, 2023	⁴⁸	RCT	65	Team: no team. Intervention: advanced nurse practitioner-led care, one patient educational session, three consultations over 6 months and telephone accessibility. Control group: care as usual	Inclusion: age ≥ 18 years, no cognitive impairments, and no cardiac electronic assist device (pacemaker, defibrillator)	AF recurrence rate at 6-month follow-up	At 6 months, AF recurrence was significantly lower in IG (13.5 vs. 39.4%, $P=0.014$). Bias: small study, open design, short follow-up, power issue	Advanced nurse practitioner-led care reduces AF recurrence after catheter ablation for AF

Evidence Table 5 for Recommendation Table 5 (Sec. 5) — Recommendations for comorbidity and risk factor management in atrial fibrillation

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Hypertension								
Pinho-Gomes, 2021	49	RCTs	22 trials with 188 570 patients of whom 13 266 (7%) had AF	Individual participant data analyses of RCTs on pharmacological BP therapy	Inclusions: trials available to the Blood Pressure Lowering Treatment Trialists' Collaboration; randomised participants to BP-lowering drugs vs. placebo; AF status recorded at baseline. Exclusions: Presence of AF	Primary outcome MACE: stroke; myocardial infarction of ischaemic heart disease; HF causing death or hospitalisation	A 5mmHg SBP reduction lowered the risk of major cardiovascular events both in patients with AF (HR=0.91; 95% CI 0.83–1.00) and in patients without AF at baseline (HR=0.91;	Pharmacological BP lowering in individuals with AF is associated with a reduction in MACE, primarily driven by a reduction in stroke

					not documented at baseline		95% CI 0.88–0.93). Bias: Not all studies were available; no pre-specified systematic evaluation of AF; no evaluation of AF endpoints. AF cohort was smaller but significant; AF patient results driven chiefly by stroke outcome	
Rienstra, 2018 (RACE 3)	⁵⁰	RCT	245	Upstream therapy with mineralocorti	Inclusion: early symptomatic persistent AF	The primary endpoint was sinus rhythm at 1 year	At 1 year, sinus rhythm was present	Upstream therapy increased the

				coid receptor antagonists (MRAs), statins, angiotensin converting enzyme inhibitors and/or receptor blockers, and cardiac rehabilitation including physical activity, dietary restrictions, and counselling versus control	patients [total AF history<5 years, total persistent AF duration>7 days but <6months, ≤1 electrical cardioversion (ECV), and early (total history<1 year); HFpEF or HfrEF]. Exclusions: LVEF<25%; NYHA IV; left atrial size>50 mm; MRA use; AF associated with surgery or acute illness	during 7 days of Holter monitoring. Underlying conditions were more successfully treated in the intervention group	in 89 (75%) patients in the intervention vs. 79 (63%) in the conventional group (OR=1.76; lower limit of 95% CI 1.02; <i>P</i> =0.04)	maintenance of sinus rhythm in mild to moderate HF
Parkash,	⁵¹	RCT	173	Intervention:	173 patients	Primary outcome	No difference	Treated in

2017 (SMAC-AF)				aggressive BP Control: standard of care	with AF and BP >130/80mmHg: 88 aggressive BP (target <120/80mmHg); 85 standard BP (target <140/90mmHg)	was symptomatic recurrence of AF /atrial tachycardia/atrial flutter lasting >30 seconds, determined 3 months beyond catheter ablation by a blinded end- point evaluation	in recurrence risk after ablation in aggressive group compared with standard group (HR=0.94; 95% CI 0.65– 1.38; <i>P</i> =0.76). More hypotension requiring drug adjustment in aggressive BP (26% vs. 0%) Bias: treatment duration possibly too	isolation, aggressive management of modest hypertension was not associated with improvement in maintaining sinus rhythm

							short to see effect. Both groups had a significant reduction in BP from baseline, dilution of positive effect of aggressive strategy	
Pathak, 2014 (ARREST-AF)	⁵²	Prospective cohort study	281	Intervention: comprehensive risk factor management (RFM) (61 patients). Control: given information on management of risk factors (88 patients)	Inclusion: BMI >27 kg/m ² and >1 risk factor (hypertension, glucose intolerance/DM, hyperlipidaemia, OSA, smoking, or alcohol excess) undergoing	AF frequency duration, symptoms, and symptom severity; Single-procedure drug-unassisted arrhythmia-free survival; Multiple-procedure arrhythmia-free survival	AF frequency duration; symptoms, and symptom severity decreased more in RFM (all $P<0.001$). Single-procedure drug-unassisted	RFM was associated with an improvement in outcomes of AF ablation by reducing AF burden and severity in conjunction with favourable changes in

					initial catheter ablation for symptomatic AF despite the use of antiarrhythmic medication. Exclusion criteria: history of MI/ cardiac surgery in the previous 12 months/ previous AF ablation/ active malignancy/ autoimmune or systemic inflammatory disease/ severe renal or hepatic failure/ <12 months' follow-		arrhythmia-free survival was greater in RFM subjects ($P<0.001$). Multiple-procedure arrhythmia-free survival was markedly better in RFM patients ($P<0.001$), with 16% and 42.4%, respectively, using antiarrhythmic drugs ($P=0.004$). Bias: Single centre study;	cardiac remodelling in these study patients. Hypertension was managed as a comprehensive program with ACEi/ARB used as first line

					up after their procedure		observational so potential for selection bias and less control of confounders; monitoring done with Holter so not continuous and could miss asymptomatic AF	
Pathak, 2015 (LEGACY)	⁵³	Prospective cohort study	355	Intervention: comprehensive risk factor management. Weight loss was categorized as: Group 1 (<3%), Group	Inclusion: patients with a BMI >27 kg/m ² Exclusion: permanent AF/ history of MI/ cardiac surgery in the previous 12-months/	Arrhythmia free with and without rhythm control; total-arrhythmia-free survival rates	45.5% of Group-1 vs. 22.2% of Group-2 and 13.4% of Group-3 (P<0.001) remained arrhythmia	Management of risk factors was associated with a graded reduction in AF recurrence. Hypertension treated as one of the risk

				2 (3–9%), and Group 3 (≥10%) Comparator: NA	significant valvopathy/ ventricular dysfunction/ active malignancy/ autoimmune or systemic inflammatory diseases/ severe renal or hepatic failure/ <24-months follow-up		free without rhythm control. Total arrhythmia- free survival rates: were 86.2% in Group-1 vs. 65.5% in Group-2 and 39.6% in Group-3 ($P<0.001$). Bias: Single centre study; potential for selection bias and less control of confounders; monitoring done with Holter so not	factors with a first line treatment with ACEi or ARB

							continuous and could miss asymptomatic AF; degree of risk factor management only evaluated by weight	
Middeldorp , 2018 (REVERSE -AF)	⁵⁴	Prospective cohort study	355	Intervention: Comprehensive risk factor management Weight loss was categorized as: Group 1 (<3%), Group 2 (3–9%), and Group 3 (≥10%) Comparator:	Inclusion: patients with a BMI >27 kg/m ² . Exclusion: permanent AF, history of MI or cardiac surgery in the previous 12-months, significant valvopathy or ventricular dysfunction,	Progression from paroxysmal to persistent AF; reversal from persistent to paroxysmal AF; freedom from AF	41% from Group 1 vs. 32% from Group 2 vs. 3% from Group 3 progressed from paroxysmal to persistent. 26% from Group 1 vs. 49% from	Weight loss and management of risk factors was associated with reverse of the natural progression of AF disease, resulting in those with persistent AF more

				NA (Sub study of LEGACY)	active malignancy, autoimmune or systemic inflammatory diseases, severe renal or hepatic failure, <24-months follow-up		Group 2 vs. 88% from Group 3 reversed from persistent to paroxysmal or no AF ($P<0.001$). Increased weight loss was significantly associated with greater AF freedom: 45 (39%) in Group 1 vs. 69 (67%) in Group 2 and 116 (86%) in Group 3 ($P\leq 0.001$). Bias: Single	frequently transiting to either paroxysmal AF or no AF. Hypertension treated as one of the risk factors with a first line treatment with ACEi or ARB

							centre study; potential for selection bias and less control of confounders; monitoring done with Holter so not continuous and could miss asymptomatic AF; degree of risk factor management only evaluated by weight	
Heart failure								
Kotecha, 2014	⁵⁵	Systematic review and meta-	18 254 (median age 64; 75%	Intervention: beta-blockers vs. placebo	Inclusion: RCT in which mortality was a	Primary outcome was all-cause mortality.	Crude death rates over a mean follow-	Beta-blockers had no significant

		analysis of RCTs; individual patient-level analysis	men). 3066 (17%) had AF on ECG at baseline	(double-blind)	primary or composite outcome of the comparison of beta-blockers vs. placebo in patients with HF. Only unconfounded head-to-head trials with recruitment of more than 300 patients and a planned follow-up of more than 6 months	The total number of hospitalisations and annualised rate per patient were higher in AF patients compared to sinus rhythm for all types, with longer average length of stay (for CV-hospitalisation 11.9 days in AF versus 9.7 days in sinus rhythm)	up of 1.5 years (SD 1.1) were 21% (633 of 3064) in patients with AF. Beta-blocker had no effect on mortality in patients with AF vs. placebo (HR=0.97; 95% CI 0.83–1.14; <i>P</i> =0.73), with a significant <i>P</i> value for interaction of baseline rhythm (<i>P</i> =0.002)	benefit on mortality or cardiovascular hospital admission in patients with HFrEF and concomitant AF

Pandey, 2021	⁵⁶	Systematic review and meta-analysis of RCTs	75 279 (18 832 with a baseline history of AF)	SGLT2 inhibitors vs. placebo or no therapy	31 RCTs reported on AF events. 3 RCTs reported on HF hospitalization or CV death stratified by a baseline history of AF	AF-related events; composite of HF hospitalisation or CV death	Reduction in the risk of serious AF events in patients who received an SGLT inhibitor (1.1% vs. 1.5%; RR=0.75; 95% CI 0.66–0.86%). SGLT inhibitors resulted in a lower risk in the composite of Lower HF hospitalization or CV death with SGLT2i,	SGLT inhibitors reduce AF events and reduce HF hospitalization/ CV death to a similar extent in patients with and without AF

							similar in AF (HR 0.70, 95% CI, 0.57–0.85) as with sinus rhythm, (HR 0.70, 95% CI 0.61–0.79); <i>P</i> for interaction=1.00	
Olsson, 2006 (CHARM)	⁵⁷	RCT	7599 patients (17% patients in the low ejection fraction group and 19% in the preserved ejection fraction	Candesartan (target dose 32 mg once daily, mean dose 24 mg) vs. placebo	Inclusion: symptomatic CHF in NYHA II to IV Exclusion: serum creatinine ≥ 265 $\mu\text{mol/l}$ (≥ 3 mg/dL), serum potassium ≥ 5.5 mmol/l	Major outcomes were cardiovascular death or hospitalization for worsening heart failure, and all-cause mortality	Patients with AF and HFpEF had a greater relative risk of the major outcomes in compared to AF patients with low EF: (HR=1.72; (95% CI,	AF is associated with an increased risk of CV outcomes in patients with CHF and either reduced EF or HFpEF

			group had AF at baseline)		(≥5.5 mEq/l), and symptomatic hypotension		1.45–2.06) versus HR=1.29; 95% CI 1.14–1.46), respectively. The same was true for the risk of all-cause mortality. Bias: unable to analyse time to event because of lack of information when onset of AF occurred	
Solomon, 2022 (DELIVER)	⁵⁸	RCT	6263 patients with heart failure	Dapagliflozin vs. placebo in addition to	Inclusion: ≥40 years; stabilized HF ± type 2	Primary outcome: composite of worsening heart	Worsening heart failure occurred in	Among patients with heart failure

			(56.1% of patients in the Dapagliflozin arm and 57.3% in the placebo arm had a history of AF)	usual therapy	diabetes mellitus; LVEF>40%; evidence of structural heart disease; elevated natriuretic peptide level	failure or cardiovascular death, as assessed in a time-to-event analysis	368 patients (11.8%) in the dapagliflozin group and in 455 patients (14.5%) in the placebo group (HR=0.79; 95% CI, 0.69–0.91); cardiovascular death occurred in 231 patients (7.4%) and 261 patients (8.3%), respectively (HR=0.88; 95% CI, 0.74–1.05).	and a mildly reduced or preserved ejection fraction, dapagliflozin resulted in a lower risk of worsening heart failure events and cardiovascular deaths, and a lower symptom burden, with no excess of adverse events

							Total events and symptom burden were lower in the dapagliflozin group than in the placebo group (1.11; 95% CI, 1.03–1.21; $P=0.009$);). The incidence of adverse events was similar (5.8%) in the two groups. Bias: all the subgroups in the DELIVER trial were underpowered	

							d; <5% of the patients enrolled were black	
McMurray, 2014 (PARADIGM-HF)	⁵⁹	RCT	8442 patients (36.2% in the LCZ696 and 37.4% in the enalapril arm had AF at baseline)	LCZ696 vs. enalapril	Inclusion: class II, III, or IV heart failure and an ejection fraction of 40% or less to receive either LCZ696 (at a dose of 200 mg twice daily) or enalapril (at a dose of 10 mg twice daily), in addition to recommended therapy	Primary outcome: a composite of death from cardiovascular causes or hospitalization for heart failure Total of 711 patients (17.0%) receiving LCZ696 and 835 patients (19.8%) receiving enalapril died (death from any cause HR=0.84; 95% CI 0.76–0.93; <i>P</i> <0.001); of these patients, 558 (13.3%) and 693	Death from cardiovascular causes or hospitalization for heart failure occurred in 914 patients (21.8%) in the LCZ696 group and 1117 patients (26.5%) in the enalapril group (LCZ696 group HR=0.80; 95% CI, 0.73	LCZ696 was superior to enalapril in reducing the risks of death and of hospitalization for heart failure

						(16.5%), respectively, died from cardiovascular causes (HR=0.80; 95% CI 0.71–0.89; $P<0.001$)	-0.87; $P<0.001$ LCZ696 also reduced the risk of hospitalization for heart failure by 21% ($P<0.001$) and decreased the symptoms and physical limitations ($P=0.001$)	
Anker, 2021 (EMPERO R-Preserved)	⁶⁰	RCT	5988 (51.5% in the Empagliflozin arm and 50.6% in the	Empagliflozin (10 mg once daily) vs. placebo, in addition to usual therapy	Inclusion: NYHA class II–IV heart failure and left ventricular ejection fraction >40%	The primary outcome was a composite of cardiovascular death or hospitalization for	The total number of hospitalizations for heart failure was lower in the	Empagliflozin reduced the combined risk of cardiovascular death or

			placebo arm had AF)			heart failure	empagliflozin group than in the placebo group (407 with empagliflozin and 541 with placebo; HR=0.73; 95% CI 0.6–0.88; $P<0.001$)	hospitalization for heart failure in patients with heart failure and a preserved ejection fraction, regardless of the presence or absence of diabetes
Bhatt, 2021 (SOLOIST-WHF)	⁶¹	RCT	1222 (576 patients had AF)	Sotagliflozin vs. placebo	Inclusion: patients with type 2 diabetes mellitus who were recently hospitalized for worsening heart failure	Primary outcome: total number of deaths from cardiovascular causes and hospitalisations and urgent visits for heart failure (first and subsequent events)In a time-to-	Primary outcome events were lower in the sotagliflozin group than in the placebo group (51.0 vs. 76.3; HR=0.67; 95% CI	In patients with diabetes and recent worsening heart failure, sotagliflozin therapy, initiated before or shortly after discharge, resulted in a

						event analysis of the original primary end point of the trial (the first occurrence of either death from cardiovascular causes or hospitalization for HF), the results were consistent with those of the revised primary end point, with a HR for death from CV causes or hospitalization for heart failure=0.71, 95% CI, 0.56–0.89	0.5f.85; $P<0.001$). The rate of death from cardiovascular causes was 10.6 in the sotagliflozin group and 12.5 in the placebo group (HR=0.84; 95% CI 0.58–1.22); the rate of death from any cause was 13.5 in the sotagliflozin group and 16.3 in the placebo	fewer number of cardiovascular deaths, hospitalizations and urgent visits for heart failure

							group (HR=0.82; 95% CI 0.59– 1.14)	
Zannad, 2011 (EMPHASIS-HF)	⁶²	RCT	2737 patients at 278 centres in 29 countries (30% of patients in the eplerenone arm and 31.7% of patients in the placebo arm had AF)	Eplerenone (up to 50 mg daily) vs. placebo, in addition to recommended therapy	Inclusion: ≥55 years, NYHA II symptoms, LVEF ≤ 30% (or, if >30 to 35%, a QRS duration of >130 msec on ECG), and treatment with an ACEi/ARB/both and a beta-blocker at the recommended dose or maximal tolerated dose. Exclusion: acute MI; NYHA class III /IV; a serum	Primary outcome: a composite of death from cardiovascular causes or hospitalization for heart failure	The primary outcome occurred in 18.3% of patients in the eplerenone group vs. 25.9% in the placebo group (HR=0.63; 95% CI 0.54–0.74; <i>P</i> <0.001). Limitations: The early stopping of the trial may	Eplerenone, as compared with placebo, reduced both the risk of death and the risk of hospitalization among patients with systolic heart failure and mild symptoms

					K ⁺ >5.0 mmol/l; eGFR<30 mL/min/ 1.73 m ² ; need for a K ⁺ - sparing diuretic, any other significant coexisting condition		have resulted in overestimation of the magnitude of the treatment effect, but the results are consistent with those seen in Randomized Aldactone Evaluation Study.	
Obesity								
Abed, 2013	⁶³	RCT	150	Intervention: comprehensive risk factor management (75 patients). Comparator: control:	Inclusion: symptomatic paroxysmal or persistent AF (in sinus rhythm at enrolment), BMI >27, waist	AF burden score; symptom score	The intervention group showed a significantly greater reduction in	Weight reduction had a positive impact on cardiac structure, reduced AF events

				written and verbal nutrition and exercise advice was provided at enrolment (75 patients)	circumference >100 cm(men) or >90 cm(women) ; and age 21 to 75 years. Exclusion: recent participation (within 3 months) in a weight loss program, unstable INR, diabetes necessitating insulin, significant cardiac valvular disease, and inability to provide informed		AF symptom burden scores (11.8 and 2.6 points, $P<0.001$), symptom severity scores (8.4 and 1.7 points, $P<0.001$), number of episodes (2.5 and no change, $P=0.01$), and cumulative duration (692-minute decline and 419-minute increase,	observed on ambulatory rhythm recordings, and reduced AF symptom burden

					consent		<i>P</i> =0.002). Limitations: did not achieve desired sample size; not continuous monitoring so could miss asymptomatic AF; counsellors could not be blinded	
Pathak, 2015 (LEGACY)	⁵³	Prospective cohort study	355	Intervention: comprehensive risk factor management; weight loss was categorized as: Group 1	Inclusion: Patients with a BMI >27 kg/m ² Exclusion: permanent AF, history of MI or cardiac surgery in the previous	Total arrhythmia- free survival rates were 86.2% in Group 1 vs. 65.5% in Group 2 vs. 39.6% in Group 3 (<i>P</i> <0.001)	At final follow-up, 45.5% of Group 1; 22.2% of Group 2 and 13.4% of Group 3	Sustained weight-loss, particularly with avoidance of weight- fluctuation, is associated with a dose-

				(<3%), Group 2 (3–9%), and Group 3 (≥10%) Comparator: NA	12-months, significant valvopathy or ventricular dysfunction, active malignancy, autoimmune or systemic inflammatory diseases, severe renal/hepatic failure and <24-months follow-up		($P<0.001$) remained free from arrhythmia without antiarrhythmic drugs or ablation. Single centre study; not randomized so potential for selection bias and better control of confounders; monitoring done with Holter so not continuous and could miss	dependent reduction in AF burden and maintenance of sinus rhythm. This occurs in conjunction with favourable changes in cardio-metabolic risk factor profile, inflammatory state, and cardiac remodelling

							asymptomatic AF	
Pathak, 2014 (ARREST-AF)	⁵²	Prospective cohort study	281	Intervention: comprehensive risk factor management (RFM) (61 patients). Comparator: control given information on management of risk factors (88 patients)	Inclusion: BMI >27 kg/m ² and >1 risk factor (hypertension, glucose intolerance/DM, hyperlipidaemia, OSA, smoking, or alcohol excess) undergoing initial catheter ablation for symptomatic AF despite the use of antiarrhythmic medication. Exclusion: history of MI or cardiac surgery	On multivariate analysis, type of AF ($P<0.001$) and RFM (HR=4.8; 95% CI 2.04–11.4; $P<0.001$) were independent predictors of arrhythmia-free survival. Single-procedure drug-unassisted arrhythmia-free survival was greater in RFM patients compared with control subjects ($P<0.001$). Multiple-procedure arrhythmia-free survival was	AF frequency, duration, symptoms, and symptom severity decreased more in the risk RFM group compared with control group (all $P<0.001$). Limitations: single centre; Observational not randomized so potential	RFM was associated with improvement in the outcomes of AF ablation by reducing AF burden and severity in conjunction with favourable changes in cardiac remodelling in these study patients

					in the previous 12 months, previous AF ablation, active malignancy, autoimmune or systemic inflammatory disease, severe renal/hepatic failure and <12 months' follow-up after their procedure	markedly better in RFM patients compared with control subjects ($P<0.001$), with 16% and 42.4%, respectively, using antiarrhythmic drugs ($P=0.004$)	for selection bias and better control of confounders. Monitoring done with Holter so not continuous and could miss asymptomatic AF	
Middeldorp , 2018 (REVERSE-AF)	⁵⁴	Prospective cohort study	355	Intervention: comprehensive risk factor management. Weight loss was categorized as: Group 1 (<3%), Group	Inclusion: Patients with a BMI >27 kg/m ² . Exclusion: permanent AF, history of MI or cardiac surgery in the previous 12-months,	41% in Group 1 vs. 32% in Group 2 vs. 3% Group 3 progressed from paroxysmal to persistent. 26% from Group 1 vs. 49% in Group 2 vs. 88% in Group 3	Increased weight loss was significantly associated with greater AF freedom: 45 (39%) in Group 1 vs.	Study suggests that weight loss and management of risk factors may reverse the natural progression of AF disease,

				2 (3–9%), and Group 3 (≥10%) Comparator: NA (Subset of LEGACY)	significant valvopathy or ventricular dysfunction, active malignancy, autoimmune or systemic inflammatory diseases, severe renal/hepatic failure and <24-months follow-up	reverse from persistent to paroxysmal or no AF ($P<0.001$)	69 (67%) in Group 2, and 116 (86%) in Group 3 ($P\leq 0.001$). Limitations: single centre study; observational not randomized so potential for selection bias and better control of confounders; monitoring done with Holter so not continuous and could miss	resulting in those with persistent AF more frequently transiting to either PAF or no AF

							asymptomatic AF	
Donnellan, 2020	⁶⁴	Retrospective cohort study	239	Arrhythmia recurrence	Inclusion: morbid obesity (BMI ≥ 40 or 35 kg/m² with obesity-related complications) and symptomatic paroxysmal or persistent AF undergoing AF ablation. Exclusion: longstanding persistent or permanent AF; active malignancy or autoimmune disease; prior AF ablation;	During a mean follow-up of 29 months, arrhythmia recurrence was observed in 65% of the morbidly obese cohort compared to 27% of the control group ($P < 0.0001$). Recurrent arrhythmia was observed in one (4%) patient who accomplished all four goals, compared to 36% who achieved 3 of 4, 85% who modified 2 of 4, and 97% of those who modified zero	Risk-factor modification (RFM) was also associated with substantial reductions in the need for repeat ablation or direct-current cardioversion and arrhythmia-related hospitalization ($P < 0.0001$). Limitations: retrospective, observational	In morbidly obese individuals, the greater number of risk factors managed the greater reduction in AF recurrence

					severe renal or hepatic impairment; or fewer than 12 months of follow-up after AF ablation. Patients who underwent bariatric surgery	or one risk-factor	study; single centre; small numbers	
Donnellan, 2019	⁶⁵	Retrospective cohort study	239	Intervention: AF patients undergoing ablation who underwent bariatric surgery (BS). 51 patients. Comparator: morbidly obese patients enrolled in	Inclusion: patients undergoing BS. Exclusion: NA	During a mean follow-up of 36 months after ablation, 10/51 patients (20%) in the BS group had recurrent AF compared with 114/188 (61%) in the non-BS group ($P<0.0001$). In the BS group, 6 patients (12%)	On multivariable analyses, only BS (HR=0.38; 95% CI 0.17–0.88; $P=0.023$) was significantly associated with reduced AF recurrence.	Bariatric surgery is associated with a marked reduction in AF recurrence rates following ablation

				medical weight management who did not undergo BS 188 patients		underwent repeat ablation compared with 77 patients (41%) in the non-BS group, ($P<0.0001$)	Limitations: retrospective, observational study; single centre; data on death of 7/8 patients who died during follow-up not available; small numbers of patients in each type of BS	
Donnellan, 2019	⁶⁶	Retrospective cohort study	253	Intervention: bariatric surgery (either Roux-en-Y gastric bypass, sleeve	Inclusion: 51 morbidly obese patients ($\text{BMI} \geq 40 \text{ kg/m}^2$) who underwent AF ablation within 2 years	During a mean follow-up of 29 ± 13 months following ablation, recurrent arrhythmia occurred in 10/51	Retrospective study; only studied patients undergoing bariatric surgery within	Arrhythmia recurrence rates in morbidly obese patients who have undergone

				gastrectomy, or laparoscopic adjustable gastric banding) Comparator: NA	following BS were matched in a 2:1 manner with 102 nonobese patients and 102 morbidly obese patients without prior BS undergoing AF ablation based on age, sex, and timing of AF ablation. Exclusion: NA	(20%) patients in the BS group compared with 25/102 (24.5%) patients in the nonobese group and 56 (55%) patients in the non-BS morbidly obese group ($P<0.0001$)	24 months before AF ablation, a longer interval would introduce event modifiers; small number of morbidly obese patients who underwent ablation, unable to match groups	prior BS are similar to those of nonobese patients following AF ablation
Obstructive sleep apnoea								
Nalliah, 2022 (SLEEP-AF)	⁶⁷	RCT	24 patients with at least moderate OSA (AHI $\geq$ 15/hr)	CPAP – 12 patients vs. standard of care – 12 patients	Exclusions: previous ablation, LVEF <50%, greater than trivial valvular	CPAP group had faster conduction velocity (0.86 ± 0.16 m/s vs. 0.69 ± 0.12 m/s; $P=0.03$), significantly higher	Small study, of 120 meeting pre-specified inclusion and exclusion	CPAP therapy results in reversal of atrial remodelling in AF and

					regurgitation, pulmonary artery hypertension (>30 mm Hg), refractory to electrical cardioversion, central sleep apnea diagnosis, past or current treatment of OSA. Excessive daytime sleepiness scores (Epworth Sleepiness Score ≥ 18) or who were considered to be at risk	voltages (2.30 ± 0.57 mV vs. 1.94 ± 0.72 mV; $P < 0.05$), and lower proportion of complex points ($8.87 \pm 3.61\%$ vs. $11.93 \pm 4.94\%$; $P = 0.01$) compared with the control group	criteria, only 24 studied. No evaluation of the impact on rhythm	provides mechanistic evidence advocating for management of OSA in AF

					because of their vocation			
Qureshi, 2015	⁶⁸	Systematic review and meta-analysis of RCTs and observational studies	8 studies on OSA (1RCT) with 698 CPAP users and 549 non-CPAP users	AF in CPAP treated patients	Inclusion: controlled study; study subjects to include patients with diagnosed OSA; study to have evaluated effect of CPAP therapy on AF recurrence; patients with OSA and symptomatic AF referred for PVI); outcome reported clinically in terms of AF recurrence; study duration	Patients treated with CPAP had a 42% decreased risk of AF (RR=0.58; 95% CI 0.47–0.70; $P<0.001$)	Low heterogeneity ($I^2=30\%$)	Decreased risk associated with CPAP users

					of more than 6 months. Exclusion: no data provided for comparison amongst CPAP users and nonusers; no report of AF recurrence			
Shukla, 2015	⁶⁹	Systematic review and meta-analysis of RCTs and observational studies	7 studies (5 studies on patients undergoing ablation; 2 studies non PVI) with 1150 patients	CPAP users vs. nonusers after pulmonary vein isolation (PVI)	Inclusion: controlled study; patients with diagnosed OSA; study to evaluate the effect of CPAP therapy on AF recurrence; patients with OSA and symptomatic AF referred for	Primary endpoint: evaluation of AF recurrence in CPAP users and nonusers in patients with OSA. CPAP use was associated with a significant reduction in AF recurrence (RR: 0.58; 95% CI 0.51–0.67; $P=0.91$; $I^2 =$	The beneficial effect of CPAP was significant in both groups of patients. In subgroup analysis these data were confirmed in PVI studies	Decreased risk of AF recurrence was associated with CPAP users

					index ablation procedure (PVI); outcome reported clinically in terms of AF recurrence; study duration>6 months. Exclusion: no data provided for comparison amongst CPAP users and nonusers; and no report of AF recurrence	0%)	and in non PVI studies	
Kadhim, 2021	⁷⁰	Systematic review and meta-analysis of RCT and	33 studies (n=23 894 patients) met the inclusion	Descriptive study evaluating the frequency of sleep	Inclusion: reported on the proportion of patients with SDB in a	The prevalence of SDB using high-risk BQ ranges from 3–58%. The pooled prevalence	However, when using SDB tests, the prevalence is	Symptom questionnaires are of limited utility for the diagnosis of

		observational studies	criteria for qualitative synthesis and 13 studies (n=2660 patients) met the meta-analysis criteria	disordered breathing (SDB) in AF. Evaluated proactiveness of symptom questionnaire in determining SDB	population with AF; included a minimum of 100 adult (≥ 18 years of age) participants; reported on the method of SDB ascertainment	of SDB with the use of questionnaires (mostly Berlin Questionnaire) was 33% (95% CI 0.18–0.47; $P<0.001$)	78% (95% CI 70–86%; $P<0.001$) for $AHI \geq 15/h$. For moderate-to-severe SDB ($AHI \geq 15/h$), the pooled SDB prevalence was 40% (95% CI 32–48%; $P<0.001$) Limitations: high heterogeneity for SDB; limited number of studies; most studies	SDB in patients with AF

							included patients with AF undergoing an intervention introducing potential bias	
Li, 2014	⁷¹	Systematic review and meta-analysis of RCTs and observational studies	3743 patients with AF (5 observational studies)	Risk of AF recurrence after catheter ablation	Inclusion: >18 years; performance of catheter ablation of AF; patients assessed for the presence of OSA; comparison of AF recurrence after single catheter ablation in patients with	Patients with OSA had a 31% greater risk of AF recurrence after catheter ablation than did patients without OSA (RR=1.31; <i>P</i> =0.00), and this risk increased by 57% in patients with OSA not undergoing CPAP therapy (RR=1.57; <i>P</i> =0.00)	The efficacy of catheter ablation for AF was similar between patients without OSA and patients with OSA undergoing CPAP treatment. Limitations: Differences	Greater associated risk of recurrence in OSA patients not treated with CPAP

					and without OSA; follow-up interval of >6 months; and performance of CPAP treatment for patients with OSA		among the evaluation methods for OSA might have accounted for the heterogeneity in the meta-analysis	
Naruse, 2013	⁷²	Prospective cohort study	153 patients with AF ablation (116 with OSA; 82 with CPAP)	CPAP vs. non-CPAP users	Inclusion: consecutive AF ablation patients Exclusion: known OSA	Follow-up period of 18.8 ± 10.3 months, 51 (33%) patients experienced AF recurrences after ablation. Cox regression analysis: the left atrial volume (HR=1.11; 95% CI 1.01–1.23; <i>P</i> <0.05)	Concomitant OSA (HR=2.61; 95% CI 1.12–6.09; <i>P</i> <0.05), and usage of CPAP therapy (HR=0.41; 95% CI 0.22–0.76; <i>P</i> <.01) were	Patients with untreated OSA were associated with a higher recurrence rate of AF after ablation. Appropriate treatment with CPAP in patients with OSA was

							associated with AF recurrences. Limitations: Single centre; observational	associated with a lower recurrence of AF
Fein, 2013	⁷³	Prospective cohort study	426 patients with AF ablation 62 OSA 32 patients "CPAP users" 30 patients "CPAP nonusers."	Selected groups	"CPAP users" had used CPAP daily for a minimum of 3 months prior to the index PVI and continued to use CPAP throughout the follow-up duration (12 months)	CPAP therapy resulted in higher AF-free survival rate (71.9% vs. 36.7%; $P=0.01$) and AF-free survival off antiarrhythmic drugs or repeat ablation following PVI (65.6% vs. 33.3%; $P=0.02$) AF recurrence rate of CPAP-treated patients was similar to a group of patients without	AF recurrence following PVI in CPAP nonuser patients was significantly higher (HR=2.4; $P<0.02$) and similar to that of OSA patients managed medically without ablation	CPAP was associated with lower AF recurrences

						OSA (HR=0.7; $P=0.46$)	(HR=2.1; $P=0.68$). Limitations: selected groups; single centre; observational	
Kadhim, 2019	⁷⁴	Prospective cohort study	442 patients with AF undergoing sleep studies	Epworth sleepiness scale versus Polysomnography	Inclusion: AF patients being considered for rhythm control. Exclusion: patients without AF or incomplete PSG	Daytime sleepiness was low (median ESS = 8/24) and the ESS poorly predicted SDB, regardless of the degree of SDB tested (area under the curve: 0.48–0.56). Excessive daytime sleepiness ($ESS \geq 11$) was present in 11.9% of the SDB population and had a negative predictive value of	SDB was present in two-thirds of the population with 33% having moderate-to-severe SDB. Single centre; observational	Excessive sleepiness is not useful in determining the presence of sleep apnea in AF patients

						43.1% and a positive predictive value of 67.5% to detect moderate-to-severe SDB		
Traaen, 2020	⁷⁵	Prospective cohort study	579 patients with paroxysmal AF	Descriptive study of occurrence of sleep apnea in AF. Evaluated the diagnostic yield of: Epworth sleepiness scale (ESS); Berlin questionnaire (BQ); STOP-Bang, these were compared to polysomnogr	Inclusion: consecutive patients with paroxysmal AF undergoing polysomnography	The mean ESS score was 7.2 ± 4 . Excessive daytime sleepiness ≥ 11 was present in 19% of all participants and did not differ by SA severity ($P=0.99$). There was no association between SA severity and daytime sleepiness ($R^2=0.003$; $P=0.37$)	When using the BQ alone to diagnose SA, 38% of patients with $AHI \geq 5$ were classified as “high risk” for OSA, compared to 23% in the group with $AHI \geq 15$. A BQ score ≥ 2 performed with a sensitivity of 46% and	Neither the ESS nor the BQ and STOP-Bang discriminated well between patients with or without SA

				aphy			56% and specificity of 75% and 70% for AHI$\geq$5 and $\geq$15. When using the STOP-Bang questionnaire to screen for OSA, 60.7% of patients with AHI $\geq$ 5 had a positive score $\geq$ 3, compared to 35.1% in the group with AHI $\geq$ 15. Limitations: single centre observational	

							study	
Holmqvist, 2015 (ORBIT AF)	⁷⁶	Prospective registry	10 132 patients with AF, 1841 had OSA	CPAP treatment on CV outcomes. The prevalence of clinician defined OSA (ie, diagnosis or history of OSA) at baseline and CPAP treatment (“currently undergoing CPAP therapy”) was captured. In ORBIT-AF, follow-up data	Inclusion: ≥18 years of age, electrocardiographic evidence of AF, providing informed consent Exclusion: life expectancy of <6 months or AF secondary to reversible conditions	Of 10 132 patients enrolled in ORBIT-AF, 18% (n=1841) had OSA at baseline no significant difference in risk was observed between patients on CPAP treatment compared with those not on CPAP for most of the outcomes	Patients with OSA on CPAP treatment were less likely to progress to more permanent forms of AF compared with patients without CPAP (HR=0.66; 95% CI 0.46–0.94; <i>P</i> =0.02)	Compared with those without, AF patients with OSA have worse symptoms and higher risks of hospitalization, but similar mortality, major adverse cardiovascular outcome, and AF progression rates

				collection occurs at 6-month intervals for a minimum of 2 years				
Pathak, 2014 (ARREST-AF)	52	Prospective cohort study	281 consecutive patients undergoing AF ablation; 165 had both BMI ≥ 27 kg/m ² and ≥ 1 risk factor. The final cohort included 149 patients: 61 RFM patients and	Risk factor management (RFM) according to American Heart Association/American College of Cardiology guidelines. After AF ablation, all 61 patients had RFM and 88 were controls	BMI ≥ 27 kg/m ² and ≥ 1 cardiac risk factor (HTN, glucose intolerance/DM, hyperlipidaemia, OSA, smoking, or alcohol excess) undergoing initial catheter ablation for symptomatic AF despite the use of antiarrhythmic medication	RFM resulted in greater reductions in weight ($P=0.002$) and blood pressure ($P=0.006$), and better glycaemic control ($P=0.001$) and lipid profiles ($P=0.01$). At follow-up, AF frequency, duration, symptoms, and symptom severity decreased more in the RFM group compared with the control group (all	RFM improved single and multiple procedure outcomes ($P<0.001$). Reduction in weight, BP, glycaemic control and lipid profile. Decrease in AF frequency, duration, symptoms	RFM was associated with improved outcomes of AF ablation by reducing AF burden and severity in conjunction with favourable changes in cardiac remodelling in these study patients

			88 control subjects		Exclusion: history of MI or cardiac surgery in the previous 12 months; previous AF ablation; active malignancy; autoimmune or systemic inflammatory disease; severe renal or hepatic failure; and <12 months FU after their procedure	$P<0.001$). On multivariate analysis, type of AF ($P<0.001$) and RFM (HR=4.8; 95% CI 2.04–11.4; $P<0.001$) were independent predictors of arrhythmia-free survival	and severity. Single centre, observational	
Middeldorp, 2018 (REVERSE-AF)	⁵⁴	Retrospective cohort study	355	Weight and risk factor management including recommendation of ≤ 3 drinks of	Inclusion: AF patients with BMI ≥ 27 kg/m ²	Progression of AF disease	Increased weight loss was significantly associated with greater AF freedom:	Obesity is associated with progression of the AF disease. Increased weight loss

				alcohol per week. Weight loss was categorized as: Group 1 (<3%), Group 2 (3–9%), and Group 3 (≥10%). Change in AF type was determined by clinical review and 7-day Holter yearly (Subset of LEGACY)			39% in Group vs. 67% in Group 2 vs. 86% in Group 3 ($P \leq 0.001$)	including less alcohol was associated with greater AF freedom
Physical activity								
Oesterle, 2022	⁷⁷	Systematic review and meta-	1155	N/A	Inclusion: supervised exercise training	The AF burden was reduced only in studies that	Exercise training reduced AF	Supervised exercise training is safe,

		analysis of RCTs and observational studies			in participants with AF	included continuous ambulatory monitoring (SMD=-0.49; 95% CI -0.96 to -0.01) but not when all studies were included (SMD=-0.12; 95% CI -0.61 to 0.38)	recurrence (RR=0.77; 95% CI 0.60–0.99), improved QoL in 5 of the 10 components of the Short Form 36 survey, and improved CRF (standardized mean difference [SMD]=0.56; 95% CI 0.27–0.85). Limitations: inherent to meta-analysis	reduces AF recurrence, and improves quality of life and CRF in participants with AF
Hegbom,	⁷⁸	RCT	30	Randomised	Inclusion:	Physical	Four of the	A significant

2007				to exercise training (n=15) or a 2-month control period (n=15)	permanent AF with less than 75 years old. Exclusion: patients who already participated in exercise training more than twice weekly, who had medical contraindications to exercise or those unable to participate for any logistic reason	functioning (82 ± 14 pre-ETP, 86 ± 10 post-ETP), bodily pain (82 ± 17 pre-ETP, 92 ± 14 post-ETP), vitality (61 ± 14 pre-ETP, 68 ± 13 post-ETP) and role-emotional (85 ± 28 pre-ETP, 94 ± 20 post-ETP). The SF-36 physical component summary scale also increased from 49 ± 6 pre-ETP to 52 ± 6 post-ETP ($P<0.05$)	eight SF-36 scales improved significantly ($P<0.05$) following training. Exercise capacity improved by $41 \pm 20\%$ and perceived exertion during testing by 1.4 points after training ($P<0.05$); Limitations: reduced N patients; single centre	improvement in HR QoL, symptoms during exercise testing and exercise capacity after a short-term exercise training program in patients with permanent AF
Osbak, 2011	⁷⁹	RCT	49	25 patients received the	Inclusion: permanent AF.	Resting pulse decreased in the	Improved exercise	Twelve weeks of exercise

				active treatment and 24 were controls	Exclusion: severe CHF (NYHA III–IV), severe refractory hypertension, previous heart valve surgery, moderate-to-severe pulmonary disease, low life expectancy, and lack of ability to exercise	active patients (94.8 ± 22.4 to 86.3 ± 22.5 b.p.m.; $P=0.05$) but remained unchanged in the controls. Cardiac output was unchanged from baseline to end-of-study period	capacity and 6MWT were observed in the active patients ($P<0.001$), with a significant difference between the active patients and the controls ($P=0.002$). The MLHF-Q score improved in the active group (21.1 ± 18.0 vs. 15.4 ± 17.5 ; $P=0.03$). Active	training increased exercise capacity and 6MWT and decreased resting pulse rate significantly in patients with AF. Overall quality of life increased significantly as measured by the cardiology-related MLHF-Q

							patients showed progress in: physical functioning ($P=0.02$), general health perceptions ($P=0.001$), and vitality ($P=0.02$). Limitations: single centre; may be self-bias toward reporting positive effect of the intervention	
Malmo, 2016	⁸⁰	RCT	51	26 patients in the intervention	Inclusion: symptomatic, ECG-	AIT improved VO2peak, left atrial and ventricular	Mean time in AF increased from 10.4%	Aerobic interval training for 12 weeks reduces

				group (aerobic interval training [AIT] for 12 weeks) vs 25 controls	documented, non-permanent AF who were referred for first AF ablation or to the outpatient clinic. Exclusion: performing endurance training at high intensity >2 times a week or at moderate intensity for >3 times a week, previous open-heart surgery, LVEF <45%, significant cardiac valve disease, implanted	ejection fraction, quality-of-life measures of general health and vitality, and lipid values compared with the control group. There was a trend toward fewer cardioversions and hospital admissions after AIT	to 14.6% in the control group and was reduced from 8.1% to 4.8% in the exercise group ($P=0.001$). AF symptom frequency ($P=0.006$) and AF symptom severity ($P=0.009$) were reduced after AIT. Limitations: single-centre; small number of participants;	the time in AF in patients with non-permanent AF. This is followed by a significant improvement in AF symptoms O₂peak, left atrial and ventricular function, lipid levels, and QoL

					cardiac pacemaker, CAD without complete revascularization, or inability to accomplish the exercise program		patients are healthy with few comorbidities;	
Elliott, 2022 (ACTIVE- AF)	⁸¹	RCT	120	Intervention: 60 patients combined home and supervised exercise over 6 months vs. controls: 60 patients	Inclusion: symptomatic paroxysmal or persistent AF patients undergoing first time ablation. Exclusions: absence of AF lasting >30 seconds in the past 3 months; previous AF ablation within	At 6 months, AF symptom severity was lower in the exercise group compared with the control group (mean difference - 2.3; 95% CI -4.3 to -0.2; <i>P</i> =0.033). This difference persisted at 12 months (-2.3; 95% CI -4.5 to -0.1; <i>P</i> =0.041). Total	By 12 months, freedom from AF was achieved in 40% of patients in the exercise group and 20% of patients in the control group (HR=0.50;	A tailored aerobic-based exercise and physical activity program among patients with symptomatic, non-permanent AF leads to a reduction in self-reported

					12 months; permanent AF, MI or cardiac surgery within the past 12 months; autoimmune or systemic inflammatory disease; LVEF<45%, moderate to severe valvular disease; and inability to participate in a structured exercise program due to a musculoskeletal condition	symptom burden was lower at 6 months in the exercise group but not at 12 months	95% CI 0.33–0.78). Limitations: single centre; intervention but ablations performed at 3 hospitals; almost 2/3 of patients screened were excluded; arrhythmia recurrence was by ambulatory monitoring and not continuous monitoring	AF symptom severity and improved maintenance of sinus rhythm without antiarrhythmic medication or AF ablation

Alcohol intake								
Voskoboini k, 2020	⁸²	RCT	140	Intervention: abstinence Comparator: standard of care	Inclusion:18–85 years old; symptomatic paroxysmal AF (≥2 episodes in the 6 months before the start of the trial) or symptomatic persistent AF with a rhythm control strategy; regular alcohol consumption (>10 standard drinks or approximately 120 g of pure alcohol/week). Exclusion: alcohol dependence or	AF burden over 6 months of follow- up was significantly lower in the abstinence group than in the control group (median percentage of time in AF, 0.5% (IQR 0.0–3.0) vs. 1.2% (IQR 0.0–10.3); <i>P</i> =0.01)	Abstinence group had a longer period before recurrence of AF than the control group (HR=0.55; 95% CI 0.36– 0.84; <i>P</i> =0.005). Significant number of screened patients refused to participate in the study. Study duration shortened as patients	Abstinence, if achievable, is associated with improved maintenance of sinus rhythm

					abuse; severe left ventricular systolic dysfunction (LVEF<35%); clinically significant noncardiac illness; psychiatric disorder		refused to maintain abstinence. Variable rhythm monitoring	
Pathak, 2015 (LEGACY)	⁵³	Prospective cohort study	355	Intervention: comprehensive risk factor management. Weight loss was categorized as: Group 1 (<3%), Group 2 (3–9%), and Group 3 (≥10%).	Inclusion: patients with a BMI>27 kg/m ² Exclusion: permanent AF, history of MI or cardiac surgery in the previous 12-months, significant valvopathy or ventricular	Total arrhythmia-free survival rates were 86.2% in Group 1 vs. 65.5% in Group 2 vs. 39.6% in Group 3 (<i>P</i> <0.001)	At final follow-up, 45.5% of Group 1 vs. 22.2% of Group 2 vs. 13.4% of Group 3 (<i>P</i> <0.001) remained free from arrhythmia	Sustained weight-loss, particularly with avoidance of weight-fluctuation, was associated with a dose-dependent reduction in AF burden and maintenance of

				Comparator: NA	dysfunction, active malignancy, autoimmune/sys temic inflammatory diseases, severe renal/hepatic failure and <24-months follow-up		without antiarrhythmi c drugs or ablation. Limitations: Single centre study; not randomized; Monitoring was not continuous and could miss asymptomatic AF	sinus rhythm. This occurs in conjunction with favourable changes in cardio- metabolic risk factor profile, inflammatory state and cardiac remodelling
Middeldorp , 2018 (REVERSE -AF)	⁵⁴	Retrospectiv e cohort study	355	Weight and risk factor management including recommenda tion of <=3 drinks of alcohol per	Inclusion: AF patients with BMI≥27 kg/m ²	Progression of AF disease	Increased weight loss was significantly associated with greater AF freedom: 39% in Group	Obesity is associated with progression of the AF disease. Increased weight loss including less

				week. Weight loss was categorized as: Group 1 (<3%), Group 2 (3–9%), and Group 3 (≥10%). Change in AF type was determined by clinical review and 7-day Holter yearly (Subset of LEGACY)			vs. 67% in Group 2 vs. 86% in Group 3 ($P \leq 0.001$)	alcohol was associated with greater AF freedom

Additional Evidence Table S4 — Comorbidity and risk factor management

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Hypertension								
Pokushalov, 2012	⁸³	RCT	27	Renal denervation	27 patients with symptomatic, drug-refractory paroxysmal AF or persistent AF and drug resistant hypertension (SBP >160mmHg despite triple drug therapy); 14 PVI only; 13 PVI+renal artery denervation	Intervention group –significant reduction in SBP (from 181±7 to 156±5, <i>P</i> <0.001) and DBP (from 97±6 to 87±4; <i>P</i> <0.001). Arrhythmia free:69% intervention group vs. 29% control group (<i>P</i> =0.033)	Small sample size, AF recurrence detection by ECG and 24-h Holter only	Renal artery denervation reduces SBP and DBP in patients with drug-resistant hypertension and reduces AF recurrences when combined with PVI

Steinberg, 2020 (ERADICATE-AF)	⁸⁴	RCT	302	Renal denervation vs. medical management	302 symptomatic paroxysmal AF with sub optimally controlled hypertension: 148 PVI only; 154 PVI +RDN	Mean SBP: PVI only (151mmHg to 147mmHg); PVI +RDN (150mmHg to 135mmHg). Risk of recurrence favoured PVI +RDN (HR=0.57; 95% CI 0.38–0.85; $P=0.006$)	PAF patients only. PVI using cryoballoon only; RDN using 3.5 mm tip Thermocool with CARTO mapping	In PAF patients with severe hypertension, renal denervation was superior to medical management for rhythm control after AF ablation
Galzerano, 2012	⁸⁵	RCT	132	Telmisartan vs. carvedilol	132 mild hypertension outpatients (SBP/DBP 140–159/90–99mmHg) in SR who had ≥ 1 ECG-documented AF episode in the previous 6 months; 70 telmisartan; 62	Mean BP not significantly different between groups: telmisartan 154/97 to 123/75 mmHg; ($P<0.001$); carvedilol 153/94 to 125/78 mmHg ($P<0.001$). Fewer AF episodes with 14.3% telmisartan vs. 37.1%	Study enrolled patients with mostly low burden AF. Possible underestimation of asymptomatic AF recurrence. No other anti-HTNs	Telmisartan was better at preventing AF recurrence in mild hypertension compared to carvedilol

					carvedilol	carvedilol ($P<0.003$)	allowed for the duration of the study and any patient failing to respond to treatment (SBP/DBP >140/90mmHg) was withdrawn from the study	
Du, 2013	⁸⁶	RCT	149	Telmisartan versus nifedipine	149 hypertensive patients with paroxysmal AF: 75 nifedipine; 74 telmisartan	Mean BP at follow up: nifedipine $125.6 \pm 4.4/75.3 \pm 4.1$ mmHg; telmisartan $127.6 \pm 4.8/76.7 \pm 4.6$ mmHg. AF recurrence: (58.7% nifedipine vs. 55.4%;	Target BP <130/80mmHg; study PAF only; absence of placebo-control group could not clarify relationship between	Compared to nifedipine, treatment of hypertension with telmisartan was not associated with a difference in maintaining sinus rhythm

						telmisartan; <i>P</i> =0.74). telmisartan treatment is an independent negative predictor of developing persistent AF (HR=0.30; 95% CI 0.09–0.97, <i>P</i> =0.045)	incidence of AF relapse and BP control	however, significantly reduced progression to persistent AF
Giannopoulos, 2014	⁸⁷	RCT	291	Moxonidine versus placebo	291 hypertension patients with symptomatic paroxysmal AF (147 moxonidine; 144 placebo)	Lower AF recurrence risk with moxonidine (HR=0.35; 95% CI 0.22–0.55, <i>P</i> <0.001)	Paroxysmal AF only. CA technique- PVI using RFA with CARTO	Treatment with moxonidine is associated with less AF recurrences after ablation treatment for drug-refractory AF in patients with hypertension. The observed

								effect does not appear to depend on the antihypertensive action of this agent
Santoro, 2015	⁸⁸	Prospective cohort study	531	Pulmonary vein ablation	531 consecutive patients undergoing ablation: 160 uncontrolled hypertension, 192 controlled hypertension, 179 no hypertension	Mean BP: uncontrolled hypertension 156.6± 7.4/ 94.9 ± 4.4mmHg; controlled hypertension 127.7±8.0/ 76.5 ± 7.5mmHg. Recurrence risk: uncontrolled hypertension (HR=1.52; 95% CI 1.01–2.29; P=0.045); controlled hypertension	Uncontrolled BP defined as BP >140/90mmHg and >3 drugs. Pulmonary vein ablation antrum and posterior wall isolation with non-pulmonary vein triggers identified during isoproterenol	Uncontrolled hypertension is associated with AF recurrence after AF ablation

						(HR=1.05; 95% CI 0.70–1.58; $P=0.82$)	infusion. No information about hypertension management at long-term follow-up	
Berruezo, 2007	⁸⁹	Prospective cohort study	148	Ablation outcome: time to first event	Patients undergoing CPVA for symptomatic drug refractory AF: 90 paroxysmal AF (60.8%); 35 persistent AF (23.6%); 23 permanent AF (15.5%)	Hypertension is one of the independent pre-procedural predictors of AF recurrence (HR=2.8; 95% CI 1.5–5.4; $P=0.002$)	Referral centre, possible inclusion bias into the study	Hypertension is associated with greater recurrence of AF after catheter ablation
Themistoclakis, 2008	⁹⁰	Prospective cohort study	1298	Ablation outcome: time to first event	Patients underwent ICE guided PV antrum	Hypertension independent predictor of: EAT (OR=1.32;	Late recurrences 1 year after ablation are	Hypertension independently predicted EAT and LAT

					isolation 699 paroxysmal AF (54%); 230 persistent AF (18%); 369 permanent AF (28%)	95% CI 1.01–1.74; $P=0.046$); LAT (OR=1.65; 95% CI 1.14–2.39; $P=0.009$)	rare	
Letsas, 2009	⁹¹	Prospective cohort study	72	Ablation outcome: time to first event	72 patients with symptomatic, drug-refractory AF, who underwent PVI: 46 paroxysmal AF (64%); 26 persistent AF (36%)	Hypertension is one of the independent pre- ablative predictors of AF recurrence (HR=3.12; 95% CI=1.26–7.71; $P=0.013$)	Small sample size, possible underestimation of recurrence	Hypertension and BMI associated with AF recurrence
Khaykin, 2011	⁹²	Prospective cohort study	385	Ablation outcome: time to first event	385 consecutive patients who had 530 PVAI: 243	History of hypertension is an independent risk factor for recurrence	ACEi/ARB use following ablation had higher recurrence in	Hypertension independently associated with recurrence of AF

					paroxysmal AF (63%); 102 persistent AF (26%); 40 permanent AF (10%)	(HR=1.43; 95% CI 1.06–1.93; <i>P</i> =0.02)	paroxysmal AF (HR=1.67; 95% CI 1.08–2.54; <i>P</i> =0.02), may be a marker for co-morbidities	
Kamioka, 2017	⁹³	Prospective cohort study	101	Ablation outcome: time to first event	101 symptomatic paroxysmal AF patients who underwent successful PVI; 46 no hypertension; 36 controlled hypertension; 19 uncontrolled hypertension	Mean BP: uncontrolled hypertension 145 ± 14/ 77 ± 12mmHg; controlled hypertension 120 ± 18/71 ± 8mmHg. Recurrence risk: uncontrolled hypertension (HR=2.35; 95% CI 1.07–5.16; <i>P</i> =0.033)	Uncontrolled BP defined as BP >140/90mmHg. Circumferential PVI for first procedure, substrate modification, such as linear ablation or complex fractionated atrial	Uncontrolled hypertension is associated with AF recurrence after AF ablation

							electrograms ablation for second procedure	
Shah, 2006	⁹⁴	Retrospective cohort study	264	Ablation outcome: time to first event	Patients who became AF-free on no AAD for at least 1 year after the ablation: 230 paroxysmal AF (87%) and 34 persistent AF (13%)	Late recurrence patients are more likely to have hypertension (HR=2.18; 95% CI 1.89–5.39; <i>P</i> =0.009)	Identified only patients with symptomatic recurrences of AF	Hypertension is associated with greater very late recurrence of AF after catheter ablation
Zylla, 2020	⁹⁵	Prospective registry	626	Ablation outcome – time to first event	626 patients undergoing AF ablation: 386 with hypertension; 240 without hypertension	No significant difference in recurrence (<i>P</i> =0.39) In persistent AF, hypertension was a predictor for: rehospitalization	CA technique: PVI with RFA (80%). More extensive use of 3-D-mapping and ablation of	Hypertension was not associated with difference in ablation outcome, however, in persistent AF

						(OR= 1.97; 95% CI 1.02–3.81; <i>P</i> =0.045); presence of dyspnea (OR=2.15; 95% CI 1.03–4.51; <i>P</i> =0.042); angina (OR=10.32; 95% CI 1.33–79.97; <i>P</i> =0.025)	additional targets in the HTN-group	was associated with greater risk of rehospitalization
Trines, 2019	⁹⁶	Prospective registry	3069	Ablation outcome	217 patients had no risk factors; all others had at least 1 risk factor	217 patients were without risk factors. Risk factor patients were older (58.4 vs. 54.1 years), more often female (32% vs. 19.8%) and had more often persistent AF (27.2% vs. 23.5%). Hypertension and	Hypertension association with recurrences of AF/AT/flutter postblanking period: univariate analysis= HR 1.163 (1.011, 1.337) <i>P</i> .035	Patients with ≥1 risk factor had a 30% higher risk for arrhythmia recurrence after ablation

						body mass index were univariate predictors of recurrence	& multivariate analysis= HR 1.129 (0.973, 1.310) <i>P</i>=0.1 11. Bias: observational ; non standardised ablation approach; non standardised follow up; ascertainmen t of risk factor variable; the group with apparently no risk factors needs further details	

Heart failure								
Martin, 2021	⁹⁷	Systematic review and meta-analysis of RCTs	41 RCTs (231 reports), 23 492 participants across all comparisons	Beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor neprilysin inhibitors, and mineralocorticoid receptor antagonists vs. placebo control	RCT with a parallel group design, enrolling adults with HFpEF, defined by LVEF >40%	ACEi: on cardiovascular mortality (RR=0.93, 95% CI 0.61–1.42), all-cause mortality (RR=1.04, 95% CI 0.75–1.45), & heart failure hospitalisation (RR= 0.86, 95% CI 0.64–1.15); ARB: cardiovascular mortality (RR=1.02; 95% 0.90–1.14), all-cause mortality (RR=1.01, 95% CI 0.92–1.11), heart failure hospitalisation (RR=0.92; 95% CI	MRA treatment reduced heart failure hospitalization (RR 0.82; 95% CI 0.69 to 0.98) however no effect on all-cause and cardiovascular mortality and quality of life measures was observed. The risk of bias was frequently unclear and only five	There is evidence that MRA treatment in HFpEF reduces heart failure hospitalization but has little or no effect on cardiovascular mortality and quality of life. BB treatment may reduce the risk of cardiovascular mortality

						0.83–1.02), quality of life (MD 0.41; 95% CI -0.86–1.67) ARNIs: cardiovascular mortality (RR=0.96; 95% CI 0.79–1.15), all-cause mortality (RR= 0.97; 95% CI 0.84–1.11)	studies had a low risk of bias in all domains	
Cleland, 2018	⁹⁸	Systematic review and meta-analysis of RCTs	11 RCTs 14 262 patients in sinus rhythm	Most of the trials had limits for LVEF as inclusion or exclusion criteria, however these were typically defined preceding	11 trials, stratified by baseline LVEF and heart rhythm	Primary outcomes were all-cause mortality and cardiovascular death over 1.3 years median follow-up, with an intention-to-treat analysis	Beta-blockers reduced all-cause and cardiovascular mortality compared to placebo in sinus rhythm, an effect that was consistent across LVEF	Beta-blockers improve LVEF and prognosis for patients with heart failure in sinus rhythm with a reduced LVEF. The data are most robust for LVEF <40%, but similar benefit was

				randomization ($<25\%$, $\leq 35\%$ $\leq 40\%$, and $<45\%$)			strata, except for those in the small subgroup with LVEF $\geq$ 50% (HR=1.79; 95% CI 0.78– 4.10; $P=0.17$). For LVEF 40– 49%, death occurred in 21/292 (7.2%)] randomized to beta- blockers compared to 35/283 (12.4%) with placebo; (HR=0.59;	observed in the subgroup of patients with LVEF 40–49%

							95% CI 0.34–1.03)	
Parkash, 2017 (SMAC-AF)	⁵¹	RCT	173	Aggressive BP control vs. standard of care	173 patients with AF and BP >130/80mmHg : 88 aggressive BP (target <120/80mmHg); 85 standard BP (target <140/90mmHg)	No difference in recurrence risk after ablation in aggressive group compared with standard group (HR=0.94; 95% CI 0.65–1.38; <i>P</i> =0.76). Mean SBP at follow-up: aggressive BP:123.2 ± 13.2mmHg; standard BP: 135.4 ± 15.7mmHg. More hypotension requiring drug adjustment in aggressive BP (26% vs. 0%)	Strategy of aggressive BP treatment for a median duration of 3.5 month, possibly too short to see effect. Both groups had a significant reduction in BP from baseline, dilution of positive effect of aggressive strategy. High burden, longer duration AF,	Treated in isolation, aggressive management of modest hypertension was not associated with improvement in maintaining sinus rhythm

							possible irreversibility of atrial myopathy	
Solomon, 2016 (TOPCAT)	⁹⁹	RCT	3444	Spironolactone vs. placebo	TOPCAT enrolled patients with HFpEF (LVEF ≥45%), who had either had a hospitalization within the past year for which heart failure was a major component or had an elevated natriuretic peptide level (BNP >150 or NT-proBNP	Ejection fraction modified the spironolactone treatment effect, particularly in the patients enrolled in the Americas, for the primary outcome ($P=$ 0.046) and for heart failure hospitalization ($P=$ 0.039), with stronger estimated benefits of spironolactone at the lower end of the ejection fraction spectrum	The incidence of the primary endpoint and cardiovascular death was highest in patients at the lower end of the ejection fraction spectrum. The primary outcome was a composite of cardiovascular death,	In patients with HFpEF enrolled in TOPCAT, patient improvements and outcomes varied substantially by LVEF. The potential efficacy of spironolactone was greatest at the lower end of the LVEF spectrum

					>360) Inclusion: ≥50 years with at least one sign and one symptom of heart failure, controlled blood pressure, and a serum potassium level of <5.0 mmol/L	with respect to the primary endpoint (LVEF <50%: HR=0.72; 95% CI 0.50–1.05; LVEF ≥60%: HR=0.97; 95% CI 0.76–1.23) and heart failure hospitalization (LVEF <50%: HR=0.76; 95% CI 0.46–1.27; LVEF ≥60%: HR=0.98, 95% CI 0.74–1.30)	aborted cardiac arrest, or hospitalization for heart failure	
Lund, 2018 (CHARM)	100	RCT	7598	Candesartan vs. placebo	Patients enrolled in the CHARM Programme HF across the spectrum of EF), characteristics, outcomes and	Over a mean follow-up of 2.9 years, the incidence rates for the primary outcome of cardiovascular death or HF hospitalization	With EF as a continuous spline variable, candesartan significantly reduced the primary outcome until	Candesartan improved outcomes in HFmrEF to a similar degree as in HFrEF

					treatment effect of candesartan according to EF was assessed	were 15.9, 8.5 and 8.9 per 100 patient-years in HFrEF, HFmrEF and HFpEF. In adjusted analyses, the rates of the primary outcome declined with increasing EF up to 50%. For recurrent HF hospitalization, the incidence rate ratios were 0.68 in HFrEF (95% CI 0.58–0.80; $P<0.001$), 0.48 in HFmrEF (95% CI 0.33–0.70; $P<0.001$), and 0.78 in HFpEF (95% CI 0.59–1.03; $P=0.08$)	EF well over 50% and recurrent HF hospitalizations until EF well over 60%. The primary outcome: cardiovascular death or HF hospitalization	

Swedberg, 2012 (EMPHASIS-HF)	¹⁰¹	RCT	1794	Eplerenone	Inclusion: NYHA class II and with LVEF≤35%	New onset AFF was significantly reduced by eplerenone: 25 of 911 (2.7%) vs. 40 of 883 (4.5%) in the placebo group (HR=0.58; 95% CI: 0.35–0.96; <i>P</i> =0.034). The reduction in the primary endpoint with eplerenone was similar among patients with and without AF at baseline (HR=0.60; 95% CI 0.46–0.79 vs. HR=0.70; 95% CI 0.57–0.85; <i>P</i> =0.41)	MRA was associated with a reduction in incident AF and recurrent AF	MRA was associated with a reduction in incident AF and recurrent AF
Type 2 diabetes								
Pathak,	⁵³	Prospective	355	Intervention:	Inclusion:	At final follow-up,	Sustained	This association

2015 (LEGACY)		cohort study		comprehensive risk factor management Weight loss was categorized as: Group 1 (<3%), Group 2 (3–9%), and Group 3 (≥10%) Comparator: NA	Patients with a BMI >27 kg/m ² . Exclusion: permanent AF, history of MI or cardiac surgery in the previous 12-months, significant valvopathy or ventricular dysfunction, active malignancy, autoimmune or systemic inflammatory diseases, severe renal/hepatic failure and	45.5% of Group-1 vs. 22.2% of Group-2 and 13.4% of Group-3 ($P<0.001$) remained free from arrhythmia without antiarrhythmic drugs or ablation. Total arrhythmia-free survival rates were 86.2% in Group-1 vs. 65.5% in Group-2 vs. 39.6% in Group-3 ($P<0.001$)	weight-loss, particularly with avoidance of weight-fluctuation, was associated with a dose-dependent reduction in AF burden and maintenance of sinus rhythm. Along with favourable changes in cardio-metabolic risk factor profile, inflammatory	between weight fluctuation and AF recurrence risk remained significant despite adjusting for baseline weight, and showed that weight fluctuation was associated with an increased risk of hypertension and diabetes, as well as an increase in other cardiometabolic traits

					<24-months follow-up		state, and cardiac remodelling. Bias: single centre study; potential for selection bias and confounders; Monitoring done with Holter so not continuous and could miss asymptomatic AF	
Pathak, 2014 (ARREST-AF)	⁵²	Prospective cohort study	281	Intervention: comprehensive risk factor management (61 patients). Comparator:	Inclusion: BMI >27 kg/m ² and >1 risk factor (hypertension, glucose intolerance/DM	AF frequency, duration, symptoms, and symptom severity decreased more in the risk factor	Single centre study; observational not randomized so potential	RFM was associated with an improvement in the outcomes of AF ablation by reducing AF

				control given information on management of risk factors (88 patients)	, hyperlipidaemia, OSA, smoking, or alcohol excess) undergoing initial catheter ablation for symptomatic AF despite the use of antiarrhythmic medication. Exclusion: history of MI or cardiac surgery in the previous 12 months, previous AF ablation, active malignancy,	management (RFM) group compared with the control group ($P<0.001$). Single-procedure drug-unassisted arrhythmia-free survival was greater in RFM patients compared with control subjects ($P<0.001$). Multiple-procedure arrhythmia-free survival was markedly better in RFM patients compared with control subjects ($P<0.001$), with 16% and 42.4%,	for selection bias and better control of confounders. Monitoring done with Holter so not continuous and could miss asymptomatic AF	burden and severity in conjunction with favourable changes in cardiac remodelling in these study patients

					autoimmune or systemic inflammatory disease, severe renal/hepatic failure and <12 months' follow-up after their procedure	using antiarrhythmic drugs ($P=0.004$). On multivariate analysis, type of AF ($P<0.001$) and RFM (HR=4.8; 95% CI 2.04 -11.4; $P<0.001$) were independent predictors of arrhythmia-free survival		
Middeldorp, 2018 (REVERSE-AF)	⁵⁴	Prospective cohort study	355	Intervention: comprehensive risk factor management; weight loss was categorized as: Group 1 (<3%); Group 2 (3–9%) and	Inclusion: patients with a BMI >27 kg/m ² . Exclusion: permanent AF, history of MI or cardiac surgery in the previous 12-	41% from Group 1 vs. 32% from Group 2 vs. 3% from Group 3, progressed from paroxysmal to persistent. 26% in Group 1 vs. 49% in Group 2 vs. 88% in Group 3 reversed	Single centre study, observational not randomized so potential for selection bias and better control of	Weight loss and management of risk factors may be associated with reversibility of the natural progression of AF disease, resulting in those with persistent

				Group 3 (≥10%). Comparator: NA (Subset of LEGACY)	months, significant valvulopathy or ventricular dysfunction, active malignancy, autoimmune or systemic inflammatory diseases, severe renal/hepatic failure and <24-months follow-up	from persistent to paroxysmal or no AF ($P<0.001$). Increased weight loss was significantly associated with greater AF freedom: 45 (39%) in Group 1 vs. 69 (67%) in Group 2 vs. 116 (86%) in Group 3 ($P\leq 0.001$)	confounders. Monitoring done with Holter so not continuous and could miss asymptomatic AF	AF more frequently transiting to either PAF or no AF
Donnellan, 2019	¹⁰²	Retrospective cohort study	298 patients with DM undergoing ablation	Diabetic control: 10% reduction in HbA1C	Inclusions: diabetic patients with AF undergoing ablation. Exclusion: patients with	AF recurrence;	68.75% of patients with HbA1c >9% at the time of ablation developed recurrent AF,	HbA1C <7% and a 10% reduction in HbA1C was associated with better maintenance of

					<12 months of follow-up and those who had only 1 HbA1C measurement at the institution		compared with 32.4% of those with HbA1c <7% ($P<0.0001$). Only 2% of patients with improvements in HbA1C of 10% or more experienced AF recurrence ($P<0.001$). Bias: Single centre; retrospective; observational	sinus rhythm
Obesity								
Di Benedetto, 2021 (EPIC-Norfolk)	¹⁰³	Prospective cohort study	21 499	Incident AF	Inclusion: 39–79 years without prior history of CVD,	1195 (12.3%) men and 960 (8.1%) women with incident AF during	Observational so could not eliminate reverse	The combined impact of 3 health behaviours,

					cancer, stroke, MI, and prevalent AF. Exclusion: Participants with incomplete data on smoking, alcohol, or BMI	average follow-up of 17.1 years. AF incidence rate and hazard ratio increased with decreasing number of health score points (including non-smoking, no or moderate alcohol consumption and being not overweight or obese)	causality; potential measurement errors in exposures; AF based on ICD discharge codes which improved 90% accurate	although modest and potentially achievable across all age groups, sex, education levels and social classes in a free-living population, was associated with an estimated 2.8-fold reduction in risk for AF
Chan, 2021	104	Retrospective cohort study	10 237	Incident AF	Inclusion: Aged >20 years with T2DM Exclusion: Using antidiabetic drugs,	Compared with those with a baseline BMI of <23.0 kg/m ² , AF risk significantly increased in patients with baseline BMI of	Retrospective observational so not be able to demonstrate causality; missing important	A baseline BMI of ≥ 27.5 kg/m ² and a ≥5% BW loss following SGLT2i treatment are independently associated with

					prevalent AF before T2DM diagnosis ≥27.5 kg/m² (HR=1.86; 95% CI 1.03–3.37) for BMI of 27.5–92.9 kg/m² (HR=2.23; 95% CI 1.24–3.98] for BMI of ≥30.0 g/m²; <i>P</i>=0.015). Compared with those without BW loss following SGLT2i treatment, AF risk significantly decreased at a BW loss of ≥ 5.0% (HR=0.39; 0.22–0.68; <i>P</i>=0.001) Use of diuretics, old age, high-dose SGLT2i, higher estimated	parameters including physical activity, smoking, dietary behaviour; potentially missing confounders so unable to adjust for these; did not account for changes in medical status; comprised of Asian population only	a significantly lower risk of new-onset AF in patients with T2DM treated with SGLT2i. The benefit of ≥ 5% BW loss following SGLT2i treatment in reduction of AF risk persisted across most T2DM subgroups, irrespective of underlying comorbidities, baseline BMI, or DM status

						glomerular filtration rate, and baseline BMI were independent factors associated with a BW loss of 5.0% following SGLT2i initiation		
Obstructive sleep apnoea								
Caples, 2019	105	RCT	1757 screened; 34 had sleep studies; 25 randomized	Intervention: CPAP. Control: usual care	Inclusions: age ≥ 18 years; AF recently underwent DCCV to sinus rhythm within the last 30 days. Exclusions: moderate to severe pulmonary disease; moderate to	AF recurred in 25% of patients in the CPAP and control groups, at 129.0 ± 166.5 versus 109.3 ± 73.2 days respectively, $P=0.98$	Very small study; significant attrition from screened to included in study	By assessing the impact of treatment of OSA on recurrence of AF post-DCCV, did not detect a difference between those treated with CPAP versus usual care

					severe valvular disease; congestive heart failure (LVEF<40%); previous diagnosis of sleep apnea or CPAP treatment; neuromuscular disease or residual neurologic impairment following stroke; previous pulmonary vein ablation procedure; pacemaker; uncontrolled			

					hypertension; sleepiness, defined as an ESS score N10			
Traaen, 2021	¹⁰⁶	RCT	109 patients with AF and OSA	5-month study evaluating the impact of CPAP vs. no CPAP on AF burden by ILR	Inclusion: 18– 75 years old; documented paroxysmal AF referred for their first/second AF catheter ablation or recruited from AF outpatient clinics; moderate to severe OSA were eligible. Exclusion: LVED<45%, BMI>40 kg/m2,	Mean time in AF	CPAP vs. no CPAP, for mean time in AF decreased from 5.6% to 4.1% vs. from 5.0% to 4.3%, adjusted between- group difference was 20.63 (95% CI 22.55–1.30) percentage points	CPAP therapy did not have an effect associated with AF burden

					or severe excessive daytime sleepiness		($P=0.52$). Serious adverse events, 13% versus two 4%. Unclear power assumptions, small series	
Hunt, 2022	107	RCT	83 patients with AF ablation, paroxysmal AF and an apnea-hypopnea index (AHI) ≥ 15 events/h	37 CPAP patients vs. 46 patients standard care. AF recurrence after PVI was defined as any episode of AF lasting >2 minutes after a 3-month	Inclusion: 18–75 years with symptomatic, documented paroxysmal AF with moderate to severe OSA, defined by an apnea-hypopnea index (AHI) ≥ 15 events/hour on	AF burden after ablation was reduced in both groups, with no between-group difference ($P=0.69$)	Small study; Study does not state prior ablation as an exclusion. In the Phase 1 of the study, they included patients referred for first or second AF	No effect associated with CPAP on AF

				blanking period	the respiratory polygraph test. Exclusion: previously diagnosed OSA, unstable coronary disease, transitory ischemic attack, stroke, structural heart disease, left ventricular systolic dysfunction (LVEF <45%), severe obesity (BMI >40 kg/m ²), severe excessive daytime		ablation; Marked attrition from screened to recruitment. Non standardised ablation technique. CPAP group had 20% greater use of RF. CPAP compliance only 3.9 ± 1.5 hours	

					sleepiness (Epworth sleepiness scale score ≥ 15), or present use of amiodarone			
Kanagala, 2003	108	Prospective cohort study	39 patients: 12 with CPAP 27 no CPAP Vs control group 79 patients Without OSA	AF recurrence	Inclusion: AF/atrial flutter referred for DC cardioversion	The recurrence rate of AF at 12 months in the 27 untreated or inappropriately treated subjects with OSA was 82%, versus 42% in the treated OSA group ($P=0.01$) and 53% in the control group without known OSA ($P=0.009$)	Patients with untreated OSA have a higher recurrence of AF after cardioversion than patients without a polysomnographic diagnosis of sleep apnea. Limitations: small population	Reduced recurrence of AF in OSA associated with patients treated with CPAP

Abumuamar, 2019	¹⁰⁹	Prospective cohort study	100 patients with AF 85 with OSA	24-h ECG Holter was performed at baseline and at 3 and 6 months after CPAP treatment	Inclusion: paroxysmal AF, patients with permanent AF	In patients with paroxysmal AF (n=29), atrial and ventricular ectopy counts/24 h significantly decreased at 3 months compared to baseline (median (IQR) 351(2049)-57 (182); $P=0.002$; 68 (105)-16 (133); $P=0.01$ respectively)	Limitations: small patient population; focus on ectopic beats	Reduced atrial ectopic beats in patients with paroxysmal AF associated with CPAP
Physical activity								
Abed, 2013	⁶³	RCT	150	Intervention: 75 patients, weight management s. Control: 75 patients	Inclusion: symptomatic paroxysmal or persistent AF (in sinus rhythm at enrolment);	Intervention groups had lower AF symptom burden scores (11.8 vs. 2.6 points; $P<0.001$) and fewer AF	Weight reduction with intensive risk factor management resulted in a reduction in	Weight reduction with intensive risk factor management resulted in a reduction in AF symptom burden

				general lifestyle advice	BMI>27; waist circumference >100 cm (men) or >90 cm (women); age 21–75 years. Exclusion: recent participation in a weight loss program; unstable INR; diabetes necessitating insulin; significant cardiac valvular disease	episodes (2.5 vs. no change; $P=0.01$) and total duration (692-min decline vs. 419-min increase; $P=0.002$)	AF symptom burden and severity and in beneficial cardiac remodelling; single centre	and severity and in beneficial cardiac remodelling
Alonso, 2015 (Look AHEAD)	¹¹⁰	RCT	5067	Intervention: 539 patients to intensive lifestyle	Intensive lifestyle intervention, including	Rates of AF were comparable in the intensive lifestyle Intervention (ILI)	In an overweight and obese population	No difference in incident AF (6.1 vs. 6.7 cases/1000

				intervention, including weight loss, increased physical activity Control: 2528 patients to DM support and education usual care group	weight loss, increased physical activity vs. DM support and education usual care group	and diabetes support and education groups (6.1 and 6.7 cases per 1000 person-years, respectively, $P=0.42$). The intervention did not affect AF incidence (HR=0.99; 95% CI 0.77–1.28). Similarly, neither weight loss nor improvement in physical fitness during the first year of the intervention was significantly associated with AF incidence for weight loss	with Type 2 diabetes, an intensive lifestyle intervention that induced modest weight loss did not reduce the risk of developing AF. AF was not a primary trial endpoint, and the specific analyses of AF were not pre-specified at the beginning of the trial	person-year, intensive lifestyle vs. control; $P=0.42$)

						(HR=0.70; 95% CI 0.41–1.18) and for physical fitness improvement (HR=0.88; 95% CI 0.55–1.43)		
Rienstra, 2018 (RACE 3)	⁵⁰	RCT	245 in patients with early persistent AF and HF	Intervention: 19 patients randomized to risk factor-driven upstream therapy with MRAs, statins, ACE inhibitors or ARBs, and cardiac rehabilitation (physical activity, dietary restrictions,	Patients with early persistent AF (AF history <5 years, total persistent AF duration >7 days and <6 months, and ≤1 previous ECV during the last 2 years; neither electrical nor chemical cardioversion ≥ 2 years ago	At 1 year, sinus rhythm was present in 75% patients in the intervention vs. 63% in the conventional group (OR=1.77; lower limit of 95% confidence interval 1.02; P=0.042)	Targeted therapy of underlying conditions improves sinus rhythm maintenance in patients with persistent AF. Absence of data on physical activity in the conventional group	Sinus rhythm at 1 y after cardioversion by 7-d Holter monitoring occurred in 75% of the upstream and 63% of the conventional group (OR=1.77; P=0.021)

				counselling). Control:126 patients to conventional therapy	are allowed) and mild to moderate early heart failure (total HF history<1 year, LVEF≥45% and NYHA class II-III with previously documented HF-related NT- proBNP elevation, or evidence of structural heart disease, or previous admission for HF, or evidence of diastolic dysfunction; or			

					LVEF<45% and NYHA class I–III)			
Pathak, 2015 (CARDIO-FIT)	¹¹¹	Prospective cohort study	308	95 in the low cardiorespiratory fitness (CRF), 134 adequate CRF, 79 high CRF	Inclusion: BMI >27 kg/m ² and undergoing an exercise stress test at baseline. Exclusion: permanent AF; history of myocardial infarction or cardiac surgery in the previous 12 months; active malignancy; autoimmune or systemic inflammatory diseases;	Arrhythmia-free survival with and without rhythm control strategies was greatest in patients with high CRF compared to adequate or low CRF ($P<0.001$). AF burden and symptom severity decreased significantly in the group with CRF gain ≥ 2 METs as compared to <2 METs group ($P<0.001$). Arrhythmia-free survival with and	CRF predicts arrhythmia recurrence in obese individuals with symptomatic AF; improvement in CRF augments the beneficial effects of weight loss; observational study Using BMI as a surrogate measure of body fatness	CRF predicts arrhythmia recurrence in obese individuals with symptomatic AF; improvement in CRF augments the beneficial effects of weight loss

					severe renal/hepatic failure; LVEF <40%; pacemaker in situ; and <24-months of follow-up, AF patients who could not perform exercise stress test because of neuromuscular or musculoskeletal problems	without rhythm control strategies was greatest in those with METs gain ≥ 2 compared to those with METs gain <2 in CRF ($P<0.001$)		
Pathak, 2014 (ARREST AF)	⁵²	Prospective cohort study	281 consecutive patients	Intervention: 69 patients who accepted a risk factor management	Inclusion: all patients. Exclusion: history of myocardial	Greater reductions in weight ($P<0.002$) and blood pressure ($P<0.006$), better	Aggressive RFM improved the long-term success of	Aggressive risk factor management improved the long-term

				(RFM). Controls: 96 patients who didn't accepted it	infarction or cardiac surgery in the previous 12 months; previous AF ablation; active malignancy; autoimmune or systemic inflammatory disease; severe renal or hepatic failure	glycemic control ($P<0.001$), lipid profiles ($P<0.01$). AF frequency, duration, symptoms, and symptom severity decreased more in the RFM group compared with the control group ($P<0.001$)	AF ablation; single centre	success of AF ablation
Pathak, 2015 (LEGACY)	⁵³	Prospective cohort study	355 consecutive patients	N/A	Inclusion: all patients BMI>27. Exclusion: permanent AF, history of myocardial infarction or cardiac	Weight loss was categorized as group 1 ($\geq 10\%$), group 2 (3–9%), and group 3 ($<3\%$). Weight loss and weight fluctuation were independent	Long-term sustained weight loss is associated with significant reduction of AF burden and	Long-term sustained weight loss is associated with significant reduction of AF burden and maintenance of sinus rhythm

					surgery in the previous 12 months, significant valvopathy or ventricular dysfunction, active malignancy, autoimmune or systemic inflammatory diseases, severe renal/hepatic failure, and <24 months of follow-up	predictors of outcomes ($P<0.001$). Weight loss $\geq 10\%$ resulted in a 6-fold (95% CI 3.4–10.3; $P<0.001$) greater probability of arrhythmia-free survival compared with the other 2 groups. Weight fluctuation $>5\%$ partially offset this benefit, with a 2-fold (95% CI 1.0–4.3; $P=0.02$) increased risk of arrhythmia recurrence	maintenance of sinus rhythm. Single centre prospective study	
Middeldorp, 2018 (REVERSE-AF)	⁵⁴	Prospective cohort study	355	N/A	Same than LEGACY	Increased weight loss was significantly associated with	Obesity is associated with progression	Obesity is associated with progression of the AF disease.

						greater AF freedom: 39% in Group 1 vs. 67% in Group 2 and 86% in Group 3 ($P \leq 0.001$)	of the AF disease. Weight-loss management and RFM reverses the type and natural progression of AF; single centre prospective study	Weight-loss management and RFM reverses the type and natural progression of AF
Alcohol intake								
Takahashi, 2021	¹¹²	Prospective cohort study	1720	All patients were requested to limit alcohol consumption to <20 g/week after the ablation	AF patients undergoing ablation	AF/atrial tachycardia (AT) recurrence-free survival without antiarrhythmic drugs beyond a 3-month blanking period. Percent reduction of	Alcohol reduction of $\geq 1\%$ from baseline to 1-year follow-up (median reduction 75%; IQR 45–100%)	Reducing alcohol consumption to a median of 70 g per week was associated with improved maintenance of sinus rhythm

						alcohol consumption from baseline to 1-year post ablation, if freed from AF/AT for 1-year, or to AF/AT recurrence was assessed	was associated with lower risk of AF/AT recurrence (HR=0.63; 95% CI 0.51–0.77; <i>P</i> <0.001), compared with alcohol reduction of <1% (median, 0% IQR –20–0%)	after catheter ablation
Pathak, 2014 (ARREST-AF)	⁵²	Prospective cohort study	281	Intervention: comprehensive risk factor management (61 patients). Comparator: control given information	Inclusion: BMI>27 kg/m ² and >1 risk factor (hypertension, glucose intolerance/DM ,	AF frequency, duration, symptoms, and symptom severity decreased more in the RFM group compared with the control group	Single centre study, observational not randomized so potential for selection bias and	RFM, including reducing alcohol consumption to ≤3 standard drinks was associated with improvement in the outcomes of

				on management of risk factors (88 patients)	hyperlipidaemia, OSA, smoking, or alcohol excess) undergoing initial catheter ablation for symptomatic AF despite the use of antiarrhythmic medication. Exclusion: history of MI or cardiac surgery in the previous 12 months, previous AF ablation, active malignancy, autoimmune or	($P<0.001$). Single-procedure drug-unassisted arrhythmia-free survival was greater in RFM patients compared with control subjects ($P<0.001$). Multiple-procedure arrhythmia-free survival was markedly better in RFM patients compared with control subjects ($P<0.001$), with 16% and 42.4%, respectively, using antiarrhythmic drugs ($P=0.004$). On multivariate	better control of confounders. Monitoring was done with Holter so not continuous and could miss asymptomatic AF	AF ablation by reducing AF burden and severity in conjunction with favourable changes in cardiac remodelling in these study patients

					systemic inflammatory disease, severe renal/hepatic failure and <12 months' follow-up after their procedure	analysis, type of AF ($P<0.001$) and RFM (HR=4.8; 95% CI 2.04–11.4; $P<0.001$) were independent predictors of arrhythmia-free survival		

Evidence Table 6 for Recommendation Table 6 (Sec. 6) — Recommendations to assess and manage thromboembolic risk in atrial fibrillation

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Healey, 2024	¹¹³	RCT	4012 Patients with subclinical AF lasting 6 minutes to 24 hours	Apixaban at a dose of 5 mg twice daily (2.5 mg twice daily when indicated) versus aspirin at a dose of 81 mg daily.	Inclusion: subclinical AF detected by an implanted pacemaker, defibrillator, or cardiac monitor, with at least one episode lasting 6	Primary efficacy outcome: stroke or systemic embolism; the primary safety outcome: major bleeding	After a mean follow-up of 3.5 ± 1.8 years, stroke or systemic embolism occurred in 55 patients in the apixaban	Among patients with subclinical AF, apixaban resulted in a lower risk of stroke or systemic embolism than aspirin but a

				minutes or longer but no episodes lasting longer than 24 hours and a CHA2DS2-VASc score of 3 or higher; minimum age 55 years and patients who were 75 years of age or older or who had a history of stroke without other risk factors. Exclusion: history of clinical AF, an ongoing indication for oral anticoagulation, a history of uncorrected major bleeding in the previous 6 months, or a creatinine clearance of less than 25 ml per minute. The concurrent use of open-label aspirin was allowed but discouraged,	group and in 86 patients in the aspirin group (HR, 0.63; 95% confidence interval [CI], 0.45 to 0.88; P=0.007). In the on-treatment population, the rate of major bleeding was 1.71% per patient-year in the apixaban group and 0.94% per patient-year in the aspirin group (HR, 1.80; 95% CI, 1.26 to 2.57; P=0.001). Fatal bleeding occurred in 5	higher risk of major bleeding.

					whereas the use of open-label dual-antiplatelet therapy was prohibited.		patients in the apixaban group and 8 patients in the aspirin group.	
Kirchhof, 2023	¹¹⁴	RCT	2536 patients with Device-detected atrial high-rate episodes (AHREs)	Edoxaban versus placebo	Inclusion: patients 65 years of age or older who had AHREs lasting for at least 6 minutes and who had at least one additional risk factor for stroke.	Primary efficacy outcome: a composite of cardiovascular death, stroke, or systemic embolism. Safety outcome: composite of death from any cause or major bleeding.	Primary efficacy outcome event occurred in 83 patients in the edoxaban group and in 101 patients in the placebo group, HR 0.81; 95% confidence interval [CI], 0.60 to 1.08; P=0.15). The incidence of stroke was approximately 1% per patient-year in both groups. A safety	The trial was terminated early on the basis of safety concerns. Among patients with AHREs detected by implantable devices, anticoagulation with edoxaban did not significantly reduce the incidence of a composite of cardiovascular death, stroke, or systemic embolism as compared with placebo, but it

						outcome event occurred in 149 patients in the edoxaban group and in 114 patients in the placebo group, HR 1.31; 95% CI, 1.02 to 1.67; P=0.03). ECG-diagnosed AF developed in 462 of 2536 patients (18.2% total, 8.7% per patient-year). Limitations: The trial was terminated early on the basis of safety concerns; incidence of	led to a higher incidence of a composite of death or major bleeding.

							stroke was low in both groups.	
Hart, 2007	115	Systematic review and meta-analysis of RCTs	29 RCTs: 28 044 participants (mean age, 71 years; mean follow-up, 1.5 years)	Adjusted-dose warfarin vs. control	Inclusion: All published randomized trials with a mean follow-up of ≥3 months that tested antithrombotic agents in patients who have nonvalvular AF	Compared with the control, adjusted-dose warfarin (6 trials, 2900 participants) and antiplatelet agents (8 trials, 4876 participants) reduced stroke by 64% (95% CI, 49–74%) and 22% (95% CI, 6–35%), respectively	Adjusted-dose warfarin was substantially more efficacious than antiplatelet therapy (risk reduction= 39%; 95% CI, 22–52%) (12 trials, 12 963 participants). Other randomized comparisons were inconclusive. Absolute increases in	Adjusted-dose warfarin and antiplatelet agents reduce stroke by approximately 60% and by approximately 20%, respectively, in patients who have AF.

							major extracranial hemorrhage were small (< or =0.3% per year). Bias: methodological features and quality varied substantially and often were incompletely reported	
Ruff, 2014	¹¹⁶	Systematic review and meta-analysis of RCTs	4 RCTs: 71 683 participants included in the RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE	New oral anticoagulant vs. warfarin	Inclusion: phase 3, randomised trials of patients with AF who were randomised to receive new oral anticoagulants or	The main outcomes were stroke and systemic embolic events, ischaemic stroke,	New oral anticoagulants significantly reduced stroke or systemic embolic	New oral anticoagulants had a favourable risk-benefit profile, with significant reductions in

			AF-TIMI 48 trials (42 411 participants received a new oral anticoagulant and 29 272 participants received warfarin)		warfarin, and trials in which both efficacy and safety outcomes were reported	haemorrhagic stroke, all-cause mortality, myocardial infarction, major bleeding, intracranial haemorrhage, and gastrointestinal bleeding	events by 19% compared with warfarin (RR 0.81, 95% CI 0.73–0.91; $P<0.0001$), mainly driven by a reduction in haemorrhagic stroke (0.49, 0.38–0.64; $P<0.0001$). New oral anticoagulant s also significantly reduced all-cause mortality (0.90, 0.85–	stroke, intracranial haemorrhage, and mortality, and with similar major bleeding as for warfarin, but increased gastrointestinal bleeding

							0.95; $P=0.0003$) and intracranial haemorrhage (0.48, 0.39–0.59; $P<0.0001$), but increased gastrointestinal bleeding (1.25, 1.01–1.55; $P=0.04$)	
Van Walraven, 2002	¹¹⁷	Systematic review and meta-analysis of RCTs	4052 patients with AF	Intervention: oral anticoagulant or aspirin with or without low-dose oral anticoagulant	Inclusion: adult patients with nonvalvular AF. Exclusion criteria: clinical indications for, or contraindications to, oral anticoagulation or aspirin. With the	Ischaemic and haemorrhagic stroke, other cardiovascular events, all-cause death and major bleeding events	Patients receiving oral anticoagulant were significantly less likely to experience any stroke: hazard ratio [HR], 0.55;	Oral anticoagulant given to patients with AF is associated with a lower risk of stroke and cardiovascular events when

					exception of the AFASAK studies patients were also excluded if they had a recent acute coronary event or cardiac revascularization; thyrotoxicosis except for AFASAK 1		95% confidence interval [CI], 0.43–0.71), ischemic stroke (HR, 0.48; 95% CI, 0.37–0.63), or cardiovascular events (HR, 0.71; 95% CI, 0.59–0.85) but were more likely to experience major bleeding HR, 1.71; 95% CI, 1.21–2.41	compared to patients receiving aspirin
Lozier, 2019	¹¹⁸	Systematic review	8479 participants with HCM and AF	Intervention: use of anticoagulation	Inclusion: human observational studies; aged ≥ 18	Thromboembolic events, major bleeding, and	Use of AC was associated	Anticoagulation is warranted in all patients with

		and meta-analysis of RCT and observational studies	(14 observational studies)	control: no anticoagulation (AC)	years old; and studies that reported data on thromboembolic events in receiving AC versus no AC or DOACs versus VKAs. Exclusion: aetiology of AF was related to valvular causes	all-cause mortality	with a lower pooled incidence rate of total thromboembolic events at 9.5% compared to 22.1% with no AC. DOAC vs. VKA: lower pooled incidence rate of thromboembolic events at 4.7% compared to 8.7% with VKAs; lower pooled incidence	concomitant HCM and AF. DOACs are associated with a lower incidence of thromboembolic events, major bleeding, and all-cause mortality when compared to VKAs

							rate of major bleeding and all-cause mortality at 3.8% versus 6.8% and 4.1% versus 16.1% respectively	
Guttmann , 2014	¹¹⁹	Systematic review and meta-analysis of RCT and observational studies	7381 patients (33 studies)	Prevalence and incidence of AF and thromboembolism in patients with HCM	Studies investigating AF and stroke in HCM as primary or secondary endpoint	Prevalence and incidence of AF and thromboembolism in patients with HCM	Overall AF prevalence of 22.45% (95% CI 20.13–24.77%),. Overall prevalence of thromboembolism in HCM patients with AF was 27.09% (95% CI 20.94–33.25%).	AF is common in HCM and associated with high thromboembolic risk. Most data suggest that AF patients should be anticoagulated

							Overall AF incidence was 3.08% per 100 patients per year (95% CI 2.63% to 3.54%, I ² =86.5%, <i>P</i> <0.001) and incidence of thromboembolism in HCM patients with AF was 3.75% per 100 patients per year (95% CI 2.88% to 4.61%)	
Hart, 2000	¹²⁰	Prospective	460 participants with intermittent	Intervention: aspirin	Inclusion: adults with documented	Stroke events	The annualized	Intermittent AF was associated

		cohort study	AF versus 1552 with sustained AF treated with aspirin		sustained or recurrent AF Exclusion: mitral stenosis; prosthetic cardiac valves; those under age 60 years without associated cardiovascular disease; heavy alcohol users Participants in the SPAF III trial assigned aspirin plus fixed, low-dose warfarin were included if the INR did not exceed 1.4 during follow-up		rate of ischemic stroke was similar for those with intermittent (3.2%) and sustained AF (3.3%). Of those with intermittent AF predicted to be high risk (24%), the observed stroke rate was 7.8% per year (95% confidence interval 4.5 to 14)	with stroke rates comparable with sustained AF. Stroke risk can be stratified using the same clinical features irrespective of the temporal pattern of AF
Vilches, 2022	¹²¹	Retrospective	1191 transthyretin	Embolic events	ATTR-CM patients from four	Embolic events and major	Incidence rate (per 100	OAC reduced the risk of

		cohort study	amyloid cardiomyopathy (ATTR-CM) patients	according to the type of oral anticoagulation (OAC) and the performance of the CHA2DS2-VASc score in this setting	international referral amyloid centres with at least two evaluations	bleeding events; cardiovascular mortality	patient-years) was 0 among patients in sinus rhythm with OAC, 1.3 in sinus rhythm without OAC, 1.7 in AF with OAC, and 4.8 in AF without OAC. CHA2DS2-VASc only predicted embolic events in patients with AF with a score ≥ 4 . There was no difference in the incidence	systemic embolism in patients with AF and ATTR-CM. Embolic rates did not differ with VKAs and DOACs. The CHA2DS2-VASc score should not be used to assess thromboembolic risk in this population

							rate of embolism between patients with AF treated VKAs and those treated with DOACs; <i>P</i> = 0.66	
Lee, 2017	¹²²	Retrospective cohort study	306 patients with apical hypertrophic cardiomyopathy (ApHCM); 77 with AF	To assess the prognostic implications of AF and to identify the predictors of AF occurrence in an ApHCM cohort	Patients with ApHCM Exclusion: follow-up duration was less than a year; initial ECG at the time of diagnostic TTE was not available	Occurrence of AF; cardiovascular death and stroke	AF prevalence= 25.2%, annual incidence= 4.6%/ year. Among 70 AF patients indicated with anticoagulation, 53 patients (76%) received warfarin.	In patients with ApHCM, AF was common and was associated with a substantial risk for strokes and mortality suggesting that AF should be carefully managed in ApHCM

							In AF patients versus those without there was a higher incidence of all-cause death (HR 6.58; 95% CI 1.65–26.16, <i>P</i> =0.007) and strokes (HR 5.13; 95% CI 1.85 to 14.18, <i>P</i> =0.002)	
Guttmann, 2015	¹²³	Retrospective, cohort study	4821 HCM patients	To determine predictors of thromboembolism (TE), the performance of the CHA2DS2-VASc score, and outcome with VKAs	Inclusion: Adult patients (≥16 years of age) with HCM Exclusion: Patients with known inherited metabolic diseases or syndromic causes of HCM; Patients	Primary endpoint: cerebrovascular accident (CVA), transient ischaemic attack (TIA), or systemic peripheral	3.6% reached the primary endpoint. A total of 27.5% of patients had a CHA2DS2-VASc score of 0, of whom	VKA treatment is associated with a reduction in TE events in patients with AF and HCM. The CHA2DS2-VASc score

					with a history of AF that had experienced TE prior to first evaluation at the centre	embolus within 10 years	9.8% developed TE during follow-up. VKA treatment was associated with a 54.8% (95% CI 31–97%, $P=0.037$) relative risk reduction in HCM patients with AF	does not appear to correlate well with the clinical outcome in patients with HCM and should not be used to assess TE risk in this population
Hsu, 2020	¹²⁴	Retrospective cohort study	18 724 HCM patients	To determine the incidence of stroke and its risk factors in HCM patients with AF	Subjects identified as having HCM from the Taiwan National Health Insurance Research Database. 3970 subjects	Incidence of AF and stroke	The AF incidence in HCM patients was 5.83 per 1000 person-years, and the overall incidence of	Taiwanese patients with concomitant HCM and AF have a high stroke risk regardless of the CHA2DS2-

					were excluded owing to use of an antiplatelet or an anticoagulation		AF-associated stroke was 24.14 per 1000 person-years. The incidence of transient ischemic attack (TIA)/ischemic stroke varied from 20.41 to 60.55 per 1000 person-years, without proportionality to CHA2DS2-VASc score increase	VASc score
Chao,	¹²⁵	Retrospective	31 039 patients	Delta	31 039 patients	Ischaemic	CHA2DS2-	Stroke risk in

2018		ective cohort study	with AF who did not have risk factors of the CHA2DS2-VASc score (except for age and sex)	CHA2DS2-VASc score versus CHA2DS2-VASc score for the prediction of ischemic stroke	with AF Exclusion: patients receiving antiplatelet agents or oral anticoagulants; comorbidities of the CHA2DS2-VASc score other than age and sex	stroke	VASc score was 1.29, which increased to 2.31 during follow-up, with a mean Delta CHA2DS2-VASc score of 1.02. The Delta CHA2DS2-VASc performed better than either the baseline or follow-up CHA2DS2-VASc scores, C-index: (0.742; 95%	AF is a dynamic process due to increasing age and incident comorbidities. A baseline CHA2DS2-VASc score alone is a poor predictor of ischaemic stroke

							CI: 0.732 to 0.750) versus (0.578; 95% CI: 0.569 to 0.587) and follow-up (0.729; 95% CI: 0.721 to 0.737) scores	
Fauchier, 2020	¹²⁶	Retrospective cohort study	608 108 patients with AF who did not have risk factors of the CHA2DS2-VASc score (except for age and sex)	Change in stroke risk profile between baseline and follow-up CHA2DS2-VASc score versus baseline CHA2DS2-VASc score for prediction of ischemic	All patients over 18 years hospitalized with a diagnosis of AF. Exclusion: risk factors of the CHA2DS2-VASc score other than age and sex	Ischemic stroke	The AUC was lower for the baseline CHA2DS2-VASc score (0.612, 95% CI 0.608–0.615) compared to that of follow-up (0.670, 95% CI 0.666–0.673) or Delta	Individualised reassessment of thromboembolic risk is recommended at periodic intervals in patients with AF to ensure anticoagulation is started in appropriate patients

				stroke risk			(0.637, 95% CI 633–640) scores ($P < 0.0001$ for DeLong test)	
Weijs, 2019	¹²⁷	Retrospective cohort study	41 idiopathic PAF patients & 45 healthy sinus rhythm (SR) control patients	To compare the development of cardiovascular disease in healthy AF patients as compared to healthy sinus rhythm patients and to assess appropriate anticoagulation treatment	Idiopathic paroxysmal AF patients and healthy SR control patients Exclusion: presence of any CVD, peripheral vascular disease, congestive heart failure, previous stroke, thyroid or pulmonary disease, preserved renal function & malignancy	Combined endpoint: all-cause death, thromboembolic complications, congestive heart failure, significant coronary artery disease, diabetes mellitus, and new onset hypertension. Major adverse cardiac and cerebrovascular events	Cardiovascular disease and all-cause death developed significantly more often in AF patients as compared to controls (63% vs. 31%, log rank $P < 0.001$). Mean duration to reach a CHA2DS2-VASc	The majority of recently diagnosed AF patients with low thromboembolic risk developed CVD with a consequent change in thromboembolic risk profile, within a short time frame. Individualised reassessment of thromboemboli

						(MACCE) were defined as cardiovascular death, stroke, myocardial infarction or repeated revascularisation, and the occurrence of acute heart failure	score > 1 among AF patients was 5.1 ± 3.0 years	c risk is recommended at periodic intervals in patients with AF to ensure anticoagulation is started in appropriate patients
Bezabhe, 2021	¹²⁸	Retrospective cohort study	2296 patients diagnosed with AF	Change in stroke risk and the proportion of patients who had a recorded prescription of an OAC	Diagnosis of AF and aged ≥ 18 Exclusion: recorded venous thromboembolism, last clinical visit or death within the screening period	Change in stroke risk and the proportion of patients who had a recorded prescription of an OAC	The CHA2DS2-VA score increased by a mean of 1.34 (95% confidence interval, 1.29–1.39) points over the study	Nearly one-third of patients with AF reclassified as being at high risk of stroke during the study were not prescribed an OAC. In addition, the

							period. Nearly two-thirds of patients (65%, 412/632) whose stroke risk changed from baseline low/moderate to high were subsequently prescribed an OAC. The median lag time from becoming high stroke risk to having OAC initiation was 2 years	delay in OAC initiation following classification as high risk was a median of 2 years, suggesting that more frequent stroke reassessment is needed
Hirota,	¹²⁹	Prospec	293 patients	To assess the	Patients with a	Sudden cardiac	At final	All patients with

2019 (Kochi RYOMA study)		tive registry	with HCM (86 with AF)	occurrence and clinical profile of thromboemboli sm in patients with HCM with a focus on the presence of AF	diagnosis of HCM Exclusion: patients with no follow-up data	death-related; composite HF events included HF-related death and hospitalization for HF; and (thromboemboli c events were a composite of embolic stroke- related death and admission for arterial thromboembolic events)	follow-up 117 patients had documented AF. The 5- year embolic event rate in those 117 patients with AF was 12.3%. The CHADS2 score did not correlate with the embolic outcome in HCM patients	HCM in whom AF develops should be given anticoagulation therapy regardless of their CHADS2 score
Nieuwlaat , 2008 (Euro Heart Survey on AF)	¹³⁰	Prospect ive registry	1509 paroxysmal, 1109 persistent, and 1515 permanent AF patients	To assess the relation between the AF subtype and thrombo- embolic events	First detected AF patients were excluded	Stroke, any thromboembolis m, myocardial infarction, peripheral embolism and cardiovascular	Paroxysmal AF had a comparable risk for thrombo- embolic events as	The temporal pattern of AF should not guide decisions for anticoagulation

						mortality	persistent and permanent AF (1.9%, 1.2% and 1.6%; <i>P</i> =0.582)	

Additional Evidence Table S5 — Institution of anticoagulation

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
SPAF, 1991	¹	RCT	1330	Intervention: warfarin (dose-adjusted) or aspirin. Control: placebo	Inclusion: AF documented on ECG in the preceding 12 months with or without history of stroke or TIA. Exclusion: prosthetic heart valves, mitral stenosis, contraindications to warfarin or aspirin	Stroke/Systemic embolism or death as primary events; bleeding	Warfarin reduced rate of stroke/systemic embolism by 67% (95% CI 28–75%, $P=0.01$) of death by 58% (95% CI 20–78%; $P=0.01$). aspirin reduced the risk of stroke/systemic by 44% (95% CI 17–62%; $P=0.02$). The risk of death was reduced by 32% (95% CI 7–50%; $P<0.01$)	Patients with AF derive benefit in terms of ischaemic stroke/systemic embolism reduction by warfarin and aspirin

Connolly, 2009 (RE-LY)	²	RCT	18 113	Intervention: dabigatran in two dosing regimens. Control: open label warfarin	Inclusion: AF documented on ECG at screening or within 6 months beforehand; history of stroke/embolism; LVEF<40%; symptomatic HF more than NYHA II in the last 6 months; ≥75 years old; ≥65 years old and CAD/HTN/DM. Exclusion: severe heart valve disease, recent stroke, a condition associated with a high bleeding	Primary outcome: stroke or systemic embolism. Primary safety outcome: major haemorrhage	1.53% in the dabigatran 110 mg (RR=0.91; 95% CI 0.74–1.11; <i>P</i> <0.001 for non-inferiority); lower bleeding risk (RR=0.8; 95% CI 0.69–0.93; <i>P</i> =0.003). 1.11% per year in the dabigatran 150 mg (RR=0.66; 95% CI 0.53–0.82; <i>P</i> <0.001 for superiority); a similar bleeding risk as warfarin (RR=0.93; 95% CI: 0.81–1.07; <i>P</i> =0.31)	In AF patients, the risk of stroke/systemic embolism in patients treated with dabigatran 110 mg was non-inferior to the risk in patients receiving warfarin. The risk of stroke/systemic embolism in patients treated with dabigatran 150 mg was non-inferior to the risk in patients receiving warfarin

					risk, CrCl<30 mL/min			
Patel, 2011 (ROCKET AF)	³	RCT	14 264	Intervention: rivaroxaban. Control: warfarin	Inclusion: patients with AF documented on ECG and a moderate to high risk of stroke (CHADS ₂ ≥2) Exclusion: prosthetic heart valves, known LA myxoma and LV thrombus, active internal bleeding, or history of increased bleeding risk, etc.	Primary efficacy outcome: composite of stroke (ischemic or hemorrhagic) and systemic embolism. Primary safety endpoint: composite of major/nonmajor or clinically relevant bleeding	Primary endpoint: rivaroxaban was non-inferior to warfarin (HR=0.79; 95% CI 0.66–0.96, <i>P</i> <0.001 for non- inferiority). Primary safety endpoint: HR=1.03; 95% CI 0.96–1.11; <i>P</i> =0.44	Rivaroxaban was not inferior to warfarin in terms of prevention of stroke and systemic embolism in patients with AF. Overall bleeding risk was not different
Granger, 2011 (ARISTOTLE	⁴	RCT	18 201	Intervention: apixaban. Control:	Inclusion: High stroke risk patient (≥75	Primary efficacy outcome:	Apixaban reduced the risk the primary	In AF patients, apixaban was superior to

)				warfarin	years old; prior stroke/TIA/systemic embolus; symptomatic CHF within 3 months or LVEF $\leq 40\%$; DM; HTN requiring treatment) with AF or AFL documented by ECG at enrolment or at least 2 weeks apart in the 12 months before enrolment. Exclusion: AF due to reversible cause, prosthetic heart valves, recent stroke, concomitant	stroke and systemic embolism. Primary safety endpoint: major bleeding as per ISTH criteria. Key secondary outcome: death from any cause	outcome (HR=0.79; 95% CI 0.66–0.95; $P<0.001$ for non-inferiority, $P=0.001$ for superiority). Apixaban reduced major bleeding risk (HR=0.69; 95% CI 0.60–0.80; $P<0.001$). Apixaban reduced the rates of all-cause mortality (HR=0.89; 95% CI 0.80–0.99; $P=0.047$)	warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality

					DAPT or ASA>165 mg, GFR<25 mL/min)			
Giugliano, 2013 (ENGAGE AF-TIMI 48)	⁵	RCT	21 105	Intervention: edoxaban (2 dosing regimens). Control: warfarin	Inclusion: patients >21years of age with high stroke risk (CHADS ₂ ≥2) and AF documented by means of an electrical tracing within 12 months before randomization. Exclusion: AF due to a reversible disorder, DAPT, high risk of bleeding, CrCl<30 mL/min	Primary efficacy endpoint: time to first adjudicated stroke or systemic embolic event. Primary safety endpoint: major bleeding as defined by ISTH	Primary efficacy endpoint: high dose edoxaban was non-inferior to warfarin (HR=0.79; 95% CI 0.63–0.99; <i>P</i> <0.001). Low dose edoxaban also was non- inferior to warfarin (HR=1.07; 95% CI 0.87–1.31; <i>P</i> =0.005). Bleeding risk reduced by edoxaban, in both dosing regimens (HR=0.80; 95%	The two dosing regimens of edoxaban were non-inferior to warfarin in terms of stroke prevention. Bleeding rates were lower

							CI 0.71–0.91; <i>P</i> <0.001) for the high dose and for the low dose (HR=0.47; 95% CI 0.41–0.55; <i>P</i> <0.001)	
Lowenstern, 2018	¹³¹	Systematic review of RCTs and observational studies	220 studies (117 unique studies involving 3 934 374 patients)	Anticoagulation, antiplatelet, and procedural interventions versus other anticoagulation therapies, antiplatelet therapies, or procedural interventions for preventing thromboembolic events	Inclusion: 20 adult patients ≥18 years of age with nonvalvular AF who were treated with anticoagulation, antiplatelet, or procedural therapies. Exclusion: known reversible AF	Stroke or systemic embolism, bleeding and mortality	Reduction in the risk of systemic embolism or stroke haemorrhagic stroke intracranial bleeding, minor bleeding, GI bleeding and all-cause mortality for patients treated with dabigatran compared with warfarin	The available DOACs are at least as effective and safe when compared to warfarin
Sanders,	¹³²	Systematic	185	DOAC versus	Inclusion: Adult	Thromboembol	Dabigatran was	Direct oral

2018		review of RCTs and observational studies	studies	warfarin	patients with AF. Exclusion: Patients with a reversible cause if AF	ic and bleeding outcomes. when compared Apixaban was superior to aspirin in preventing stroke or systemic embolism (HR=0.45; 95% CI 0.32–0.62), with similar risk for major bleeding (HR=1.13; 95% CI 0.74–1.75)	superior to warfarin in preventing stroke or systemic embolism (RR=0.66; 95% CI 0.53–0.82), with no difference in the occurrence of major bleeding (RR 0.93; 95% CI 0.81–1.07). Edoxaban reduced hemorrhagic stroke and major bleeding compared to warfarin but had no evidence of a difference in stroke or systemic	anticoagulants demonstrate reductions in stroke events and reductions or similar rates in bleeding events when compared with warfarin

							embolism. Rivaroxaban was similar to warfarin in preventing stroke or systemic embolism (HR=0.88, 95% CI 0.74–1.03), with similar rates of major bleeding	
Tomita, 2015 (J-RHYTHM)	¹³³	Prospective registry	997 AF patients	Incidence of thromboembolic events in patients not on warfarin	Patients not on warfarin	Thromboembolic events: In patients with CHA2DS2-VASc scores 0 and 1 (n=374), there were markedly significant c-statistic difference (0.053, Z=6.6,	No sex difference was found in patient groups stratified by CHA2DS2-VASc and CHA2DS2-VA scores. There were significant c-statistic difference (0.029, Z=2.3, <i>P</i> =0.02) and NRI (0.11, 95% CI	CHA2DS2-VA score may be more useful in risk stratification for thromboembolic events than CHA2DS2-VASc score, especially in identifying truly low-risk

						$P<0.0001$) and NRI (0.11, 95% CI 0.07–0.14, $P<0.0001$), supporting superiority of CHA2DS2-VA to CHA2DS2-VASc	0.01–0.20, $P=0.02$), with the CHA2DS2-VA score being superior to the CHA2DS2-VASc score	patients

Evidence Table 7 for Recommendation Table 7 (Sec. 6) — Recommendations for oral anticoagulation in atrial fibrillation

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Cardoso, 2022	134	Systematic review and meta-analysis of RCTs	1379	DOACs vs. warfarin	AF patients with bioprosthetic valves or valve repair	Efficacy and safety	Stroke or systemic embolism was significantly lower in patients treated with DOACs (1.9%) compared with warfarin (3.7%) (OR=0.43; 95% CI 0.22–0.85; <i>P</i> =0.02). Ischemic stroke (OR=0.72; 95% CI 0.18–2.93), haemorrhagic stroke (OR=0.18; 95% CI 0.03–1.05), cardiovascular death (OR=0.78; 95% CI 0.38–1.62), and all-	In patients with AF and bioprosthetic valves or valve repair, DOAC are associated with a reduced incidence of thromboembolic events and major bleeding as compared with warfarin. Thus, DOACs may be considered a preferred option for this

							cause mortality (OR=0.94; 95% CI 0.55–1.62) were not significantly different among groups. Major bleeding was significantly lower in patients treated with DOAC (2.8%) compared with warfarin (4.7%) (OR=0.49; 95% CI 0.28–0.88; <i>P</i> =0.02)	patient population
Kotecha, 2018	¹³⁵	Systematic review and meta-analysis of RCTs	5203 patients were included (2850 randomized to receive DOACs and 2353	DOAC vs. VKA in patients with AF undergoing cardioversion	Inclusion: trials that have randomized patients with AF undergoing cardioversion to DOAC or VKA	DOAC therapy considerably reduced primary outcome events compared with VKA, with a pooled RR=0.42 (95%	The primary outcome was the composite of stroke, systemic embolism, myocardial infarction, and cardiovascular death. Bias: included trials studied the short-	In combination with integrated approaches to AF care and stratification of therapy, the routine use of DOACs for cardioversion can improve

			randomized to receive VKAs)			CI 0.21-.86; $P=0.017$) and no heterogeneity between trials ($I^2=0\%$; $P=0.84$)	term effects of anticoagulation; none of the trials were individually powered for clinical outcomes, more than 90% of patients underwent electrical cardioversion, and although there is no a priori reason to suspect a difference with pharmacological cardioversion, data in this context are scarce	safety for patients undergoing cardioversion
Carnicelli, 2022	¹³⁶	Meta-analysis from RCTs	COMBINE AF database: individual patient data from	DOAC vs. warfarin (n=29 362 randomized to standard-dose DOAC,	Individual patient data from the COMBINE AF (A Collaboration Between	Compared with warfarin, standard-dose DOACs were associated with a lower	The primary efficacy outcome was a composite outcome of any stroke (ischemic, haemorrhagic, or	Compared with warfarin, DOACs have more favourable efficacy and

			the 4 DOACs trials (RE-LY; ROCKET AF; ARISTOTLE; ENGAGE AF-TIMI 48) vs. warfarin in AF patients A total of 71 683 patients were included in these analyses	n=13 049 randomized to lower-dose DOAC, and n=29 272 randomized to warfarin)	Multiple Institutions to Better Investigate Non-Vitamin K Antagonist Oral Anticoagulant Use in AF) database, which includes all patients randomized in 4 trials of DOACs versus warfarin in AF (RE-LY, ROCKET AF, ARISTOTLE and ENGAGE AF-TIMI 48) comparing standard-dose DOAC, lower-dose DOAC,	rates of stroke or systemic embolism (883/29 312 [3.01%] vs. 1080/29 229 [3.69%]; HR=0.81; 95% CI 0.74–0.89), death (2276/29 312 [7.76%] vs. 2460/29 229 [8.42%]; HR=0.92 95% CI 0.87–0.97), and intracranial bleeding (184/29 270 [0.63%] vs. 409/29 187 [1.40%];	other) or systemic embolism (ie, stroke or systemic embolism). The primary safety outcome was major bleeding as defined by the International Society on Thrombosis and Haemostasis. Bias: type I error inflation attributable to multiplicity; aggregating trials with different study drugs and doses for meta-analyses may obscure subtle differences between outcomes that are specific to individual study drugs	safety profiles among AF patients

					and warfarin	HR=0.45; 95% CI 0.37–0.56])		
Heneghan, 2012	¹³⁷	Systematic review and meta-analysis of individual patients data from RCTs	11 trials, 6417 participants	Self-monitoring (self-testing) or self-management (self-testing and self-dosage) of anticoagulation versus control and dosage by personal physician, anticoagulation management clinics, or managed services	RCTs including adults on anticoagulant therapy irrespective of the indication for treatment, with no language restrictions	Primary outcomes were time to death, first major haemorrhage, and first thromboembolic event	Significant reduction in thromboembolic events in the self-monitoring group (hazard ratio 0.51; 95% CI 0.31–0.85) but not for major haemorrhagic events (0.88, 0.74–1.06) or death (0.82, 0.62–1.09). Participants <55 years showed a reduction in thrombotic events (hazard ratio 0.33, 95% CI 0.17–0.66), as did participants with mechanical heart valve (0.52, 0.35–0.77). No	Self-monitoring and self-management of oral coagulation is a safe option for suitable patients of all ages

							significant adverse effects of the intervention for all outcomes in the very elderly (age ≥ 85 years, n=99)	
Joosten, 2024	138	RCT	1330 older patients with AF living with frailty (≥ 75 years of age plus a Groningen Frailty Indicator score ≥ 3)	To switch from international normalized ratio-guided VKA treatment to an DOAC versus to continue VKA treatment	Inclusion: age ≥ 75 years; currently managed on INR-guided VKA treatment for AF; a Groningen Frailty Indicator (GFI) ≥ 3 ; and willingness to switch from VKA management to an DOAC-based treatment strategy. Exclusion: valvular AF; an	Primary outcome: major or clinically relevant nonmajor (CRNM) bleeding complication. Secondary outcomes: all-cause mortality, major bleeding complications; CRNM bleeding	662 patients switched from a VKA to an DOAC and 661 patients continued VKAs in the intention-to-treat population. After 101 CRNM events in the switch arm versus 62 in the continue arm, the trial was stopped for futility according to a prespecified futility analysis. The HR CRNM was 1.69 (95% CI, 1.23–2.32).	In frail older patients with AF switching from well controlled VKA treatment to a DOAC increase bleeding complications and does not reduce thromboembolic complications

					eGFR <30 mL·min ⁻¹ ·1.73 m ⁻² ; taking part in another medical scientific research program; and unwilling or unable to provide written informed consent	complications; all-cause thromboemboli c events; composite of thromboemboli c events and major or CRNM bleeding; and the composite of ischemic and haemorrhagic stroke	The HR for thromboembolic events was 1.26 (95% CI, 0.60–2.61)	
Connolly, 2022 (INVICTUS)	139	RCT	4565 patients with AF and echocardio graphically documente d	Intervention: standard doses of rivaroxaban Control: dose- adjusted vitamin K	Inclusion: patients with AF and echocardiograp hically documented rheumatic heart disease who	The primary efficacy outcome was a composite of stroke, systemic embolism, myocardial	In the intention-to- treat analysis, 560 patients in the rivaroxaban group and 446 in the vitamin K antagonist group had a primary-outcome	Among patients with rheumatic heart disease- associated AF, vitamin K antagonist therapy led to

			rheumatic heart disease	antagonist	had any of the following: a CHA ₂ DS ₂ VASc score of at least 2 (on a scale from 0 to 9, with higher scores indicating a higher risk of stroke), a mitral-valve area of no more than 2 cm ² , left atrial spontaneous echo contrast, or left atrial thrombus	infarction, or death from vascular (cardiac or noncardiac) or unknown causes. The primary safety outcome was major bleeding according to the International Society of Thrombosis and Hemostasis	event. Survival curves were nonproportional. The restricted mean survival time was 1599 days in the rivaroxaban group and 1675 days in the vitamin K antagonist group (difference, -76 days; 95% confidence interval [CI], -121 to -31; <i>P</i> <0.001). A higher incidence of death occurred in the rivaroxaban group than in the vitamin K antagonist group (restricted mean survival time, 1608 days vs. 1680 days;	a lower rate of a composite of cardiovascular events or death than rivaroxaban therapy, without a higher rate of bleeding

							difference, -72 days; 95% CI, -117 to -28). No significant between-group difference in the rate of major bleeding was noted	
Patel, 2011 (ROCKET AF)	³	RCT	14 264	Intervention: rivaroxaban (at a daily dose of 20 mg). Control: dose-adjusted warfarin	AF patients with NVAf who were at increased risk for stroke	Stroke, systemic embolism; major bleeding	The primary end point occurred in 188 patients in the rivaroxaban group (1.7% per year) and in 241 in the warfarin group (2.2% per year) (for rivaroxaban HR=0.79; 95% CI 0.66–0.96; <i>P</i> <0.001 for noninferiority). Major and nonmajor clinically relevant bleeding occurred in 1475 patients in the	In AF patients, rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism. There was no significant between-group difference in the risk of major bleeding

							rivaroxaban group (14.9% per year) and in 1449 in the warfarin group (14.5% per year) (HR=1.03; 95% CI 0.96–1.11; <i>P</i>=0.44), with significant reductions in intracranial haemorrhage (0.5% vs. 0.7%; <i>P</i>=0.02) and fatal bleeding (0.2% vs. 0.5%, <i>P</i>=0.003) in the rivaroxaban group	
Granger, 2011 (ARISTOTLE)	⁴	RCT	18 201	Intervention: apixaban (5 mg twice daily). Control: warfarin (target INR,	Patients with AF and at least one additional risk factor for stroke	The primary outcome was ischemic or haemorrhagic stroke or systemic embolism. Key	The rate of the primary outcome was 1.27% per year in the apixaban group, as compared with 1.60% per year in the warfarin group	Apixaban was superior to warfarin in preventing stroke or systemic embolism,

				2.0 to 3.0)		secondary objectives of testing for superiority with respect to the primary outcome and to the rates of major bleeding and death from any cause. Follow up 1,8 years	(with apixaban HR=0.79; 95% CI 0.66–0.95; $P<0.001$ for noninferiority; $P=0.01$ for superiority). The rate of major bleeding was 2.13% per year in the apixaban group, as compared with 3.09% per year in the warfarin group (HR=0.69; 95% CI 0.60–0.80; $P<0.001$), and the rates of death from any cause were 3.52% and 3.94%, respectively (HR=0.89; 95% CI 0.80–0.99; $P=0.047$)	caused less bleeding, and resulted in lower mortality
Giugliano, 2013	⁵	RCT	21 105	Intervention: Two once-	Patients with moderate-to-	The primary efficacy end	The annualized rate of the primary end	Both once-daily regimens

(ENGAGE AF-TIMI 48)				daily regimens of edoxaban. Control: warfarin	high-risk AF	point was stroke or systemic embolism. The principal safety end point was major bleeding. Follow-up, 2.8 years	point during treatment was 1.50% with warfarin, as compared with 1.18% with high- dose edoxaban (HR=0.79; 95% CI 0.63–0.99; <i>P</i> <0.001 for noninferiority) and 1.61% with low- dose edoxaban (HR=1.07; 95% CI 0.87–1.31; <i>P</i> =0.005 for noninferiority). The annualized rate of major bleeding was 3.43% with warfarin versus 2.75% with high- dose edoxaban (HR=0.80; 95% CI 0.71–0.91; <i>P</i> <0.001) and 1.61% with low-	of edoxaban were noninferior to warfarin with respect to the prevention of stroke or systemic embolism and were associated with significantly lower rates of bleeding and death from cardiovascular causes

							dose edoxaban (HR=0.47; 95% CI 0.41–0.55; <i>P</i> <0.001). Follow- up, 2.8 years	
SPAF II, 1994	140	RCT	715 patients aged 75 years or less and 385 patients older than 75	Warfarin (prothrombin time ratio 13– 18, international normalised ratio 2.0–4.5) versus aspirin 325 mg	Inclusion: adults with AF in the previous 12 months. Exclusion: prosthetic heart valves, mitral stenosis, or requirements for or contraindication s to aspirin or warfarin. Ischaemic stroke or transient ischaemic attack more	Primary events: ischaemic stroke and systemic embolism	The primary event rate per year was 1.3% with warfarin and 1.9% with aspirin (RR= 0.67, <i>P</i> =0.24). Among older patients, warfarin decreased the absolute rate of primary events by 1.2% per year (95% CI -1.7 to 4.1). The primary event rate per year was 3.6% with warfarin and 4.8% with aspirin (RR 0.73, <i>P</i> =0.39)	In older patients the rate of stroke (ischaemic and haemorrhagic) was substantial, irrespective of which agent was given. Patient age and the inherent risk of thromboemboli sm should be considered in the choice of antithrombotic

					than 2 years before entry were eligible			prophylaxis for patients with AF
SPAF III, 1996	¹⁴¹	RCT	1044 patients with AF and with at least one thromboembolic risk factor	Combination of low-intensity, fixed-dose warfarin (INR 1.2–1.5 for initial dose adjustment) and aspirin (325 mg/day) or adjusted-dose warfarin (INR 2.0–3.0)	Inclusion: e adults with AF documented in the 6 months preceding the study. Exclusion: similar to those of the earlier SPAF studies, except that patients who had had a non-disabling stroke or transient ischaemic attack were eligible after 30 days of the insult, and	Rate of ischaemic stroke and systemic embolism	The mean INR during follow-up of patients taking combination therapy 1.3, compared with 2.4 for those taking adjusted-dose warfarin. The primary events in patients given combination therapy (7.9% per year) was significantly higher than in those given adjusted-dose warfarin (1.9% per year), an absolute reduction of 6.0% per year (95% CI 3.4, 8.6) by	Low-intensity, fixed-dose warfarin plus aspirin is insufficient for stroke prevention in patients with non-valvular AF at high-risk for thromboembolism; adjusted-dose warfarin (target INR 2.0–3.0) importantly reduces stroke for high-risk patients

					participants who had taken part in previous SPAF studies or similar clinical trials were not eligible		adjusted-dose warfarin. The annual rates of disabling stroke (5.6% vs. 1.7%, $P=0.0007$) and of primary event or vascular death (11.8% vs. 6.4%, $P=0.002$), were also higher with combination therapy. The rates of major bleeding were similar in both treatment groups	
Gullov, 1998	142	RCT	677	Warfarin sodium, 1.25 mg/d; warfarin sodium, 1.25 mg/d, plus aspirin, 300 mg/d;	Inclusion: ≥ 18 years or nonvalvular chronic AF. Exclusion: Patients younger than 60 years with lone	Stroke or a systemic thromboembolic event was the primary outcome event. Transient	The cumulative primary event rate after 1 year was 5.8% in patients receiving minidose warfarin; 7.2%, warfarin plus aspirin; 3.6%, aspirin; and	Adjusted-dose warfarin seemed superior to minidose warfarin and to warfarin plus aspirin after 1

				and aspirin, 300 mg/d versus adjusted-dose warfarin therapy (international normalized ratio of prothrombin time [INR], 2.0–3.0)	AF; systolic or diastolic blood pressure above 180/100 mm Hg, stroke, or a TIA within 6 months; risk factors for bleeding; or contraindications for warfarin or aspirin therapy	ischemic attack, acute myocardial infarction, and death were secondary events	2.8%, adjusted-dose warfarin ($P = .67$). After 3 years, no difference among the groups was seen. Major bleeding events were rare	year of treatment. The results do not justify a change in the current recommendation of adjusted-dose warfarin (INR, 2.0–3.0) for stroke prevention in AF
Singer, 1990	143	RCT	420 patients entered the trial (212 in the warfarin group and 208 in the control group)	Low-dose warfarin therapy (target prothrombin-time ratio, 1.2 to 1.5) versus control group who were not given	Inclusion: Adults with chronic sustained or intermittent AF who had no evidence of mitral stenosis. Exclusion: transient AF or if cardioversion	Primary end point was ischemic stroke; all bleeding events	Prothrombin times in the warfarin group were in the target range 83% of the time. There were 2 strokes in the warfarin group versus 13 in the control group, for a reduction of 86% in	Long-term low-dose warfarin therapy is highly effective in preventing stroke in patients with nonrheumatic AF, and can be quite safe with

				warfarin but could choose to take aspirin	was planned. Evidence of an intracardiac thrombus, a left ventricular aneurysm, or the presence of severe congestive heart failure or prosthetic heart valves. Neurologic reasons; clinical indication or contraindication for anticoagulation, or if they required aspirin therapy		the risk of stroke (warfarin:control incidence ratio=0.14; 95% CI 0.04 to 0.49; $P=0.0022$). Death rate was 2.25% in the warfarin group versus 5.97% in the control per year, for an incidence ratio of 0.38 (95% CI, 0.17 to 0.82; $P=0.005$). The frequency of bleeding events that led to hospitalization or transfusion was essentially the same in both groups	careful monitoring
Macaluso, 2022	¹⁴⁴	Post-hoc analysis of	604 HeartWare	HVAD System	Evaluable subjects (n =	The primary endpoint was	Low TTR patients experienced higher	There was a significant

		RCT	HVAD system Destination Therapy patients from ENDURAN CE and ENDURAN CE supplemental trials	compared with a control (HeartMate II Left Ventricular Assist System, HMII, Abbott Inc., Abbott Park, IL)	495) had >1 INR value recorded 1–24 months postimplant and were categorized as: low TTR (10–39%), moderate TTR (40–69%), and high TTR (≥70%)	noninferiority and survival at 24 months alive on originally implanted device, free from disabling stroke, and free from explant for myocardial recovery or transplant	rates of major bleeding (1.69 vs. 0.54 events per patient year [EPPY]; $P<0.001$), GI bleeding (1.22 vs. 0.38 EPPY; $P<0.001$), stroke (0.47 vs. 0.17 EPPY; $P<0.001$), thrombus requiring exchange (0.05 vs. 0.01 EPPY; $P=0.02$), infection (1.44 vs. 0.69 EPPY; $P<0.001$), and renal dysfunction (0.23 vs. 0.05 EPPY; $P<0.001$) compared with high TTR. Moderate TTR had higher rates of major	reduction in morbidity and mortality in destination therapy HVAD patients with well-controlled TTR (≥70%)

							bleeding (0.75 vs. 0.54 EPPY; $P<0.001$), thrombus requiring exchange (0.05 vs. 0.01 EPPY; $P=0.007$), cardiac arrhythmia (0.32 vs. 0.24 EPPY; $P=0.04$), and infection (0.90 vs. 0.69 EPPY; $P=0.001$) compared with high TTR. Two year survival was greater among moderate and high versus low cohorts (Log-rank $P=0.001$)	
Alexander, 2016	¹⁴⁵	Post-hoc analysis of an RCT	17 322 in the ARISTOTLE trial	5 mg twice daily dose of apixaban or warfarin	Patients with AF and at least 1 additional risk factor for stroke or systemic	Stroke or systemic embolism and bleeding	Of the patients with 1 or no dose-reduction criteria assigned to receive the 5 mg twice daily	The 5 mg twice daily dose of apixaban is safe, efficacious,

					embolism		dose of apixaban or warfarin, 3966 had 1 dose-reduction criterion; these patients had higher rates of stroke or systemic embolism (HR, 1.47; 95% CI, 1.20–1.81) and major bleeding (HR, 1.89; 95% CI, 1.62–2.20) compared with those with no dose-reduction criteria (n = 13 356). The benefit of the 5 mg twice daily dose of apixaban (n = 8665) compared with warfarin (n = 8657) on stroke or systemic embolism in patients with 1	and appropriate for patients with only 1 dose-reduction criterion

							dose-reduction criterion (HR, 0.94; 95% CI, 0.66–1.32) and no dose-reduction criterion (HR, 0.77; 95% CI, 0.62–0.97) were similar (<i>P</i> for interaction = 0.36). Similarly, the benefit of 5 mg twice daily dose of apixaban compared with warfarin on major bleeding in patients with 1 dose-reduction criterion (HR, 0.68; 95% CI, 0.53–0.87) and no dose-reduction criterion (HR, 0.72; 95% CI, 0.60–0.86) were similar (<i>P</i> for	

							interaction =0.71). Similar patterns were seen for each dose-reduction criterion and across the spectrum of age, body weight, creatinine level, and creatinine clearance	
Wan, 2008	146	Systematic review and meta-analysis of RCTs and observational studies	33 976 participants (47 studies: 27 retrospective, 5 prospective cohorts, and 15 RCTs)	Systematic examination of the relationship between international normalized ratio (INR) control measurements and the prediction of adverse events in	Studies of AF patients receiving vitamin-K antagonists that reported INR control measures (percentage of time in therapeutic range [TTR] and percentage of INRs in range)	TTR=29–75%; percentage of INRs=34–84%. From studies reporting both measures, TTR significantly correlated with percentage of INRs in range ($P<0.001$). TTR negatively correlated with	Randomized controlled trials had better INR control than retrospective studies (64.9% vs. 56.4%; $P=0.01$). For retrospective studies, a 6.9% improvement in the TTR significantly reduced major haemorrhage by 1 event per 100 patient-years of	In AF patients receiving orally administered anticoagulation treatment, TTR and percentage of INRs in range was associated with an effectively prediction of INR control

				patients with AF on oral anticoagulation	and major haemorrhage and thromboembolic events	major haemorrhage ($r=-0.59$; $P=0.002$) and thromboembolic rates ($r=-0.59$; $P=0.01$)	treatment (95% CI 0.29–1.71 events)	
Vestergaard, 2017	¹⁴⁷	Systematic review and meta-analysis of RCTs and observational studies	35 studies; >100 000 patients with AF on warfarin therapy	For AF patients on warfarin therapy to examine the association between mean TTR and complication rates with adjustment for differences	Studies reporting on use of warfarin therapy in patients with non-valvular AF and the occurrence of thromboembolism and haemorrhage. Exclusion: valvular AF	Major bleeding and stroke/systemic embolism	Increasing mean TTR was significantly associated with a decreased rate of both major bleeding and stroke/systemic embolism ($P=0.03$)	The safety of warfarin therapy increases with higher mean TTR
Szumner, 2017	¹⁴⁸	Retrospective cohort	7738 newly diagnosed	Relation between	Newly diagnosed AF	Composite of ICH, ischemic	TTR was 70% among patients with	AF patients with severe

		study	AF patients initiating treatment with warfarin	eGFR and TTR in patients taking warfarin	patients initiating warfarin treatment	stroke, MI, or death	eGFR <30, around 10% lower than in those with normal renal function. During observation, adverse events occurred in 4.0% of patients, and those with TTR ≤75% were at higher adverse event risk: adjusted odds ratio (OR) 1.84 (95% CI, 1.41–2.40) for TTR 75% to 60% and adjusted OR 2.09 (1.59–2.74) for TTR <60%. No interaction was observed between eGFR and TTR in association to adverse events	chronic kidney disease patients have worse INR control while on warfarin. An optimal TTR (>75%) is associated with lower risk of adverse events, independently of underlying renal function

							(P=0.2)	
Sjalander, 2018	¹⁴⁹	Retrospective cohort study	64 382 patients	Investigate efficacy and safety of apixaban, dabigatran or rivaroxaban compared with warfarin in clinical practice	Inclusion: AF patients initiated on apixaban, dabigatran, rivaroxaban or warfarin between 20131–01 and 201n2–31	Main outcome measures were all-cause stroke and systemic embolism, all-cause stroke, ischemic stroke, hemorrhagic stroke; major bleeding, intracranial bleeding, gastrointestinal bleeding, other bleeding (fatal or requiring hospital care); all-cause mortality; myocardial	After propensity score matching, there was no significant difference in risk of stroke or systemic embolism between DOAC and warfarin treated patients. Major bleeding events were for apixaban HR=0.63; 95% CI 0.52–0.75; for dabigatran HR=0.74; 95% CI 0.62–0.87 and for rivaroxaban HR=1.06; 95% CI 0.92–1.23 compared with warfarin. Bias: retrospective OS	Apixaban, dabigatran, or rivaroxaban was similar compared to high TTR warfarin treatment regarding its association to stroke prevention. However, fewer bleeding events were associated with apixaban and dabigatran, but not with rivaroxaban

						infarction		
Yao, 2017	¹⁵⁰	Registry	14 865 patients with AF taking DOACs	Patients taking DOACs	Nonvalvular AF patients taking apixaban, dabigatran, or rivaroxaban between October 1, 2010, and September 30, 2015, and had creatinine test results before treatment initiation. Exclusion: valvular heart disease; an eGFR <15 mL/min/1.73 m ² ; other indications for DOACs	Primary effectiveness outcome was ischemic stroke or systemic embolism, and the primary safety outcome was major bleeding	Among the 1473 patients with a renal indication for dose reduction, 43.0% were potentially overdosed, which was associated with a higher risk of major bleeding (HR: 2.19; 95% confidence interval: 1.07 to 4.46) but no statistically significant difference in stroke. Among the 13 392 patients with no renal indication for dose reduction, 13.3% were potentially underdosed; underdosing was	Underdosing of DOAC therapy is associated with an increased risk of stroke

							associated with a higher risk of stroke (HR: 4.87; 95% confidence interval: 1.30 to 18.26) but no statistically significant difference in major bleeding in apixaban-treated patients	
Krittayaphong, 2020	¹⁵¹	Registry	2233 patients	To study antithrombotic patterns, clinical outcomes, and the quality of OAC control	Adult patients with AF who were on warfarin with at least 2 INR readings. Exclusion: ischemic stroke during the past 3 months; thrombocytopenia or myeloproliferativ	Ischemic stroke or transient ischemic attack (TIA), major bleeding, intracerebral haemorrhage (ICH), and death	When patients with a TTR <65% were compared with those with TTR ≥ 65%, the adjusted hazard ratios (aHR) for the increased risks of ischemic stroke/TIA, major bleeding, ICH, and death were 3.07, 1.90, 2.34, and 2.11, respectively	Poor TTR control is associated with adverse clinical outcomes in patients with NVAf who were on warfarin. Efforts to ensure good TTR (≥65%) after initiation

					e disorders; rheumatic mitral valve disease; prosthetic valve or valve repair; AF related to a transient reversible cause; participation in a clinical trial; pregnancy; (8) limited life expectancy to less than 3 years; not available to attend follow-up; refusal to participate; hospitalization within 1 month prior to			of warfarin are mandatory to minimize the risk of adverse clinical outcomes

					enrollment			
Steinberg, 2016	¹⁵²	Registry	5738	DOAC off-label dose therapy	Patients treated with a DOAC	Longitudinal outcomes: stroke or systemic embolism, myocardial infarction, major bleeding (International Society of Thrombosis and Haemostasis criteria), cause-specific hospitalization, and all-cause mortality	541 DOAC-treated patients (9.4%) were underdosed, 197 were overdosed (3.4%), and 5000 were dosed according to U.S. labeling (87%). Compared with patients receiving the recommended dose, those who were receiving off-label doses were older (median: 79 and 80 years of age vs. 70 years of age, respectively; $P<0.0001$), more likely female (48% and 67% vs. 40%, respectively;	DOAC over- and underdosing are associated with increased risk for adverse events

							<i>P</i><0.0001), less likely to be treated by an electrophysiologist (18% and 19% vs. 27%, respectively; <i>P</i><0.0001), and had higher CHA2DS2-VASc scores (96% and 97% ≥2 vs. 86%, respectively; <i>P</i><0.0001) and higher ORBIT bleeding scores (25% and 31% >4 vs. 11%, respectively; <i>P</i><0.0001). After dose adjustment, DOAC overdosing was associated with increased all-cause mortality compared	

							with recommended doses (adjusted hazard ratio: 1.91; 95% confidence interval [CI]: 1.02 to 3.60; $P=0.04$). Underdosing was associated with increased cardiovascular hospitalization (adjusted hazard ratio: 1.26; 95% CI: 1.07 to 1.50; $P=0.007$)	

Additional Evidence Table S6 — Direct oral anticoagulants

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Song, 2022	¹⁵³	Systematic review and meta-analysis of RCTs	Ten RCTs	Intervention: shared decision-making facilitated by the decision aids (DAs) vs. Control: usual care; disseminations of didactic materials; evidence-based paper guidelines	Inclusion: ≥18 years old with AF; studies that considered DAs as the intervention	Evaluate the effects of DAs on AF patients' knowledge, decisional conflict, OAC uptake, and adherence and on the incidence of stroke and bleeding; and explore characterizing factors associated with enhanced DAs effectiveness	Pooling results indicated that DAs reduce decisional conflict related to warfarin use (mean difference = -0.10; 95% CI -0.18 to -0.02; <i>P</i> =0.01) and enhance OAC uptake (RR=1.03; 95% CI 1.01–1.05; <i>P</i> =0.004). The effects of DAs on adherence and incidence of stroke and bleeding were unclear	DAs are promising in promoting shared decision-making and OAC uptake in patients with AF. The evidence on adherence and incidence of stroke and bleeding remains uncertain

Shaikh, 2021	¹⁵⁴	Systematic review and meta-analysis of RCTs	5 articles	DOAC in overweight/obese	Only systematic reviews with meta-analyses that examined the effect of DOAC in overweight or obese adults with AF, published in the English language, were included. Only RCTs included in meta-analysis	Primary outcomes assessed were stroke (ischemic or hemorrhagic) or systemic or pulmonary embolism. Secondary outcomes assessed included all-cause mortality, transient ischemic attack, myocardial infarction, major bleed, all-cause hospitalization, and cardiovascular mortality	The results did not show any significant difference between all body mass index (BMI) groups for all outcomes at both 12 months and for the entire trial duration. Non-significant differences were seen among the different types of DOAC	There was no difference between the BMI classes in any of the outcomes assessed

Additional Evidence Table S7 — Vitamin K antagonists

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion
Grymonprez, 2022	¹⁵⁵	Systematic review and meta-analysis of observational studies	9 758 637 (21 cohort studies)	Different oral anticoagulants in AF patients	Non-selected AF patients 2010–2018	Prevalence of OAC use time trends	Prevalent and incident VKA use decreased from 0.42 (95% CI 0.22–0.65) and 0.42 (95% CI 0.36–0.49) in 2010 to 0.32 (95% CI 0.32–0.32) and 0.06 (95% CI 0.06–0.07) in 2018, respectively	The proportion of OAC users worldwide almost doubled following DOAC introduction
Sjalander, 2014	¹⁵⁶	Retrospective cohort study	115 185 patients	Investigate if AF patients benefit from	AF patients in the National Swedish	Endpoints were ischaemic	Treatment with ASA was associated	Acetylsalicylic acid as monotherapy

				ASA as monotherapy for stroke prevention	Patient register, matched with data from the National Prescribed Drugs register	stroke, thrombo-embolic event, intracranial haemorrhage, and major bleeding	with higher risk of ischaemic stroke and thrombo-embolic events compared with no antithrombotic treatment. Bias: retrospective OS; confounding by indication	in stroke prevention of AF was no associated with protective effect against stroke, and may be associated with an increase in the risk of ischaemic stroke in elderly patients
Vora, 2022	¹⁵⁷	Retrospective cohort study	3,5 million from 9 databases	Different oral anticoagulants in AF patients	Adults with AF and a first OAC prescription, either vitamin K antagonist (VKA) or	Use of VKA and DOAC, time trends	In 2010, 87.5–99.8% of patients started on a VKA. By 2017, the majority started on a	From 2010 to 2017, VKA use had declined and DOAC use had increased in the US and

					direct oral anticoagulant (DOAC), from 2010 to 2017. US and some European countries		DOAC: 87.0% (US), 88.3% (Belgium), 93.1% (France), 88.4% (Germany), and 86.1–86.7% (UK)	Europe

Additional Evidence Table S8 — Anticoagulation in the context of chronic kidney disease

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Reinecke, 2022 (AXADIA-AFNET 8)	¹⁵⁸	RCT	97 patients	Randomised in an open-labelled, 1:1 design: apixaban 2.5 mg bid or the vitamin K antagonist (VKA)	Inclusion: end-stage kidney disease with chronic haemodialysis treatment 3 times/week;	Non-inferiority, composite primary safety outcome: first event of major bleeding, clinically relevant non-major bleeding, or all-	Comparing apixaban and VKA in patients with AF on haemodialysis with long follow-up, no differences were observed in	No differences in safety or efficacy outcomes. Patients with AF on haemodialysis

				phenprocoumon (INR 2.0–3.0)	documented AF; CHA ₂ DS ₂ -VASc score of ≥2 as an indication for OAC. Exclusions: AF or atrial flutter due to reversible causes; new onset of haemodialysis within the last three months; moderate/severe aortic and mitral stenosis; conditions other than AF that require chronic anticoagulation	cause death. Primary efficacy outcome: composite of ischemic stroke, all-cause death, myocardial infarction, deep vein thrombosis and/or pulmonary embolism	safety or efficacy outcomes	remain at high risk of cardiovascular events

Randhawa, 2020	¹⁵⁹	Systematic review and meta-analysis of observational studies	47 480 patients with AF and end-stage renal disease (, MOOSE guidelines were followed)	Warfarin vs. no anticoagulation	Inclusion: AF patients with end-stage renal disease receiving warfarin and with hazard ratios (HRs) of at least 1 primary outcome. Exclusion: a lack of information on outcomes and unreliable 95% CIs of the results	Incidence of ischemic stroke, haemorrhagic stroke, major bleeding, and mortality	Warfarin use had no significant change for the risk of ischemic stroke (HR=0.96; 95% CI 0.82–1.13), with a significantly higher risk of haemorrhagic stroke (HR=1.49; 95% CI 1.03–1.94), with no significant difference in the risk of major bleeding (HR=1.20; 95% CI 0.99–1.47), no change in overall mortality (HR=0.95; 95% CI 0.83–1.09). Bias: heterogeneity,	Warfarin was associated with higher risk of haemorrhagic stroke in end-stage renal disease

							non-harmonized outcomes	
Rhee, 2022	¹⁶⁰	Systematic review and meta-analysis of RCT and observational data	124 628 patients	DOACs vs. warfarin	OAC in AF patients with renal impairment, including advanced chronic kidney disease (CKD) with CrCl <30 mL/min	Stroke or thromboembolism, major bleeding, and all-cause death edoxaban and apixaban presented the highest rank probability to reduce the risk of stroke or thromboembolism	In patients with AF and CKD, DOACs presented significantly lower risks of stroke or thromboembolism [HR pooled=0.78, 95% CI=0.73–0.85, I2 = 16.6%] and major bleeding [HR pooled=0.76 (0.64–0.89), I2 = 85.7%] when compared with warfarin, regardless of the severity of renal impairment	DOACs, particularly apixaban and edoxaban, were associated with higher efficacy and safety rates, apixaban with lowest bleeding HR

Evidence Table 8 for Recommendation Table 8 (Sec. 6) — Recommendations for combining antiplatelet drugs with anticoagulants for stroke prevention on oral anticoagulation in atrial fibrillation

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Connolly, 2009, (ACTIVE)	¹⁶¹	RCT	7554 AF patients	Intervention: Clopidogrel (75 mg) once daily, in addition to aspirin Control: placebo in addition to aspirin	Inclusion: AF at enrolment; or ≥ 2 episodes of intermittent AF in the previous 6 months; ≥ 75 years; systemic HTN during treatment; previous stroke, TIA, or non–central nervous system systemic embolism; LVEF<45%; peripheral vascular disease; 55–74	The primary outcome was the composite of stroke, myocardial infarction, non-central nervous system systemic embolism, or death from vascular causes	Stroke occurred in 296 patients receiving clopidogrel (2.4% per year) and 408 patients receiving placebo (3.3% per year) (RR=0.72; 95% CI 0.62–0.83; $P<0.001$). Myocardial infarction occurred in 90	In AF patients, the addition of clopidogrel to aspirin reduced the risk of major vascular events, especially stroke, and increased the risk of major hemorrhage

					years and DM or CAD. Exclusion: VKA or clopidogrel or documented peptic ulcer disease within the previous 6 months; a history of intracerebral hemorrhage; significant thrombocytopenia (platelet count $<50 \times 10^9/l$); or ongoing alcohol abuse		patients receiving clopidogrel (0.7% per year) and in 115 receiving placebo (0.9% per year) (RR=0.78; 95% CI, 0.59 -1.03; $P=0.08$). Major bleeding occurred in 251 patients receiving clopidogrel (2.0% per year) and in 162 patients receiving placebo (1.3% per year) (RR=1.57; 95%	

							CI 1.29–1.92; <i>P</i> <0.001)	
Yasuda, 2019 (AFIRE)	¹⁶²	RCT	2236 AF patients	Intervention: rivaroxaban. Control: combination therapy with rivaroxaban plus a single antiplatelet agent	Inclusion: ≥20 years with AF and stable CAD in Japan; CHADS ₂ ≥1; a history of PCI, including angioplasty ± stenting at ≥1 year before enrollment; a history of angiographically confirmed CAD (with stenosis of ≥50%) not requiring revascularization; or a history of CABG at ≥1 year before enrolment. Exclusion: a	The primary efficacy end point was a composite of stroke, systemic embolism, myocardial infarction, unstable angina requiring revascularization, or death from any cause; this end point was analyzed for noninferiority with a noninferiority margin of 1.46. The primary safety end point was major bleeding, according to the	Rivaroxaban monotherapy was noninferior to combination therapy for the primary efficacy end point, with event rates of 4.14% and 5.75% per patient-year, respectively (HR=0.72; 95% CI 0.55–0.95; <i>P</i> <0.001 for noninferiority). Rivaroxaban monotherapy was superior to combination therapy for the	As antithrombotic therapy, rivaroxaban monotherapy was noninferior to combination therapy for efficacy and superior for safety in AF patients and stable coronary artery disease

					history of stent thrombosis, coexisting active tumor, and poorly controlled hypertension	criteria of the International Society on Thrombosis and Hemostasis; this end point was analyzed for superiority	primary safety end point, with event rates of 1.62% and 2.76% per patient-year, respectively (HR=0.59; 95% CI 0.39–0.89; <i>P</i> =0.01 for superiority). Limitations: The choice of antiplatelet regimen (aspirin/P2Y12 inhibitor) was at the discretion of the treating physicians, a factor that makes it uncertain	

							whether the benefit of rivaroxaban monotherapy applies equally to the two combination regimens. The early termination of the trial because of an increased risk of death from any cause in the combination-therapy group may overestimate the efficacy data	
Lip, 2011	¹⁶³	Review	N/A	Intervention:	Inclusion: AF	Primary outcome:	Aspirin use	Aspirin

				anticoagulant Control: aspirin	patients	stroke prevention	should continue in the early stages following presentation of a patient with AF and acute coronary syndrome, and after stenting, in combination with oral anticoagulant drugs and clopidogrel, as appropriate	combined with clopidogrel shows only modest benefit in stroke prevention compared with aspirin monotherapy in patients with AF who refuse oral anticoagulant drugs (including warfarin), or in those individuals who have difficulties in anticoagulation monitoring, and can be used where bleeding risk is not

								excessive

Additional Evidence Table S9 — Antiplatelet drugs and combinations with anticoagulants

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Shin, 2022	¹⁶⁴	Retrospective cohort study	1068 from a Korean hospital	DOAC only vs. combined antiplatelet	Inclusion: NVAf patients who were taking DOACs and some of them were taking APT. Exclusion: <18 years, with a history of DOAC therapy, mechanical prosthetic valves or moderate-to-	Primary outcome: major bleeding and any bleeding events: Secondary outcomes: stroke/systemic emboli events and MACE	Incidence of any bleeding was associated with higher rates in the combination therapy group than in the monotherapy group ($P<0.001$). The rate of major bleeding, stroke/SE, and MACE between the two groups was similar.) Hospital cohort,	Combination therapy group was associated with higher rates of any bleeding events vs. DOAC monotherapy in patients with appropriate dosing($P<0.0001$) . No difference in stroke/SE, and MACE. The bleeding risk in AF patients taking the combination of DOACs and

					severe mitral stenosis, and impaired renal function (CrCl <30 mL/min and dialysis)		small N patients/outcomes, Korean only	APT should be carefully evaluated
Ruiz, 2019.	¹⁶⁵	Retrospective cohort study	2361	DOAC vs. antiplatelet (APT)	Inclusion: consecutive NVAf patients initiating DOAC. Exclusion: patients with an acute ischaemic event within the last 12 months (acute coronary syndrome,	Primary outcome: was major bleeding. Secondary outcome: stroke, nonfatal MI, ICB, death	Concomitant APT was associated with higher risk for major bleeding (HR=3.62; 95% CI 1.32–9.89; <i>P</i> =0.012) but was not associated with a higher risk of other clinical outcomes. Bias: retrospective study; confounding by	APT higher risk of bleeding, no benefit

					stroke or revascularization), DOAC initiation, NVAf, ischemic event during last 3 months		indication; the power is limited to detect differences in clinical outcomes between groups and it is therefore insufficient to reach robust conclusions due to the low frequency of the study events	
Fox, 2020 (GARFIELD-AF)	¹⁶⁶	Prospective registry	24 436	OAC vs. OAC plus antiplatelet	New onset AF	Stroke, ischemic events, bleeding, mortality	Incidence rates of stroke (HR=1.49; 95% CI 1.01–2.20), bleeding event (HR=1.41; 95% CI 1.17–1.70) than those	No indication for OAC plus AP unless there is a clear indication for adding AP to OAC therapy in newly diagnosed AF

							treated with OAC alone; II-cause mortality (HR= 1.22; 95% CI 0.98–1.51). Bias: variables known to influence outcomes, differences between patients treated with either OAC plus AP or OAC alone may be subject to unmeasured confounders related to treatment selection by physicians	
Verheugt,	¹⁶⁷	Prospective	51 270		Inclusion:	Proportion of	20.7% of	APT prescription

2018 (GARFIELD -AF)		registry	patients from 35 countries		≥18 years, NVAF diagnosed within the previous 6 weeks, and with at least one risk factor for stroke. Exclusion: a transient reversible cause of NVAF and those for whom follow- up is not envisaged or possible	treatment APT, AC, APT+DOAC and comorbidities	patients received APT monotherapy, 52.1% AC monotherapy, and 14.1% AP + AC. Bias: inherent selection bias; other factors that may have specifically precluded the use of AC like frailty have not been prospectively taken into account	in newly diagnosed AF has declined, but substantial proportion still have no indication for APT

Evidence Table 9 for Recommendation Table 9 (Sec. 6) — Recommendation on thromboembolism despite anticoagulation

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Seiffge, 2020	¹⁶⁸	Systematic review and meta-analysis of observational studies	5413 patients	Intervention: oral anticoagulants (VKA or DOAC) prior to index event Control: without prior oral anticoagulation	Inclusion: recent ischemic stroke or TIA; nonvalvular AF; information on anticoagulation therapy prior to and after index event available; and systematic follow-up for at least 3 months or longer after the index event. Exclusion: mechanical heart valves;	The primary outcome: recurrent acute ischemic stroke	Group without prior OAC was associated with an increased risk of acute ischemic stroke (HR = 1.6, 95% CI 1.2–2.3, <i>P</i> =0.005). Limitations: observational study rather than a randomized trial, and allocation to the type of oral anticoagulant is	Patients with AF who have an ischemic stroke despite previous oral anticoagulation are at a higher risk for recurrent ischemic stroke despite a CHA ₂ -VASc score similar to those without prior oral anticoagulation

					rheumatic or severe mitral valve stenosis		likely to be affected by biases	
Polymeris, 2022	¹⁶⁹	Prospective cohort study	2946 patients (median age 81 years; 48% women; 43% VKA, 57% DOAC)	VKA versus DOAC	Patients with AF with an index imaging-proven ischaemic stroke despite vitamin K-antagonist (VKA) or direct oral anticoagulant (DOAC) treatment across 11 stroke centres	Primary outcome: composite of recurrent ischemic stroke, major bleeding, and all-cause death. Only DOAC (vs. VKA) treatment after index stroke showed lower odds for both endpoints (primary: adjusted OR (aOR) (95% CI:0.49 (0.32 to 0.73)); secondary: 0.44	Adding antiplatelets showed higher odds for both endpoints (primary: OR (95% CI:1.99 (1.25–3.15)); secondary: 2.66 (1.40–5.04))	While DOAC were associated with better outcomes than VKA, adding antiplatelets was linked to worse outcomes in these high-risk patients

						(0.24 to 0.80)), but not switching between different DOAC types		
Paciaroni, 2019	¹⁷⁰	Prospective cohort study	713 cases and 700 controls	Non-vitamin K antagonist oral anticoagulants	Inclusion: consecutive patients with AF who had acute cerebrovascular ischemic events during DOAC treatment. Controls were consecutive patients with AF who did not have cerebrovascular events during DOACs treatment	On multivariable analysis, ischemic events were associated with: off-label low dose of DOACs (OR =3.18; 95% CI 1.95–5.85), atrial enlargement (OR=6.64; 95% CI= 4.63–9.52), hyperlipidemia (OR=2.40; 95% CI 1.83–3.16), and CHA ₂ DS ₂ - VASc score	Among the CHA ₂ DS ₂ -VASc components, age was older and presence of diabetes mellitus, congestive heart failure, and history of stroke or transient ischemic attack more common in patients who had acute cerebrovascular ischemic events. Paroxysmal AF	In patients with AF treated with DOACs who had a cerebrovascular event off-label low dose, atrial enlargement, hyperlipidemia, and high CHA ₂ DS ₂ -VASc score were associated with increased risk of cerebrovascular events

						(OR=1.72 for each point increase; 95% CI, 1.58–1.88)	was inversely associated with ischemic events (OR=0.45; 95% CI 0.33–0.61)	
Paciaroni, 2022	¹⁷¹	Prospective cohort study	1300 patients who suffered an acute ischemic stroke while on treatment with DOACs	DOAC therapy	Patients with AF who suffered an acute cerebrovascular ischemic event while on DOAC treatment. Exclusion: Patients who had suspended anticoagulant therapy at least 24 hours before the cerebrovascular event for any reason and patients who did	Primary outcome: composite of ischemic stroke, systemic embolism, intracranial bleeding, and major extracranial bleeding	192 out of 1240 patients (15.5%) had 207 ischemic or bleeding events corresponding to an annual rate of 13.4%. Predictive factors of recurrent ischemic events included CHA2DS2-VASc score after the index event (odds ratio [OR], 1.2 [95% CI,	Patients having a stroke despite being on therapy with DOACs are at high risk of recurrent ischemic stroke and bleeding

					not guarantee adherence to treatment		1.0–1.3] for each point increase; $P=0.05$) and hypertension (OR, 2.3 [95% CI, 1.0–5.1]; $P=0.04$). Predictive factors of bleeding events included age (OR, 1.1 [95% CI, 1.0–1.2] for each year increase; $P=0.002$), history of major bleeding (OR, 6.9 [95% CI, 3.4–14.2]; $P=0.0001$) and the concomitant administration of	

							an antiplatelet agent (OR, 2.8 [95% CI, 1.4–5.5]; $P=0.003$)	

Evidence Table 10 for Recommendation Table 10 (Sec. 6) — Recommendations for percutaneous left atrial appendage occlusion

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Reddy, 2013 (ASAP)	172	Prospective cohort study	150	Intervention: WATCHMAN LAA closure device	Inclusion: >18 years, NVAF CHADS2 score >0, a contraindication for even short-term oral anticoagulation therapy, and eligibility for 6 months of treatment with a thienopyridine antiplatelet agent and lifelong aspirin. Exclusion:	Composite primary efficacy endpoint: ischemic stroke, hemorrhagic stroke, systemic embolism, and cardiovascular/unexplained death. Serious procedure- or device-related safety events	All-cause stroke or systemic embolism occurred in 4 patients (2.3% per year), ischemic stroke in 3 patients (1.7% per year), and hemorrhagic stroke in 1 patient (0.6% per year). Serious procedure- or device-related safety events	LAA closure with the Watchman device can be safely performed without a warfarin transition and is a reasonable alternative to consider for patients at high risk for stroke but with contraindications to systemic oral

					LVEF <30%, intracardiac thrombus/ dense spontaneous contrast by TOE, a PFO with atrial septal aneurysm, complex atheroma with mobile plaque in the ascending aorta/aortic arch, significant mitral stenosis, or an existing pericardial effusion >3 mm		occurred in 8.7% of patients (13 of 150). Bias: absence of a control or alternative treatment group; prone to selection bias	anticoagulation

Boersma, 2019 (EWOLUTION)	¹⁷³	Prospective cohort study	1020	Intervention: WATCHMAN implant procedure	Eligible to receive the WATCHMAN device according to the appropriate local and international guidelines Exclusion: participating in another trial, were pregnant or of childbearing age; able, to provide informed consent	Bleeding and incidence of stroke/TIA/SE	161 patients (16.4%) died, 22 strokes were observed (1.3/100 patient-years, 83% reduction versus historic data), and 47 major nonprocedural bleeding events (2.7/100 patient-years, 46% reduction versus historic data). Stroke and bleeding rates were consistently lower than historic data in those with prior	Left atrial appendage occlusion device had consistently low rates of stroke and nonprocedural bleeding, although most were contraindicated to oral anticoagulation and used only single antiplatelet therapy or nothing

							ischemic (-76% and -41%) or hemorrhagic (-81% and 67%) stroke and prior bleeding (-85% and -30%)	
Tzikas, 2016	¹⁷⁴	Prospective cohort study	1047	Intervention: AMPLATZER Cardiac Plug	Patients eligible for a LAAO	Procedural success; all-cause mortality; stroke; TIA; systemic thromboembolism; major bleeding	Procedural success was 97.3%. There were 52 (4.97%) periprocedural major adverse events. One-year all-cause mortality was 4.2% (not device-related). There were 9 strokes (0.9%) and 9 transient ischaemic	LAAO showed high procedural success and a favourable outcome for the prevention of AF-related thromboembolism

							attacks (0.9%). The annual rate of systemic thromboembolism was 2.3%, which is a 59% risk reduction. There were 15 major bleedings (1.5%) during follow-up. The annual rate of major bleeding was 2.1%, which is a 61% risk reduction	
Boersma, 2016 (EWOLUTION)	¹⁷⁵	Prospective registry	1021	Intervention: LAAO device implantation	Inclusion: Subjects eligible to receive WATCHMAN device who were of legal	Data on procedural success and complications and long-term patients' outcomes, including bleeding and incidence of	Successful device deployment in 98.5%. 99.3% patients with TOE data available had	Left atrial appendage closure with the WATCHMAN device has a high success rate in complete

					age to provide consent	stroke/TIA/SE	successful procedural closure of LAA. Bias: Lack of control group, clinical FU and responsibility of complete reporting left to participating centres; postprocedural antithrombotic regimen was not uniform	LAAC with low peri-procedural risk in a population with a higher risk of stroke and bleeding, and multiple comorbidities

Additional Evidence Table S10 — Percutaneous left atrial appendage occlusion

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Lakkireddy, 2021 (Amulet-IDE)	176	RCT	1878	Intervention: percutaneous LAAO device implantation with the Amulet occluder. Control group: percutaneous LAAO device implantation with the WATCHMAN occluder	Inclusion: ≥18 years with NVAf, CHADS ₂ score ≥2 or a CHA ₂ DS ₂ -VASc score ≥3, suitable LAA anatomy for implanting both devices, suitable for anticoagulation therapy for 6 months	Primary safety end point: composite of procedure-related complications, all-cause death, or major bleeding through 12 months. Primary effectiveness end point: composite of ischemic stroke or systemic embolism through 18 months	The Amulet occluder was noninferior to the Watchman device for the primary safety end point (14.5% vs. 14.7%; <i>P</i> <0.001 for noninferiority) and the primary effectiveness end point (2.8% versus 2.8%;	The Amulet occluder was noninferior for safety and effectiveness of stroke prevention for NVAf compared with the Watchman device and superior for LAA occlusion

							<i>P</i> <0.001 for noninferiority)	
Reddy, 2014 (PROTECT-AF)	¹⁷⁷	RCT	707	Intervention: WATCHMAN LAA closure device. Comparator: warfarin (targeting an INR between 2–3)	Inclusion: >18 years; NVAf; ≥1 CHADS2 risk factors and eligibility for long-term anticoagulation with warfarin. Exclusion: atrial septal defect, mechanical prosthetic heart valve, PFO with atrial septal aneurysm, LVEF <30%, intracardiac thrombus, morphologically complex aortic atheroma, or symptomatic carotid artery disease	Composite primary efficacy end point: stroke, systemic embolism, and cardiovascular death	Primary efficacy event rates were 3.0% in the Watchman and 4.3% in the warfarin groups, respectively (RR=0.71; 95% CI 0.44–1.30% per year). More primary safety events 5.5% per year, in the Watchman group than 3.6% per year in the control	The WATCHMAN device was noninferior to warfarin for the primary composite endpoint of stroke, cardiovascular mortality, and systemic embolism, but was also associated with significantly higher rates of ischemic stroke and procedural

							group (RR=1.53; 95% CI 0.95– 2.70). Bias: lenient non inferiority margin	complications
Osmancik, 2020 (PRAGUE- 17)	178	RCT	402	Intervention: LAA closure device (WATCHMAN 39%, AMULET 61%) Comparator: DOAC (rivaroxaban, apixaban, or dabigatran at the manufacturer- recommended dose)	Inclusion: NVA patients with history of: bleeding requiring intervention/ hospitalization, cardioembolic event while taking anticoagulation agents or CHA2DS2-VASc >2 plus HAS-BLED >1 Exclusion: mechanical valve prosthesis, mitral stenosis, other	Primary endpoint was a composite of stroke (ischemic or hemorrhagic) or TIA; systemic embolism; clinically significant bleeding; cardiovascular death; a significant peri- procedural or device-related complications	Primary endpoint: 35 patients with LAAC (10.99% per 100 patient- years) compared to 41 patients with DOACs (13.42% per 100 patient- years; HR=0.84; 95% CI 0.53– 1.31; P=0.44).	Among patients with NVA at high risk for stroke and increased risk of bleeding, mechanical LAAC was noninferior to DOACs for the composite of cardioembolic events, cardiovascular death,

					comorbidities mandating anticoagulation, PFO with large atrial septal aneurysm, mobile aortic plaque, symptomatic carotid arterial atherosclerosis, clinically significant bleeding within 30 days, cardioembolic event within 30 days, CrCl <30 mL/min		The study met the criteria for noninferiority ($P<0.004$ for noninferiority). Safety data: 4.5% procedure-related complication rate and 1% procedure or device-related death	clinically significant bleeding, or procedure-/device-related complications
Holmes, 2014 (PREVAIL)	¹⁷⁹	RCT	407	Intervention: WATCHMAN LAA closure device. Comparator: warfarin, (targeting an	Inclusion: >18 years, NVAF and CHADS2 ≥ 2 . Exclusion: Need for long-term AC therapy for reasons other than AF,	3 co-primary endpoints: Primary efficacy-composite of hemorrhagic/ ischemic stroke, systemic	The first coprimary efficacy endpoint did not achieve the prespecified	LAA occlusion was noninferior to warfarin for ischemic stroke prevention or

				INR: 2–3)	contraindications to warfarin or ASA, previous stroke or TIA within 90 d of enrolment, symptomatic carotid disease, or a PFO or ASD requiring Tx, and patients with an indication for clopidogrel	embolization, and CV/unexplained death. Late-ischemic efficacy: composite of systemic embolization/ ischemic stroke, excluding the first 7 d of randomization. Early safety: composite of all-cause death, ischemic stroke, systemic embolization, or device/procedure-related events requiring open CV surgery, or major endovascular Tx	criteria of noninferiority (RR=1.07; 95% CI 0.57–1.89). The second coprimary efficacy endpoint was 0.03 versus 0.02 (risk difference 0.01; 95% CI -0.02–0.03) achieving noninferiority. Safety primary endpoint result: % (n/N) 2.2% (6/269) (95% CI upper bound	SE >7 days' post procedure. Noninferiority was not achieved for overall efficacy

							2.65%)	
Freeman, 2020 (NCDR LAAO registry)	¹⁸⁰	Prospective, registry	38 158	Intervention: WATCHMAN LAAO device implantation	Inclusion: patients undergoing WATCHMAN device implantation	Data on patient, hospital and operator characteristics, procedural success rates and in-hospital adverse events	In 98.1% of patients LAAO was implanted successfully. Major in-hospital adverse events occurred in 2.16% of patients; the most common complications were pericardial effusion requiring intervention (1.39%) and major bleeding	Major in-hospital adverse event rates were lower than reported in pivotal trials with the WATCHMAN device, although patients were generally older with more comorbidities

							(1.25%). Under-reporting bias cannot be excluded	
Kar, 2021 (PINNACLE FLX)	¹⁸¹	Prospective, registry	400	Intervention: WATCHMAN FLX LAAO device implantation	Inclusion: NVAf patients with a CHA ₂ DS ₂ -VASc score of ≥2 for men or ≥3 for women, able to take the prescribed postimplant antithrombotic medication regimen, rationale for a nonpharmacological approach to stroke prevention, and no other diagnoses that would require long-term anticoagulation	Primary effectiveness end point: incidence of effective LAA closure, (any peri-device flow with jet size ≤5 mm) assessed by TOE at 12 months. Primary safety end point: between the time of implant and within 7 days after the procedure or by hospital discharge: death, ischemic stroke,	The incidence of the primary safety end point was 0.5% meeting the performance goal of 4.2% (<i>P</i> <0.001). The incidence of the primary effectiveness end point was 100%, meeting the performance goal of 97.0% (<i>P</i> <0.001)	LAA closure with WATCHMAN FLX was associated with a low incidence of adverse events and a high incidence of anatomic closure

						systemic embolism, or device/procedure-related events requiring open cardiac surgery or major endovascular intervention		

Evidence Table 11 for Recommendation Table 11 (Sec. 6) — Recommendations for surgical left atrial appendage occlusion

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Whitlock , 2021 (LAAOS III)	¹⁸²	RCT	4811	LAAO vs. no LAAO	Inclusion: to undergo cardiac surgery with cardiopulmonary bypass; history of AF; CHA ₂ DS ₂ -VASc≥2.	Ischemic stroke or systemic embolism occurred in 4.8% participants in the occlusion group and in 7.0% in	Stroke or systemic embolism occurred in 4.8% participants in the occlusion group and in 7.0% in the no-occlusion group (HR=0.67;	Among participants with AF who had undergone cardiac surgery, most of whom

					Exclusion: off-pump surgery; mechanical valve implantation; heart transplantation, surgery for complex congenital heart disease, or implantation of a LVAD; previous surgery that involved opening the pericardium; previous LAA closure device	the no occlusion group (HR=0.67; 95% CI 0.53– 0.85; <i>P</i> =0.001). Death occurred in 22.6% participants in the occlusion group and in 22.5% in the no-occlusion group (HR=1.00; 95% CI 0.89– 1.13). The effect of left atrial appendage occlusion on the risk of ischemic stroke or systemic embolism was consistent across subgroups	95% CI 0.53–0.85; <i>P</i> =0.001)	continued to receive ongoing antithrombotic therapy, the risk of ischemic stroke or systemic embolism was lower with concomitant left atrial appendage occlusion performed during the surgery than without it
Whitlock	¹⁸³	RCT	51 patients	LAA	Patients	(1) Safety of LAA	No patient with	LAA occlusion

, 2013 (LAAOS II)			with AF and increased stroke risk	occlusion (n = 26) or no occlusion and oral anticoagulation (n = 25)	undergoing any cardiac surgical procedure using cardiopulmonary bypass and had a history of AF with increased stroke risk. Exclusion: undergo redo surgery; planned: surgical atrial ablation/ implantation of a mechanical valve/ aortic arch repair/ heart transplantation/ complex congenital heart surgery/ or planned insertion of a ventricular assist device;	amputation and closure (as indicated by the rate of life-threatening atrial tears and the need for re-exploration for haemorrhage) and (2) to estimate the rate of death, MI, stroke, noncerebral systemic emboli, and major bleeding at 1 year	occlusion had significant bleeding at the LAA site. At 1 year, 4 patients (15.4%) in the occlusion arm and 5 patients (20.0%) in the no-occlusion arm experienced death, myocardial infarction (MI), stroke, noncerebral systemic emboli, or major bleeding (relative risk [RR], 0.71; 95% confidence interval [CI], 0.19–2.66; <i>P</i> =0.61)	can be safely performed at the time of cardiac surgery

					absolute contraindication to transesophageal echocardiography			
Park- Hansen, 2018 (LAACS)	¹⁸⁴	RCT	205 (22.4%) were enrolled. Of those, 187 (91.2%) were randomize d and 141 (75.4%) ultimately followed the treatment protocol	Concomitant LAACS or standard care	Inclusion: consecutive patients undergoing planned first-time open-heart surgery living within 40 km from the hospital. Exclusion: endocarditis and implanted pacemaker	Primary endpoint: composite of post-operative symptomatic ischemic stroke, transient ischemic attack or imaging findings of silent cerebral ischemic (SCI) lesions	5% primary events in the LAACS-group and 16% in the control group (HR=0.3; 95% CI 0.1–0.8; $P=0.02$). No detectable difference in all- cause mortality ($P=0.79$) between the LAACS group (n=12; 12%) vs. the controls (n=12;14%). Bias: study is not powered to demonstrate a protection against stroke	LAACS in addition to first- time open- heart surgery (CABG, valve or combination of both) seems to protect against post- operative cerebral ischemic events several years after surgery

Caliskan , 2018	¹⁸⁵	RCT	291 (40 patients from a first-in-man device trial and 251 patients from a consecutive institutional registry thereafter)	Epicardial LAA occlusion using the AtriClip device	Inclusion: elective cardiac surgery in adult patients with AF. Exclusion: reoperation, known LAA-thrombus, patients from the intensive care unit, history of pericarditis, recent myocardial infarction, (<90 days) and a known allergy to the device components	Primary efficacy endpoint: ischaemic or haemorrhagic neurological events during FU. The primary safety endpoint was any device-related event. In the subgroup analysis of 166 patients without OAC (mean CHA ₂ DS ₂ -VASc score of 3.2) only two ischaemic strokes could be observed accounting for an observed rate of 0.5/100 patient-years (95% CI	Peri-operatively, 5 strokes were observed with 3 of ischaemic (embolism from a large left-atrial thrombus, intraoperative hypoxia during cardiopulmonary-bypass and intraoperative air-embolism) and 2 of haemorrhagic origin (under OAC and antiplatelet therapy with biventricular assist-device and secondary intracranial bleeding after preoperative ischaemic stroke due to septic	The long-term results from the prospective human trial plus institutional registry of epicardial LAA occlusion with the AtriClip in patients with AF undergoing cardiac surgery was associated with safety and durability of the procedure. In addition, data are associated with suggestive for the potential efficacy of LAA occlusion in

						0.1–1.7)	emboli)	reducing the incidence of stroke
Nso, 2022	¹⁸⁶	Systematic review and meta-analysis of RCT and observational studies	26 878 who underwent LAAO and 16 753 who underwent cardiac surgery without LAAO	S-LAAO vs. no LAAO	Inclusion: PubMed/Medline, Cochrane Central Register of Controlled Trials, and JSTOR databases for relevant studies published between 1 January 2003, and 15 August 2021. Exclusion: opinion papers, review articles, meta-analyses, systematic reviews, and scientific	Primary clinical outcomes: all-cause mortality, embolic events, and stroke. Secondary clinical outcomes: major adverse cardiac events (MACE), postoperative AF, postoperative complications, reoperation for bleeding, and major bleeding	34% reduction in embolic events (OR=0.66; 95% CI 0.57–0.77; $P<0.001$) and a 42% decrease in MACE (OR 0.58, 95% CI 0.38–0.88, $P=0.01$) in patients who underwent cardiac surgery and received LAAO compared with their counterparts who did not. In those who underwent LAAO versus those who did not receive LAAO RD (HR=-0.01; 95% CI -0.03 to -0.00; $P=0.02$) for	LAAO is potentially superior to no LAAO in terms of reducing the incidence of embolic events and MACE in patients with AF

					correspondence articles		embolic events between patients	
Ibrahim, 2019	¹⁸⁷	Systematic review and meta-analysis of RCT and observational studies	13 352	S-LAAO vs. no S-LAAO	Inclusion: studies compared all forms of cardiac surgery performed with or without left atrial appendage occlusion; Exclusion: studies that did not include outcomes including ischemic stroke or systemic embolism, postoperative AF, and all-cause mortality	There was no difference of postoperative AF between S-LAAO and non-LAAO (OR=0.13; 95% CI 0.81–2.06; <i>P</i> =0.28). S-LAAO group was associated with reduced risk of all-cause mortality compared with the non-LAAO group (OR=0.74; 95% CI 0.55–0.99; <i>P</i> =0.041)	The S-LAAO group was associated with a reduced risk of stroke (OR=0.66; 95% CI 0.52–0.83; <i>P</i> =0.001) compared with the non-LAAO group. Bias: variations of surgical techniques; successful closure of the LAA varies between different techniques; only 3 RCTs with small sample sizes	S-LAAO has shown to be an effective technique in preventing ischemic stroke or systemic embolism and all-cause mortality when compared with the non-LAAO cohort
Soltesz, 2022	¹⁸⁸	Retrospective	4210 from Medicare	Isolated CABG (i.e.,	Inclusion: age≥65 at the time of	In the IPT-weighted 2-year	In a Medicare cohort of patients with AF	Concomitant LAA exclusion

		registry	data	without ablation) with (n=931) or without (n=3279) left atrial appendage clip exclusion	CABG admission and presented with either persistent or paroxysmal AF. Exclusion: patients not continuously eligible for Medicare 2015–2017 or with missing records; a major cardiac procedure (including surgical ablation) concomitant to or one year before the index CABG	time-to-event analysis thromboembolism risk was reduced by 26% in the CABG + LAACE group (HR=0.74; 95% CI 0.54–1.00; <i>P</i> =0.05). IPT weighted ischemic stroke did not differ (HR=0.74; 95% CI 0.49–1.11, <i>P</i> =0.14). Late follow-up period IPW weighted mortality was significantly lower for the CABG + LAACE group (HR=0.55; 95% CI 0.32–0.95;	undergoing cardiac surgery without concomitant ablation, CABG + LAACE compared with isolated CABG was associated with a significantly lower risk of thromboembolism, all-cause mortality, and hospital readmissions. While observational in nature, this analysis supports the use of LAACE in patients with AF at the time of CABG surgery	via an epicardial closure device is associated with reduced CABG mortality, thromboembolic events, and readmissions in patients with pre-existing AF. CABG + LAACE was associated with a decrease in thromboembolic event rate, fewer hospital readmits and lower all-cause mortality in Medicare

						$P=0.031$)		beneficiaries with AF compared with isolated CABG patients in a real-world setting

Additional Evidence Table S11 — Surgical left appendage occlusion

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Zhang, 2022	¹⁸⁹	Systematic review and meta-analysis of RCT and observational studies	1958	Catheter left atrial appendage occlusion combined with ablation (COA) versus thoracoscopic surgical left atrial appendage clipping combined with ablation (TCA)	Inclusion: Patients with AF after at least 12 months of follow-up studies; patients undergoing COA or TCA (including hybrid ablation) due to isolated AF; reporting outcomes of interest Exclusion: case reports, abstracts, as well as editorial	Stroke and all-cause mortality during follow-up as well as complications and mortality occurring in the postprocedural period	No significant difference in stroke and all-cause mortality (stroke: $P=0.504$; all-cause mortality: $P=0.611$). COA group had a higher acute success rate compared with TCA group ($P=0.001$). COA placed the patients at a higher risk of hemorrhage during the postprocedural period compared with TCA	No significant difference in stroke prevention was found in patients undergoing COA versus TCA after at least 12-month follow-up. COA and TCA were similar in terms of all-cause mortality during the follow-up period. The COA group had a higher acute success

					comments and review articles; studies unpublished or with insufficient data; follow-up less than 12 months; surgical procedures concomitant with other intra-cardiac interventions, such as mitral valve or CABG		($P=0.023$). A similar risk of other postprocedural complications was found in the COA group in comparison with TCA group ($P>0.05$)	rate than TCA group. COA placed the patients at a higher risk of haemorrhage during the perioperative period
Van Laar, 2018	¹⁹⁰	Prospective cohort study	222	Thoracoscopic LAA clipping	Inclusion: consecutive patients who underwent thoracoscopic LAA clipping in 4 major referral centres in the	Complete closure was achieved in 95.0% (211 of 222) as assessed by CT scan or TOE after a median period of 6 months after the LAA clipping procedure	The high LAA closure rates (95.0%), the absence of clip-related complications, and a low rate of cerebrovascular	Thoracoscopic LAA clipping is a feasible and safe LAA closure approach with lower-than-expected rates of stroke after

					Netherlands and the United States; all patients had symptomatic, drug-refractory AF, and their cases were discussed by the multidisciplinary AF care team (the AF Heart Team) consisting of dedicated cardiac surgeons and electrophysiologists	(IQR: 3–8 months). No patients died during 30-day follow-up. Overall freedom from any 30-day complication was 96.4%. The freedom from the combined endpoint of ischemic stroke, hemorrhagic stroke, or TIA was 99.1% over 369 patient-years of follow-up	events at 0.5 per 100 patient-years. To put these findings into context, for a CHA ₂ DS ₂ -VASc=2 is 0.7 per 100 patient-years for those receiving full anticoagulation therapy	deployment
Fu, 2019	¹⁹¹	Prospective cohort study	492	Prospective study comparing	Inclusion: ≥18 years; history of paroxysmal,	Thoracoscopic LAA occlusion was associated with a	Thoracoscopic LAA occlusion was associated with a	Thoracoscopic LAA occlusion is a reasonable

				thoracoscopic LAA occlusion and warfarin therapy	persistent, and permanent AF; CHADS₂≥1. Exclusion: diseases that required long-term anticoagulant therapy except AF; surgical LAA occlusion combined with CABG or valve replacement; diseases that could cause embolism except AF (include atrial septal defect, mechanical heart valve prosthesis,	lower risk to warfarin for the primary efficacy composite endpoint of preventing stroke, SE, and cardiovascular/unexplained death; the thoracoscopic LAA occlusion was superior to warfarin for the occurrence of late ischemic events, such as stroke or SE >7 days' post-operation to exclude the effect of early periprocedural events; the surgical group also had significantly lower bleeding risk	lower risk to warfarin for the primary efficacy composite endpoint of preventing stroke, SE, and cardiovascular/unexplained death. Bias: single centre	alternative to chronic long-term warfarin therapy for stroke/systemic embolization prevention in patients with NVAf

					patent foramen ovale with atrial septal aneurysm, LVEF<30%, intracardiac thrombus, complex (mobile or ulcerated) atherosclerotic aorta, symptomatic carotid artery disease), contraindication to warfarin or aspirin			
Cartledge, 2022	¹⁹²	Retrospective cohort study	175	Standalone thoracoscopic LAAE	Inclusion: NVAF who underwent isolated thoracoscopic LAAE at 3 US and European	Perioperative: complete LAAE was achieved intraoperatively in 99.4% patients and no periprocedural	Predicted annual ischaemic stroke rate of 4.8/100 patient-years (based on median CHA ₂ DS ₂ -VASc	Standalone totally thoracoscopic LAAE is feasible, safe and durable option for AF

					centres	complications in 92% of patients. Long term outcomes: in patients with successful LA AE, no ischaemic strokes occurred during follow-up. Based on the CHA₂DS₂-VASc score [IQR 3.0–5.0], predicted ischaemic stroke rate for this population was 4.8/100 patient-years. The actual stroke rate (95% CI 0–2.0/100 patient-years) was significantly reduced from predicted level ($P<0.001$). During follow-up, no major bleeding was	score of 4.0) was significantly higher than stroke risk observed in follow-up after LA AE	patients with contraindications /intolerance for routine DOAC. AF-related thromboembolism risk including stroke may be potentially reduced with this new method

						reported		

Evidence Table 12 for Recommendation Table 12 (Sec. 6) — Recommendations for assessment of bleeding risk factors

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Harskamp , 2022	¹⁹³	Systematic review and meta-analysis of RCTs	71 527 (5 studies)	Hypertension (HTN) vs. no-HTN in patients randomised to DOAC vs. VKA	Populations with AF randomised to DOAC/VKA, in which the comparative safety and efficacy was stratified by HTN status and/ or blood pressure control	Stroke or systemic embolism, haemorrhagic stroke, intracranial bleeding, and major bleeding	Patients with HTN haemorrhagic stroke (HR=1.98; 1.24–3.16) compared with patients without HTN at baseline. No difference on intracranial hemorrhage and major bleeding	Patients with HTN on anticoagulant are at greater risk of haemorrhagic stroke

							events in those with vs. without HTN	
White, 2007 (SPORTI F III and V)	194	RCTs	3587	Patients were randomized to receive a fixed dosage of the oral direct thrombin inhibitor Ximelagatran or adjusted-dose warfarin in an open-label fashion	Inclusion: persistent or paroxysmal AF and: previous stroke, SEE, or transient ischemic attack (TIA); hypertension and LVEF <40% or symptomatic systolic or diastolic heart failure); 75 years or older, or ≥ 65 years with known coronary disease or	Outcomes would be analysed according to INR control: major bleeding, hemorrhagic strokes & minor bleeding	Major bleeding rates were lower with moderate and good INR control compared with poor INR control ($P<0.01$). All bleeds (major and minor combined) were less frequent with good INR control compared with moderate or poor INR	Patients with poor INR control were associated with increased rates of death, bleeding, MI, and stroke or SEE compared with patients with good INR control. Assiduous INR control with warfarin administration is likely to be associated with better patient outcomes

					diabetes mellitus		control ($P<0.01$)	
DiMarco, 2005 (AFFIRM)	¹⁹⁵	RCT	4060	Rate-control vs. rhythm-control strategy	Inclusion: recurrent persistent AF or flutter, in whom oral anticoagulation was not contraindicated . Exclusion: arrhythmia had lasted longer >1 year; usual exclusion criteria for ECV; patients with NYHA class IV HF; current or previous treatment with	Major bleeding events	Diabetes at baseline for risk of major bleeding (HR=1.44; 95% CI 1.07–1.93); $P=0.02$)	Diabetes increases the risk of major bleeding when treated with warfarin

					amiodarone, or a pacemaker; patients were required to have undergone one ECV during the previous two years, with a maximum of two			
Gallego, 2012	¹⁹⁶	Prospective cohort study	965 consecutive anticoagulated outpatients with permanent or paroxysmal AF who were	The usefulness of the HAS-BLED score for predicting both major bleeding and cardiovascular events in a cohort of anticoagulated patients with	Inclusion: permanent or paroxysmal AF on OAC; INR between 2.0 and 3.0 during the previous 6 months of clinic visits. Exclusion: prosthetic heart valves,	Independent predictors for adverse cardiovascular events were age >75 years (HR=2.20; 95% CI, 1.40–3.46; <i>P</i> =0.001), heart failure (HR=1.78;	The incidence of both bleeding and adverse cardiovascular events was higher as HAS-BLED score increased, and crude bleeding rates only exceeded	The HAS-BLED score not only is useful in the assessment of bleeding risk, but is increased with the incidence of both bleeding and adverse

			stabilized for at least 6 months on oral anticoagulation	AF	acute coronary syndrome, stroke (ischemic or embolic), valvular AF, or any hemodynamic instability as well as patients who had hospital admission or surgical intervention in the preceding 6 months	95% CI, 1.20–2.86; $P=0.001$), and previous stroke (HR=1.85; 95% CI, 1.20–2.86; $P<0.001$). The HAS-BLED score was highly predictive for major bleeding events (HR=2.04; 95% CI, 1.68–2.49; $P<0.001$) and adverse cardiovascular events (HR=1.51; 95% CI, 1.27–	thrombotic events at a HAS-BLED score >3 . The HAS-BLED score also predicted all-cause mortality (HR=1.68; 95% CI, 1.40–2.01; $P<0.001$). Bias: selection bias;	cardiovascular events

						1.81; $P<0.001$)		
Bouillon, 2016	¹⁹⁷	Retrospective cohort study	90 826	Bridging risks during vitamin K antagonist initiation in outpatient settings (individuals starting oral anticoagulation for nonvalvular AF managed in outpatient care and identified from French healthcare insurance)	Inclusion: ≥ 18 years who had their first VKA. Exclusion: history of heart valve disease or surgery, cancer, dialysis for renal failure, any lesion or condition posing a high risk of major bleeding such as anemia, hepatic impairment/ liver disease, current or recent gastroduodena	Primary outcome was bleeding	At 1 month of follow-up, the incidence of bleeding was higher in the bridged group compared with the non-bridged group (0.47% vs. 0.30%; $P<0.001$), and this increased risk persisted after adjustment for covariates (HR=1.60; 95% CI 1.28–2.01)	Bridging therapy was associated with a higher risk of bleeding in patients taking a VKA

					l ulceration, dementia, and recent lower limb surgery			
Schulman , 2008	¹⁹⁸	Part of Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines	N/a	VKA therapy, targeted international normalized ratio (INR) of 2.5 (range, 2.0–3.0), is associated with a lower risk of bleeding than therapy targeted at an INR >3.0	Bleeding is the major complication of anticoagulant and fibrinolytic therapy. The criteria for defining the severity of bleeding vary considerably between studies, accounting in part for the variation in the rates of bleeding reported. The	Low-molecular-weight heparin (LMWH) is associated with less major bleeding compared with UFH in acute venous thromboembolism. Higher doses of UFH and LMWH are associated with important increases in major bleeding in ischemic	Both major bleeding and mortality rates are significantly higher in patients with time in therapeutic range (TTR) <60% (3.85–4.20%) compared with those with TTR >75% (1.58–1.69%)	Incidence of major bleeding for patients with a target international normalized ratio (INR)>3.0 is twice as high as in those with a target INR between 2.0–3.0

					major determinants of vitamin K antagonist (VKA)-induced bleeding are the intensity of the anticoagulant effect, underlying patient characteristics, and the length of therapy	stroke		
Olesen, 2011	¹⁹⁹	Registry	132 372 discharged with non-valvular AF in Denmark	Vitamin K antagonists (VKAs) and acetylsalicylic acid (ASA)	All patients with non-valvular AF. Exclusion: if they died, had a thromboembolism, or had a	Hospitalisation or deaths from i) thromboembolism or ii) bleeding	In patients with CHA2DS2-VASc score of 2–9 and HAS-BLED score ≥ 3 , the net clinical benefit for VKA	In patients with AF and at risk of stroke, VKA treatment is associated with a net clinical benefit in patients with a

					bleeding event in this seven days 'quarantine' period		treatment versus no treatment is 2.21 (95% CI 1.93 to 2.50)	high bleeding risk

Additional Evidence Table S12 — Bleeding risk factors

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Hypertension								
Kirchhof, 2020	²⁰⁰	Prospective registry	4127	Uncontrolled HTN (>160/90mmHg) vs. not	Unselected adult patients (aged ≥18 years) with AF who had been newly prescribed rivaroxaban for stroke/systemic embolism prevention in routine clinical practice	Bleeding events	Uncontrolled HTN at baseline vs. not for risk of major bleeding (HR=1.79; 95% CI 1.05–3.05; <i>P</i> =0.034)	Uncontrolled hypertension was associated with increased risk of major bleeding when treated with rivaroxaban
Concomitant antiplatelet/NSAID								
Shireman, 2004	²⁰¹	Retrospective cohort study	10 093 patients on	19.4% received antiplatelet therapy	Inclusion: confirmed AF during chart	Occurrence and time to major bleeding events	2.0% for the warfarin-only group and	Combined warfarin-antiplatelet

			warfarin		review, age 65 years or older, and warfarin. Exclusion: if they were transferred to another acute-care hospital, died during hospitalization, or were discharged against medical advice; managed care enrolment during the 90-days post-index AF hospitalization because CMS did not routinely process these		2.8% for the combined group; the 3-fold difference in ICH remained (0.3% vs. 0.9%; OR=2.95; 95% CI 1.58–5.51). Limitations: observational (unable to exclude prescription bias); unable to track medication use after hospitalization; inability to determine INR or aspirin	therapy was associated with a relative increase in major bleeding risks, although absolute rates remained low

					hospitalization claims		doses; insufficient patient numbers to assess potential increased risk with concomitant aspirin- clopidogrel	
Kirchhof, 2020	²⁰⁰	Prospective registry	4127	Concomitant antiplatelet, NSAIDs or paracetamol vs. not	Inclusion: unselected adult patients (aged ≥18 years) with AF who had been newly prescribed rivaroxaban for stroke/systemic embolism prevention in routine clinical	Bleeding events	Concomitant antiplatelet, NSAIDs or paracetamol at any time during the study vs. not for risk of major bleeding (HR=1.80; 95% CI 1.24–2.61; <i>P</i> =0.002)	Concomitant antiplatelet, NSAIDs or paracetamol was associated with increased risk of major bleeding when treated with rivaroxaban

					practice			
Excessive alcohol intake								
Kirchhof, 2020	²⁰⁰	Prospective registry	4127	Heavy (>80 g alcohol/day) vs. abstinent/mild alcohol consumption	Inclusion: unselected adult patients (aged ≥18 years) with AF who had been newly prescribed rivaroxaban for stroke/systemic embolism prevention in routine clinical practice	Bleeding events	Major bleeding (HR=2.37; 1.24–4.53; P=0.009)	Heavy alcohol consumption was associated with increased risk of major bleeding when treated with rivaroxaban
Inappropriate choice of OAC and incorrect dosing								
Zerah, 2021	²⁰²	Prospective cohort study	22 220	Exposure to oral AT and inappropriate oral AT combinations were defined as deliveries not	Inclusion: ≥ 45 years old and had a first delivery of oral AT from 1 January 2013 to 31 December	Secondary outcomes: the appropriateness of oral AT combinations; major bleeding including	In total, 64% of OAC combinations were inappropriate. However no increased risk	64% of oral AT combinations used had no recommended indication for use with an increased risk

				complying with the guidelines, according to the synthesis of international guidelines	2017. Exclusion: individuals under the age of 45	intracranial	of major bleeding when compared to those on appropriate combinations: (HR=0.83; 0.41–1.68; <i>P</i> =0.62)	of major bleeding. People aged ≥ 80 years were most exposed to this inappropriate prescribing despite also being most at risk of bleeding
Risk of falls								
Donze, 2012	²⁰³	Prospective cohort study	515	Consecutive patients treated with a VKA	Inclusion: adult inpatients and outpatients treated with a vitamin K antagonist. Exclusion: those unwilling or unable (due to severe cognitive impairment) to	First major bleed within 12 months of follow-up	First major bleed rates did not differ significantly between the patients at low risk of falls versus those at high risk of falls: (HR=1.09; 95% CI 0.54–	High risk of falls was not associated with a higher risk of major bleeds compared with low falls risk patients

					provide informed consent		2.21)	
Age								
DiMarco, 2005 (AFFIRM)	¹⁹⁵	RCT	4060	Rate-control vs. rhythm-control strategy	Inclusion: Only patients with recurrent persistent AF or flutter, in whom oral anticoagulation was not contraindicated. Exclusion: arrhythmia had lasted longer than one year; usual exclusion criteria for studies of ECV;	Major bleeding events	Increased age at entry increases risk of major bleeding events (HR=1.05; 95% CI 1.04–1.07; <i>P</i> <0.001)	Increased age increases risk of bleeding in patients treated with warfarin

					patients with NUHA class IV HF; current or previous treatment with amiodarone, or a pacemaker. Patients were required to have undergone one ECV during the previous two years, with a maximum of two			
Gallego, 2012	¹⁹⁶	Prospective cohort study	965	Age ≥75 years	Inclusion: permanent or paroxysmal AF patients on OAC from an outpatient anticoagulation clinic; patients who had an INR	Major haemorrhagic events	HR=1.74; 95% CI 1.05–2.87; <i>P</i> =0.03	An age ≥75 was associated with an increased risk for major bleeding in anticoagulated patients

					2.0–3.0 during the previous 6 months. Exclusion: patients with prosthetic heart valves, ACS, stroke (ischemic or embolic), valvular AF or any hemodynamic instability; patients who had hospital admission or surgical intervention in the preceding 6 months			
Kirchhof, 2020	²⁰⁰	Prospective registry	4127	Increasing age	Unselected adult patients (aged ≥18	Bleeding events	For a 5-year increased risk of major	Increasing age was associated with increased

					years) with AF who had been newly prescribed rivaroxaban for stroke/systemic embolism prevention in routine clinical practice		bleeding (HR=1.25; 95% CI 1.12–1.38; $P<0.001$)	risk of major bleeding when treated with rivaroxaban
Heart Failure								
DiMarco, 2005 (AFFIRM)	¹⁹⁵	RCT	4060	Rate-control vs. rhythm-control strategy	Inclusion: Only patients with recurrent persistent AF or flutter, in whom oral anticoagulation was not contraindicated. Exclusion: arrhythmia had lasted longer	Major bleeding events	Presence of congestive HF increases bleeding risk (HR=1.43; 95% CI 1.09–1.89; $P=0.01$)	Presence of congestive HF increases bleeding risk

					than one year; usual exclusion criteria for studies of ECV; patients with NYHA class IV HF; current or previous treatment with amiodarone, or a pacemaker. Patients were required to have undergone one ECV during the previous two years, with a maximum of two			
Kirchhof, 2020	²⁰⁰	Prospective registry	4127	Presence of heart failure vs. not	Unselected adult patients (aged ≥18 years) with AF who had been	Bleeding events	Presence of HF vs. not at baseline for risk of major bleeding	Presence of HF was associated with increased risk of major bleeding when

					newly prescribed rivaroxaban for stroke/systemic embolism prevention in routine clinical practice		(HR=1.97; 95% CI 1.36–2.86; $P<0.001$)	treated with rivaroxaban
Vascular disease								
Kirchhof, 2020	²⁰⁰	Prospective registry	4127	Presence of vascular disease vs. not	Unselected adult patients (aged ≥ 18 years) with AF who had been newly prescribed rivaroxaban for stroke/systemic embolism prevention in routine clinical practice	Bleeding events	Presence of vascular disease vs. not baseline for risk of major bleeding (HR=1.91; 95% CI 1.32–2.77; $P<0.001$)	Presence of vascular disease was associated with increased risk of major bleeding when treated with rivaroxaban
Renal or hepatic impairment								

DiMarco, 2005 (AFFIRM)	¹⁹⁵	RCT	4060	Rate-control vs. rhythm-control strategy	Inclusion: patients with recurrent persistent AF or flutter, in whom oral anticoagulation was not contraindicated. Exclusion: arrhythmia had lasted longer than one year; exclusion criteria for studies of ECV; patients with NYHA class IV HF; current or previous treatment with amiodarone, or a pacemaker.	Major bleeding events	Hepatic or renal disease risk of major bleeding, (HR=1.93; 95% CI 1.27–2.93; <i>P</i> =0.002)	Hepatic or renal disease increases risk of major bleeding

					Patients were required to have undergone one ECV during the previous two years, with a maximum of two			

Additional Evidence Table S13 — Bleeding risk scores

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Hilken, 2017 (RE-LY)	²⁰⁴	RCT	3623	Randomized patients to dabigatran (110/150 mg BID) or warfarin	Inclusion: documented AF in the preceding 6 months and 1 additional risk factor	Major bleeding	During 6922 person-years of follow-up, 266 major bleedings occurred (rate=3.8; 95% CI 3.4–4.3 per 100 person-years). C statistics for HEMORR2HAGES, Shireman, HAS-BLED, ATRIA, ORBIT SCORE ranged from 0.62 to 0.67 at 1 year and were comparable	Performance of prediction models for major bleeding is modest. Bleeding risk scores cannot guide treatment decisions for oral anticoagulants but may still be useful to identify modifiable risk factors for bleeding. Clinical usefulness may be best for ORBIT, which is

							at 2 years	based on a limited number of easily obtainable variables and showed reasonable performance
Gao, 2021	²⁰⁵	Systematic review and meta-analysis of RCTs and observational studies	589 271 patients. 39 studies (10 post-hoc analysis of RCT)	Diagnostic accuracy of the HAS-BLED score in anticoagulated (VKAs or DOACs) patients with AF and compare the performances of the HAS-BLED score with other risk scores to determine the most	Inclusion: anticoagulated NVAf (≥18 years); RCT/observational studies reporting the diagnostic performance of HAS-BLED; primary outcome of bleeding events. Exclusion: studies that	HAS-BLED score vs. other risk prediction models for bleeding (the HEMORR2HAGES, the ATRIA, the ORBIT, the CHADS2, the CHA2DS2-VASc, the GARFIELD-AF, or the ABC scores)	Pooled analysis for HAS-BLED C-statistic for major bleeding=0.63 (0.6–0.65), any clinically relevant bleeding=0.58 (0.56–0.61), any bleeding=0.57 (0.53–0.61), intracranial bleeding= 0.58 (0.53–0.62), and gastrointestinal bleeding= 0.67	The HAS-BLED score has moderate discrimination for bleeding risks in patients with AF regardless of type of oral anticoagulants. Current evidence support that the HAS-BLED score is at least similar discrimination to the HEMORR2HAG

				appropriate tool for predicting bleeding risks	focused on the non-AF population or patients with AF with specific diseases; patients with AF with certain interventions; other bleeding risk prediction tools then HAS-BLED score; studies reporting the modified HAS-BLED score version; certain publication with insufficient data		(0.55–0.82). Limitations: only 5 RCTs included	ES, the ATRIA, the ORBIT, the GARFIELD-AF, the CHADS2, the CHA2DS2-VASc, or the ABC scores
Caldeira, 2014	²⁰⁶	Systematic review and meta-	5 studies; 253 937	Compare the value added by ATRIA and	Studies with a longitudinal design (either	Sensitivity, specificity, and diagnostic odds	Five studies evaluated simultaneously	The 'high-risk' categories of the evaluated major

		analysis of observational studies	AF patients	HEMORR ₂ HAGES compared to HAS-BLED	prospective or retrospective), evaluating major bleedings and reporting the HAS-BLED score/categories and at least one of HEMORR ₂ HAGES and ATRIA scores in patients with AF (treated or not with anticoagulant drugs)	ratio)	HAS-BLED and HEMORR ₂ HAGES. Sensitivity, specificity, and diagnostic odds ratio were respectively, 0.65 (0.65–0.65) and 2.11 (1.91–2.35) for HAS-BLED, and 0.27 (0.26–0.27), 0.89 (0.89–0.89) and 2.90 (2.77–3.04) for HEMORR ₂ HAGES. Four studies compared HAS-BLED with ATRIASensitivity, specificity, and DOR were respectively 0.41	bleeding-risk scores are not sensitive. HAS-BLED, due to its sensitivity (compared to other scores) and ease to apply, is recommended for the assessment of AF patient" major bleeding risk

							(0.35–0.48); 0.78 (0.76–0.79) and 2.22 (1.08–4.55) for HAS-BLED, and 0.23 (0.17–0.29), 0.91 (0.90–0.91) and 1.98 (1.29–3.03) for ATRIA	
Borre, 2018	²⁰⁷	Systematic review and meta-analysis of observational studies	38 studies	Comparing bleeding risks	Inclusion: NVAF (including atrial flutter) that reported the efficacy of clinical or imaging tools, or patient risk factors, on predicting thromboembolic and/or bleeding	In patients with NVAF, what are the comparative diagnostic accuracy and impact on clinical decision-making of clinical tools and associated risk factors for predicting bleeding events	BRI (4 studies, n=11 939), c statistic range= 0.56–0.65 HEMORR ₂ HAGES (10 studies, n=115 348), c statistic range= 0.53–0.78 HAS-BLED (11 studies, n=194 839), c statistic range= 0.50–0.80	HAS-BLED provides discrimination for bleeding risk

					outcomes. Exclusion: studies that evaluated patients exclusively from Asia, Africa, or the Middle East		ATRIA (7 studies, n=76 163), c statistic range insufficient data ABC (1 study, n= 22 998), c statistic= 0.65	
Loewen, 2011	²⁰⁸	Systematic review and meta-analysis of observational studies	6 studies	Evaluate the performance of clinical prediction rules (CPR) for estimating bleeding risk in patients on OAC therapy based on research published since 2006	Inclusion: evaluated the ability of a CPR using only readily available clinical parameters to distinguish between patients at high and low risk of experiencing major bleeding	Individual trial and pooled analyses using likelihood ratios for mOBRI and HAS-BLED showed they have weak discrimination accuracy. A RIETE score of 0 point was moderately predictive of the	None of the CPRs exhibited sufficient predictive accuracy or had sufficient validation to be recommended for routine use in practice. None of the available CPRs exhibit sufficient predictive	None of the available CPRs exhibit sufficient discrimination accuracy or have trials evaluating the impact of their use on patient outcomes

					on warfarin, ximelagatran, rivaroxaban, apixaban, or dabigatran therapy for any indication. Exclusion: studies did not report observed bleeding rates in the CPR risk strata	absence of major bleeding	accuracy or have trials evaluating the impact of their use on patient outcomes	
Prioetti, 2020	²⁰⁹	Systematic review and meta-analysis of observational studies	50 studies; 669 217 patients	Clinical risk scores and mortality	Inclusion: only risk scores built with routinely evaluated clinical criteria; AF original studies with data available on at least one of the risk	Main outcome: all-cause death	HAS-BLED (HR=1.38; 95% CI 1.27–1.49). Risk scores as high-risk category: HAS-BLED ≥3 (HR=2.69; 95% CI 2.36–3.07); ATRIA ≥4 (HR=2.09; 95%	HAS-BLED and ATRIA have modest predictive performance

					scores considered; a study cohort comprising at least 500 patients; and available data on mortality events over at least one year of follow-up observation		CI 1.38–3.16). Limitations: limited data for other scores (mostly CHADS ₂ and CHA ₂ DS ₂ -VASc)	
Sanders, 2018	¹³²	Systematic review and meta-analysis of observational studies	13 studies; 197 312 patients	Comparison of different risk scores (Bleeding Risk Index [BRI], HEMORR ₂ HAGES, HAS-BLED, ATRIA, ABC) in predicting major bleeding events	Inclusion: adult patients with AF; assessment of clinical and imaging tool efficacy for predicting thromboembolic risk and bleeding	Major bleeding events	Limitations: high heterogeneity in populations and bleeding rates. Measures of tool calibration, strength of association, and diagnostic accuracy were inconsistently	Evidence favours HAS-BLED based on two studies demonstrating that it has statistically significantly higher prediction (by c-statistic) for major bleeding

					events; RCTs, prospective and retrospective observational studies. Exclusion: patients with reversible causes of AF		reported	events than other scores among patients on warfarin, but the majority of comparative studies which evaluated HAS-BLED showed no statistically significant differences in prediction abilities, reducing the strength of evidence (moderate SOE)
Wang, 2017	²¹⁰	Systematic review and meta-analysis of observational	7 studies; 8079 patients	Systematic review and meta-analysis to compare the predictive ability of bleeding risks	Inclusion: prospective or retrospective studies reporting the HAS-BLED and	Outcomes: major bleeding was defined based on the 2005 International Society on	Pooled C-statistic of continuous variables for major bleeding were 0.65 (95%	Compared with HAS-BLED, the ORBIT score does not perform better in predicting major

		nal studies		using the ORBIT and HAS-BLED scores	ORBIT scores for predicting the bleeding risk; non-valvular AF patients with VKA and DOAC	Thrombosis and Haemostasis [ISTH] criteria	CI 0.60–0.69) for ORBIT and 0.63 (95% CI 0.60–0.66) for HAS-BLED. Compared with HAS-BLED, more anticoagulated AF patients (88.45% vs. 32.59%) and major bleeding events (75.57% vs. 25.57%) were categorized as low risk. The ORBIT score had an elevated risk of major bleeding in the low=1.21, intermediate=1.73 and 1.44-fold	bleeding events in anticoagulated AF patients. More anticoagulated AF patients and major bleeding events were categorized as low risk when using ORBIT

							high-risk strata. Calibration analysis demonstrated that the ORBIT score under-predicted major bleeding in the low (OR=0.64; 95% CI 0.37–1.10), intermediate (OR=0.63; 95% CI 0.38–1.05) and high-risk (OR=0.64; 95% CI 0.38–1.06) stratifications	
Zeng, 2020	²¹¹	Systematic review and meta-analysis of	9 studies	To compare the occurrence of major bleeding events across 3 risk categories	Inclusion: studies post hoc ancillary analysis of randomized	Outcome: major bleeding	Compared with HEMORR ₂ HAGE S, there were 87% and 39% reduced rates of	Compared with any of HEMORR ₂ HAGE S, ATRIA, or ORBIT scores,

		observational studies		between HAS-BLED and any of HEMORR ₂ HAGES, ATRIA, or ORBIT scores	clinical trials (RCTs) and observational studies focusing on the HAS-BLED score for predicting the bleeding risk; adult NVAf patients with anticoagulation therapy. Exclusion: studies that reported AF patients with certain interventions (e.g., cardioversion, catheter ablation,		major bleeding in the HAS-BLED “low-risk” and “moderate-risk” groups, respectively. Compared with ATRIA, there was an 89% decreased rate of major bleeding in the HAS-BLED “low-risk” group. Compared with ORBIT, there were 84% and 44% reduced rates of major bleeding in the HAS-BLED “low-risk” and “moderate-risk” groups,	the HAS-BLED score distributed more major bleeding events into the "low" or "moderate" risk categories

					coronary interventions, or left-atrial appendage closure)		respectively. Patients with HAS-BLED scores ≥ 3 showed an approximately 3-fold greater risk of major bleeding compared with patients with scores < 3 (OR=3.00; 95% CI 1.21–7.43)	
Zhu, 2015	²¹²	Systematic review and meta-analysis of observational studies	11 studies	To compare the diagnostic accuracy between the HAS-BLED score and any of HEMORR ₂ HAGES, ATRIA, CHADS ₂ , or	Inclusion: the studies reported the comparative diagnostic performance between the HAS-BLED score and any of the	The patient outcomes (major bleeding, defined as fatal bleeding requiring a transfusion of ≥ 2 units of whole blood or red cells, or hemorrhage into	C-statistic for major bleeding: HAS-BLED (7 studies) C=0.65 (0.61–0.69) HEMORR ₂ HAGES (5 studies) C=0.63 (0.61–0.66) ATRIA (3	The HAS-BLED score not only performs better than the HEMORR ₂ HAGES and ATRIA bleeding scores, but it also is superior to the CHADS ₂ and

				CHA ₂ DS ₂ -VASc scores in anticoagulated patients with AF	HEMORR ₂ HAGES, ATRIA, CHADS ₂ , or CHA ₂ DS ₂ -VASc scores Exclusion: studies including valvular AF patients or individuals who received ablation or PCI procedures; clinically relevant non-major bleeding events (eg, ischemic stroke and minor bleed)	a critical area or organ, or an overt bleed causing a fall in haemoglobin level of ≥ 2 g/dL)	studies) C= 0.63 (0.56–0.72) CHADS ₂ (3 studies) C= 0.55 (0.49–0.61); CHA ₂ DS ₂ -VASc (3 studies) C= 0.56 (0.53–0.59)	CHA ₂ DS ₂ -VASc stroke scores for bleeding prediction. The HAS-BLED score should be the optimal choice to assess major bleeding risk in clinical practice
Prioetti, 2021	²¹³	Prospective registry	3018	To compare the HAS-BLED and	Inclusion: AF documented	Primary outcome: major	HAS-BLED score: those with	In this real-life contemporary

				ORBIT bleeding risk scores in AF patients actually treated with DOACs	within 12 months of enrolment based on objective ECG evaluation; age≥18 years and provided written informed consent	bleeding	high baseline bleeding risk ≥ 3 had more than two-fold increase in risk (HR=2.26; 95% CI 1.23–4.15) compared with the low-bleeding risk group. Major bleeding prediction: AUC=0.65; 95% CI 0.59–0.71. ORBIT score: high baseline bleeding risk (i.e. ORBIT ≥ 4) had more than four-fold increase in risk (HR=4.62, 95% CI 2.25–9.46) compared	cohort of AF patients treated with DOACs, the ORBIT score did not provide reclassification improvement, showing even poorer calibration compared to HAS-BLED. The findings do not support the preferential use of ORBIT in DOAC-treated AF patients

							with ORBIT score <4. Major bleeding prediction: AUC =0.60; 95% CI 0.53–0.68. Limitation: evaluation of bleeding outcomes were performed by each investigator and not adjudicated centrally	
Fox, 2017 (GARFIELD-AF)	²¹⁴	Prospective registry	39 898	GARFIELD-AF risk model	Inclusion: NVAf adults (aged ≥18 years) within the previous 6 weeks and had at least one risk factor for stroke	All-cause mortality, ischaemic stroke/systemic embolism (SE); any major bleed	All-cause mortality c=0.77; Ischaemic stroke/ SE, c=0.69 (95% CI 0.65–0.67); Major bleeding (n=25 677),	GARFIELD-AF risk score is superior to HAS-BLED for bleeding, overall and in lower risk patients

					as judged by the investigator. Exclusion: patients with a transient reversible cause of AF		c=0.66 (95% CI 0.62–0.69) Bias: observational study	

Evidence Table 13 for Recommendation Table13 (Sec. 6) — Recommendations for management of bleeding in anticoagulated patients

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
DOACs								
Milling, 2016	215	RCTs	181	4F-PCC versus plasma	Inclusion: INR ≥2.0 receiving VKA therapy and needing an urgent surgical or invasive procedure within 24 hrs. Exclusion: requirement for a procedure for which an accurate estimate of blood loss was not possible (eg, ruptured	Primary endpoint was haemostasis during urgent surgical or invasive procedures in the intention-to-treat efficacy (ITT-E) population	Effective haemostasis was achieved in 90% patients in the 4F-PCC group compared with 75% patients in the plasma group, demonstrating both non-inferiority and superiority of 4F-PCC over plasma	4F-PCC is non-inferior and superior to plasma for rapid INR reversal and effective haemostasis in patients needing VKA reversal for urgent surgical or invasive procedures

					aneurysm or trauma) or coagulopathy that could be corrected solely through administration of vitamin K and withdrawal of VKA therapy		(difference 14.3%, 95% CI 2.8–25.8)	
Pollack, 2017 (RE-VERSE AD)	²¹⁶	Prospective cohort study	503	5 g of intravenous idarucizumab would be able to reverse the anticoagulant effect of dabigatran in patients who had uncontrolled bleeding (group A) or	Inclusion: adults who were receiving dabigatran	Primary efficacy end point was the maximum percentage reversal of the anticoagulant effect of dabigatran	The median maximum percentage reversal of dabigatran was 100% (95% CI 100–100), on the basis of either the diluted thrombin time or the ecarin clotting time. In	In emergency situations, idarucizumab rapidly, durably, and safely reversed the anticoagulant effect of dabigatran

				were about to undergo an urgent procedure (group B)			group A, 137 patients (45.5%) presented with gastrointestinal bleeding and 98 (32.6%) presented with intracranial hemorrhage; among the patients who could be assessed, the median time to the cessation of bleeding was 2.5 hours. In group B, the median time to the initiation of the intended procedure was	

							1.6 hours; periprocedural hemostasis was assessed as normal in 93.4% of the patients, mildly abnormal in 5.1%, and moderately abnormal in 1.5%	
Connolly, 2019 (ANNEXA-4)	²¹⁷	Prospective cohort study	352	Bolus of Andexanet, followed by a 2-hour infusion	Inclusion: ≥18 years, presented with acute major bleeding, and had received within 18 hours one of the following: apixaban, rivaroxaban, or edoxaban at any dose or	The coprimary outcomes were the percent change in anti-factor Xa activity after Andexanet treatment and the percentage of patients with excellent or good haemostatic	In patients who had received apixaban, the median anti-factor Xa activity decreased from 149.7 ng/mL at baseline to 11.1 ng/mL after the	In patients with acute major bleeding associated with the use of a factor Xa inhibitor, treatment with Andexanet markedly reduced anti-

					Enoxaparin at a dose of at least 1 mg/kilogram of body weight/day. Exclusion: planned surgery within 12 hours after Andexanet treatment; intracranial haemorrhage in a patient with GCS score of less than 7 to 3 or an estimated hematoma volume of more than 60 cc; expected survival of less than 1 month; the occurrence of a thrombotic event	efficacy at 12 hours after the end of the infusion, with haemostatic efficacy adjudicated on the basis of prespecified criteria	Andexanet bolus (92% reduction; 95% CI 91–93); in patients who had received rivaroxaban, the median value decreased from 211.8 ng/mL to 14.2 ng/mL (92% reduction; 95% CI 88–94). Excellent or good haemostasis occurred in 82% of the patients who could be evaluated	factor Xa activity, and 82% of patients. Had excellent or good haemostatic efficacy at 12 hours

					within 2 weeks before enrolment; or use of any of the following agents within the previous 7 days: VKA, dabigatran, prothrombin complex concentrate, recombinant factor VIIa, whole blood, or plasma			
Fanikos, 2020	²¹⁸	Retrospective cohort study	359	Potential sites where idarucizumab was dispensed	Inclusion: ≥ 18 years receiving idarucizumab as part of their clinical care were eligible, regardless of prior OAC use. Exclusion: patients	Characteristics of patients and sites receiving idarucizumab	Real-world information from the RE-VECTO surveillance program adds to the data obtained from idarucizumab clinical trials	The RE-VECTO study confirmed that 5 g of idarucizumab was used appropriately in > 98% of dabigatran-treated patients

					participating in a dabigatran or idarucizumab clinical trial		and provides valuable insights into the current strategies employed to reverse the anticoagulation effects of dabigatran in emergency situations. Usage patterns of idarucizumab were aligned with idarucizumab prescribing information, with minimal off-label use	with life-threatening bleeding or in need of emergency surgery

Additional Evidence Table S14 — Management of bleeding

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
DOACs								
Milling, 2023 (ANNEXA-4)	219	Prospective cohort study	479	Bolus of Andexanet, followed by a 2-hour infusion	Inclusion: those ≥18 years of age presenting with acute major bleeding and having received one of the following within 18 hours: apixaban, rivaroxaban, edoxaban, or	The 2 co-primary efficacy end points: percent change from baseline in anti-FXa activity after andexanet alfa treatment and percentage of patients with	In evaluable apixaban patients (n=172), median anti-FXa activity decreased from 146.9 ng/mL to 10.0 ng/mL (reduction, 93% [95% CI, 94–93]); in rivaroxaban	In patients with major bleeding associated with the use of FXa inhibitors, treatment with andexanet alfa reduced anti-FXa activity and was associated with good or excellent haemostatic efficacy in 80% of patients

					enoxaparin (the latter at a therapeutic dose of ≥ 1 mg/kg). Exclusion: patients on low-dose FXa inhibitors for coronary or peripheral vascular disease	excellent or good haemostatic efficacy at 12 hours after andexanet alfa infusion	patients (n=132), it decreased from 214.6 ng/mL to 10.8 ng/mL (94% [95% CI, 95–93]); in edoxaban patients (n=28), it decreased from 121.1 ng/mL to 24.4 ng/mL (71% [95% CI, 82–65]); and in enoxaparin patients (n=17), it	

							decreased from 0.48 IU/mL to 0.11 IU/mL (75% [95% CI, 79–67]). Excellent or good haemostasis occurred in 274 of 342 evaluable patients (80% [95% CI, 75–84])	

Evidence Table 14 for Recommendation Table 14 (Sec. 7) — Recommendations for heart rate control in patients with atrial fibrillation

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings	Conclusion(s)
Rate Control: Indications								
Ziff, 2015	220	Systematic review and meta-analysis of both RCT and observational studies	Patients: 621 845	Intervention: treatment with digoxin compared with placebo or no treatment	Inclusion: studies published from 1960 to July 2014 that examined treatment with digoxin compared with control (placebo or no treatment); all cardiovascular outcomes and all populations Exclusion: studies that did not provide comparative outcomes	Primary outcome: all-cause mortality. Secondary outcomes: cardiovascular mortality; admission to hospital for any cause; cardiovascular causes and heart failure; incident stroke; incident	Digoxin had no effect on death in adjusted analyses and RR=0.99 (95% CI 0.93–1.05) in RCTs. Baseline differences between treatment groups had a significant impact on mortality associated with digoxin (P=0.004).	Digoxin is associated with a neutral effect on mortality in randomized trials and a lower rate of admissions to hospital across all study types. Regardless of statistical analysis, prescription biases limit the value of observational

						myocardial infarction	Across all study types, digoxin led to a reduction in all cause hospital admission (RR=0.92; 95% CI 0.89–0.95; $P<0.001$; n=29 525). Studies with higher bias reported a greater association of digoxin with death ($P<0.001$)	data
Van Gelder, 2010 (RACE II)	²²¹	RCT	Patients: 614 patients (mean age 68 ± 8 years, 66%	Intervention: Group 1 (n=311): Lenient rate control, target resting heart rate <110	Inclusion: a current episode of permanent AF ≤12 months documented on two consecutive ECGs; ≤80 years; mean resting heart	Primary outcome: composite of cardiovascular death, hospitalization for heart	Primary outcome: 12.9% in the lenient-control group and 14.9% in the strict control group; an	Lenient rate control was noninferior to strict rate control in the prevention of major

			men)	b.p.m. Group 2 (n=303): Strict rate control. Target resting heart rate <80b.p.m. and a target heart rate <110 b.p.m. during moderate exercise	rate >80 b.p.m. with or without rate control medication; current use of oral anticoagulation therapy Exclusion: paroxysmal AF; known contraindications for either strict or lenient rate control; unstable heart failure; cardiac surgery <3 months; any stroke; current or foreseen pacemaker, ICD, and/or CRT; signs of sick sinus syndrome or AV conduction disturbances; untreated hyperthyroidism or <3 months euthyroidism;	failure, and stroke, systemic embolism, major bleeding, and arrhythmic events Secondary outcome: the components of the primary outcome; death from any cause; symptoms; functional status	absolute difference of -2.0 percentage points (90% CI - 7.6 to 3.5) and a HR=0.84 (90% CI 0.58–1.21). As compared with strict rate control, lenient rate control was noninferior with regard to the prevention of the primary outcome, for both the criteria of the difference in risk ($P<0.001$) and the HR ($P=0.001$)	cardiovascular events in patients with permanent AF. For both patients and health care providers, lenient rate control is more convenient, since fewer outpatient visits and examinations are needed

					inability to walk or bike			
Brignole, 2021 (APAF-CRT)	²²²	RCT	Patients 133 patients (mean age 73 ± 10 years, 53% men)	Intervention Group 1 (n=63): AV junction ablation and biventricular pacing. Group 2 (n=70): optimal pharmacological rate control therapy	Inclusion: severely symptomatic permanent AF (>6months), which has been considered unsuitable for AF ablation or in which AF ablation had failed; narrow QRS (≤110 ms); at least one hospitalization for HF in the previous year. Exclusion: Hospital NYHA class IV and SBP ≤80 mmHg despite optimized therapy; severe concomitant non- cardiac disease; need for surgical intervention; MI within	Primary outcome: time to all-cause mortality. Secondary outcome: Time to the composite of all-cause mortality or hospitalization due to heart failure, whatever came first	All-cause mortality occurred in 7 patients in the ablation + CRT arm and in 20 patients in the drug arm (HR=0.26; 95% CI 0.10–0.65; P=0.004). The secondary endpoint was significantly lower in the ablation + CRT arm: 18 vs. 36 (HR=0.40; 95% CI 0.22–0.73; P=0.002). A benefit in all-	Ablation + CRT was superior to pharmacologi cal therapy in reducing mortality in patients with permanent AF and narrow QRS who were hospitalized for HF, irrespective of their baseline ejection fraction

					the previous 3 months; previously implanted devices (pacemaker/ICD/CRT) with $\geq 5\%$ pacing function		cause mortality was observed in patients with EF $>35\%$ (HR=0.27; 95% CI 0.08–0.84; P=0.024) with no interaction with patients with EF $\leq 35\%$ (HR=0.34; 95% CI 0.06–1.92; P=0.22)	
Karth, 2001	²²³	RCT	Patients: 60 (mean age 67 ± 10 years, 72% men)	Intervention: Group 1 (n=20): diltiazem in a 25 mg bolus followed by a continuous infusion of 20 mg/hr for 24 hours. Group 2 (n=20): amiodarone in a	Inclusion: critically ill patients with recent-onset tachycardic AF (AF with a rate consistently >120 b.p.m. over a 30-min period). Exclusion: concurrent treatment with class I-IV antiarrhythmic drugs; severe hepatic	Primary outcome: success was defined as a sustained heart; rate reduction of $\geq 30\%$ within a 4-hr period and maintenance	Rate reduction $\geq 30\%$ rate reduction within 4 hours was achieved in 70%, 55% and 75% of patients in groups 1, 2, and 3, respectively (P=0.38). Hypotension,	Sufficient rate control can be achieved in critically ill patients with atrial tachyarrhythmias using either diltiazem or amiodarone.

				300 mg bolus. Group 3 (n=20): amiodarone in a 300 mg bolus followed by 45 mg/hr for 24 hours	failure; severe thyroid dysfunction; uncorrected low serum potassium (<3.5 mmol/L) and/or magnesium levels (<0.7 mmol/L); age <19 years	of this reduction until the end of the 4-hr period. Secondary outcome: controlled tachycardia was defined as a heart rate of ≤120 b.p.m.; uncontrolled tachycardia was deemed present if the heart rate could not be reduced below 120 b.p.m. within 4 hr after study drug	which necessitated a premature discontinuation of the study medication, occurred more often in the diltiazem group (30%, 0%, 5%, <i>P</i>=0.01)	Although diltiazem allowed for significantly better 24-hr heart rate control, this effect was offset by a significantly higher incidence of hypotension requiring discontinuation of the drug. Amiodarone may be an alternative in patients with severe hemodynamic

						administration; hypotension		compromise
Brignole, 2018 (APAF-CRT)	²²⁴	RCT	Patients: 102 (mean age 72 ± 10 years, 55% men)	Intervention: Group 1 (n=50): AV junction ablation and biventricular pacing. Group 2 (n=52): Optimal pharmacological rate control therapy	Inclusion: severely symptomatic permanent AF (>6months), which has been considered unsuitable for AF ablation or in which AF ablation had failed; narrow QRS (≤110 ms); at least one hospitalization for heart failure in the previous year. Exclusion: hospital NYHA class IV and SBP ≤80 mmHg despite optimized therapy; severe concomitant non- cardiac disease; need for surgical	Primary outcome: composite of death due to heart failure, or hospitalization due to heart failure, or worsening heart failure, whichever occurred first. Secondary outcome: total mortality; hospitalization for heart failure; worsening heart failure	Primary outcome: 10 patients in the ablation+CRT arm and in 20 patients in the Drug arm (HR 0.38; 95% CI 0.18–0.81; P=0.013). A total of 5 patients receiving ablation+CRT and 13 patients receiving drugs had hospitalization for heart failure (HR=0.30; 95% CI 0.11–0.78; P=0.024). The	The strategy of AV junction ablation and CRT is both safe and superior to conventional medical strategy in relieving symptoms of heart failure and reducing hospitalization for heart failure in elderly patients affected by permanent AF and

					intervention; myocardial infarction within the previous 3 months; previously implanted devices (pacemaker/ICD/CRT) with ≥5% pacing function		greatest improvements in symptoms were observed in ablation and CRT patients with EF >35%, P=0.003, with a ≥ 1 point reduction in EHRA score in 90% of cases (P=0.003)	narrow QRS
Andrade, 2016	²²⁵	RCTs	5164 patients (34.8% female, age 68.2 ± 8.3 years)	Intervention: strategy of rate control with beta- blockers, non- dihydropyridine calcium channel blockers and/or digoxin, or rhythm control (antiarrhythmic drugs with or	Inclusion: history of non- permanent AF and either a high risk of stroke or death (AFFIRM), or symptomatic or severe left ventricular systolic dysfunction	The primary outcome was mortality based (ie, all-cause mortality in AFFIRM and cardiovascular mortality in AF- CHF)	An elevated baseline heart rate in sinus rhythm was associated with increased all- cause mortality (HR=1.24 per 10 b.p.m. increase; 95% CI 1.14– 1.36; <i>P</i> <0.0001).	In patients with a history of AF, an elevated baseline heart rate in sinus rhythm is independently associated with mortality. In contrast, the

				without electrical cardioversion)	(ejection fraction $\leq 35\%$)		Bias: retrospective study in nature; subject to the limitations inherent to post hoc analyses; possibility of residual confounding	baseline heart rate in AF is not associated with mortality but predicts hospitalizations
Olshanksy, 2004 (AFFIRM)	²²⁶	RCT	2027 patients (mean age 70 $\pm$ 9 years, 59% men)	Intervention: rate-control in AF patients at high risk of stroke or death	Inclusion: patients assigned to the rate-control arm in the AFFIRM trial. Exclusion: not mentioned	Primary outcome: adequate “overall” pharmacologic rate control at rest and with exercise while taking the initial drug class chosen, after dose optimization by the treating	% of patients who achieved rate control at rest: beta-blocker (with or without digoxin)=75%, digoxin alone= 68% & calcium channel blocker (with or without digoxin)= 66%. % of patients who achieved	Rate control in AF is possible in the majority of patients with AF. Beta-blockers were the most effective drugs. To achieve the goal of adequate rate control in all patients,

						physician	adequate overall rate control: first drug combination or combination= 58%. 37% patients required a change in or the addition of another drug. More patients taking digoxin or a calcium channel blocker were changed to another drug, as compared with patients taking beta-blockers ($P<0.0001$)	frequent medication changes and drug combinations were needed
Kotecha, 2020 (RATE-AF)	¹¹	RCT	160 patients (mean age 76 $\pm$ 8	Intervention: Group 1 (n=80): digoxin, dose range, 62.5–250 μ g/d; mean dose, 161 μ g/d).	Inclusion: $\geq$ 60 years; permanent AF in need for heart rate control from a clinician's	Primary outcome: quality of life using the 36-Item Short Form Health	Primary outcome: no significant between-group difference in the mean SF-36 PCS	Low-dose digoxin as monotherapy is effective for heart rate

			years, 54% men)	Group 2 (n=80): bisoprolol, dose range, 1.25–15 mg/d; mean dose, 3.2 mg/d). Alternative β -blocker treatments were acceptable for those with an intolerance to bisoprolol	perspective; NYHA $\geq$ class II. Exclusion: an established indication for bisoprolol within the last 6 months; baseline heart rate <60 b.p.m.; a second- or third-degree heart block; other arrhythmias; pacemaker dependency or planned implantation; obstructive hypertrophic cardiomyopathy; myocarditis or pericarditis; had received or were	Survey physical component summary score. Secondary outcomes: heart rate, modified European Heart Rhythm Association [EHRA] symptom classification, N-terminal pro-brain natriuretic peptide [NT-proBNP] level; adverse events	in the digoxin versus bisoprolol group (HR=1.4; 95% CI -1.1 to 3.8; $P=0.28$). Secondary outcomes: At 12 months, 8 of 20 outcomes were significantly different (all favouring digoxin). Adverse events were less common with digoxin; 25% of patients vs 64% in bisoprolol group; $P<.001$	control and symptom relief in permanent AF with symptoms of heart failure, and is associated with less adverse events than β -blockers

					planning to undergo heart transplant; major surgery within prior 3 months; any non-cardiovascular disease expected to reduce life expectancy; decompensated heart failure in the last 14 days; receiving kidney replacement therapy			
Tisdale, 1998	²²⁷	RCT	40 patients (diltiazem: mean age 65 ± 8	Intervention: Group 1 (n=20): intravenous diltiazem (a 20 mg bolus dose over a 2-minute period and a 25 mg bolus fifteen minutes later,	Inclusion: patients in whom AF developed within 7 days after isolated CABG surgery. Exclusion: SBP <100mmHg;	Primary outcome: proportion of patients in each group who achieved ventricular rate	Those who received diltiazem achieved ventricular rate control (≥20% decrease in pretreatment	Ventricular rate control occurs more rapidly with intravenous diltiazem than digoxin in AF

			years, 80% men. digoxin: 68 ± 9 years, 80% men) followed by a maintenance infusion of 10 mg/hr. In patients who did not achieve a therapeutic response within 1 hour, the maintenance infusion was increased to 15 mg/hr) Group 2 (n=20): intravenous digoxin (0.5 mg bolus over a 2-minute period, followed by a placebo bolus and maintenance infusion fifteen minutes later)	severe congestive heart failure; serum creatinine >2.0 mg/dL; serum potassium concentration <3.0 mg/dL; serum magnesium concentration <1.0 mg/dL; myocardial infarction within 7 days; history of sinus node dysfunction or second- or third-degree AV block in the absence of a functioning pacemaker; WPW syndrome; digoxin, verapamil, diltiazem, or class	control, which was defined as a ≥20% decrease in pretreatment ventricular rate; time to achieve ventricular rate control, measured from the start of the first bolus	ventricular rate) in a mean of 10 ± 20 (median 2) minutes compared with 352 ± 312 (median 228) minutes for patients who received digoxin ($P<0.0001$). However, response rates associated with diltiazem and digoxin at 12 and 24 hours were not significantly different. In patients who remained in AF, similar results were found. At 12 and 24 hours,	after CABG. However, 12- and 24-hour response rates and duration of postoperative hospital stay associated with the two drugs were similar

					1A, 1C, or III antiarrhythmic agents within five half-lives before administration of the study drug; mechanically ventilated patients; patients receiving dopamine, dobutamine, or norepinephrine		response rates in the two treatment groups were not significantly different ($P>0.05$)	
Ulimoen, 2013 (RATAF)	228	RCT	Patients : 60	Intervention: Group 1: diltiazem sustained-release capsules 360 mg/day. Group 2: verapamil modified-release tablets 240 mg/day. Group 3: metoprolol slow-release tablets 100 mg/day.	Inclusion: >18 years; permanent AF≥ 3 months; heart rate at rest of ≥ 100b.p.m. during the day. Exclusion: congestive HF or ischemic heart disease with concomitant	Heart rate at rest and 24-hour heart rate measured at baseline and at the last day of each of the 4 treatment periods. The Symptom Checklist-	All drugs reduced the heart rate compared to baseline ($P<0.001$ for all). diltiazem and verapamil were equally effective in reducing the daytime heart rate, performing better	All 4 drug regimens reduced the mean 24-hour heart rate significantly. At the standard dosages tested, calcium channel blockers performed

				Group 4: carvedilol immediate-release tablets 25 mg/day	treatment with beta-blockers; hypotension; treatment with class I /III antiarrhythmic drugs; severe renal or hepatic failure; pregnancy	Frequency and Severity (SCL) at baseline and at the last day of each of the 4 treatment periods	than the beta-blockers ($P<0.001$ for all). Compared to baseline, treatment with diltiazem significantly reduced both symptom frequency ($P<0.001$) and severity ($P=0.005$)	better than beta-blockers on heart rate and arrhythmia-related symptoms in patients with permanent, rapidly conducted AF
Figulla,1996	229	RCT	Patients : 186 patients (92 receiving diltiazem, 94 receiving placebo	Intervention: the effect of adjunct diltiazem (60 to 90 mg TID) on standard treatment	Inclusion: 18–70 years; idiopathic dilated cardiomyopathy (IDC) diagnosed within the last 6 months and LVEF was <0.50 , independent of the patient's symptomatic	Primary end point: mortality, listing for heart transplantation during the 2-year study period	After 24 months, only diltiazem significantly increased cardiac index at rest ($P=0.01$) and under a workload ($P=0.02$), systolic and diastolic pressures ($P=0.003$ and	In patients with IDC, the adjunct therapy of diltiazem improves cardiac function, exercise capacity, and subjective status without

			)		status. Exclusion: hypertension; a valvular or congenital heart disease, except for first- or second-degree mitral or tricuspid regurgitation by ventriculography; ongoing myocarditis; coronary artery disease; insulin-dependent diabetes mellitus; systemic diseases such as collagenosis, malignancies, thyroid diseases, and		$P=0.004$), stroke volume index ($P=0.003$), and stroke work index ($P=0.000$) and decreased both pulmonary artery pressure under workload ($P=0.007$) and heart rate ($P=0.001$)	deleterious effects on transplant listing-free survival

					pheochromocytoma; pregnancy; severe liver/kidney disease; alcohol or drug dependency; multimorbidity; previous treatment with any calcium antagonist or β -blocker agent for more than 3 months; second- or third-degree AV block			
Khand, 2003	230	RCT	47 patients (mean age 68 years, 62% men)	Intervention: Phase 1 (duration 4 months): digoxin alone (n=23) versus a combination of digoxin and carvedilol (n=24). The starting dose of carvedilol was	Inclusion: patients with persistent AF (>1 month) and heart failure who receive digoxin and diuretics. Exclusion: resting <60 b.p.m.; SBP <90mmHg; sick	Primary outcome: LVEF; ventricular rate control by 24-h ambulatory ECG; symptoms at the end of phase 2 study. Secondary	The addition of carvedilol to digoxin reduced the mean 24-h ventricular rate ($P<0.0001$), improved symptoms scores ($P<0.05$), LVEF	The combination of carvedilol and digoxin appears generally superior, leads to better ventricular rate control than

				3.125 mg bid, and this was increased at two-week intervals to the target dose of 25 mg bid (up-titration period of two months) or, for patients weighing more than 85 kg, 50 mg bid	sinus syndrome or complete heart block; current treatment with a beta-blocker or heart rate lowering calcium channel antagonist or >200 mg amiodarone; recent major cardiovascular event or procedure; asthma or reversible obstructive airways disease; serum creatinine >250 $\mu\text{mol/l}$ or significant hepatic disease; uncorrected significant valvular	outcome: exercise tolerance; ventricular rate control during steady-state bicycle exercise test; plasma concentration of BNP	($P<0.05$), improve NYHA functional class ($P=0.08$), lowered the mean 24-h ventricular rate during both day and night & reduced the ventricular rate at rest and throughout steady-state exercise (peak ventricular rate 106 vs. 123 b.p.m. on digoxin; $P<0.05$)	either agent alone and therefore should be considered the standard treatment for HF patients with persistent AF

					heart disease; any life-threatening noncardiac disease			
Mulder, 2014 (RACE II)	²³¹	RCT	Patients : digoxin group (n=284) : mean age 68 ± 8 years, 60% men. No-digoxin group (n=324) : mean age 68 ± 8 years,	Intervention: digoxin in patients with permanent AF	Inclusion: patients enrolled in RACE II; completed the dose-adjustment phase. Exclusion: not mentioned	Primary outcome: composite of death from cardiovascular causes, hospitalization for heart failure, and stroke, systemic embolism, major bleeding, and arrhythmic. Secondary outcome: cardiovascular hospitalization; all-cause mortality or heart failure	Primary outcome: the 3-year estimated cumulative incidence was 12.9% in the digoxin group and 13.4% in the no-digoxin group (HR=0.97; 95% CI 0.62–1.52). For the outcomes cardiovascular hospitalization (HR= 1.00; 95% CI 0.69–1.45) and all-cause mortality or heart failure hospitalization	In patients enrolled in the RACE II trial with permanent AF and without severe HF, the use of digoxin was not associated with increased cardiovascular morbidity and mortality

			70% men			hospitalization	(HR=0.62; 95% CI 0.34–1.13), no differences were observed	
Nikolaidou, 2009	²³ 2	Systematic review of RCT and observational studies	Patient s: N/A	Intervention: medical heart rate control in chronic AF	Inclusion: all study designs evaluating or comparing oral digoxin, beta-blockers and calcium antagonists, alone or in combination, for rate control in chronic AF. Exclusion: did not specify concurrent use of digoxin, used single doses of medication or scored “poor” on	Heart rate; symptoms; exercise tolerance	Heterogeneous effects on heart rate control	The combination of calcium antagonists with digoxin or beta-blockers with digoxin has been consistently shown to improve HR control at rest, exercise and over 24 h compared with digoxin alone

					quality assessment			
Scheuermeyer, 2013	²³³	Retrospective cohort study	Patients : 259 (mean age 67 ± 13 years, 56% men)	Intervention: Group 1 (n=100): calcium channel blockers. Group 2 (n=159): beta-blockers	Inclusion: patients with a primary emergency care diagnosis of AF; patients treated only with calcium channel blockers or beta-blockers. Exclusion: patients who had cardiac procedures within 7 days prior to index ED visit; attended the ED only to monitor their anticoagulation; with: sepsis, shock, pneumonia, ACS, acute	Hospital admission after emergency department visit; emergency department length of stay; 7- and 30-day emergency department visits and hospital admission; adverse events	For beta-blockers versus calcium-channel blocker respectively: admission to hospital 27% vs. 31% (difference=4.0%, 95% CI -7.7 to 6.1%); median length of stay of 326 minutes (IQR=199–482 minutes) vs. 302 minutes (IQR=182–55), difference=24 minutes; 95% CI -11–62 minutes; no significant difference in 7- or	Both calcium channel blocker or beta-blocker agents may be considered acceptable in patients with acute AF who do not have underlying medical causes and are not candidates for rhythm control

					decompensated congestive HF, PE, COPD, thyrotoxicosis, hypertensive emergency, drugs overdose, acute valvular disease, or hypothermia		30-day ED revisits or hospital admissions; adverse events 6 vs. 4	
Hess, 2020	²³⁴	Retrospective cohort study	Patients 13 981 patients (median age 82 years, 38% men)	Intervention Strict rate control (n=9100), lenient rate control (n=4617) or poor rate control (n=264)	Inclusion: patients admitted to the hospital between 1 July 2011 until 30 September 2014. Exclusion: patients without a diagnosis of AF or atrial flutter; missing discharge heart rate; missing LVEF assessment; patients who were	Primary outcome: all-cause death at 90 days. Secondary outcome: all-cause death at 365 days; all-cause readmission at 90 and 365 days; all-cause death or all-cause readmission at	Lenient versus strict rate control was associated with higher adjusted risks of death (HR=1.21; 95% CI 1.11–1.33; $P<0.001$), all-cause readmission (HR=1.09; 95% CI 1.03–1.15; $P<0.002$), death or all-cause readmission	In a contemporary cohort of patients admitted with HF, many patients with AF achieved strict-control heart rate goals by the day of discharge. Those who did not were at

					not Medicare fee-for-service beneficiaries and thus could not be linked to the follow-up outcomes data	90 and 365 day; cardiovascular readmission at 90 days and 365 days	(HR=1.11; 95% CI 1.05–1.18; $P<0.001$), but not cardiovascular readmission (HR=1.08; 95% CI 1.00–1.16; $P=0.05$) at 90 days. Associations were comparable in patients with poor rate control & in the presence or absence of reduced ejection fraction	elevated risk of death and readmission. These adverse outcomes were observed irrespective of the presence or absence of reduced LVEF

Additional Evidence Table S15 — Rate control: Drugs

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings	Conclusion(s)
Kotecha, 2014	⁵⁵	Systematic review and meta-analysis of RCTs	Patients: 18 254 (median age 64; 75% men)	Intervention: beta-blockers in patients with HF and AF	Inclusion: RCT in which mortality was a primary or composite outcome of the comparison of beta-blockers vs. placebo in patients with HF. Only unconfounded head-to-head trials with recruitment of more than 300 patients and a planned follow-up of more than 6	Mortality	Beta-blocker therapy led to a significant reduction in all-cause mortality in patients with sinus rhythm (HR=0.73; 95% CI 0.67–0.80; <i>P</i> <0.001), but not in patients with AF (HR=0.97; 95% CI 0.83–1.14; <i>P</i> =0.73), with a significant <i>P</i> value for interaction of	In contrast with the beneficial effects noted for patients with sinus rhythm, beta-blocker therapy has no impact on mortality or cardiovascular hospital admission in patients with HFrEF and AF

					months were eligible to make the project technically feasible and clinically relevant		baseline rhythm ($P=0.002$). The lack of efficacy for the primary outcome was noted in all subgroups of AF, including age, sex, LVEF, NYHA class, heart rate, and baseline medical therapy	
Perrett, 2023	²³⁵	Systematic review and meta-analysis of RCTs	12 studies (1152 participants)	Intervention: intravenous beta-blockers Control: alternative pharmacological agents/ placebo	Inclusion: RCTs, patients ≥ 18 years with AF/AFL requiring acute treatment with at least one arm assessing	No difference between beta-blockers and comparators for: conversion to sinus rhythm (RR	No difference in heart rate control: Heart rate reduction (standardised mean difference –	Across all intravenous beta-blockers, there was no difference with other medications

					intravenous beta-blocker therapy. Exclusion: where intravenous beta-blockers were given in combination to other pharmacological agents, or as prophylactic therapy	1.15, 0.90–1.46; $P = 0.28$), hypotension (RR 1.85, 0.87–3.93; $P = 0.11$), bradycardia (RR 1.29, 0.25–6.82; $P = 0.76$) or adverse events leading to drug discontinuation (RR 1.03, 0.49–2.17; $P = 0.93$)	0.65 beats/minute compared to control, 95% CI – 1.63 to 0.32; $P = 0.19$); proportion that achieved target heart rate (risk ratio [RR] 0.85, 95% CI 0.36–1.97; $P = 0.70$). Limitations: high heterogeneity	for acute heart rate control in AF and flutter. Efficacy and safety may be improved by choosing beta-blockers with higher beta-1 selectivity
Segal, 2000	²³⁶	Systematic review of RCTs	Patients: N/A	Intervention: ventricular rate control for AF	Inclusion: RCT of drugs used for heart rate control in adults with AF. Articles had to address the	Heart rate at rest; heart rate during exercise; exercise tolerance	All comparisons showed that calcium channel blockers were	The calcium-channel blockers verapamil or diltiazem, or select beta-

					management of non-postoperative AF or atrial flutter, include human data, adult subjects and present original data		associated with more efficacy than placebo at reducing heart rate both at rest and during exercise. An improvement in exercise tolerances was almost always seen. All of the tested beta-blockers were associated with a reduction in heart rate with exercise compared with placebo. However, these trials suggest that	blockers are efficacious for heart rate control at rest and during exercise for patients with AF without a clinically important decrease in exercise tolerance. digoxin is useful when rate control during exercise is less a concern

							beta-blockers may be associated with a reduction in exercise tolerance in patients with AF. An improved heart rate control may be associated with calcium channel blockers both at rest and with exercise compared to digoxin	
Van Gelder, 2010 (RACE II)	²²¹	RCT	Patients: 614 patients (mean age 68 ± 8)	Intervention: Group 1 (n=311): lenient rate control,	Inclusion: a current episode of permanent AF ≤12 months	Primary outcome: a composite of death from	Primary outcome: the 3-year estimated	Lenient rate control was noninferior to strict rate

			years, 66% men)	target resting heart rate <110 b.p.m. Group 2 (n=303): strict rate control. Target resting heart rate <80 b.p.m. and a target heart rate <110 b.p.m. during moderate exercise	documented on two consecutive ECGs (without known spontaneous conversion); aged ≤ 80 years; mean resting heart rate >80 b.p.m. with or without rate control medication; current use of oral anticoagulation therapy. Exclusion: paroxysmal AF; known contraindications for either strict or lenient rate control; unstable	cardiovascular causes, hospitalization for HF, and stroke, systemic embolism, major bleeding, and arrhythmic events including syncope, sustained VT, cardiac arrest, life-threatening adverse effects of rate-control drugs, and implantation of a pacemaker or	cumulative incidence of the primary outcome was 12.9% in the lenient-control group and 14.9% in the strict control group, with an absolute difference between lenient control and strict control of -2.0 percentage points (HR=0.84; 95% CI 0.58–1.21). As compared with strict rate control, lenient	control in the prevention of major cardiovascular events in patients with permanent AF. For both patients and health care providers, lenient rate control is more convenient, since fewer outpatient visits and examinations are needed

					HF; cardiac surgery <3 months; any stroke; current or foreseen pacemaker, ICD, and/or CRT; signs of sick sinus syndrome or AV conduction disturbances; untreated hyperthyroidism or <3 months euthyroidism; inability to walk or bike	cardioverter-defibrillator. Secondary outcome: the components of the primary outcome; death from any cause; symptoms; functional status	rate control was noninferior with regard to the prevention of the primary outcome, for both the criteria of the difference in risk ($P<0.001$) and the hazard ratio ($P=0.001$). The HR=0.80; 95% CI 0.55–1.17) after statistical adjustment for the unbalanced distribution of the presence of coronary artery disease, the use of statins,	

							and the DBP	
Siu, 2009	²³⁷	RCT	150 patients (mean age 72 ± 12 years, 56% men)	Intervention: Group 1 (n=50): intravenous diltiazem Group 2 (n=50): intravenous digoxin Group 3 (n=50): intravenous amiodarone	Inclusion: patients who presented to the emergency department of the hospital with symptomatic acute AF for <48 hours and rapid ventricular rate >120 b.p.m. necessitating hospitalization. Exclusion: ventricular rate >200 b.p.m.; pre- excitation syndrome; hypotension (SBP <90 mm Hg); congestive heart failure;	Primary outcome: ventricular rate control within the first 24 hours, defined as sustained ventricular reduction <90 b.p.m. for ≥ 4 hours	90% of patients assigned to diltiazem achieved ventricular rate control, which was more than those assigned to digoxin (74%, <i>P</i> =0.047) and amiodarone (74%, <i>P</i> =0.047). Patients assigned to diltiazem had persistently the lowest mean ventricular rate after the first hour of drug	As compared with digoxin and amiodarone, intravenous diltiazem was safe and effective in achieving ventricular rate control to improve symptoms and to reduce hospital stay in patients with acute AF

					implanted pacemaker and/or ICD; recent myocardial infarction; unstable angina; stroke or thromboembolism within the past 6 months; use of antiarrhythmic and/or atrioventricular nodal blocking drug within the last 7 days (in case of amiodaron, within past 3 months); other major medical conditions including renal		administration compared with the other two groups ($P=0.05$). Substantial reductions in both AF symptom frequency score and severity score were observed in all three groups 24 hours following initiation of ventricular rate control agents (all $P<0.001$). At 24 hours, patients receiving	

					failure, respiratory failure and bleeding disorders		diltiazem had the greatest reduction in both AF symptom frequency score (12.7 ± 6.1 , $P=0.001$) and severity score (9.8 ± 5.7 , $P<0.0001$) compared with those who received digoxin (8.6 ± 5.5 and 6.1 ± 4.7) or amiodarone (9.0 ± 5.9 and 6.1 ± 4.7)	
Schreck, 1997	²³⁸	RCT	30 patients (mean age 72 ± 16)	Intervention: Group 1 (n=11): intravenous	Inclusion: patients with acute onset of AF	Ventricular rate control (heart rate	At time 0, the heart rate was 150 ± 19	Intravenous diltiazem is superior to

			years, 33% men)	diltiazem. Group 2 (n=9): intravenous digoxin. Group 3 (n=10): intravenous diltiazem and digoxin	or atrial flutter. Exclusion: SBP <100 mm Hg; objection of the patient's private physician; treatment with calcium channel blockers other than diltiazem; acute myocardial infarction with pulmonary congestion; acute congestive heart failure (NYHA functional class 3 or 4); cardiogenic shock; sick sinus syndrome; intravenous beta-blocker treatment in the preceding	<100 b.p.m.); conversion to sinus rhythm	b.p.m. in the diltiazem group and 144 ± 12 in the digoxin group ($P=0.432$). The decrease in heart rate from time 0 reached statistical significance at time 5 minutes in the diltiazem group ($P=0.0006$); the mean rates at time 5 minutes were 111 ± 26 b.p.m. for diltiazem and 144 ± 13 b.p.m. for digoxin. The	intravenous digoxin in the emergency control of ventricular rate in acute AF/atrial flutter and should be considered as a drug of choice for this condition. This study was not large enough to adequately assess adverse effects, and further studies may be warranted for clinical validation

					hour; evidence of WPW syndrome; rhythm other than AF/atrial flutter		decrease in heart rate achieved with digoxin did not reach statistical significance until time 180 minutes ($P=0.009$), at which time the rates were 90 ± 13 for diltiazem and 117 ± 22 for digoxin	
Hou, 1995	²³⁹	RCT	50 patients (mean age 70 ± 7 years, 86% men)	Intervention: Group 1 (n=26): amiodarone (infused over 24 h according to the following dosage regimen for a 70-kg subject:	Inclusion: persistent AF or atrial flutter with ventricular rates >130 b.p.m. for less than 10 days. Exclusion: cardiogenic	Primary outcome: conversion to sinus rhythm within 24 h from initiation of treatment. Secondary outcome:	In the digoxin group, 71% converted to sinus rhythm within 24 h at a median of 6.5 h (range: 1–20 h). In the amiodarone	The present study showed that intravenous infusion of amiodarone, using the dosing regimen

				5 mg/min⁻¹ for the first hour, 3 mg/min⁻¹ for the next 3 hours, 1 mg/min⁻¹ for the next 6 hours and 0.5 mg/min⁻¹ for the remaining 14 hours). Group 2 (n=24): digoxin (0.013 mg/kg⁻¹ was infused intravenously in three divided doses, each dose 2 hours apart and infused over 30 minutes)	shock or hypotension (SBP <80 mm Hg); Wolff-Parkinson-White syndrome with AF or atrial flutter and RR intervals <270 ms; sick sinus syndrome; episodes of paroxysmal AF or atrial flutter that had lasted less than 24 h in previous events; consumption of any antiarrhythmic drug; serum potassium <3.5 mEq/l; severe hypoxia, severe	ventricular rates after medication administration; adverse events	group, 92% cases converted to sinus rhythm within 24 h, with a median time to conversion of 2.5 h (range: 0.5–21.5 h). Significantly more patients in the amiodarone group were converted during the 24 h period (P=0.005). The mean heart rates in the amiodarone	proposed, was more efficient than digoxin in controlling the heart rate and conversion to sinus rhythm. However, intravenous amiodarone may precipitate heart failure and induce death infrequently, while digoxin appears to be safer. Therefore, in such cases, the use of digoxin as the

					metabolic acidosis or thyrotoxicosis; onset of AF or atrial flutter within 24 h after or during surgery		group decreased significantly from 157 ± 20 b.p.m. to 122 ± 25 b.p.m. after 1h ($P<0.05$ vs. baseline), and then decreased further to stabilize at 96 ± 25 b.p.m. after 6 h ($P<0.05$). In the amiodarone group, there were 2 serious complications:1 patient eventually died	first line drug for acute treatment of recent-onset AF/atrial flutter is suggested and reserve amiodarone for those who are refractory to, or not suitable for, use of digoxin
Roth, 1986	²⁴⁰	RCT	Patients:12 (48 ± 7 years, 25%	Intervention: treatments were assigned	Inclusion: patients with chronic AF.	Heart rate; blood pressure;	Combined therapy of digoxin and	Medium-dose diltiazem when combined with

			men)	according to the following order: 1) digoxin+ diltiazem. 2) diltiazem alone. 3) patients resumed their regular digoxin therapy and were treated in addition with diltiazem	Exclusion: MI or angina pectoris in the preceding 3 months; severe HF; HTN uncontrolled by diuretics alone; significant renal or hepatic dysfunction; known conduction system disease; Wolff-Parkinson-White syndrome	pressure rate-product. These variables were measured at rest, after 1 min of exercise, after 50% of exercise time, maximal exercise, and 2 min after termination of exercise	diltiazem enhanced the effect of digoxin alone and resulted in significantly better control of heart rate at rest (67 ± 16 b.p.m. with medium-dose and 65 ± 15 b.p.m. with high-dose diltiazem) and during peak exercise (132 ± 32 and 121 ± 24 b.p.m., respectively)	digoxin is an effective and safe regimen for the treatment of patients with chronic AF and enhances digoxin-mediated control of heart rate both at rest and during exercise
David, 1979	²⁴¹	RCT	Patients:28 (mean age 66 years,	Intervention: treatments were assigned	Inclusion: patients with chronic AF.	Mean heart rate during rest; mean	The addition of timolol to the low-dose	Digoxin alone may not suffice to

			82% men)	according to the following order: 1) Low-dose digoxin: 0.25 to 0.5 mg/day 2) Low-dose digoxin + timolol 3) High-dose digoxin + timolol. 4) High-dose digoxin 5) timolol:	Exclusion: signs of congestive heart failure of physical examination and on the chest X-ray film; renal failure; diabetes mellitus; chronic lung disease	heart rate during exercise	digoxin treatment resulted in a significant reduction of the heart rate both at rest (68 ± 15 vs. 91 ± 19, $P < 0.001$) and during exercise (94 ± 9 vs. 135 ± 23, $P < 0.001$) in all patients. The response to the addition of timolol was comparable during high digoxin maintenance (67 ± 13 vs. 91 ± 19 at rest, $P < 0.001$ and	control excessive heart rate in patients with chronic AF. The additional beta-adrenergic blockade actually normalizes the heart rate response in these patients

							92 ± 15 vs. 135 ± 23 during exercise, $P<0.001$)	
Hao, 2022	²⁴²	Systematic review and Meta-analysis of RCTs and observational studies	1349 patients (within 13 RCTs and 4 cohorts)	Intervention: perioperative administration of the intravenous beta-blocker landiolol hydrochloride to prevent AF after cardiothoracic surgery	Inclusion: RCT or cohort studies; studies had to be relevant. Exclusion: review, case report, single sample experiments, comments and editorials; studies with no human subjects	Occurrence of AF; complications; length of hospital stay; mortality rates	Compared with control group, landiolol administration was associated with a significant reduction of the occurrence of AF after cardiothoracic surgery (OR=0.32; 95% CI 0.23–0.43; $P<0.001$). In addition, the results demonstrated that	Landiolol was associated with effectiveness in the prevention of AF after cardiothoracic surgery and was not associated with an increase in the risk of major postoperative complications

							perioperative administration of landiolol hydrochloride minimized the occurrence of postoperative complications (OR=0.48; 95% CI 0.33–0.70; <i>P</i> =0.002)	
Gosselink, 1992	²⁴³	Prospective cohort study	Patients: 89 (mean age 63 ± 10 years, 60% men)	Intervention: 600 mg of amiodarone daily during a 4-week loading period. Patients who did not convert to sinus rhythm during loading underwent ECV. After	Inclusion: consecutive patients having chronic AF or atrial flutter and eligible for cardioversion; patients had failed previous treatment aimed at maintaining sinus rhythm.	Recurrence of AF or atrial flutter during follow-up; side effects not amenable to dose reduction and leading to discontinuation of amiodarone	After loading with amiodarone, 15 patients converted to sinus rhythm. The remaining 74 patients underwent electrical cardioversion, which was	Low-dose amiodarone is effective for maintaining sinus rhythm in patients with difficult to treat chronic AF or atrial flutter and is associated with a low

				cardioversion, patients were maintained on a dose of 204 ± 66 of amiodarone per day, guided by serum drug levels to maintain a concentration between 1.0–2.5 mg/ L25 and by the occurrence of side effects	Exclusion: paroxysmal AF; MI prior 6 months; unstable angina; severe systemic disease; sick sinus syndrome or atrioventricular conduction disturbances without an artificial pacemaker; hyperthyroidism		successful in 65. The cumulative percentages of patients remaining in sinus rhythm during 1, 2, and 3 years after cardioversion were 61%, 56%, and 53%, respectively. Of all arrhythmia recurrences, the majority occurred during the first 6 months. Serious side effects occurred in	incidence of serious side effects

							three patients (4%) and were the reason for discontinuation of amiodarone in only 1	

Additional Evidence Table S16 — Rate control: Role of pacing

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcomes	Key findings	Conclusion(s)
Lim, 2007 (AIRCRAFT)	²⁴⁴	RCT	Patients:48 (mean age 74 ± 8 years, 52% men)	Intervention: Group 1: AVJAP (n=28) atrioventricular junction ablation and pacing) Group 2: MED (n=35): pharmacologic therapy	Inclusion criteria: AIRCRAFT patients recruited in either Royal Perth or Hollywood Private Hospitals. Age >40 years; symptomatic permanent AF with uncontrolled ventricular rate defined as resting heart rate (HR) >80 and exercise HR >150 after a screening period of 3 months.	Primary outcome: cardiac function measured by echocardiographic and exercise tolerance. Secondary outcomes: ventricular rate control; quality of life measured by Assessment of Quality of Life Questionnaire, the CAST Quality of Life Questionnaire,	In the MED group, LVEF was 62 ± 1% at baseline and 59 ± 12% at 5 years (<i>P</i> <0.01). In the AVJAP group LVEF was 54 ± 19% at baseline and 51 ± 17% at 5 years (<i>P</i> =0.02).	In this long-term follow-up of the AIRCRAFT cohort, similar decline in LVEF and NYHA class was observed in both treatment groups. AVJAP patients have better quality of life with fewer symptoms

					Exclusion: AIRCRAFT Unwillingness or inability to cooperate or to give informed consent	and the Sickness Impact Profile; adverse events; survival	NYHA functional class was not statistically different between MED and ($P=0.48$). The CAST quality of life questionnaire revealed that patients in the AVJAP group had fewer symptoms of irregular heart beat ($P<0.001$),	

							chest pain ($P=0.02$), and difficulty breathing ($P=0.02$)	
Weerasooriya, 2003 (AIRCRAFT)	²⁴⁵	RCT	Patients:99 (mean age 68 ± 9 years, 71% men)	Intervention: Group 1: AVJAP (n=49) atrioventricular junction ablation and pacing. Group 2: MED (n=50): pharmacologic therapy	Inclusion: age>40; symptomatic permanent AF with uncontrolled ventricular rate in which a good rate control could be achieved by drugs during a three-month screening period; ability to perform a treadmill test. Exclusion: clinical indication for ablation and pacing; the	Primary outcome: cardiac function measured by echocardiographic and exercise tolerance. Secondary outcomes: ventricular rate control, evaluated by 24-h ambulatory electrocardiographic monitoring. Quality of life according to the	At 12 months follow-up there was no significant difference in LVEF (AVJAP: 54 ± 17%; MED: 61 ± 13%, $P=NS$). At 12 months follow-up there was	AVJAP for patients with mild to moderately symptomatic permanent AF did not worsen cardiac function during long-term follow-up, and quality of life was improved

					likelihood of surgery or transcatheter valvuloplasty within 12 months of enrolment; untreated resting mean ventricular rate <80b.p.m. and <150b.p.m. during maximum exercise; unstable angina pectoris; WPW syndrome; severe tricuspid valvular regurgitation or tricuspid prosthetic valve; NYHA functional class IV despite pharmacologic treatment; an	Assessment of Quality of Life Questionnaire (aQoL), the CAST Quality of Life Questionnaire, and the Sickness Impact Profile (SIP)	no significant difference in exercise duration on treadmill testing (AVJAP: 4.1 ± 2 min; MED: 4.6 ± 2 min; $P=NS$). The peak ventricular rate was lower in the AVJAP group during exercise 112 ± 17 b.p.m. vs. 153 ± 36	

					occupation or hobby that precluded permanent pacing		b.p.m., $P<0.05$). The CAST quality-of-life questionnaire revealed that patients in the AVJAP group had fewer symptoms at six months ($P=0.003$) and at 12 months ($P=0.004$)	

Wood, 2000	²⁴⁶	Systematic review and meta-analysis of RCT and observational studies	Patients:1181 (21 studies) (2 RCTs)	Intervention: radiofrequency ablation of the AVN and permanent pacing in patients with medically refractory AF	Inclusion: studies that use radiofrequency catheter ablation (CA) to produce complete heart block in the setting of medically refractory atrial tachyarrhythmia or explicit separation of radiofrequency ablation data from direct-current CA in comparative studies; Exclusion: abstracts; studies using only direct current ablation; studies examining only AVN modification for ventricular rate	Exercise duration; cardiac function; quality of life; symptoms; healthcare use; mortality	Significant improvement after ablation and pacing therapy in all outcome measures except fractional shortening. Ejection fraction did show significant improvement ($P<0.001$). The calculated 1-year total and sudden death	Ablation and pacing therapy improve a broad range of clinical outcomes for patients with medically refractory AF. The calculated 1-year mortality rates after this therapy are low and comparable with medical therapy

					slowing rather than complete AV junctional ablation		mortality rates after ablation and pacing therapy were 6.3% (95% CI 5.5–7.2%) and 2.0% (95% CI 1.5–2.6%)	
Huang, 2017	²⁴⁷	Prospective cohort study	52 patients (mean age 73 ± 8, 62% men)	Intervention Heart failure patients underwent attempted AVN ablation and his bundle pacing (HBP) for symptomatic AF	Inclusion: patients had symptomatic HF and long-lasting persistent or permanent AF even though their heart rate was controlled with pharmacological treatment during AF; NYHA class II/III; patients had	LVEF; LVEDd; NYHA class; diuretic use	LVEDd and LVEF improved at 3 months of HBP: (52.7 ± 5.3 vs. 55.8 ± 8.1; <i>P</i> <0.001 and 56.5 ± 8.7 vs. 44.0 ± 14.6; <i>P</i> <0.001),	Permanent HBP post-AVN ablation were associated with improved echocardiographic measurements and NYHA classification and reduced diuretics use

					at least 1 HF related hospitalization in the last 12 months despite optimal HF therapy; ≥ 18 years; not pregnant. Exclusion: intraventricular conduction block or delay on 12-lead ECG; severe mitral or aortic valve regurgitation; congenital heart disease requiring cardiac surgery; chronic kidney disease with dialysis; severe COPD		and more improvement was observed over 1 year of HBP (50.6 ± 5.4 vs. 55.8 ± 8.1; $P > 0.001$ and 59.7 ± 9.8 vs. 44.9 ± 14.6, $P < 0.001$). In patients with HFpEF, there was an improvement in LVEF (63.2 ± 8.2 vs. $56.6 \pm$	for HF management in AF patients with narrow QRS who suffered from HFpEF

							9.9; $P=0.010$). NYHA classification improved to 1.4 ± 0.4 after 1 year of HBP from the baseline 2.7 ± 0.6 in HFpEF patients ($P<0.001$). In both hFrEF and HFpEF the reduction in diuretic use was significant	
Vijayaraman, 2017	²⁴⁸	Retrospective cohort	Patients:42 (mean age $74 \pm$	Intervention: AVN ablation	Inclusion: all patients who had	LVEF; his bundle pacing	His bundle pacing in	AVN ablation and his bundle

		study	11 years, 45% men)	and his bundle pacing	undergone attempts at permanent his bundle pacing and AVN ablation either simultaneously or at different times. Exclusion: not mentioned	lead characteristics; lead-related complications; NYHA functional class; mortality and heart failure hospitalization	the setting of AVN ablation was successful in 40 of 42 (95%) patients. LVEF significantly improved to $50 \pm 10\%$ during follow-up vs. $43 \pm 13\%$ at baseline ($P=0.01$). The increase in LVEF was primarily in patients	pacing were associated with a success in 95% of patients. His bundle pacing lead characteristics remained relatively stable. LVEF was associated with an improvement during follow-up. His bundle pacing was associated with feasible, safe and effective rates in patients undergoing

							with LVEF $\leq 40\%$ at baseline (33 ± 7 to $45 \pm 9\%$; $P < 0.001$). Three patients required heart failure hospitalization during follow-up, despite an improvement in LV function in two patients. Five patients died during follow-up	AVN ablation

Wang, 2013	249	Retrospective cohort study	Patients: 520 (mean age 73.6 ± 10.3 years). Control cohort: n=334): mean age 68.1 ± 1.1 years	Intervention: pacemakers were programmed to a lower rate of 90 b.p.m. after the procedure, with a monthly decrement of 10 b.p.m. until 60 b.p.m. was reached. Control group: pacemakers were programmed to a lower rate of 60	Inclusion: patients with AF who underwent AVN ablation and pacemaker implantation between January 2005 and December 2009. Inclusion control group: previously reported patients who underwent AVN ablation and pacemaker implantation from July 1990 to December 1998	Sudden death	The rate of sudden death likely or possibly related to ablation in the study cohort (0.2%) was significantly lower than that in the control group (2.1%) ($P=0.007$). Sudden death deemed likely or possibly related to ablation	In patients with AF who have undergone an AVN ablation, programming their pacemaker to a faster lower rate was associated with fewer sudden death events compared to patients who had their pacemakers programmed at a slower lower rate following AVN ablation.

				b.p.m. immediately after ablation			and pacemaker implantatio n occurred in 1 patient in the study cohort (0.2%) and in 7 patients (2.1%) in the control group ($P=0.007$)	
Ozcan, 2011	²⁵⁰	Retrospecti ve cohort study	Patients: 350 (mean age 68 ± 11 years, 53% men)	Intervention: patients with AVN ablation and implantation of a permanent pacemaker for AF (study	Inclusion: all patients with AF who underwent radiofrequency ablation of the AVN and implantation of a permanent pacemaker at the	Long-term survival	Observed survival among patients without these three risk factors did not differ to	Long-term survival did not differ for patients with AF, whether they receive AVN ablation or drug therapy

				population) are compared with two control populations: age- and sex-matched members; consecutive AF patients who received drug therapy	Mayo Clinic between July 1990 and December 1998. Inclusion control group 1: age- and sex-matched members of the general Minnesota population. Inclusion control group 2: consecutive patients who received drug therapy for AF at the Mayo Clinic in 1993		expected survival ($P=0.43$). The observed survival rate among patients who underwent ablation was similar to that among 229 controls with AF who received drug therapy ($P=0.44$). None of the 26 patients	

							with lone AF died during follow-up (37 ± 27 months)	
Queiroga, 2003	²⁵¹	Retrospective cohort study	Patients: 114 (mean age 65 ± 9 years, 48% men)	Intervention AVN ablation and dual chamber mode switching pacing	Inclusion: patients undergoing AVN ablation plus implantation of a dual chamber mode switching pacemaker for drug refractory paroxysmal AF were included. Exclusion: not mentioned	Mortality; progression of AF	Overall mortality was 10.5% at 72 months. There was no difference in mortality between subjects who had purely paroxysmal AF and those who had both	Ablate and pace is associated with a low overall mortality. No predictors of permanent AF were identified, but 48% of patients were still in sinus rhythm at 72 months. These results support the use of dual chamber pacing for

							AF and atrial flutter (log rank statistic 0.63, $P=0.43$)	paroxysmal AF patients after ablate and pace

Evidence Table 15 for Recommendation Table 15 (Sec. 7) — Recommendations for general concepts in rhythm control

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Kotecha, 2018	135	Systematic review and meta-analysis of RCTs	5203 patients were included (2850 randomized to receive DOACs and 2353 randomized	DOAC vs. VKA in patients with AF undergoing cardioversion	Inclusion: trials that have randomized patients with AF undergoing cardioversion to DOAC or VKA	DOAC therapy considerably reduced primary outcome events compared with VKA, with a pooled RR=0.42 (95% CI 0.21-.86; $P=0.017$) and no heterogeneity between trials	The primary outcome was the composite of stroke, systemic embolism, myocardial infarction, and cardiovascular death. Bias: included trials studied the short-	In combination with integrated approaches to AF care and stratification of therapy, the routine use of DOACs for cardioversion can improve safety for patients

			ed to receive VKAs)			(I ² =0%; <i>P</i> =0.84)	term effects of anticoagulation; none of the trials were individually powered for clinical outcomes, more than 90% of patients underwent electrical cardioversion, and although there is no a priori reason to suspect a difference with pharmacological cardioversion, data in this context are scarce	undergoing cardioversion
Hart, 2007	¹¹⁵	Systemati	29	Adjusted-	Inclusion: All	Compared with	Adjusted-dose	Adjusted-dose

		c review and meta- analysis of RCTs	RCTs: 28 044 participa nts (mean age, 71 years; mean follow- up, 1.5 years)	dose warfarin vs. control	published randomized trials with a mean follow-up of ≥ 3 months that tested antithrombotic agents in patients who have nonvalvular AF	the control, adjusted-dose warfarin (6 trials, 2900 participants) and antiplatelet agents (8 trials, 4876 participants) reduced stroke by 64% (95% CI, 49–74%) and 22% (95% CI, 6– 35%), respectively	warfarin was substantially more efficacious than antiplatelet therapy (risk reduction= 39%; 95% CI, 22– 52%) (12 trials, 12 963 participants). Other randomized comparisons were inconclusive. Absolute increases in major extracranial hemorrhage were small ($< 0.3\%$ per year). Bias:	warfarin and antiplatelet agents reduce stroke by approximately 60% and by approximately 20%, respectively, in patients who have AF.

							methodological features and quality varied substantially and often were incompletely reported	
Telles-Garcia, 2018	252	Systematic review and meta-analysis of RCTs	7 trials with 7588 patients	DOACs versus warfarin	RCTs comparing the outcomes of DOACs and warfarin in adult patients who underwent cardioversion for AF were selected for meta-analysis. Primary studies and the post-hoc analyses of primary studies reporting on at	Mortality, major bleeding and ischemic and haemorrhagic stroke	DOACs, as compared to warfarin, resulted in similar risk of ischemic stroke [odds ratio (OR): 0.49 (95% confidence interval (CI): 0.20–1.19); $P=0.12$], major bleeding [0.71 (0.37–1.38), $P=0.32$], mortality [0.73 (0.32–1.67);	DOACs and warfarin have comparable efficacy and safety in patients with AF undergoing cardioversion

					least one outcome of interest were included. Studies that did not compare DOACs versus warfarin were excluded		$P=0.45$], and hemorrhagic stroke [0.96 (0.11–8.70); $P=0.97$]	
Brunetti, 2018	²⁵³	Meta-analysis of RCTs	8564	Safety and efficacy of DOACs in the clinical setting of non-valvular AF cardioversion	7 randomized, controlled trials reporting early outcome data of AF patients randomized to DOACs or VKAs and treated with cardioversion: RELY, ARISTOTLE, ROCKET-AF, ENGAGE AF-TIMI 48, and	Two co-primary end points were stroke/systemic embolism and major bleeding	When compared with patients receiving vitamin-K antagonists (VKAs), patients receiving DOACs had a lower risk of stroke/systemic embolism (RR 0.70, 95% CI 0.33–1.546, $P = 0.34$), as well	DOACs are as effective and as safe as VKAs for thromboembolic prevention in non-valvular AF in the setting of cardioversion

					data from the X- VeRT, ENSURE-AF and EMANATE trials		as of Major Bleeding (RR 0.86; 95% CI 0.47–1.58, <i>P</i> = 0.62), although both were non- significant	
Steinberg, 2004 (AFFIRM)	²⁵⁴	RCT	2033 to rhythm control and 2027 to rate control	Rhythm control versus rate control strategy	AF in patients who were at least 65 years of age or who had other risk factors for either stroke or death	Cause-specific modes of death	During a mean follow-up of 3.5 years, there were 356 deaths in the rhythm-control patients and 310 deaths in the rate-control patients (<i>P</i> =0.07). In the rhythm-control group, 129 patients (9%) died of a cardiac cause, and in the	Drug-based management of AF with a rhythm- control strategy conferred no advantage over a rate-control strategy in cardiac or vascular mortality and may be associated with an increased noncardiovascular death rate

							rate-control group, 130 patients (10%) died ($P=0.95$). Both groups had similar rates of arrhythmic and nonarrhythmic cardiac deaths & vascular deaths. No differences in the rates of ischemic stroke and central nervous system hemorrhage. Whereas in the rate-control arm, there were 113 noncardiovascular deaths (36.5% of the total number of	

							deaths) ($P=0.0008$). Differences in noncardiovascular death rates were due to pulmonary and cancer-related death	
Klein, 2001	²⁵⁵	RCT	1222	Treatment guided by the findings on transesophageal echocardiography versus conventional treatment (warfarin for anticoagulation for three weeks before cardioversion		Composite primary end point was cerebrovascular accident, transient ischemic attack, and peripheral embolism within eight weeks. Secondary end points were functional status, successful	There was no significant difference between the two treatment groups in the rate of embolic events (0.8% in the transesophageal- echocardiography group vs. 0.5% in the conventional- treatment group,	Transesophageal echocardiography to guide the management of AF may be considered a clinically effective alternative strategy to conventional therapy for patients in whom elective cardioversion is

				)		restoration and maintenance of sinus rhythm, haemorrhage, and death	$P=0.50$). Rate of hemorrhagic events was significantly lower in the transesophageal-echocardiography group (2.9% vs. 5.5%, $P=0.03$). Patients in the transesophageal-echocardiography group also had a shorter time to cardioversion (mean $\pm$ SD, 3.0 $\pm$ 5.6 vs. 30.6 $\pm$ 10.6 days, $P<0.001$) and a greater rate of successful restoration of	planned

							sinus rhythm (71.1% vs. 65.2%, $P=0.03$). At 8 weeks, there were no significant differences between the two groups in the rates of death or maintenance of sinus rhythm or in functional status	
Pluymaekers, 2019 (RACE 7-ACWAS)	²⁵⁶	RCT	437	Intervention: delayed cardioversion Control: early cardioversion	Inclusion: >18 years presenting to the ER; AF on ECG; heart rate >70b.p.m.; symptoms due to AF; duration of AF <36 h;	Primary endpoint: Sinus rhythm at ECG at the 4 weeks' visit. Secondary endpoints: duration of the index visit at the emergency department,	Delayed CV (wait-and-see approach) non-inferior to early CV in terms of the primary endpoint: (-2.9; 95% CI -8.2 to 2.2; $P=0.005$ for	In patients with recent onset AF, presenting to the ER a wait-and-see approach is non-inferior to early cardioversion in terms of achieving SR at 4 weeks

					willingness to undergo telemonitoring. Exclusion: haemodynamic instability; ECG signs of MI; history of persistent AF; ventricular preexcitation; sick sinus syndrome; history of unexplained syncope	emergency department visits related to AF, cardiovascular complications, time until recurrence of AF	noninferiority). AF recurred in 30% and 29% of the patients for the two groups, respectively. No difference in safety between the two arms. Study underpowered to assess safety outcomes	
Ezekowitz, 2018 (EMANATE)	²⁵⁷	RCT	1500	Apixaban vs. heparin/vitamin K antagonist (VKA)	Patients with AF and ≤48 h anticoagulation prior to randomization undergoing cardioversion	Rates of strokes, systemic emboli, deaths, and bleeds	Comparing apixaban to heparin/VKA, there were 0/753 vs. 6/747 strokes (RR=0; 95% CI 0–0.64; <i>P</i>=0.02),	Rates of strokes, systemic emboli, deaths, and bleeds were low for both apixaban and heparin/VKA

							no SE, and 2 vs. 1 death (RR=1.98; 95% CI 0.19–54.00; $P>0.99$). In the safety population, there were 3/735 vs. 6/721 major (RR=0.49; 95% CI 0.10–2.07; $P=0.34$) and 11 vs. 13 CRNM bleeding events (RR=0.83; 95% CI 0.34–1.89; $P=0.69$)	
Cappato, 2014 (X- VeRT)	²⁵⁸	RCT	1504	Patients assigned to rivaroxaban (20 mg once daily, 15 mg if creatinine	Inclusion: ≥ 18 years scheduled for elective electrical or pharmacological cardioversion.	The primary efficacy outcome was the composite of stroke, transient ischaemic attack,	In the rivaroxaban group, four patients experienced primary efficacy	Oral rivaroxaban appears to be an effective and safe alternative to VKAs and may allow prompt

				clearance = 30–49 mL/min) or dose-adjusted vitamin K antagonists (VKAs) in a 2:1 ratio	Exclusion: haemodynamically significant mitral valve stenosis, prosthetic heart valves, known LA thrombi, severe disabling stroke within the previous 3 months, and any stroke or transient ischaemic attack up to 2 weeks or 3 days, respectively, prior to randomization	peripheral embolism, myocardial infarction, and cardiovascular death. The primary safety outcome was major bleeding. The primary efficacy outcome occurred in 5 (two strokes) of 978 patients (0.51%) in the rivaroxaban group and in 5 (two strokes) of 492 patients (1.02%) in the VKA group (RR=0.50; 95% CI 0.15–1.73)	events following early cardioversion (0.71%) and one following delayed cardioversion (0.24%). In the VKA group, three patients had primary efficacy events following early cardioversion (1.08%) and two following delayed cardioversion (0.93%). Major bleeding occurred in six patients (0.6%) in the rivaroxaban group and four	cardioversion

							patients (0.8%) in the VKA group (RR=0.76; 95% CI 0.21–2.67)	
Kirchhof, 2012	²⁵⁹	RCT	635	Randomization to: no treatment following CV vs. flecainide for 4 weeks vs. flecainide for 6 months	Inclusion: >18 years with persistent AF scheduled for ECV Exclusion: patients unsuitable for flecainide therapy or those already treated with other AADs	Primary outcomes: time to first persistent AF recurrence or death from any cause Secondary outcomes: time to first documented AF; number and total duration of paroxysmal or persistent AF episodes documented on ECG, AF hospitalization; serious adverse events, QoL	In the per-protocol population short-term flecainide treatment is not non-inferior to long term treatment after cardioversion; (mean difference 7.9%; 95% CI -1.9–17.7; $P=0.28$ for non-inferiority). In a post-hoc analysis of patients who did not reach the primary endpoint in the first month	Short-term antiarrhythmic drug treatment after cardioversion is less effective than is long-term treatment, but can prevent most recurrences of AF

							long-term treatment with flecainide was superior to short-term treatment (HR=0.31; 95% CI 0.18–0.56; <i>P</i> =0.001)	
Goette, 2016	260	RCT	2199 patients undergoing electrical cardioversion of non-valvular AF	Edoxaban 60 mg per day with enoxaparin–warfarin	Non-valvular AF (of duration no shorter than 48 h and no longer than 12 months) and who were planned for electrical cardioversion and anticoagulation therapy	Primary efficacy objective: composite endpoint of stroke, systemic embolic event, myocardial infarction, and cardiovascular mortality. Primary safety objective: composite endpoint of major and clinically	Mean CHA2DS2-VASc score was 2.6 (SD 1.4). Mean time in therapeutic range on warfarin was 70.8% (SD 27.4). The primary efficacy endpoint occurred in five (<1%) patients in the edoxaban group versus 11 (1%) in the	Edoxaban is an effective and safe alternative to the best possible conventional treatment with enoxaparin and VKA strategy, and might allow prompt cardioversion to be performed

						relevant non-major bleeding	enoxaparin–warfarin group (OR 0.46, 95% CI 0.12–1.43). The primary safety endpoint occurred in 16 (1%) of 1067 patients given edoxaban versus 11 (1%) of 1082 patients given enoxaparin–warfarin (OR 1.48, 95% CI 0.64–3.55)	
Kirchhof, 2020	¹⁰	RCT	2789 patients with early AF (median time since	Early rhythm control versus usual care		The primary safety outcome was a composite of death, stroke, or serious adverse events related to rhythm-	A first-primary-outcome event occurred in 249 of the patients assigned to early rhythm control (3.9 per 100	Early rhythm-control therapy was associated with a lower risk of adverse cardiovascular outcomes than

			diagnosis, 36 days) underwent randomization			control therapy. Secondary outcomes, including symptoms and left ventricular function, were also evaluated	person-years) and in 316 patients assigned to usual care (5.0 per 100 person-years) (hazard ratio, 0.79; 96% confidence interval, 0.66 to 0.94; $P=0.005$). The mean number of nights spent in the hospital, the percentage of patients with a primary safety outcome and symptoms and left ventricular function at 2 years did not	usual care among patients with early AF and cardiovascular conditions

							differ significantly between the groups. Serious adverse events related to rhythm-control therapy occurred in 4.9% of the patients assigned to early rhythm control and 1.4% of the patients assigned to usual care	
Stellbrink, 2004	²⁶¹	RCT	496 patients scheduled for cardioversion of AF of >48	Enoxaparin administered subcutaneously with intravenous UFH followed by the oral anticoagulant	AF patients ≥18 years old and weighed at least 45 kg, AF associated with clinical symptoms for at least 48 hours	Incidence of embolic events, all-cause death, and major bleeding complications. Secondary end points included	Enoxaparin was noninferior to UFH+phenprocoumon with regard to the incidence of the composite primary end point in a per-protocol	Enoxaparin is noninferior to UFH+phenprocoumon for prevention of ischemic and embolic events, bleeding complications, and

			hours' and < or =1 year's duration	phenprocoumon	before study inclusion, or persistent AF had to be documented during the previous 3 months on resting or long-term ECG if the patient presented without clinical symptoms. Exclusion: acute neurological deficits, acute clinical signs of systemic thromboembolic events or thrombosis, known left	successful cardioversion, maintenance of sinus rhythm until study end, and minor bleeding complications	analysis (7 of 216 patients versus 12 of 212 patients, respectively; $P=0.016$) and in an intention-to-treat analysis (7 of 248 patients versus 12 of 248 patients, respectively; $P=0.013$). There was no significant difference between the 2 groups in the number of patients reverted to sinus rhythm	death in TOE-guided cardioversion of AF

					ventricular or aortic thrombus, blood coagulation disorders or (suspected) internal bleeding, a platelet count $<100 \times 10^9/L$, a history of heparin- associated thrombocytopen ia (type II), severe chronic hepatic or renal disease, cerebral or gastrointestinal bleeding during the previous 6 months, or			

					severe arterial hypertension resistant to treatment			
Zhu, 2022	²⁶²	Meta-analysis of RCTs and observational studies	8 studies involving 447 202 AF patients	Early rhythm control (defined as within 12 months of AF diagnosis)	RCTs and observational studies assessing the associations of early rhythm control (defined as within 12 months of AF diagnosis) with adverse outcomes	The primary outcome was a composite of death, stroke, admission to hospital for heart failure (HF), or acute coronary syndrome (ACS)	23.5% of participants underwent an early rhythm-control therapy. In the pooled analysis using the random-effects model, compared with rate control, the early rhythm-control strategy was significantly associated with reductions in the primary composite outcome	Early initiation of rhythm control treatment was associated with improved adverse effectiveness outcomes in patients who had been diagnosed with AF within 1 year

							(HR=0.88, 95% CI: 0.86–0.89) and secondary outcomes, including stroke or systemic embolism (HR=0.78, 95% CI: 0.71–0.85), ischemic stroke (HR=0.81, 95% CI: 0.69–0.94), cardiovascular death (HR=0.83, 95% CI: 0.70–0.99), HF hospitalization (HR=0.90, 95% CI: 0.88–0.92), and ACS (HR=0.86, 95% CI: 0.76–0.98)	
Sandhu,	¹⁸	Prospecti	100	Consecutive	Inclusion:	Primary endpoint:	Patients who	ECV is associated

2017		ve cohort study		patients undergoing AF were enrolled	consecutive patients undergoing elective electrical cardioversion at two centres	change in quality of life assessed by AFEQT and SF-36 scores at 3 months post cardioversion	remained in sinus rhythm had a significant improvement in SF-36 and AFEQT scores. Patients who remained in AF by 3 months demonstrated improvements in the AFEQT treatment concern score and emotional role value probably because of treatment of expectations related to ECV. Limitation: observational	with a significantly improved QoL in patients who maintain sinus rhythm following ECV

							study	
Crijns, 2014	²⁶³	Prospective cohort study	3940	Cardioversion (whether pharmacological or electrical) vs. no cardioversion	Inclusion: >18 with recent onset AF documented on ECG considered for ECV	Outcomes: sinus/atrial rhythm in 24 h following initiation of therapy (for PCV); sinus/atrial rhythm for at least 10 min following the last shock	Total CV success rate: 82.6% of the patients (ECV 89.7% vs. PCV 69.1%). Class IC drugs enhanced conversion as compared to amiodarone	Both PCV and ECV were safe and effective. Class IC drugs more effective for conversion
Lip, 2016	²⁶⁴	Prospective cohort study		Rivaroxaban treatment for 6 weeks for LA/LAA thrombus resolution in patients with nonvalvular AF or atrial flutter and LA/LAA thrombus	VKA/DOAC naïve or untreated within 1 month prior to signing the informed consent form	Primary end point: complete LA/LAA thrombus resolution rate on the centrally adjudicated end-of-treatment TOE after 6 weeks' treatment with rivaroxaban	The adjudicated thrombus resolution rate was 41.5% (22/53 modified intention-to-treat [mITT] patients, 95% CI 28.1–55.9%) based on central TOE assessments. Resolved or	Rivaroxaban seems to be a potential option for the treatment of TOE-detected LA/LAA thrombi in patients with AF or atrial flutter

				confirmed at baseline on a transesophageal echocardiogram (TOE)			reduced thrombus was evident in 60.4% (32/53 mITT patients, 95% CI 46.0–73.6%) of patients	
Bonfanti, 2019	²⁶⁵	Retrospective cohort study	419	Electrical cardioversion of acute-onset AF performed by emergency physicians in the ED vs. no rhythm control strategy	Inclusion: AF onset <48 h treated at the ER	Effectiveness and safety of ECV of AF of acute onset in the setting of emergency department	ECV successfully restored SR in 403 patients (96.2%). Effectiveness is dependent upon age-100% effectiveness in the age group 18–39 years, 97.3% in the group 65–80 years and <80% in patients >80 years	ECV in the emergency setting is a safe and effective procedure. The success rates of ECV decrease with age

Additional Evidence Table S17 — General principles and anticoagulation in rhythm control

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Um, 2022	²⁶⁶	Systematic review and meta-analysis of RCTs	4348	Intervention: pre-treatment with an AAD of any type and route of administration before elective ECV Control: no treatment, rate control or placebo	N/A for this analysis	Outcomes of interest: acute SR restoration; maintenance of SR during follow-up	Acute restoration of SR: class III medications beneficial compared to no-treatment or rate control (OR=2.82; 95 CI 1.61–4.98). amiodarone beneficial compared to no-treatment or rate control (OR=2.41; 95% CI 1.37–4.62). Classes IC, III and amiodarone beneficial in maintenance of	Before ECV of AF, pre-treatment with class III AADs or amiodarone is associated with improved likelihood for acute restoration of SR. amiodarone most likely to improve the maintenance of sinus rhythm after ECV, but class Ic and class III AADs

							SR. Of these amiodarone associated with highest likelihood for SR maintenance	are also effective
Schmidt, 2021	²⁶⁷	RCT	468	Intervention: antero-lateral positioning of the pads. Control: antero-posterior position	Inclusion: ≥18 years scheduled for ECV Exclusion: arrhythmias other than AF; presence of a CIED; haemodynamically unstable AF; hyperthyroidism	Primary outcome: proportion of patients in SR 1 min after the last shock. Secondary outcome: ECV effectiveness at 2 hours post procedure. Safety outcomes: N patients with arrhythmic effects; Pain (patient	Larger proportion of patients met the primary endpoint with antero-lateral position (RR=1.69; 95% CI 1.35–2.11; <i>P</i> <0.001). Significantly less number of shocks in the A-L arm with lower median total energy usage. No difference in safety outcome as well as in the patient reported pain. The investigators were	Anterior–lateral electrode positioning was found to be more effective than anterior–posterior electrode positioning for AF cardioversion. Safety outcomes were not different between the two arms

						reported)	not blinded	
Kirchhof, 2002	²⁶⁸	RCT	108	Anterior-lateral or anterior-posterior	Inclusion: age 18–80 years who were undergoing cardioversion. Excluded: patients with atrial flutter or rapid atrial tachycardias	The primary endpoint was cardioversion success rate. Secondary endpoints included cardioversion success rate for each of the predefined shock energies and success rates after cross-over	Cardioversion was successful in a higher proportion of the anterior-posterior than the anterior-lateral group 96% vs. 78%, difference 23.7% (95% CI 91–37.8, <i>P</i> =0.009)	Anterior-posterior electrode position is more effective than the anterior-lateral position for external cardioversion of persistent AF
Squara, 2021	²⁶⁹	RCT	100	Intervention: active compression over the anterior electrode during application of the standard	Inclusion: ≥18 years scheduled for elective ECV of persistent (>7 days) AF Exclusion:	Primary endpoint was defibrillation threshold (defined as the lowest defibrillation	Primary endpoint: Defibrillation threshold lower in the active compression arm: (103.1 ± 49.9 J vs. 130.4 ± 47.7 J;	Active compression applied to the anterior defibrillation electrode was more effective

				step-up protocol. Comparator: standard step-up protocol with increasing energy without compression	arrhythmias other than AF; multiple myeloma; previous sternotomy; osteoporosis	energy required for the successful termination of AF)	$P=0.008$)	for ECV in persistent AF cardioversion with the anterior-posterior position
Schmidt, 2020 (CHESS)	²⁷⁰	RCT	276	Intervention: maximal (360 J) energy for ECV Comparator: low escalating (125–150–200 J) energy for ECV	Inclusion: ≥ 18 years scheduled for elective ECV ECG-documented AF. Exclusion: haemodynamically unstable AF; hyperthyroidism	Primary endpoint: the presence of sinus rhythm 1 min after ECV. Secondary endpoints: first shock efficacy (125 vs. 360 J). Safety endpoints: any arrhythmia on 4 h ECG-surveillance; myocardial	Primary endpoint: 88% in the maximal energy group vs. 66% in the low escalating energy ($P<0.001$); Relative intergroup difference (low escalating energy as Ref) in presence of sinus rhythm 1.3 (95% CI 1.2–1.5). No difference in the safety endpoints	Maximum fixed-energy shocks more effective than low escalating energy without compromising safety

						injury measured by hsTnI; skin discomfort or pain 2 h post procedure; skin redness after removal of electrodes	between the arms	
Schmidt, 2017	²⁷¹	RCT	134	Pulsed biphasic shock vs. bipolar truncated exponential waveform, both in escalating energy protocol, up to 4 shocks	Inclusion: all patients scheduled for elective ECV. Exclusion: age<18; arrhythmias other than AF; active hyperthyroidism	Primary endpoint: sinus rhythm at 4 hours post ECV. Secondary endpoints: sinus rhythm at 1 min and 30 min post ECV. Safety endpoint: change in hsTnI levels at 4 hours after ECV vs. preprocedural complications of	The primary endpoint was achieved in 86% of the patients in the BTE waveform vs. 62% in the PB group ($P<0.002$). No difference in the safety endpoint. Study terminated prematurely because of a side effect	Cardioversion using BTE waveform was more effective when compared with a PB waveform. There was no difference in safety between the 2 waveforms, as judged by changes in troponin I levels

						the procedure		
Glover, 2007 (BEST AF)	²⁷²	RCT	380	Escalating energy protocol (protocol A: 100 J, 150 J, 200 J, 200 J), vs. a non-escalating energy protocol (protocol B: 200 J, 200 J, 200 J)	Inclusion: history of persistent AF who were routinely referred for an outpatient DC cardioversion of AF. Exclusion: inadequate anticoagulation, known intracardiac thrombus, significant electrolyte imbalance, digoxin toxicity, cardiogenic shock, refractory	Shock success; number of shocks, cumulative energy, sedation and duration of procedure; post-shock arrhythmia	First-shock success was significantly higher for those randomised to 200 J than 100 J (71% vs. 48%; $P<0.01$) and for patients with a BMI >25 kg/m ² (75% vs. 44%; $P=0.01$). In patients with a normal BMI there was no significant difference in first-shock success. There was also no significant difference between subsequent	Fewer shocks were required for an energy selection protocol that begins at 200 J. Although this approach is safe and not associated with any additional complications, no significant difference in the duration of the procedure or amount of sedation required was demonstrated in this study. It is therefore

					pulmonary oedema, uncontrolled thyrotoxicosis, a permanent pacemaker which would result in an altered pad position, any incapable of giving informed consent or any other condition thought to increase the risk of the procedure		shocks or overall success. The use of a non-escalating protocol (protocol B) resulted in fewer shocks but with a higher cumulative energy. There was no difference in duration of procedure, amount of sedation administered or post-shock erythema between the groups	reasonable to recommend higher biphasic energies as a first DCCV shock for patients, particularly in patients who are overweight or have a higher transthoracic impedance
Trendafilov a, 2021	²⁷³	RCT	78 adult patients admitted for elective	Intervention: pulsed biphasic (PB) vs. biphasic truncated	Inclusion: age ≥18 years and had symptomatic (EHRA score	Primary endpoint estimated CVS efficacy as the sum of energies	Success rates were similar (BTE-HE vs. PB): 1min first-shock (84.2 vs. 82.9%), 1min	Both PB and BTE-HE waveforms used for cardioversion of AF with fixed

			CVS of AF	exponential (BTE) waveforms	2–4) persistent AF or symptomatic first detected AF or persistent AF after successful causal therapy. Exclusion: atrial flutter or were unable/unwilling to sign the informed consent	delivered by all shocks during one intervention. Secondary: success rate, number of delivered shocks and energy delivered	CVS (97.4 vs. 94.3%), 2h CVS (94.7 vs. 94.3%), 24h CVS (92.1 vs. 94.3%), $P>0.05$. Safety analysis did not find CVS hazards, reporting insignificant changes of myocardial-specific biomarkers, transient and rare ST-segment deviations, and no case of harmful tachyarrhythmias and apnea	energy protocol 200–200–200 J show similarly high efficacy and safety
Stiell, 2021 (RAFF-3)	²⁷⁴	RCT	603 patients/ 718 visits	Intervention: introduction of the CAEP checklist to	Inclusion: acute AF/AFL of at least 3 hours duration	Primary endpoint: length of stay in the ED.	There was a reduction in the length of stay in the intervention	Optimised care of AF/AFL patients with decreased ED

				manage AF Control: usual care	but less than 7 days Exclusion: permanent AF; haemodynamic instability; death in the ED from nonacute AF related causes; presentation for another condition; spontaneous restoration of SR before any therapy initiated	Secondary endpoints: use of cardioversion in the ED; use of rate control; consultations done in the ED by cardiology or internal medicine services; appropriate prescription of anticoagulants on discharge; adverse events attributable to medical management; admission to a hospital unit; return visit to ED visits and	arm: relative decrease of 20.9% (95% CI 5.5– 33.8%; $P=0.01$). The intervention arm more likely to receive rhythm control (OR= 4.5; 95% CI 1.8–11.6; $P=0.002$). There was a decrease in use of rate-control medications (OR=0.5; 95% CI 0.2–0.9; $P=0.02$). Adverse events were not different in the two arms	lengths of stay, increased ED rhythm control by drug or electricity, and resulted in similar incidence of adverse events

						admissions for acute AF/AFL or other CV problems in the subsequent 30 days		
Guerra, 2014	²⁷⁵	RCT	204	Propofol use for anaesthesia/sedation administered by anaesthesiologist vs. midazolam administered by the cardiologist as a means of sedation	Inclusion: >18; scheduled for elective ECV of persistent AF Exclusion: known allergy to midazolam or propofol	Primary safety endpoint: incidence of adverse events requiring intervention. Primary efficacy endpoint: procedure tolerability by the VAS. Secondary endpoints: variations of vital status parameters; total duration of	Primary safety endpoint: incidence: 13% vs. 9.6%, <i>P</i> =NS. Primary efficacy endpoint: no difference in the two arms. midazolam administered by cardiologists demonstrates lower costs. Bias due to lack of blinding to the intervention and also reporting bias	Sedation with midazolam administered by cardiologist-only appears to be as safe as sedation with propofol and anesthesiologist assistance

						the procedure; monitoring time; procedural delay; length of hospitalization, assessed in hours; incidence of AF recurrence up to 24h after ECV	due to self-reporting of one of the outcomes by the study subjects	
Stronati, 2020	²⁷⁶	RCT	69	Propofol use for anaesthesia/sedation administered by anaesthesiologist vs. midazolam administered by the cardiologist as a means of sedation	Inclusion: age >18; with high-rate AF and requiring emergency ECV Exclusion: known allergy to midazolam or propofol	Primary safety endpoint: A composite of death and peri-procedural adverse events requiring medical intervention: bradycardia, severe hypotension, severe hypoxia,	Primary endpoint occurred in 22.9% of the patients in the midazolam arm and in 29.4% in the propofol arm ($P=NS$). No difference in the other safety endpoints including the variation in the vital parameters.	A cardiologist-only approach to sedation with midazolam could represent a feasible and safe option for DCCV even in the emergency/urgent setting. It is associated with lower costs

						stroke, TIA and need for orotracheal intubation. Other safety endpoints: variations in vital parameters during the procedure. Cost-effectiveness also analysed	Longer procedure duration in the propofol arm. Higher costs in the propofol arm	
Stiell, 2021 (RAFF)	²⁷⁷	Meta-analysis of RCTs and observational studies	1736	N/A for this study	Inclusion: acute AF/AFL of at least 3 hours duration but less than 7 days. Exclusion: permanent AF; haemodynamic instability;	Main outcome: serious adverse event occurring prior to discharge	13.9% (12.3–15.7%) of cases exhibited important adverse events which required treatment; 0.4% were life-threatening. In the logistic regression	ECV for acute AF/AFL in the ED is associated with rare serious adverse events although there were a concerning number of events

					death in the ED from nonacute AF related causes; presentation for another condition; spontaneous restoration of SR before any therapy initiated		analysis age ≥85 years (OR=2.1), coronary artery disease (OR 1.5), midazolam (OR=1.9), and fentanyl (OR=1.5) were associated with important adverse events	associated with sedation which required intervention
Schnabel, 2018	¹⁷	Prospective registry	6196	Consecutive patients with AF were enrolled at 461 centres. Interventions: pharmacological or ECV as well as catheter ablation upon follow-up	Inclusion: ≥18 years; with AF	Outcomes: presence of sinus rhythm on the follow-up ECG; adequate heart rate control. Disease outcomes: ischemic stroke/transient ischemic	EHRA score presented in a dichotomized manner (intermediate/frequent symptoms as compared to occasional/absent symptoms) was associated with: cardioversions	Higher symptom burden as assessed by the EHRA score predicts rhythm control interventions

						attack/arterial embolism, coronary events (acute coronary syndrome/coronary revascularization), heart failure, and major bleeding	(OR=1.21; 95% CI 1.01–1.45) catheter ablation (OR=1.97; 95% CI 1.44–2.69) and HF incidence (OR=1.65; 95% CI 1.16–2.34)	

Evidence Table 16 for Recommendation Table 16 (Sec. 7) — Recommendations for electrical cardioversion of atrial fibrillation

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Sandhu, 2017	¹⁸	Prospective cohort study	100 patients underwent electrical cardioversion	The global Short-Form Health Survey (SF-36) and the AFEQT questionnaire	Inclusion: AF referred for outpatient electrical cardioversion at 2 hospitals in Edmonton from 2013–2014	Outcomes: the impact of electrical cardioversion on quality of life (QoL) outcomes in clinical practice	There were significant improvements in the vast majority of the SF-36 and AFEQT domains for the 51 patients who maintained sinus rhythm at 3 months. Patients who were in AF by 3 months demonstrated improvements	There are significant QoL benefits for patients who maintain sinus rhythm after electrical cardioversion

							in the AFEQT treatment concern score ($P=0.02$) and SF-36 emotional role value ($P<0.01$) compared with baseline values, which may be the result of treatment expectations related to cardioversion	
Bonfanti, 2019	²⁶⁵	Retrospective cohort study	419	Electrical cardioversion of acute-onset AF performed by emergency physicians in the ED vs. no	Inclusion: AF onset <48 h treated at the ER	Effectiveness and safety of ECV of AF of acute onset in the setting of emergency department	ECV successfully restored SR in 403 patients (96.2%). Effectiveness is dependent	ECV in the emergency setting is a safe and effective procedure. The success rates of ECV

				rhythm control strategy			upon age-100% effectiveness in the age group 18–39 years, 97.3% in the group 65–80 years and <80% in patients >80 years	decrease with age
Schnabel, 2018	¹⁷	Prospective registry	6196 AF patients	Intervention: European Heart Rhythm Association score symptoms Control: the standardized health status questionnaire (EQ-5D-5 L). Interventions	Inclusion: patients from the Prevention of Thromboembolic Events–European Registry in AF who had completed the European Heart Rhythm	Outcomes: the presence of sinus rhythm on the follow-up ECG and adequate heart rate control. Disease outcomes were ischemic stroke/transient ischemic attack/arterial embolism,	The European Heart Rhythm Association score was associated with cardioversions (OR=1.21; 95% CI 1.01–1.45) and catheter ablation	A higher symptom burden, in particular palpitations, predicted interventions to restore sinus rhythm

				included cardioversions (pharmacological and electrical cardioversion) and catheter-based ablation (pulmonary vein isolation) Control: adequate heart rate control	Association score symptoms	coronary events (acute coronary syndrome/coronary revascularization), heart failure, and major bleeding	(OR=1.97; 95% CI 1.44–2.69), and inversely related with heart rate control (OR=0.80; 95% CI 0.70–0.92) and heart failure incidence (OR=1.65; 95% CI 1.16–2.34). Palpitations were positively associated with cardioversion (OR=1.32; 95% CI 1.08–1.61) and ablation	

							therapy (OR=2.02; 95% CI 1.48– 2.76). Limitations: bias attributable to enrollment decisions, quality of data collection, and follow-up may have been introduced, despite training of the participating cardiologists and central data management. EHRA score calculation in	

							practice is more subjective, and it shows less measurement accuracy	
Kotecha, 2016	²⁷⁸	Review	N/A	Intervention: echocardiographic parameters in AF patients Control: invasive pulmonary capillary wedge pressure and clinical outcomes	Inclusion: AF patients with echocardiographic parameters	Outcomes: treatments of concomitant HFpEF and AF aim to reduce symptoms and improve quality of life	AF is associated with changes in echocardiographic parameters and circulating natriuretic peptides that confound HFpEF diagnosis. Symptomatic improvement with diuretic therapy	Adequate treatment of comorbidities and risk factors may improve symptom burden, quality of life, and exercise capacity. HFpEF (i.e., the presence of elevated LV filling pressure and HF symptoms) does exist in

							supports the presence of HFpEF in patients with concomitant AF	patients with AF and can be diagnosed, albeit from small observational studies with highly selective inclusion

Additional Evidence Table S18 — Electrical cardioversion

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Eid, 2022	²⁷⁹	Systematic review and meta-analysis of RCTs	1677 patients (10 RCT)	Examined the outcomes of anterior-posterior (AP) versus anterior-lateral (AL) electrodes position during cardioversion of (AF)	Inclusion: RCTs that examined the outcomes of AP versus AL electrode positioning during cardioversion of AF; must have reported the success rate of cardioversion among the study groups. Exclusion: non-randomized studies	Success rate of cardioversion	There was no difference in the rate of successful cardioversion between the AP versus AL groups (86.6 vs. 87.9%; RR=1.00; 95% CI 0.95–1.06). There was lower transthoracic impedance with AP versus AL electrode position (SMD-0.28; 95% CI -0.47 to -0.10)	No difference between AP and AL electrode positions in the success rate of DC cardioversion of AF. Either AP or AL electrode positions should be acceptable approaches for elective DC cardioversion of patients with AF
Um, 2022	²⁶⁶	Systematic	4348	Intervention:	N/A for this	Outcomes of	Acute restoration	Before ECV of

		review and meta-analysis of RCTs		pre-treatment with an AAD of any type and route of administration before elective ECV Control: no treatment, rate control or placebo	analysis	interest: acute SR restoration; maintenance of SR during follow-up	of SR: class III medications beneficial compared to no-treatment or rate control (OR=2.82; 95 CI 1.61–4.98). amiodarone beneficial compared to no-treatment or rate control (OR=2.41; 95% CI 1.37–4.62). Classes IC, III and amiodarone beneficial in maintenance of SR. Of these amiodarone associated with highest likelihood for SR maintenance	AF, pre-treatment with class III AADs or amiodarone is associated with improved likelihood for acute restoration of SR. amiodarone most likely to improve the maintenance of sinus rhythm after ECV, but class Ic and class III AADs are also effective

Stiell, 2021 (RAFF)	²⁷⁷	Pooled analysis of RCTs and observational studies	1736	N/A for this study	Inclusion: acute AF/AFL of at least 3 hours duration but less than 7 days. Exclusion: permanent AF; haemodynamic instability; death in the ED from nonacute AF related causes; presentation for another condition; spontaneous restoration of SR before any therapy initiated	Main outcome: serious adverse event occurring prior to discharge	13.9% (12.3–15.7%) of cases exhibited important adverse events which required treatment; 0.4% were life-threatening. In the logistic regression analysis age ≥ 85 years (OR=2.1), coronary artery disease (OR 1.5), midazolam (OR=1.9), and fentanyl (OR=1.5) were associated with important adverse events	ECV for acute AF/AFL in the ED is associated with rare serious adverse events although there were a concerning number of events associated with sedation which required intervention
Schmidt, 2021	²⁶⁷	RCT	468	Intervention: antero-lateral	Inclusion: ≥ 18 years	Primary outcome:	Larger proportion of patients met the	Anterior–lateral electrode

				positioning of the pads. Control: antero-posterior position	scheduled for ECV Exclusion: arrhythmias other than AF; presence of a CIED; haemodynamically unstable AF; hyperthyroidism	proportion of patients in SR 1 min after the last shock. Secondary outcome: ECV effectiveness at 2 hours post procedure. Safety outcomes: N patients with arrhythmic effects; Pain (patient reported)	primary endpoint with antero-lateral position (RR=1.69; 95% CI 1.35–2.11; $P<0.001$). Significantly less number of shocks in the A-L arm with lower median total energy usage. No difference in safety outcome as well as in the patient reported pain. The investigators were not blinded	positioning was found to be more effective than anterior–posterior electrode positioning for AF cardioversion. Safety outcomes were not different between the two arms
Kirchhof, 2002	²⁶⁸	RCT	108	Anterior-lateral or anterior-posterior	Inclusion: 18–80 years who were undergoing cardioversion. Excluded: patients with atrial flutter or	The primary endpoint was cardioversion success rate. Secondary endpoints included	Cardioversion was successful in a higher proportion of the anterior-posterior than the anterior-lateral group 96% vs.	Anterior-posterior electrode position is more effective than the anterior-lateral position

					rapid atrial tachycardias	cardioversion success rate for each of the predefined shock energies and success rates after cross-over	78%, difference 23.7% (95% CI 91–37.8, $P=0.009$)	for external cardioversion of persistent AF
Squara, 2021	²⁶⁹	RCT	100	Intervention: active compression over the anterior electrode during application of the standard step-up protocol. Comparator: standard step-up protocol with	Inclusion: ≥ 18 years scheduled for elective ECV of persistent (>7 days) AF Exclusion: arrhythmias other than AF; multiple myeloma; previous sternotomy; osteoporosis	Primary end point was defibrillation threshold (defined as the lowest defibrillation energy required for the successful termination of AF)	Primary endpoint: Defibrillation threshold lower in the active compression arm: (103.1 ± 49.9 J vs. 130.4 ± 47.7 J; $P=0.008$)	Active compression applied to the anterior defibrillation electrode was more effective for ECV in persistent AF cardioversion with the anterior-posterior position

				increasing energy without compression				
Schmidt, 2020 (CHESS)	²⁷⁰	RCT	276	Intervention: maximal (360 J) energy for ECV Comparator: low escalating (125–150–200 J) energy for ECV	Inclusion: ≥18 years scheduled for elective ECV ECG- documented AF Exclusion: haemodynamically unstable AF; hyperthyroidism	Primary endpoint: the presence of sinus rhythm 1 min after ECV. Secondary endpoints: first shock efficacy (125 vs. 360 J). Safety endpoints: any arrhythmia on 4 h ECG-surveillance; myocardial injury measured by hsTnI; skin discomfort or pain 2 h post	Primary endpoint: 88% in the maximal energy group vs. 66% in the low escalating energy ($P<0.001$); Relative intergroup difference (low escalating energy as Ref) in presence of sinus rhythm 1.3 (95% CI 1.2–1.5). No difference in the safety endpoints between the arms	Maximum fixed-energy shocks more effective than low escalating energy without compromising safety

						procedure; skin redness after removal of electrodes		
Schmidt, 2017	²⁸⁰	RCT	134	Pulsed biphasic shock vs. bipolar truncated exponential waveform, both in escalating energy protocol, up to 4 shocks	Inclusion: all patients scheduled for elective ECV. Exclusion: age<18; arrhythmias other than AF; active hyperthyroidism	Primary endpoint: sinus rhythm at 4 hours post ECV. Secondary endpoints: sinus rhythm at 1 min and 30 min post ECV. Safety endpoint: change in hsTnI levels at 4 hours after ECV vs. preprocedural complications of the procedure	The primary endpoint was achieved in 86% of the patients in the BTE waveform vs. 62% in the PB group ($P<0.002$). No difference in the safety endpoint. Study terminated prematurely because of a side effect	Cardioversion using BTE waveform was more effective when compared with a PB waveform. There was no difference in safety between the 2 waveforms, as judged by changes in troponin I levels
Glover, 2007	²⁷²	RCT	380	Escalating energy protocol	Inclusion: history of persistent AF	Shock success; number of shocks,	First-shock success was significantly higher	Fewer shocks were required for an energy

				(protocol A: 100 J, 150 J, 200 J, 200 J), vs. a non-escalating energy protocol (protocol B: 200 J, 200 J, 200 J)	who were routinely referred for an outpatient DC cardioversion of AF. Exclusion: inadequate anticoagulation, known intracardiac thrombus, significant electrolyte imbalance, digoxin toxicity, cardiogenic shock, refractory pulmonary oedema	cumulative energy, sedation and duration of procedure; post-shock arrhythmia	for those randomised to 200 J than 100 J (71% vs. 48%; $P<0.01$) and for patients with a BMI >25 kg/m² (75% vs. 44%; $P=0.01$). In patients with a normal BMI there was no significant difference in first-shock success. There was also no significant difference between subsequent shocks or overall success. The use of a non-escalating protocol	selection protocol that begins at 200 J. Although this approach is safe and not associated with any additional complications, no significant difference in the duration of the procedure or amount of sedation required was demonstrated in this study. It is therefore reasonable to recommend higher biphasic energies as a

							(protocol B) resulted in fewer shocks but with a higher cumulative energy. There was no difference in duration of procedure, amount of sedation administered or post-shock erythema between the groups	first DCCV shock for patients, particularly in patients who are overweight or have a higher transthoracic impedance
Trendafilova, 2021	²⁸¹	RCT	78 adult patients admitted for elective CVS of AF	Intervention: pulsed biphasic (PB) vs. biphasic truncated exponential (BTE) waveforms	Inclusion: ≥18 years with symptomatic (EHRA score 2–4) persistent AF or symptomatic first detected AF or persistent AF after	Primary endpoint estimated CVS efficacy as the sum of energies delivered by all shocks during one intervention. Secondary:	Success rates were similar (BTE-HE vs. PB): 1min first-shock (84.2 vs. 82.9%), 1min CVS (97.4 vs. 94.3%), 2h CVS (94.7 vs. 94.3%), 24h CVS (92.1 vs. 94.3%), $P>0.05$.	Both PB and BTE-HE waveforms used for cardioversion of AF with fixed energy protocol 200–200–200 J show similarly high efficacy and safety

					successful causal therapy. Exclusion: atrial flutter	success rate, number of delivered shocks and energy delivered	Safety analysis did not find CVS hazards, reporting insignificant changes of myocardial-specific biomarkers, transient and rare ST-segment deviations, and no case of harmful tachyarrhythmias and apnea	
Pluymaekers, 2019 (RACE 7-ACWAS)	²⁵⁶	RCT	437	Intervention: delayed cardioversion Control: early cardioversion	Inclusion:>18 years presenting to the ER; AF on ECG; heart rate >70b.p.m.; symptoms due to AF; duration of AF<36 h;	Primary endpoint: Sinus rhythm at ECG at the 4 weeks' visit. Secondary endpoints: duration of the index visit at the	Delayed CV (wait-and-see approach) non-inferior to early CV in terms of the primary endpoint: (-2.9; 95% CI -8.2 to 2.2; $P=0.005$ for noninferiority).	In patients with recent onset AF, presenting to the ER a wait-and-see approach is non-inferior to early cardioversion in terms of

					willingness to undergo telemonitoring. Exclusion: haemodynamic instability; ECG signs of MI; history of persistent AF; ventricular preexcitation; sick sinus syndrome; history of unexplained syncope	emergency department, emergency department visits related to AF, cardiovascular complications, time until recurrence of AF	AF recurred in 30% and 29% of the patients for the two groups, respectively. No difference in safety between the two arms. Study underpowered to assess safety outcomes	achieving SR at 4 weeks
Stiell, 2021	²⁷⁴	RCT	603 patients/ 718 visits	Intervention: introduction of the CAEP checklist to manage AF Control: usual care	Inclusion: acute AF/AFL of at least 3 hours duration but less than 7 days. Exclusion:	Primary endpoint: length of stay in the ED. Secondary endpoints: use of cardioversion	There was a reduction in the length of stay in the intervention arm: relative decrease of 20.9% (95% CI 5.5–	Optimised care of AF/AFL patients with decreased ED lengths of stay, increased ED rhythm control

					permanent AF; haemodynamic instability; death in the ED from nonacute AF related causes; presentation for another condition; spontaneous restoration of SR before any therapy initiated	in the ED; use of rate control; consultations done in the ED by cardiology or internal medicine services; appropriate prescription of anticoagulants on discharge; adverse events attributable to medical management; admission to a hospital unit; return visit to ED visits and admissions for acute AF/AFL or other CV	33.8%; $P=0.01$). The intervention arm more likely to receive rhythm control (OR= 4.5; 95% CI 1.8–11.6; $P=0.002$). There was a decrease in use of rate-control medications (OR=0.5; 95% CI 0.2–0.9; $P=0.02$). Adverse events were not different in the two arms	by drug or electricity, and resulted in similar incidence of adverse events

						problems in the subsequent 30 days		
Guerra, 2014	²⁷⁵	RCT	204	Propofol use for anaesthesia/sedation administered by anaesthesiologist vs. midazolam administered by the cardiologist as a means of sedation	Inclusion: age >18; scheduled for elective ECV of persistent AF Exclusion: known allergy to midazolam or propofol	Primary safety endpoint: incidence of adverse events requiring intervention. Primary efficacy endpoint: procedure tolerability by the VAS. Secondary endpoints: variations of vital status parameters; total duration of the procedure; monitoring time; procedural	Primary safety endpoint: incidence: 13% vs. 9.6%, <i>P</i> =NS. Primary efficacy endpoint: no difference in the two arms. midazolam administered by cardiologists demonstrates lower costs. Bias due to lack of blinding to the intervention and also reporting bias due to self-reporting of one of the outcomes by	Sedation with midazolam administered by cardiologist-only appears to be as safe as sedation with propofol and anaesthesiologist assistance

						delay; length of hospitalization, assessed in hours; incidence of AF recurrence up to 24h after ECV	the study subjects	
Stronati, 2020	²⁷⁶	RCT	69	Propofol use for anaesthesia/ sedation administered by anaesthesiologist vs. midazolam administered by the cardiologist as a means of sedation	Inclusion: age >18; with high-rate AF and requiring emergency ECV Exclusion: known allergy to midazolam or propofol	Primary safety endpoint: A composite of death and peri-procedural adverse events requiring medical intervention: bradycardia, severe hypotension, severe hypoxia, stroke, TIA and need for orotracheal	Primary endpoint occurred in 22.9% of the patients in the midazolam arm and in 29.4% in the propofol arm ($P=NS$). No difference in the other safety endpoints including the variation in the vital parameters. Longer procedure duration in the propofol arm.	A cardiologist-only approach to sedation with midazolam could represent a feasible and safe option for DCCV even in the emergency/urgent setting. It is associated with lower costs

						intubation. Other safety endpoints: variations in vital parameters during the procedure. Cost-effectiveness also analysed	Higher costs in the propofol arm	
Singh, 2005	282	RCT	665	Patients with persistent AF randomized to receive amiodarone, sotalol or placebo	Inclusion: AF>72 hours and receiving OAC Exclusion: paroxysmal AF, atrial flutter, NYHA class III/IV, CrCl<60 mL/min, long QT, intolerance to beta blockers	Primary outcome: time to first recurrence of AF after SR restoration	Total SR restoration rate was 79.8% in the amiodarone group and 79.9% in the sotalol group ($P=NS$) and 68.1% in the placebo group ($P<0.01$ vs. sotalol, amiodarone). Both medications were similarly effective	Amiodarone and sotalol are equally effective in converting AF to SR. amiodarone is superior to sotalol for SR maintenance. SR but both drugs have similar efficacy in patients with

							in ischemic heart disease. Restoration of SR was associated with a significant improvement of QoL and exercise tolerance	ischemic heart disease. Sustained SR was associated with better QoL and exercise tolerance
Kirchhof, 2012	²⁵⁹	RCT	635	Randomization to: no treatment following CV vs. flecainide for 4 weeks vs. flecainide for 6 months	Inclusion: >18 years with persistent AF scheduled for ECV Exclusion: patients unsuitable for flecainide therapy or those already treated with other AADs	Primary outcomes: time to first persistent AF recurrence or death from any cause Secondary outcomes: time to first documented AF; number and total duration of paroxysmal or persistent AF episodes	In the per-protocol population short-term flecainide treatment is not non-inferior to long term treatment after cardioversion; (mean difference 7.9%; 95% CI -1.9 to 17.7; $P=0.28$ for non-inferiority). In a post-hoc analysis of patients who did	Short-term antiarrhythmic drug treatment after cardioversion is less effective than is long-term treatment, but can prevent most recurrences of AF

						documented on ECG, AF hospitalization; serious adverse events, QoL	not reach the primary endpoint in the first month long-term treatment with flecainide was superior to short-term treatment (HR=0.31; 95% CI 0.18–0.56; <i>P</i> =0.001)	
Sandhu, 2017	¹⁸	Prospective cohort study	100	Consecutive patients undergoing AF were enrolled	Inclusion: consecutive patients undergoing elective electrical cardioversion at two centres	Primary endpoint: change in quality of life assessed by AFEQT and SF-36 scores at 3 months post cardioversion	Patients who remained in sinus rhythm had a significant improvement in SF-36 and AFEQT scores. Patients who remained in AF by 3 months demonstrated improvements in the AFEQT	ECV is associated with a significantly improved QoL in patients who maintain sinus rhythm following ECV

							treatment concern score and emotional role value probably because of treatment of expectations related to ECV. Limitation: observational study	
Crijns, 2014	²⁶³	Prospective cohort study	3940	Cardioversion (whether pharmacological or electrical) vs. no cardioversion	Inclusion: >18 with recent onset AF documented on ECG considered for ECV	Outcomes: sinus/atrial rhythm in 24 h following initiation of therapy (for PCV); sinus/atrial rhythm for at least 10 min following the last shock	Total CV success rate: 82.6% of the patients (ECV 89.7% vs. PCV 69.1%). Class IC drugs enhanced conversion as compared to amiodarone	Both PCV and ECV were safe and effective. Class IC drugs more effective for conversion

Schnabel, 2018	¹⁷	Prospective registry	6196	Consecutive patients with AF were enrolled at 461 centres. Interventions: pharmacological or ECV as well as catheter ablation upon follow-up	Inclusion: ≥18 years; with AF	Outcomes: presence of sinus rhythm on the follow-up ECG; adequate heart rate control. Disease outcomes: ischemic stroke/transient ischemic attack/arterial embolism, coronary events (acute coronary syndrome/coronary revascularization), heart failure, and major bleeding	EHRA score presented in a dichotomized manner (intermediate/frequent symptoms as compared to occasional/absent symptoms) was associated with: cardioversions (OR=1.21; 95% CI 1.01–1.45) catheter ablation (OR=1.97; 95% CI 1.44–2.69) and HF incidence (OR=1.65; 95% CI 1.16–2.34)	Higher symptom burden as assessed by the EHRA score predicts rhythm control interventions

Evidence Table 17 for Recommendation Table 17 (Sec. 7) — Recommendations for pharmacological cardioversion of atrial fibrillation

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Markey, 2018	²⁸³	Systematic review and meta-analysis of RCTs	11 RCT	Intervention: use of i.v. flecainide in acute AF	Inclusion: RCTs of i.v. flecainide for acute conversion of recent-onset AF were selected for meta-analysis	Flecainide had high efficacy for cardioversion within 2 h (number needed to treat [NNT] = 1.8)	Efficacy was superior to propafenone, amiodarone, Procainamide, ibutilide, and sotalol (NNT = 4.3)	Intravenous flecainide cardioversion could be a safe and effective option for emergency physicians to restore sinus rhythm in selected patients with acute AF
Camm, 2011	²⁸⁴	RCT	254 adult patients	10-min infusion of vernakalant (3 mg/kg) followed by a	Inclusion: 18–85 years with symptomatic recent-onset AF	Conversion from AF to sinus rhythm within the first	Vernakalant resulted in rapid conversion	Vernakalant infusion was superior to amiodarone

				15-min observation period and a second 10-min infusion (2 mg/kg) if still in AF, plus a sham amiodarone infusion, versus a 60-min infusion of amiodarone (5 mg/kg) followed by a maintenance infusion (50 mg) over an additional 60 min, plus a sham vernakalant infusion	(duration of 3 to 48 h) who were eligible for cardioversion, hemodynamically stable (systolic blood pressure >100 but <160 mm Hg and diastolic blood pressure <95 mm Hg) and taking adequate anticoagulation therapy. Exclusion: ventricular rate <50 beats/min; or QRS interval >140 ms; patients with a pacemaker; atrial flutter (AFL); atrial thrombus; unstable	90 min (primary end point) was achieved in 60 of 116 (51.7%) vernakalant patients compared with 6 of 116 (5.2%) amiodarone patients ($P<0.0001$)	(median time of 11 min in responders) and was associated with a higher rate of symptom relief compared with amiodarone (53.4% of vernakalant patients reported no AF symptoms at 90 min compared with 32.8% of amiodarone patients; $P=0.0012$).	infusion for the conversion of recent-onset AF. Both vernakalant and amiodarone were safe and well tolerated. vernakalant has low proarrhythmic potential and provides a rapidly acting therapeutic alternative for the conversion of AF

					congestive heart failure, NYHA IV HF, or HF requiring inotropes; recent myocardial infarction, ACS, stroke or cardiac surgery		Bias: short follow-up period for efficacy (90 min) and the short infusion period (i.e., <24 h) for amiodarone	
Deedwania , 1998	²⁸⁵	RCT	103 patients with CHF and AF	Amiodarone versus placebo	Established history of heart failure (≥ 3 months), LVEF $\leq 40\%$ and NYHA functional class II, III, or IV. Exclusion: women of childbearing age; myocardial infarction or revascularization within 3 months; heart failure due to uncorrected	Rate control, spontaneous conversion to sinus rhythm, new-onset AF, Effects of Conversion to Sinus Rhythm on Survival	The mean ventricular response during AF over 24 hours was reduced by amiodarone at 2 weeks (20%, $P=0.001$), at 6 months (18%, $P=0.001$), and at 12 months	In patients with CHF and AF, amiodarone is effective in spontaneously converting patients in AF to sinus rhythm, with patients who convert having a lower mortality rate than those who

					primary valvular disease or restrictive or infiltrative cardiomyopathy; a history of aborted sudden death, symptomatic ventricular arrhythmia, or need for continuing antiarrhythmic therapy; QRS duration of ≥ 180 milliseconds or QTc of ≥ 500 milliseconds; active drug or alcohol abuse; uncontrolled thyroid disease; noncardiac conditions or		(16%, $P=0.006$). Sixteen of 51 patients on amiodarone and 4 of 52 on placebo converted to sinus rhythm during the study ($\chi^2=9.23$, $P=0.002$). During follow-up, 11 of 268 patients in sinus rhythm on amiodarone at baseline and 22 of the 263 in sinus rhythm on	do not. Amiodarone also prevented the development of new-onset AF and significantly reduced the ventricular response in those with persistent AF

					malignancy that was likely to be fatal within 3 years; and symptomatic hypotension or systolic blood pressure of <90 mm Hg		placebo developed AF; the difference was significant ($\chi^2=12.88$, $P=0.005$). Analysis of total mortality during follow-up showed a significantly lower mortality rate ($P=0.04$) in patients in AF at baseline who subsequently converted to sinus rhythm on	

							amiodarone than in those who did not convert to sinus rhythm on the drug	
Hou, 1995	²³⁹	RCT	50 patients	Amiodarone intravenously (n = 26) versus digoxin (n = 24)	Recent-onset, persistent, AF, and flutter with ventricular rates above 130 beats. Exclusion: cardiogenic shock or hypotension ; Wolff-Parkinson-White syndrome; sick sinus syndrome; episodes of paroxysmal AF/ AFI that had lasted less than 24 h in previous events;	Primary outcome: conversion to sinus rhythm. Alterations in heart rate and blood pressure	The mean heart rates in the amiodarone group decreased significantly from 157 ± 20 beats. min ⁻¹ to 122 ± 25 beats. min ⁻¹ after 1 h (<i>P</i> <0.05 vs. baseline), and then decreased further to	Amiodarone is effective in the treatment of AF/ AFI. Digoxin, while not as effective as amiodarone in the treatment of recent-onset AF and flutter, appears to be safer

					consumption of any antiarrhythmic drug; 0 serum K<3–5mEq. l ⁻¹ ; severe hypoxia, severe metabolic acidosis or thyrotoxicosis; onset of AF/ AFI 24 h after or during surgery		stabilize at 96 ± 25 beats. min ⁻¹ after 6 h (<i>P</i> <0.05). The digoxin group had fewer dramatic alterations in heart rates, compared to the amiodarone group, in the first 8h (<i>P</i> <0.05, respectively). Overall, 24 of 26 patients (92%) in the amiodarone group and 17 of 24 (71%) in	

							the digoxin group were restored to sinus rhythm within 24 h. The accumulated rates of conversion over 24 h were significantly different between the two groups ($P=0.0048$)	
Conde, 2013	²⁸⁶	RCT	32 patients	Oral dose of flecainide 300 mg versus intravenous vernakalant	Inclusion: hemodynamically stable patients with recent onset AF without structural heart disease were prospectively and	Time to conversion to sinus rhythm was of 163 min (120–300) in the flecainide group versus 10	Time to conversion of AF to sinus rhythm was significantly shorter in the vernakalant	Time to conversion of AF to sinus rhythm was significantly shorter in the vernakalant

					consecutively included in two periods, one for each drug	min (6–18) in the vernakalant group ($P=0.0001$)	group	group compared with the flecainide group, and was associated with shorter hospital stay
Reisinger, 2004	²⁸⁷	RCT	207 patients	Flecainide versus ibutilide	Inclusion: AF of recent onset ($<$ or $=$ 48 h)	The conversion rates were 56.4% in patients given flecainide and 50.0% in patients given ibutilide ($P=0.34$)	Multivariate analysis revealed that a lower age for women independently increased the probability of conversion. None of the other variables, including left atrial size, left ventricular systolic	There was no significant difference in the cardioversion efficacy or in the risk of adverse events between flecainide and ibutilide in patients with AF of recent onset

							function, presence of left ventricular hypertrophy, plasma levels of potassium or magnesium at baseline, or concomitant use of digoxin, beta-blocker, diltiazem or verapamil were predictors of conversion	
Roy, 2008 (ACT I)	²⁸⁸	RCT	336 patients (short duration, n=220; long	Vernakalant versus placebo	Inclusion: sustained AF for 3 hours to 45 days, be ≥18 years of age, have a body weight of 45 to	The primary end point was conversion of AF to sinus rhythm for at least 1 minute	Of the 145 vernakalant patients, 75 (51.7%) in the short-duration AF group	Vernakalant demonstrated rapid conversion of short-duration AF and was

			duration, n=116)		136 kg, be receiving adequate anticoagulation, and have a systolic blood pressure >90 mm Hg and <160 mm Hg and a diastolic blood pressure <95 mm Hg. Exclusion: sick-sinus syndrome or QRS >0.14 seconds without a pacemaker; ventricular rate of <50 b.p.m.; uncorrected QT >0.440 seconds; typical atrial flutter; NYHA IV HF; ACS, myocardial infarction, or	within 90 minutes of the start of drug infusion in the short-duration AF group	converted to sinus rhythm (median time, 11 minutes) compared with 3 of the 75 placebo patients (4.0%; $P<0.001$). Overall, in the short- and long-duration AF groups, 83 of the 221 vernakalant patients (37.6%) experienced termination of AF compared with 3 of the 115 placebo	well tolerated

					cardiac surgery within 30 days before enrollment; an investigational drug within 30 days before enrollment; a reversible cause of AF; end-stage disease; previously failed electric conversion; uncorrected electrolyte imbalance; or digoxin toxicity		patients (2.6%; $P<0.001$)	
Zhang, 2005	²⁸⁹	RCT	82 patients	Ibutilide and propafenone	Inclusion: <75 years; normal serum K ⁺ and stopping treatment of other class III or class I antiarrhythmic	Ibutilide had a significantly higher rate of cardioversion than propafenone (70.73 vs.	The patients with shorter AF duration or smaller left atrium diameter had a higher	Ibutilide is more effective than intravenous propafenone for the cardioversion

					agents beyond five half-metabolism periods of the corresponding agents. Exclusion: QTc ≥ 440 ms; 60 kg > body weight > 100 kg; ventricular rate < 55 beats per minute; unstable hemodynamic status; clinical evidence of acute or chronic congestive heart failure (NYHA class III or IV); acute myocardial infarction; sick sinus node syndrome, second	48.78%, $P=0.043$)	success rate. Bias: single blinded study; the administered dose was not modified according to individual body weight	of recent onset AF, and the adverse effects are rare and transient

					degree or complete atrioventricular block without protection of an implanted pacemaker; hepatic/renal insufficiency; history of ventricular tachycardia; history of bronchial asthma other severe respiratory disease			
Martinez-Marcos, 2000	²⁹⁰	RCT	150 patients	Intervention: intravenous flecainide, propafenone, or amiodarone	Inclusion: consecutive symptomatic patients with acute (≤ 48 hours' duration) AF	By the end of a 12-hour observation period, conversion to sinus rhythm was achieved in	Only after administering the second bolus was there a significant difference	Flecainide is more effective than propafenone and amiodarone for conversion of

						45 patients (90%) in the flecainide group, 36 (72%) in the propafenone group, and 32 (64%) in the amiodarone group ($P=0.008$ for the overall comparison, $P=0.002$ for flecainide vs. amiodarone, $P=0.02$ for flecainide vs. propafenone, and $P=0.39$ for propafenone vs. amiodarone)	between flecainide and propafenone	acute AF to sinus rhythm. propafenone and amiodarone have similar conversion rates, although propafenone was faster in achieving the conversion to sinus rhythm
Khan, 2001	²⁹¹	Systematic review of	7 studies	Oral loading propafenone	Trials evaluating the use of oral	Conversion rate and time to	The success rates ranged	The single oral loading dose of

		RCT and observational studies		with placebo, intravenous propafenone or other oral loading antiarrhythmic agents	loading propafenone for pharmacological cardioversion of recent-onset AF	sinus rhythm; adverse effects	from 56% to 83% & conversion time ranged from 110 ± 59 to 287 ± 352 min, depending on the duration of observation after drug administration . The single dose oral loading regimen of propafenone was significantly more efficacious than placebo in the first 8 h	propafenone appears to be highly effective for conversion of recent-onset AF, with a relatively rapid effect within 2 to 3 hrs and freedom from serious adverse effects

							after administration but not at 24 h. Compared with the intravenous regimen, the oral regimen resulted in fewer conversions in the first 2 h, but both regimens were equally efficacious afterward. The oral propafenone regimen was as efficacious as the single dose oral	

							loading regimen of flecainide but was superior to those of quinidine and amiodarone. The adverse effects reported were transient arrhythmia, reversible QRS-complex widening, transient hypotension and mild noncardiac side effects	
Hofmann, 2004	²⁹²	Prospective cohort study	78 consecutive patients	450 mg amiodarone given as a	39 patients suffered from advanced	Ventricular heart rate and cardiac rhythm;	Twenty-five patients (32%)	Amiodarone, given as a single

			with AF and heart rate above 135 beats/min	single intravenous bolus	congestive heart failure, 26 patients had pulmonary oedema, and 13 patients were in cardiogenic shock	site of venous access	converted to normal sinus rhythm within 30 minutes. Another 15 (19%) reverted into sinus rhythm during the following 24 hours. Within 30 minutes after amiodarone administration , ventricular heart rate decreased significantly from 152 +/- 12 to 88 +/- 17 (P<0.0001)	intravenous bolus through a peripheral vein rapidly reduced ventricular rate and was well tolerated in patients with AF, even in the presence of congestive heart failure and cardiogenic shock

							beats/min in patients who converted to sinus rhythm and from 157 +/- 14 to 98 +/- 16 beats/min in patients who did not. The degree of reduction in heart rate was similar among patients presenting with exacerbated congestive heart failure, pulmonary edema, or cardiogenic	

							shock. Systolic blood pressure decreased in two patients, from 115 to 80 mmHg and from 130 to 100 mmHg, but was reversible after 10 and 90 minutes respectively without specific intervention. No proarrhythmia or clinically relevant bradycardia was	

							observed, and no inflammation detected at the site of venous access	
Alboni, 2004	²⁹³	Prospective cohort study	268 patients with mild heart disease or none who came to the emergency room with AF of recent onset that was hemodynamically	Flecainide or propafenone	18 to 75 years, emergency room intervention for AF of recent onset (<48 hours earlier), a mean heart rate of more than 70 beats/min, and a systolic pressure of 100 mm Hg or more. Additional criteria were history of palpitations with an abrupt onset that were	Conversion to sinus rhythm; arrhythmia episodes	During a mean follow-up of 15+/-5 months, 79% had a total of 618 episodes of arrhythmia; of those episodes, 92% were treated 36+/-93 minutes after the onset of symptoms. Treatment	Pill-in-the-pocket treatment is feasible and safe, with a high rate of compliance by patients, a low rate of adverse events, and a marked reduction in emergency room visits and hospital admissions

			well tolerated		hemodynamically well tolerated. Exclusion: electrical or structural contraindications to flecainide or propafenone; previous thromboembolic episodes, acute disease, very severe chronic diseases; renal or hepatic insufficiency; previous hypokalemia; suspected or known pregnancy; a known intolerance of flecainide or		was successful in 94%; the time to resolution of symptoms was 113+/-84 minutes. Among the 165 patients with recurrences, the drug was effective during all the arrhythmic episodes in 139 patients (84%). Adverse effects were reported during one or more	

					current propafenone, or current prophylactic antiarrhythmic treatment		arrhythmic episodes by 7%, including atrial flutter at a rapid ventricular rate in 1 patient and noncardiac side effects in 11 patients. The numbers of monthly visits to the emergency room and hospitalization s were significantly lower during follow-up than during the year before	

							the target episode ($P<0.001$ for both comparisons)	
Alboni, 2010	²⁹⁴	Prospective cohort study	120 patients with AF of recent onset who were successfully treated (conversion of AF within 2 h without major adverse effects)	Tolerance to intravenous administration of flecainide or propafenone's relation to pill-in-the pocket treatment	Aged >18 years requiring ER intervention for recent episode of AF with a mean heart rate >70 beats/min and a systolic blood pressure ≥ 100 mmHg & history of palpitations. Exclusion: ECG or structural abnormalities contraindicating them to flecainide or propafenone; previous	Arrhythmic recurrences	During a mean follow-up of 11 ± 4 months, 79 patients self-treated 213 arrhythmic episodes; treatment was successful in 201 episodes (94%). Major adverse events occurred in five patients (6%) and in four (5%) of	The study was prematurely terminated because of the high incidence of major adverse effects during the first out-of-hospital treatment.. The patient's tolerance of intravenous administration of flecainide or propafenone does not seem to predict

					thromboembolic episodes; acute disease; very severe general diseases; renal or hepatic insufficiency; hypokalaemia; suspected or known pregnancy; known intolerance of flecainide or propafenone; prophylactic antiarrhythmic treatment or cognitive skills inadequate for self-treatment		these during the first oral treatment	adverse effects during out-of-hospital self-administration of these drugs

Evidence Table 18 for Recommendation Table 18 (Sec. 7) — Recommendations for antiarrhythmic drugs for long-term maintenance of sinus rhythm

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Valembois, 2019	²⁹⁵	Systematic review and meta-analysis of RCTs	59 RCTs: 20 981 participants studying quinidine, disopyramide, propafenone, flecainide, metoprolol, amiodarone, dofetilide, dronedarone and sotalol	Quinidine, disopyramide, propafenone, flecainide, metoprolol, amiodarone, dofetilide, dronedarone and sotalol	Inclusion: RCTs comparing any antiarrhythmic drug with a control (no treatment, placebo, drugs for rate control) or with another antiarrhythmic drug in AF adults and in whom sinus rhythm was restored, spontaneously or by any	High-certainty evidence from five RCTs indicated that treatment with sotalol was associated with a higher all-cause mortality rate compared with placebo or no treatment (RR 2.23, 95% CI 1.03–4.81; participants = 1882). The	Moderate-certainty evidence showed increased RR for mortality but with very wide CIs for metoprolol (RR 2.02, 95% CI 0.3711.05, 2 RCTs, participants = 562) and amiodarone (RR 1.66, 95% CI 0.55–4.99,	There is high-certainty evidence of increased mortality associated with sotalol treatment, and low-certainty evidence suggesting increased mortality with quinidine, when used for maintaining sinus rhythm in

					intervention. Exclusion: postoperative AF	number need to treat for an additional harmful outcome (NNTH) for sotalol was 102 participants treated for one year to have one additional death. Low- certainty evidence from six RCTs suggested that risk of mortality may be higher in people taking quinidine (RR 2.01, 95% CI	2 RCTs, participants = 444), compared with placebo; little or no difference in mortality with dofetilide (RR 0.98, 95% CI 0.76–1.27; moderate- certainty evidence) or dronedarone (RR 0.86, 95% CI 0.68–1.09; high-certainty evidence) compared to placebo/no treatment. There were	AF patients. Few data on mortality in people taking disopyramide, flecainide and propafenone, so it was not possible to make a reliable estimation of the mortality risk for these drugs. However, moderate- certainty evidence of marked increases in proarrhythmia and adverse effects with

						0.84 to 4.77; participants = 1646)	few data on mortality for disopyramide, flecainide and propafenone, making impossible a reliable estimation for those drugs	flecainide was seen. Overall, there is evidence showing that antiarrhythmic drugs increase adverse events, increase proarrhythmic events and some antiarrhythmics may increase mortality
Kochiadakis, 2000	²⁹⁶	RCT	214 with recurrent symptomatic AF	Amiodarone, propafenone and sotalol	Age >18 years, ECG documentation of AF, and symptoms such as light-headedness, palpitations,	Recurrent AF	Recurrent AF occurred in 25/ 75 patients treated with amiodarone compared to 51/ 75 patients treated with	Amiodarone and propafenone were superior to sotalol in maintaining long-term normal sinus

					chest pain, and dyspnoea in association with AF. Exclusion: acute myocardial infarction <6 months before entry into the trial, cardiogenic shock, thyroid disease, AF secondary to an active underlying disorder, recent cardiac surgery, uncontrolled congestive heart failure, un-stable angina, hepatic or renal failure, an LVEF <40%, an estimated life		sotalol and 24/64 patients treated with propafenone. 14 patients treated with amiodarone, 5 with sotalol, and 1 with propafenone experienced adverse effects while in sinus rhythm, necessitating discontinuation of treatment ($P<0.001$ for amiodarone and propafenone vs. sotalol). If the analysis	rhythm in patients with AF. Amiodarone tended to be superior to propafenone, but its long-term efficacy was limited by adverse side effects

					expectancy of <1 year; and previous exposure to amiodarone, propafenone or sotalol		was limited to recurrent AF events, amiodarone was more effective than propafenone ($P<0.05$)	
Roy, 2000	²⁹⁷	RCT	403	Amiodarone (201) versus sotalol (101) or propafenone (101)	Patients who had had at least one episode of AF within the previous six months	Primary end point was the length of time to a first recurrence of AF	After a mean of 16 months of follow-up, 35% patients assigned to amiodarone 63% of those who were assigned to sotalol or propafenone had a recurrence of AF ($P<0.001$). Adverse	Amiodarone is more effective than sotalol or propafenone for the prevention of recurrences of AF

							events requiring the discontinuation of drug therapy occurred in 18% of the patients receiving amiodarone, versus 11% of those treated with sotalol or propafenone ($P=0.06$)	
Hohnloser, 2009 (ATHENA)	⁷	RCT	4628	Intervention: dronedarone Control: placebo	Inclusion: patients with AF and additional risk factors for death	The primary outcome: first hospitalization due to CV events or death. Secondary outcomes: death from	The primary outcome occurred in 734 patients (31.9%) in the dronedarone group and in 917 patients (39.4%) in the	Dronedarone reduced the incidence of hospitalization due to cardiovascular events or death in patients with AF

						any cause, death from CV causes, and hospitalization due to CV events	placebo group (for dronedarone HR=0.76;95% I CI 0.69–0.84; $P<0.001$)	
Kirchhof, 2012	259	RCT	635	Randomization to: no treatment following CV vs. flecainide for 4 weeks vs. flecainide for 6 months	Inclusion: >18 years with persistent AF scheduled for ECV Exclusion: patients unsuitable for flecainide therapy or those already treated with other AADs	Primary outcomes: time to first persistent AF recurrence or death from any cause Secondary outcomes: time to first documented AF; number and total duration of paroxysmal or persistent AF episodes	In the per-protocol population short-term flecainide treatment is not non-inferior to long term treatment after cardioversion; (mean difference 7.9%; 95% CI- 1.9–17.7; $P=0.28$ for non-inferiority). In a post-hoc	Short-term antiarrhythmic drug treatment after cardioversion is less effective than is long-term treatment, but can prevent most recurrences of AF

						documented on ECG, AF hospitalization; serious adverse events, QoL	analysis of patients who did not reach the primary endpoint in the first month long-term treatment with flecainide was superior to short-term treatment (HR=0.31; 95% CI 0.18–0.56; <i>P</i> =0.001)	
Stroobandt, 1997	²⁹⁸	RCT	160 patients with persistent AF	Propafenone 2 mg/kg over 30 minutes, followed by oral propafenone 150 mg 3 times daily or	Aged >18 years with either recent-onset AF or chronic AF occurring either as a first episode or as a recurrent	Number of patients Who maintained sinus rhythm after 6 months. Secondary	Pharmacologic conversion to sinus rhythm was achieved in 29% of the patients taking propafenone and in 17% of	Oral propafenone at a low dosage 150 mg 3 times daily is well tolerated and effective in maintaining

				matching placebo	episode. Exclusion: NYHA class >2 or symptoms of heart failure on physical examination, recent myocardial infarction or cardiac surgery , cardiogenic shock or hypotension, angina pectoris, significant arrhythmias, or severe obstructive lung disease, pulmonary embolism, metabolic	objectives were (1) the evaluation of the efficacy of initial intravenous propafenone therapy and (2) the safety of propafenone in long term treatment	patients taking placebo ($P>$ or $=0.10$). Subsequent direct-current cardioversion in nonresponders was equally successful (70%) in both groups ($P>$ or $=0.10$). The proportion of patients free from recurrent symptomatic arrhythmia at 6 months was 67% for the propafenone and 35% for the placebo	sinus rhythm for 6 months after pharmacologic or electrical restoration of sinus rhythm

					disturbances or known thyroid dysfunctions, unstable hepatic or renal function, and evidence of digitalis intoxication and hypokalemia; treated with amiodarone within the preceding 6 months, or were currently receiving treatment with antiarrhythmic or cardiovascular drugs such as b blockers, verapamil, or diltiazem not	group ($P<0.01$). Time to AF relapse was more favorable with propafenone than with placebo ($P<0.001$). The incidence of drug-related side effects was 10% in the propafenone group and 14% in the placebo group	

					discontinued 5 half-lives before the start of the study			
Singh, 2005 (SAFE-T)	²⁸²	RCT	665	Patients with persistent AF randomized to receive amiodarone, sotalol or placebo	Inclusion: AF>72 hours and receiving OAC Exclusion: paroxysmal AF, atrial flutter, NYHA class III/IV, CrCl<60 mL/min, long QT, intolerance to beta blockers	Primary outcome: time to first recurrence of AF after SR restoration	Total SR restoration rate was 79.8% in the amiodarone group and 79.9% in the sotalol group ($P=NS$) and 68.1% in the placebo group ($P<0.01$ vs. sotalol, amiodarone). Both medications were similarly effective in ischemic heart	Amiodarone and sotalol did not show differences in converting AF to SR. amiodarone is superior to sotalol for SR maintenance. SR but both drugs have similar efficacy in patients with ischemic heart disease. Sustained SR was associated with better QoL

							disease. Restoration of SR was associated with a significant improvement of QoL and exercise tolerance	and exercise tolerance
Ehrlich, 2019	²⁹⁹	Retrospective cohort study	3498 individuals who had received dronedarone and 17 724 individuals who had received other antiarrhythmic drugs	Dronedarone, amiodarone, flecainide, propafenone, or sotalol	Patients who had received a first prescription of dronedarone, amiodarone, flecainide, propafenone, or sotalol in 1 258 general and 62 cardiology practices	The main outcomes of this study were the percentages of patients with myocardial infarction and stroke in the dronedarone group and in the group of individuals	At the end of the follow-up period, 7.4% of individuals with dronedarone prescriptions and 8.3% of those who had been prescribed other antiarrhythmic drugs had	In our study, dronedarone was associated with a lower risk of myocardial infarction and stroke in patients with AF compared to other antiarrhythmics

						who had received other antiarrhythmic drugs within six years of the index date. After six years of follow-up, 3.9% of patients who had received dronedarone and 5.2% of patients who had received other antiarrhythmic drugs had been diagnosed with myocardial infarction (log-	been diagnosed with a stroke (log-rank P-value=0.003). dronedarone was associated with a significant decrease in the risk of developing myocardial infarction (HR=0.78) and suffering a stroke (HR=0.84) compared to other antiarrhythmics	

						rank P - value=0.002)		

Additional Evidence Table S19 — Recommendations for antiarrhythmic drugs for long-term maintenance of sinus rhythm

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Valembois, 2019	²⁹⁵	Systematic review and meta-analysis of RCTs	59 RCTs: 20 981 participants studying quinidine, disopyramide, propafenone, flecainide, metoprolol, amiodarone, dofetilide, dronedarone and sotalol	Quinidine, disopyramide, propafenone, flecainide, metoprolol, amiodarone, dofetilide, dronedarone and sotalol	Inclusion: RCTs comparing any antiarrhythmic drug with a control (no treatment, placebo, drugs for rate control) or with another antiarrhythmic drug in AF adults and in whom sinus rhythm was restored, spontaneously or by any intervention.	High-certainty evidence from five RCTs indicated that treatment with sotalol was associated with a higher all-cause mortality rate compared with placebo or no treatment (RR 2.23, 95% CI 1.03–4.81; participants = 1882). The number need	Moderate-certainty evidence showed increased RR for mortality but with very wide CIs for metoprolol (RR 2.02, 95% CI 0.3711.05, 2 RCTs, participants = 562) and amiodarone (RR 1.66, 95% CI 0.55–4.99, 2 RCTs,	There is high-certainty evidence of increased mortality associated with sotalol treatment, and low-certainty evidence suggesting increased mortality with quinidine, when used for maintaining sinus rhythm in AF patients.

					Exclusion: postoperative AF	to treat for an additional harmful outcome (NNTH) for sotalol was 102 participants treated for one year to have one additional death. Low- certainty evidence from six RCTs suggested that risk of mortality may be higher in people taking quinidine (RR 2.01, 95% CI 0.84 to 4.77;	participants = 444), compared with placebo; little or no difference in mortality with dofetilide (RR 0.98, 95% CI 0.76–1.27; moderate- certainty evidence) or dronedarone (RR 0.86, 95% CI 0.68–1.09; high-certainty evidence) compared to placebo/no treatment. There were few data on	Few data on mortality in people taking disopyramide, flecainide and propafenone, so it was not possible to make a reliable estimation of the mortality risk for these drugs. However, moderate- certainty evidence of marked increases in proarrhythmia and adverse effects with flecainide was

						participants = 1646)	mortality for disopyramide, flecainide and propafenone, making impossible a reliable estimation for those drugs	seen. Overall, there is evidence showing that antiarrhythmic drugs increase adverse events, increase proarrhythmic events and some antiarrhythmics may increase mortality
Chevalier, 2003	³⁰⁰	Meta-analysis of RCTs	13 RCTs: Six studies randomizing amiodarone versus placebo (595 patients) and seven studies	Amiodarone with placebo and class Ic drugs	Inclusion: RCT on recent-onset AF comparing amiodarone to placebo or class Ic drugs	The primary end point was the rate of conversion at 24 h. There was no significant difference	Efficacy with amiodarone was inferior to class Ic drugs for up to 8 h (RR=0.67, $P<0.001$) but no difference	Amiodarone is superior to placebo for cardioversion of AF, and even though the onset of conversion is

			versus class Ic drugs (579 patients)			between amiodarone and placebo at 1 to 2 h, but significant efficacy was found after 6 to 8 h (RR=1.23, $P=0.022$) and at 24 h (RR=1.44, $P<0.001$)	was seen at 24 h (RR=0.95, $P=0.50$). There were no major adverse effects	delayed, its efficacy is similar at 24 h compared with class Ic drugs
Kochiadakis, 2000	²⁹⁶	RCT	214 with recurrent symptomatic AF	Amiodarone, propafenone and sotalol	Age >18 years, ECG documentation of AF, and symptoms such as light-headedness, palpitations, chest pain, and dyspnoea in	Recurrent AF	Recurrent AF occurred in 25/75 patients treated with amiodarone compared to 51/75 patients treated with sotalol and 24/64 patients	Amiodarone and propafenone were superior to sotalol in maintaining long-term normal sinus rhythm in patients with

					association with AF. Exclusion: acute myocardial infarction <6 months before entry into the trial, cardiogenic shock, thyroid disease, AF secondary to an active underlying disorder, recent cardiac surgery, uncontrolled congestive heart failure, un-stable angina, hepatic or renal failure, an LVEF <40%, an estimated life expectancy of <1 year; and		treated with propafenone. 14 patients treated with amiodarone, 5 with sotalol, and 1 with propafenone experienced adverse effects while in sinus rhythm, necessitating discontinuation of treatment ($P<0.001$ for amiodarone and propafenone vs. sotalol). If the analysis was limited to recurrent AF	AF. Amiodarone tended to be superior to propafenone, but its long-term efficacy was limited by adverse side effects

					previous exposure to amiodarone, propafenone or sotalol		events, amiodarone was more effective than propafenone ($P<0.05$)	
Roy, 2000	²⁹⁷	RCT	403	Amiodarone (201) versus sotalol (101) or propafenone (101)	Patients who had had at least one episode of AF within the previous six months	Primary end point was the length of time to a first recurrence of AF	After a mean of 16 months of follow-up, 35% patients assigned to amiodarone 63% of those who were assigned to sotalol or propafenone had a recurrence of AF ($P<0.001$). Adverse events requiring the	Amiodarone is more effective than sotalol or propafenone for the prevention of recurrences of AF

							discontinuation of drug therapy occurred in 18% of the patients receiving amiodarone, versus 11% of those treated with sotalol or propafenone ($P=0.06$)	
Hohnloser, 2009 (ATHENA)	⁷	RCT	4628	Intervention: dronedarone Control: placebo	Inclusion: patients with AF and additional risk factors for death	The primary outcome: first hospitalization due to CV events or death. Secondary outcomes: death from any cause, death from CV	The primary outcome occurred in 734 patients (31.9%) in the dronedarone group and in 917 patients (39.4%) in the placebo group (for	Dronedarone reduced the incidence of hospitalization due to cardiovascular events or death in patients with AF

						causes, and hospitalization due to CV events	dronedarone HR=0.76;95% I CI 0.69–0.84; <i>P</i> <0.001)	
Kirchhof, 2012	²⁵⁹	RCT	635	Randomization to: no treatment following CV vs. flecainide for 4 weeks vs. flecainide for 6 months	Inclusion: >18 years with persistent AF scheduled for ECV Exclusion: patients unsuitable for flecainide therapy or those already treated with other AADs	Primary outcomes: time to first persistent AF recurrence or death from any cause Secondary outcomes: time to first documented AF; number and total duration of paroxysmal or persistent AF episodes documented on ECG, AF	In the per-protocol population short-term flecainide treatment is not non-inferior to long term treatment after cardioversion; (mean difference 7.9%; 95% CI- 1.9–17.7; <i>P</i> =0.28 for non-inferiority). In a post-hoc analysis of patients who	Short-term antiarrhythmic drug treatment after cardioversion is less effective than is long-term treatment, but can prevent most recurrences of AF

						hospitalization; serious adverse events, QoL	did not reach the primary endpoint in the first month long-term treatment with flecainide was superior to short-term treatment (HR=0.31; 95% CI 0.18–0.56; $P=0.001$)	
Stroobandt, 1997	²⁹⁸	RCT	160 patients with persistent AF	Propafenone 2 mg/kg over 30 minutes, followed by oral propafenone 150 mg 3 times daily or matching placebo	Aged >18 years with either recent-onset AF or chronic AF occurring either as a first episode or as a recurrent episode. Exclusion:	Number of patients Who maintained sinus rhythm after 6 months. Secondary objectives were	Pharmacologic conversion to sinus rhythm was achieved in 29% of the patients taking propafenone and in 17% of patients taking placebo ($P>$	Oral propafenone at a low dosage 150 mg 3 times daily is well tolerated and effective in maintaining sinus rhythm for 6 months

					NYHA class >2 or symptoms of heart failure on physical examination, recent myocardial infarction or cardiac surgery , cardiogenic shock or hypotension, angina pectoris, significant arrhythmias, or severe obstructive lung disease, pulmonary embolism, metabolic disturbances or known thyroid	(1) the evaluation of the efficacy of initial intravenous propafenone therapy and (2) the safety of propafenone in long term treatment	or=0.10). Subsequent direct-current cardioversion in nonresponders was equally successful (70%) in both groups ($P>0.10$). The proportion of patients free from recurrent symptomatic arrhythmia at 6 months was 67% for the propafenone and 35% for the placebo group ($P<0.01$). Time	after pharmacologic or electrical restoration of sinus rhythm

					dysfunctions, unstable hepatic or renal function, and evidence of digitalis intoxication and hypokalemia; treated with amiodarone within the preceding 6 months, or were currently receiving treatment with antiarrhythmic or cardiovascular drugs such as b blockers, verapamil, or diltiazem not discontinued 5 half-lives before		to AF relapse was more favorable with propafenone than with placebo ($P<0.001$). The incidence of drug-related side effects was 10% in the propafenone group and 14% in the placebo group	

					the start of the study			
Singh, 2005 (SAFE-T)	²⁸²	RCT	665	Patients with persistent AF randomized to receive amiodarone, sotalol or placebo	Inclusion: AF>72 hours and receiving OAC Exclusion: paroxysmal AF, atrial flutter, NYHA class III/IV, CrCl<60 mL/min, long QT, intolerance to beta blockers	Primary outcome: time to first recurrence of AF after SR restoration	Total SR restoration rate was 79.8% in the amiodarone group and 79.9% in the sotalol group ($P=NS$) and 68.1% in the placebo group ($P<0.01$ vs. sotalol, amiodarone). Both medications were similarly effective in ischemic heart disease. Restoration of	Amiodarone and sotalol did not show differences in converting AF to SR. amiodarone is superior to sotalol for SR maintenance. SR but both drugs have similar efficacy in patients with ischemic heart disease. Sustained SR was associated with better QoL and exercise

							SR was associated with a significant improvement of QoL and exercise tolerance	tolerance
Ehrlich, 2019	²⁹⁹	Retrospective cohort study	3498 individuals who had received dronedarone and 17 724 individuals who had received other antiarrhythmic drugs	Dronedarone, amiodarone, flecainide, propafenone, or sotalol	Patients who had received a first prescription of dronedarone, amiodarone, flecainide, propafenone, or sotalol in 1258 general and 62 cardiology practices	The main outcomes of this study were the percentages of patients with myocardial infarction and stroke in the dronedarone group and in the group of individuals who had received other	At the end of the follow-up period, 7.4% of individuals with dronedarone prescriptions and 8.3% of those who had been prescribed other antiarrhythmic drugs had been diagnosed with	In our study, dronedarone was associated with a lower risk of myocardial infarction and stroke in patients with AF compared to other antiarrhythmics

						antiarrhythmic drugs within six years of the index date. After six years of follow-up, 3.9% of patients who had received dronedarone and 5.2% of patients who had received other antiarrhythmic drugs had been diagnosed with myocardial infarction (log-rank <i>P</i>-value=0.002)	a stroke (log-rank <i>P</i>-value=0.003). dronedarone was associated with a significant decrease in the risk of developing myocardial infarction (HR=0.78) and suffering a stroke (HR=0.84) compared to other antiarrhythmics	

Evidence Table 19 for Recommendation Table 19 (Sec. 7) — Recommendations for catheter ablation of atrial fibrillation

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Paroxysmal AF								
Jais, 2008 (A4)	³⁰¹	RCT	112	Intervention: catheter ablation. Control group: treatment with antiarrhythmic drugs	Inclusion: adult patients with symptomatic, documented paroxysmal AF ≥2 episodes during the preceding month. Exclusion: contraindications to >2 AADs in different classes or to OAC, prior AF ablation, intracardiac thrombus, AF from a potentially reversible cause,	Primary end point: proportion of patients free of recurrent AF between months 3–12 Secondary end points: time to recurrent AF, complications and adverse effects, change in left heart dimensions and function, QoL, exercise capacity, AF	At the 1-year follow-up, 23% and 89% had no recurrence of AF in the antiarrhythmic drug and ablation groups, respectively (<i>P</i> <0.001). Symptom score, exercise capacity, and quality of life were significantly higher in the	Superiority of catheter ablation over antiarrhythmic drugs in patients with AF with regard to maintenance of sinus rhythm and improvement in symptoms, exercise capacity, and quality of life

					pregnancy, or a contraindication to the discontinuation of OAC	burden, and efficacy of amiodarone when used for the first time during the study	ablation group	
Wilber, 2010 (Thermocool AF)	³⁰²	RCT	167	Intervention: Catheter ablation. Control group: treatment with antiarrhythmic drugs	Inclusion: ≥3 symptomatic paroxysmal AF episodes (≥1 episode verified by ECG) within the 6 months before randomization, and not responding to at least 1 antiarrhythmic. Exclusion: AF>30 days,<18 years, LVEF<40%, previous ablation for AF, documented left atrial thrombus,	Primary end point: freedom from protocol-defined treatment failure, which included documented symptomatic paroxysmal AF, repeat ablation after day 80 after the initial ablation, absence of entrance block confirmed in all	At the end of the 9-month effectiveness evaluation period, 66% of patients in the catheter ablation group remained free from protocol-defined treatment failure compared with 16% of patients treated with ADT (HR=0.30;	Among patients with paroxysmal AF who had not responded to at least 1 antiarrhythmic drug, the use of catheter ablation compared with ADT resulted in a longer time to treatment failure during the 9-month follow-up period

					amiodarone therapy in the previous 6 months, NYHA class III or IV, myocardial infarction within the previous 2 months, CABG in the prior 6 months, prior valvular surgery, ICD, contraindication to antiarrhythmic or anticoagulation medications, life expectancy of <12 months IAd >50 mm	PVs at the end of the ablation procedure, or changes in specified drug regimen post blanking even if they remained free from symptomatic paroxysmal AF	95% CI 0.19–0.47; $P<0.001$). Major 30-day treatment-related adverse events occurred in 8.8% treated with ADT and 4.9% treated with catheter ablation	
Packer, 2013 (STOP-AF)	³⁰³	RCT	245	Intervention: Cryoballoon ablation. Control group: treatment with	Inclusion: >2 episodes of symptomatic paroxysmal AF in the 2 months prior	Primary effectiveness endpoint: freedom from treatment	At 12 months, treatment success was 69.9% of cryoablation	The STOP AF trial demonstrated that cryoballoon ablation is a safe

				antiarrhythmic drugs	to randomization and previously failed therapy with ≥ 1 antiarrhythmic drug. Exclusion: LAd ≥ 5.0 cm; LVEF $< 40\%$; NYHA class III/IV congestive HF, CAD warranting intervention, stroke or transient ischemic attack (TIA) within 6 months, previous LA ablation or surgery for AF, a prosthetic heart valve, amiodarone therapy in the preceding 3 months, > 2	failure, as defined by the absence of: any detectable AF after the blanking period; use of a non-study, antiarrhythmic drug; or any non-protocol intervention for AF (i.e., RF ablation)	patients compared with 7.3% of antiarrhythmic drug patients (absolute difference, 62.6% $P < 0.001$)	and effective alternative to antiarrhythmic medication for the treatment of patients with symptomatic paroxysmal AF, for whom at least one antiarrhythmic drug has failed, with risks within accepted standards for ablation therapy

					cardioversions within 2 years, an implantable rhythm device			
Packer, 2019 (CABANA)	³⁰⁴	RCT	2204	Intervention: catheter ablation Control group: State of the art drug therapy	Inclusion: AF ≥ 65 years or <65 years with 1 or more risk factors for stroke (hypertension, heart failure, history of stroke, diabetes, or other heart problems), had ≥2 episodes of paroxysmal AF or 1 episode of persistent AF in the prior 6 months, and were suitable for catheter-based treatment or rhythm and/or rate control drug therapy.	Primary endpoint: composite of death, disabling stroke, serious bleeding, or cardiac arrest. Prespecified secondary end points: all-cause mortality; total mortality or cardiovascular hospitalization; and AF recurrence	Intention-to-treat analysis: over a median follow-up of 48.5 months, the primary end point occurred in 8.0% of patients in the ablation group vs. 9.2% of patients in the drug therapy group (HR=0.86; 95% CI 0.65–1.15; <i>P</i> =0.30). Outcomes in the ablation	The strategy of catheter ablation, compared with medical therapy, did not significantly reduce the primary composite end point of death, disabling stroke, serious bleeding, or cardiac arrest

					Exclusion: prior left atrial catheter ablation for AF or had failed ≥ 2 antiarrhythmic drugs		group vs. the drug therapy group were 5.2% vs. 6.1% for all-cause mortality (HR=0.85; 95% CI 0.60–1.21; $P=0.38$). Bias: high treatment crossovers	
Wazni 2005 (RAAFT)	³⁰⁵	RCT	70	Intervention: PVI using radiofrequency ablation. Control group: treatment with antiarrhythmic drugs (class I or III agents)	Inclusion: Patients with monthly symptomatic AF episodes for at least 3 months. (95.7% paroxysmal AF) Exclusion: <18 years and >75 years, previous history of atrial flutter or AF	Main outcome measures: recurrence of AF, hospitalization, and quality of life assessment	At the end of 1-year follow-up, 63% of patients in the AAD vs. 13% in the PVI group had at least 1 recurrence of symptomatic AF ($P<.001$). Hospitalization during 1-year	PVI is a feasible first-line approach for the treatment of selected patients with symptomatic AF

					ablation, previous history of open-heart surgery, previous AAD treatment and contraindication to long-term anticoagulation treatment		follow-up occurred in 54% patients in the AAD group compared with 9% in the PVI group ($P<0.001$). Limitation: small N patients	
Cosedis-Nielsen, 2012 (MANTRA-PAF)	306	RCT	294	Intervention: radiofrequency catheter ablation. Control group: treatment with antiarrhythmic drugs (class I or III agents)	Inclusion: ≥ 2 episodes of symptomatic paroxysmal AF within the preceding 6 months Exclusion: age >70 , previous or ongoing treatment with class IC or class III AADs, contraindication to both class IC and	Primary study end points: AF burden (percentage of time in AF on each Holter recording) and the cumulative AF burden (percentage of time in AF on all the Holter recordings	No significant difference between the ablation and drug-therapy groups in the cumulative burden of AF or the burden at 3, 6, 12, or 18 months. At 24 months, the burden of AF	No significant difference between the two treatment strategies in the cumulative burden of AF over a period of 2 years

					class III agents, previous AF ablation, IAd >50 mm, LVEF <40%, contraindication to OAC, moderate-to-severe mitral valve disease, severe heart failure (NYHA III–IV), expected surgery for structural heart disease, and secondary AF (due to cardiac surgery, infection, or hyperthyroidism)	obtained during follow-up). Secondary outcome measures: freedom from any AF and freedom from symptomatic AF at 24 months of follow-up, cumulative and per-visit burden of symptomatic AF, time to first recurrence of AF after the blanking period	was significantly lower in the ablation group than in the drug-therapy group (90th percentile, 9% vs. 18%; $P=0.007$). More patients in the ablation group were free from any AF (85% vs. 71%; $P=0.004$) and from symptomatic AF (93% vs. 84%; $P=0.01$). Limitation: Significant cross-over	

Morillo, 2014 (RAAFT-2)	307	RCT	127	Intervention: radiofrequency catheter ablation. Control group: treatment with antiarrhythmic drugs (class I or III agents)	Inclusion: >18 years and <75 years with symptomatic, recurrent paroxysmal AF without previous AAD treatment. Exclusion: documented LVEF <40%; IAd>5.5 cm; had moderate to severe left ventricular hypertrophy (wall thickness >1.5 cm), valvular disease, coronary artery disease, or postcardiac surgery within 6 months; previous left heart ablation, complete	Primary efficacy endpoint: first recurrence of symptomatic or asymptomatic AF, atrial flutter, or atrial tachycardia lasting more than 30 seconds documented by ECG or trans telephonic monitor. Secondary outcome: first documented recurrence of AF, atrial flutter, and atrial tachycardia episodes;	Primary efficacy endpoint: 72% in the AAD group vs. 54.5% in the ablation group (HR=0.56; 95% CI 0.35–0.90; <i>P</i>=0.02). Secondary outcomes: 59% in the AAD group vs. 47% in the ablation group (HR=0.56; 95% CI 0.33–0.95; <i>P</i>=0.03)	Among patients with paroxysmal AF without previous antiarrhythmic drug treatment, radiofrequency ablation compared with antiarrhythmic drugs resulted in a lower rate of recurrent atrial tachyarrhythmias at 2 years

					contraindication for the use of heparin, warfarin, or both	repeated episodes of symptomatic or asymptomatic AF, atrial flutter, and atrial tachycardia episodes		
Wazni, 2021 (STOP AF)	³⁰⁸	RCT	203	Intervention: pulmonary vein isolation with a cryoballoonControl group: treatment with antiarrhythmic drugs (class I or III agents)	Inclusion: 18 to 80 years, with recurrent symptomatic paroxysmal AF. Exclusion: previous treatment with an antiarrhythmic drug (class I or III) for 7 or more days, an enlarged left atrial diameter (>5 cm), or a previous left atrial ablation or left atrial surgical	Primary efficacy end point: treatment success (freedom from the following events: initial failure of the procedure; any subsequent AF surgery or ablation in the left atrium; atrial arrhythmia recurrence,	Treatment success at 12 months was 74.6% (95% CI 65.0–82.0) in the ablation group and 45.0% (95% CI 34.6–54.7) in the drug-therapy group ($P<0.001$ by log-rank test). Two primary safety end-point	Cryoballoon ablation was superior to antiarrhythmic drug therapy for the prevention of atrial arrhythmia recurrence in patients with paroxysmal AF who had not previously received rhythm-control therapy. Serious

					procedure	cardioversion; or use of class I or III antiarrhythmic drugs outside the 90-day blanking period)	events occurred in the ablation group (annual event rate=1.9%). Limitations: limited FU (1 year), intermittent rhythm monitoring, unblinded nature of the trial	procedure-related adverse events were uncommon
Andrade, 2021 (EARLY-AF)	³⁰⁹	RCT	303	Intervention: catheter cryoballoon ablation. Control group: Antiarrhythmic drug therapy	Inclusion: >18 years who had symptomatic paroxysmal AF and ≥1 episode of AF detected on electrocardiography within 24 months before	Primary end point: first recurrence of any atrial tachyarrhythmia lasting 30 seconds or longer after the 3-month	At 1 year, recurrence of atrial tachyarrhythmia occurred in 42.9% of patients in the ablation group and 67.8% in	Among patients receiving initial treatment for symptomatic, paroxysmal AF, there was a significantly lower rate of AF recurrence with

					randomization. Exclusion: history of regular (daily) use of a class I or class III antiarrhythmic drug at therapeutic doses, LA diameter >55 mm	blanking period or performance of repeat ablation. Secondary endpoints: first recurrence of symptomatic atrial tachyarrhythmia after the 3-month blanking period, arrhythmia burden, success of multiple ablation procedures, QoL, health care utilization, and serious adverse events	the AAD group (HR=0.48; 95% CI 0.35–0.66; $P<0.001$). Serious adverse events occurred in 3.2% of patients who underwent ablation and in 4.0% of patients who received antiarrhythmic drugs	catheter cryoballoon ablation than with antiarrhythmic drug therapy, as assessed by continuous cardiac rhythm monitoring
Kuniss,	³¹⁰	RCT	218	Intervention:	Inclusion: 18 to 75	Primary end	Freedom from	Cryoballoon CA

2021 (Cryo-FIRST)				pulmonary vein isolation with cryoballoon. Control group: antiarrhythmic drug therapy (Class I or III)	years old with a normal ECG, structurally normal heart (LVEF >50%), IAd (short axis) <46 mm] and recurrent symptomatic paroxysmal AF, no previous treatment with Class I or III AAD for >48h	point: freedom from any atrial arrhythmia recurrence lasting >30 s at 12 months documented by 7-day Holter ECG or any other ECG recording outside of the 90-day blanking period or cardioversion or repeat catheter ablation for atrial arrhythmia recurrence outside of the 90-day blanking period. Secondary	AA was achieved in 82.2% of subjects in the cryoballoon arm and 67.6% of subjects in the AAD arm (HR=0.48; $P<0.01$). There were no group differences in the time-to-first (HR=0.76; $P=0.28$) or overall incidence (IRR=0.79; $P=0.28$ of SAEs	was superior to AAD therapy, significantly reducing arrhythmia recurrence in treatment naive patients with PAF. Cryoballoon CA was associated with lower symptom recurrence and a similar rate of SAEs compared with AAD therapy

						endpoints: rate of serious adverse events (SAEs) and recurrence of patient-reported symptomatic palpitations		
Persistent AF								
Mont, 2014 (SARA)	³¹¹	RCT	146	Intervention: catheter ablation. Control group: treatment with antiarrhythmic drugs	Inclusion: symptomatic persistent AF refractory to at least one class I or class III antiarrhythmic drug. Exclusion: age<18 or >70 years, long-standing persistent AF, first AF, hyper- or hypothyroidism, hypertrophic	Primary outcome: episode of AF or flutter lasting >24h or requiring cardioversion after a 3-month blanking period. Secondary outcomes: any recurrence of AF or flutter >30 s after the	In an intention-to-treat analysis, 70.4% in the CA group and 43.7% in the ADT group were free of the primary endpoint ($P=0.002$). The proportion of patients free of any recurrence	Catheter ablation is superior to medical therapy for the maintenance of sinus rhythm in patients with persistent AF at 12-month follow-up

					cardiomyopathy, implanted pacemaker or defibrillator, moderate or severe mitral disease or mitral prosthesis, LVEF<30%, LAd>50 mm, prior ablation procedure, contra-indication for oral anticoagulation, left atrial thrombus, active infection or sepsis, pregnancy, unstable angina, acute myocardial infarction during previous 3 months, life expectation <12 months	3-month blanking period, hospitalization related to arrhythmia, electrical or pharmacological cardioversion, therapeutic crossover, AV node ablation, re-ablation, health-related QoL, complications	(>30 s) was higher in the CA group than in the ADT group (60.2 vs. 29.2%; $P<0.001$) and cardioversion was less frequent (34.7 vs. 50%; $P=0.018$)	
Winkle,	³¹²	Prospective	843	Catheter ablation	Symptomatic	Freedom from	For each AF	For patients with

2011		cohort study			patients undergoing AF ablation	AF	type, repeat ablations were more successful than initial ablations ($P = .01$ to 0.001). Procedure times (139.1 ± 49.1 vs. 135.3 ± 45.6 minutes, $P = .248$) and major complications (1.66% vs. 2.87%, $P = .216$) were similar. Patients with either successful initial ablations or undergoing repeat ablations	persistent AF repeat ablations are more successful than initial ablations, have similar procedure times and complication. For the best outcomes, patients may need a repeat ablation

							had late AF recurrence rates of 0% to 1.5% a year	
Mohanty, 2014	³¹³	Prospective cohort study	1257	Catheter ablation	Patients with metabolic syndrome (MS) or obstructive sleep apnoea (OSA) undergoing first catheter ablation for AF. Exclusion: patients with central sleep apnoea or previous continuous positive airway pressure breathing therapy users	Freedom from AF, atrial flutter (AFL), or atrial tachycardia (AT) of >30 seconds duration off AAD at follow-up	After 34 ± 8 months of first procedure, 66 (52%) in Group 1 (MS and OSA) and 386 (34%) in Group 2 (either MS or OSA) had recurrence ($P<0.001$). Recurrence rate in only-MS, only-OSA, and without MS/OSA groups were 40%, 38%, and 29%,	In patients with OSA and MS, repeat ablation or compliant lifestyle modifications increase freedom from recurrent AF

							respectively. Patients with MS+OSA experienced substantially higher recurrence compared to those with lone MS or OSA (52% vs. 40% vs.38%; $P=0.036$). Of the 452 patients having recurrence, 250 underwent redo-ablation and 194 remained on AAD and lifestyle modifications.	

							At 20 ± 6 months, 76% of the redo group remained arrhythmia-free off AAD whereas 74% of the LSM group were free from recurrence ($P=0.71$), 33% of which were off AAD	
Bhargava, 2009	³¹⁴	Retrospective cohort study	1404 underwent catheter ablation for AF	Role of repeat catheter ablation	Symptomatic, drug-resistant AF. Exclusion: <18 years old or >85 years old or if they had a contraindication to oral anticoagulation	AF recurrence	At mean follow-up of 57 +/- 17 months, 565 of 728 patients with PAF and 454 of 676 patients with NPAF (77.6% vs. 67.2%, $P<.001$) had	Pulmonary vein antrum isolation guided by intracardiac echocardiography results in significant freedom from AF. At least moderate efficacy can be

							freedom from AF after a single ablation procedure. For arrhythmia recurrences, 74.2% (121/163) patients with PAF and 74.8% (166/222) with NPAF underwent repeat ablation, after which 92.4% patients with PAF and 84.0% patients with NPAF remained free from AF	achieved in patients with NPAF, although the success rate is lower than in patients with PAF. Considerably higher success can be achieved in both groups with repeat ablation
HF								
Chen, 2020	315	Systematic	3598	Intervention group:	Inclusion: AF and	Primary	CA rhythm	

		review and meta analysis of RCTs	Trials with HFrEF and HFpEF	rhythm control using AADs (Subset A) or catheter ablation vs. rate control. Subset B: rhythm control using catheter ablation vs. medical therapy. (Subset B); the control group: rate control (Subset A) or medical therapy (Subset B); outcome: major cardiovascular endpoints	HF RCT;	outcomes: all-cause mortality, re-hospitalization, stroke, and thromboembolic events. Secondary outcomes: LVEF, recurrence of AF/atrial tachycardia (AT) QoL: Minnesota Living with Heart Failure Questionnaire (MLHFQ) score	control was associated with significantly lower all-cause mortality (OR=0.51; $P=0.003$), reduced re-hospitalization rate (OR=0.44; $P=0.003$), similar rate of stroke events (OR=0.59; $P=0.27$). Compared with medical rate control, the AADs rhythm control was associated with similar all-cause mortality (OR=0.96;	

							<i>P</i> =0.65), significantly higher rate of re-hospitalization (OR=1.25; <i>P</i> =0.01), and similar rate of stroke and thromboembolic events (OR=0.91; <i>P</i> =0.76)	
Sohns, 2023 (CASTLE-HTx)	³¹⁶	RCT	194	Intervention: catheter ablation and guideline directed medical therapy; control: medical therapy alone	Inclusion: symptomatic AF, ≥NYHA II, LVEF ≤35%, impaired functional capacity, as assessed with the use of the 6-minute walk test Exclusion: left atrial diameter >6 cm;	Primary end point: composite of death from any cause, implantation of a left ventricular assist device, or urgent heart transplantation	Primary end-point event had occurred in 8 patients (8%) in the ablation group and in 29 patients (30%) in the medical-therapy group (HR= 0.24;	In patients with end-stage heart failure catheter ablation alongside medical therapy is more effective in improving survival, reducing the need for

					contraindication for chronic anticoagulation therapy or heparin; previous ablation; ACS; cardiac surgery, angioplasty, or cerebrovascular accident within 2 months prior to enrolment; untreated hypothyroidism/ hyperthyroidism; mental or physical inability to participate in the study; Listed as 'high urgent' for heart transplantation; cardiac assist		95% CI 0.11–0.52; $P<0.001$). Death from any cause occurred in 6 patients (6%) in the ablation group and in 19 patients (20%) in the medical-therapy group (HR=0.29; 95% CI 0.12–0.72)	ventricular assist device implantation and heart transplant, than medical therapy alone

					device implanted; planned cardiovascular intervention; life expectancy ≤12 months; uncontrolled hypertension; requirement for dialysis due to end- stage renal failure			
Packer, 2021 (CABANA trial)	³¹⁷	RCT	778	Ablation with pulmonary vein isolation versus drug therapy including rate or rhythm control drugs	Patients with AF who were ≥65 years old or <65 years old with ≥1 risk factor for and NYHA class >II	Primary end point was a composite of death, disabling stroke, serious bleeding, or cardiac arrest. All-cause mortality; AF recurrence; Quality of life measured by	The ablation arm had a 36% relative reduction in the primary composite end point (HR= 0.64 [95% CI, 0.41– 0.99]) and a 43% relative reduction in all- cause mortality	In patients with AF and heart failure, catheter ablation had a greater improvement on survival, freedom from AF and quality of life when compared to rhythm control drug therapy

						the AFEQT summary score and MAFSI (Mayo Atrial Fibrillation-Specific Symptom Inventory) frequency score	(HR, 0.57 [95% CI, 0.33–0.96]) compared with drug therapy alone over a median follow-up of 48.5 months. AF recurrence was decreased with ablation (HR, 0.56 [95% CI, 0.42–0.74]). The adjusted mean difference for the AFEQT summary score averaged over the entire 60-month follow-up was 5.0 points, favouring the	

							ablation arm (95% CI, 2.5–7.4 points), and the MAFSI frequency score difference was -2.0 points, favouring ablation (95% CI, -2.9 to -1.2)	
Hunter, 2014 (CAMTAF)	³¹⁸	RCT	50	Intervention: catheter ablation for AF. Control group: medical rate control	Inclusion: Persistent AF, symptomatic HF (NYHA class II–IV), LVEF <50%. Exclusion: HF with a suspected reversible cause, previous LA ablation, any contraindication to catheter ablation, symptoms that	Primary endpoint: LVEF at 6 months. Secondary endpoints: % reduction in LV end systolic volume, VO ₂ max, plasma BNP, NYHA class, MLWHF score, and 36-SFS	Significantly higher LVEF at 6 months in the ablation group compared with the rate control group (40 ± 12% vs. 31 ± 13%, <i>P</i> =0.015). Ablation was associated with better peak oxygen	Catheter ablation is effective in restoring sinus rhythm in selected patients with persistent AF and HF, and can improve LV function, functional capacity, and HF symptoms compared with

					were clearly attributable to AF rather than HF, any event during the past 6 months that might continue to effect on LV function (including implantation of a pacemaker or CRT-D, cardiac surgery, MI, or coronary revascularization), or a realistic expectation of these occurring within the next year		consumption (22 ± 6 vs. 18 ± 6 mL/kg per minute; <i>P</i> =0.014) and Minnesota living with HF questionnaire score (24 ± 22 vs. 47 ± 22; <i>P</i> =0.001) compared with rate control. Limitations: single centre study	rate control
Di Biase, 2016 (AATAC)	³¹⁹	RCT	203	Intervention: CA for AF. Control group: medical therapy with amiodarone	Inclusion: ≥18 years with persistent AF, dual-chamber ICD or CRT-D, NYHA class II–III, and	Primary end point: AF recurrence. Secondary endpoints: all-cause	Significantly higher risk of treatment failure in the AMIO group: (HR=2.5; 95%	Catheter ablation of AF is superior to AMIO in achieving freedom from AF at long-term

					LVEF ≤40% within the past 6 months. Exclusion: AF due to a reversible etiology, valvular or coronary heart disease requiring surgical intervention, early postoperative AF or a life expectancy ≤2 years, prolonged QT interval, hypothyroidism, history of severe pulmonary disease, and liver failure	mortality and unplanned hospitalization rate	CI 1.5–4.3; $P<0.001$) than CA. Significantly lower unplanned hospitalization rate (RR=0.55; 95% CI 0.39–0.76) and significantly lower mortality (8% vs. 18%, $P=0.037$) in CA vs. AMIO group	follow-up and reducing unplanned hospitalization and mortality in patients with HF and persistent AF
Prabhu, 2017 (CAMERA-MRI)	³²⁰	RCT	68	Intervention: catheter ablation with PVI and posterior wall isolation.	Inclusion: 18–85 years; NYHA class ≥ II; persistent AF; (4) LVEF ≤45% on baseline cardiac	Primary endpoint: change in LVEF from baseline to 6 months on	LVEF improved by $+18 \pm 13\%$ in the CA group compared to $+4.4 \pm 13\%$ in	The restoration of sinus rhythm with catheter ablation is associated with considerable

				Control group: medical rate control	MRI (CMR); exclusion of coronary artery disease via conventional or CT guided angiography or functional imaging and no other identifiable cause explaining the LV dysfunction. Exclusion: contraindication to AF ablation; contra- indication to cardiac MRI or paroxysmal AF	CMR. Secondary endpoints: change in CMR chamber dimensions, NYHA class, BNP, 6MWT distance, physical and mental composite scores (SF-36), AF recurrence, AF burden, and procedural complications	MRC group, ($P<0.001$) and normalized (LVEF $\geq 50\%$) in 58% vs. 9%; $P=0.002$	improvements in LVEF, cardiac remodelling and functional capacity. The absence of CMR detected ventricular fibrosis identifies “super responders” to catheter ablation
Marrouche, 2018 (CASTLE- AF)	³²¹	RCT	363	Intervention: catheter ablation. Control group: medical therapy	Inclusion: paroxysmal or persistent AF; resistant, intolerant or unwilling to take	Primary endpoint: composite of death from any cause or	Primary composite end point in significantly fewer patients	Catheter ablation for AF in patients with HF was associated with a significantly lower

					AADs; NYHA II–IV and LVEF<35%; implanted ICD or CRT-D with automatic daily remote-monitoring capabilities (17.9% paroxysmal AF). Exclusion: Candidacy for heart transplantation or planned cardiovascular intervention	worsening of HF that led to an unplanned overnight hospitalization. Secondary endpoints: death from any cause, unplanned hospitalization related to heart failure, death from CV disease, cerebrovascular accident, unplanned hospitalization for CV disease, and any hospitalization; procedure-	in the ablation group than in the medical-therapy group (28.5% vs. 44.6%; HR=0.62; 95% CI 0.43–0.87; <i>P</i>=0.007). Significant reduction in all-cause mortality: 13.4% vs. 25.0%; (HR=0.53; 95% CI 0.32–0.86; <i>P</i>=0.01), hospitalization for worsening HF (20.7% vs. 35.9%; HR=0.56; 95% CI 0.37–0.83;	rate of a composite end point of death from any cause or hospitalization for worsening HF than was medical therapy

						related adverse events in the ablation group	<i>P</i> =0.004), or cardiovascular mortality (11.2% vs. 22.3%; HR= 0.49; 95% CI 0.29–0.84; <i>P</i> =0.009). Limitation: highly selected patient population	

Additional Evidence Table S20 — Catheter ablation

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Kuck, 2019 (AMICA)	³²²	RCT	202	Intervention: AF catheter ablation. Control group: Best medical therapy (rate or rhythm control)	Inclusion: 18 to 75 years, persistent or longstanding persistent AF, NYHA class II–III HF, indication for an ICD or a CRT-D, LVEF ≤ 35% under optimal medical treatment for HF for at least 1 month. Exclusion: Left atrial diameter of >60 mm in parasternal axis, an underlying valvular heart disease (without correction) and	Primary study end point: absolute increase in LVEF from baseline to 1 year after randomization. Secondary end points: 6-minute walk distance, self-assessed QoL, BNP or NTproBNP levels, AF burden, adverse events, and mortality	No change in LVEF at 1 year in ablation patients 8.8% (95% CI 5.8–11.9%) vs. BMT patients 7.3% (95% CI 4.3–10.3%; <i>P</i> =0.36). No difference in secondary end point outcome between ablation patients and BMT patients. Limitation: early termination: one	The trial did not reveal any benefit of catheter ablation in patients with AF and advanced HF

					previous PV isolation procedures		year FU and unexpected EF increase in control arm	
Andrade, 2023 (EARLY-AF (3-year FU))	323	RCT	303	Intervention: catheter cryoballoon ablation. Control group: antiarrhythmic drug therapy	Inclusion: >18 years who had symptomatic paroxysmal AF and ≥1 episode of AF detected on electrocardiography within 24 months before randomization. Exclusion: history of regular (daily) use of a class I or class III antiarrhythmic drug at therapeutic doses, LAd >55 mm	Primary endpoint: first occurrence of persistent AF (episode of continuous atrial tachyarrhythmia lasting ≥7 days or 48hours-7 days but necessitating cardioversion for termination). Secondary end points: arrhythmia burden (% of time in AF); quality of life;	Over 36 months of follow-up, 3 patients (1.9%) in the ablation group had an episode of persistent AF, as compared with 11 patients (7.4%) in the antiarrhythmic drug group (HR=0.25; 95% CI 0.09–0.70)	Initial strategy of catheter cryoballoon ablation is associated with a lower incidence of persistent AF, as determined by implantable cardiac devices capable of continuous rhythm monitoring, than pharmacologic rhythm control

						health care utilization as determined by ED visits, hospitalizations, cardioversion, or non-protocol ablation; and serious adverse events		
Parkash, 2022 (RAFT-AF)	³²⁴	RCT	411	Intervention: catheter ablation. Control group: Medical therapy for rate control	Inclusion: high-burden paroxysmal (>4 episodes in 6 months) or persistent (duration <3 years) AF, NYHA class II–III heart failure, and elevated NT-proBNP (≥600 pg/mL if in sinus rhythm, or ≥900 pg/mL if in AF). Exclusion:	Primary outcome measure: composite of all-cause mortality and all HF events. Secondary outcome measure: LVEF, 6-minute walk test, and NT-proBNP	Significant reduction in the primary outcome (23.4% in the ablation-based rhythm-control group vs. 32.5% in the rate-control group; HR=0.71; 95% CI 0.49–1.03; <i>P</i> =0.07).	In patients with high-burden AF and HF, there was no statistical difference in all-cause mortality or HF events with ablation-based rhythm control versus rate control; however, there was a nonsignificant

					LA>55 mm, rheumatic heart disease, severe aortic or mitral valve disease or life expectancy less than one year. LVEF ≤45% (in 58.4%)		Significant LVEF increase in the ablation-based group ($10.1 \pm 1.2\%$ versus $3.8 \pm 1.2\%$, $P=0.017$), significant improvement in 6-min walk test; $P=0.025$; significant decrease in NT-proBNP; $P<0.001$. Similar serious adverse events in both groups. Limitation: Early termination because of apparent futility	trend for improved outcomes with ablation-based rhythm control over rate control

Evidence Table 20 for Recommendation Table 20 (Sec. 7) — Recommendations for anticoagulation in patients undergoing catheter ablation

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Brockmeyer, 2020	³²⁵	Meta analysis of RCTs	6 RCTs, 2369 patients	Comparison of uninterrupted DOAC vs. VKA Uninterrupted OAC during catheter ablation for AF	Online databases were searched for RCTs comparing uninterrupted DOAC to VKA in patients undergoing catheter ablation of AF	Primary safety outcome major bleeding. Primary efficacy outcome stroke or TIA. 2 nd composite major bleeding and stroke or TIA, minor bleeding, acute stroke on MRI and mortality	No sign difference in DOAC vs. VKA for major bleeding, stroke and TIA nor for 2 nd outcome. Bleeding outcome as per study definition (4 with IST)	Uninterrupted DOAC not superior to VKA in patients undergoing ablation for AF
DiMonaco, 2020	³²⁶	Meta analysis of RCTs	6 RCTs n=2369	Safety and efficacy of	Inclusion: eligible RCTs	Safety and efficacy of	Nonsignificant in DOACs vs. VKA	Uninterrupted DOAC is safe

			(1288 DOAC and 1081 VKA)	uninterrupted direct oral anticoagulants (DOACs) to uninterrupted vitamin K antagonists (VKAs) during AF	from 2009 to 2019	uninterrupted direct oral anticoagulants (DOACs) to uninterrupted vitamin K antagonists (VKAs) during AF	of composite outcome of major bleeding, stroke, or transient ischemic attack, and mortality (HR=0.69; 95% CI 0.28–1.71; 31 vs. 45 events), major bleeding alone (HR=0.66; 95% CI 0.30–1.47; 27 vs. 41 events), and silent cerebral thromboembolic events (HR=1.12; 95% CI 0.75–1.66); 72 vs. 58 among 442 and 376 patients	alternative to VKA

							performing MRI study. Sensitivity analyses confirmed overall results: pooled OR=0.56–1.00 for the composite outcome and OR=0.54–0.92 for major bleedings	
Noubiap, 2021	³²⁷	Systematic review and meta-analysis of RCT and observational studies	56 660 AF patients	Data on rates and predictors of LA or LAA thrombus by TOE before intervention (cardioversion or ablation) (all – not only OACs)	Inclusion: studies reporting on the prevalence or predictors of LAT or LAAT, SEC, or sludge identified	In patients undergoing CA and ECV, the pooled prevalence of LAT/LAAT was 1.8% and 7.5% in those not on oral anticoagulation	Pooled prevalence of LAT/LAAT was assessed. The risks of thrombus were higher amongst patients undergoing cardioversion.	Prevalence and RF varies for detection of LAA thrombus

					using TOE done before ECV or CA in patients with AF, or enough data to compute these estimates. Exclusion: Studies including less than 100 patients	(OAC), 1.8% and 5.5% in those taking OAC, and 1.3% and 4.9% in case of adequate OAC, respectively. According to the type of OAC, the prevalence was 2.0% and 7.6% for vitamin K antagonist, 1.3% and 3.5% for direct oral anticoagulant	For CA the overall pooled prevalence of LAT/LAAT was 1.8%, and lower in case of OAC at 1.3%. Risks were higher in patients with non-paroxysmal AF and RF	
Lurie, 2021	³²⁸	Systematic review and meta-analysis of observational	14 653 patients	Prevalence of among patients with AF/AFL undergoing TOE following	Inclusion: from inception to July 2020; studies	Prevalence of LAA thrombus after 3 w OAC on TOE CHA2DS2-	Prevalence LA thrombus 2.73% (95% CI 1.95–3.8%). Similar for VKA and	LA thrombus prevalence is high in subgroups of anticoagulated

		studies		at least 3 weeks of continuous therapeutic oral anticoagulation and to identify high-risk subgroups	reporting on LA thrombus prevalence among patients with AF/AFL undergoing TOE following at least 3 w of VKA/DOAC. Exclusion: studies including <100 patients	VASc reported	DOAC. Higher risk if non-paroxysmal (4.81% vs. 1.03); higher prevalence if undergoing cardioversion compared to ablation (5.55 vs. 1.65%). If high CHA2DS2-VASc >3 also increased risk 6.31% vs. 1.06. High inter-study Heterogeneity	patients with AF/AFL. TOE imaging in select patients at an elevated risk of LA thrombus, despite anticoagulation status, may be a reasonable approach to minimize the risk of thromboembolic complications following cardioversion or catheter ablation

Additional Evidence Table S21 — Left atrial appendage thrombus peri-ablation

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Liu, 2020	³²⁹	Systematic review and meta-analysis of RCT and observational studies	6860 patients	DOAC vs. VKA in LAA thrombus formation	Searched PubMed, Embase, and the Cochrane Library databases	There was no difference between the DOACs and VKAs groups with respect to the odds of LAT/LAAT formations	No difference between the DOACs and VKAs groups with respect to the odds of LAT/LAAT formations (OR=0.79; 95% CI 0.52–1.21; <i>P</i> =0.29)	The rate of thrombus formation did not differ between DOAC and VKA
Yang, 2019	³³⁰	Systematic review and meta-analysis of observational studies	7 016 patients	Incidence of left atrial thrombi (LAT) on TOE between different anticoagulants	The incidence of LAT and dense spontaneous echocardiographic contrast were extracted as the basis of the meta-	Subgroup analysis showed that the incidence of LAT among three types of DOACs have no	Incidence of LAT did not differ between patients anticoagulated with DOACs and those	Patients anticoagulated with DOACs may have lower incidence of LAT than patients on

					analysis	significant difference (dabigatran vs. rivaroxaban, OR=1.16; 95% CI 0.75–1.81; rivaroxaban vs. apixaban, OR=0.97; 95% CI 0.54–1.74]; dabigatran vs. apixaban, OR=1.09; 95% CI 0.55–2.16)	anticoagulated with VKAs (OR=0.74; 95% CI 0.55–1.00). After excluding the heterogeneous article by sensitivity analysis, we found the incidence of LAT in patients anticoagulated with DOACs is lower than VKAs (OR=0.59; 95% CI 0.42–0.84)	VKAs. The incidence of LAT among different type of DOACs did not differ
Diab, 2020	³³¹	Prospective cohort study	900 patients were included. median CHA ₂ DS ₂ -	Catheter ablation for AF	Inclusion: all consecutive patients presenting in AF or AFL on the day	Thromboembolic complication within 3 months	Thromboembolic complications occurred in 4 patients. all with no further	In this large prospective cohort of patients with novel DOACs

			VASc score was 2 (interquartile range 1–3). All were on DOACs (333 rivaroxaban, 285 dabigatran, 281 apixaban, and 1 edoxaban). Presenting rhythm on the day of ablation was AF in 698 patients (77.56% no preprocedural imaging was performed)		of the procedure and who had been treated with a novel DOAC (rivaroxaban, dabigatran, apixaban, or edoxaban) for at least 3 consecutive weeks and without interruption were included. Exclusion: patients presenting in AF or AFL but with <3 weeks of anticoagulation or interruption of their anticoagulants		complications. Bleeding complications occurred in 5 patients none required interventions. In all, it was noted that the risk of thromboembolic complication was 0.1% in patients with preserved LV systolic function (1 event in 710 patients with EF≥50%) and 1.6% in patients with reduced LV systolic function (3 events in 190	and presenting in AF or AFL, performing left atrial ablations without preprocedural or intraprocedural imaging of the LAA was feasible and with very low risk of thromboembolic or bleeding complications. Reasonable to image perhaps in reduced LVEF and persistent AF

					were required to undergo preprocedural TOE and were not included in the current study CT scans <3 weeks		patients with EF<50%)	
Patel, 2020	³³²	Prospective registry	6186 patients (5120 (82.8%)) patients had persistent and long-standing persistent AF; 4194 patients (67.8%) were male. The mean CHA2DS2-VASc scores were 2.86	Catheter ablation without TOE – all had ICE	All patients undergoing radiofrequency CA for AF on an uninterrupted DOAC regimen (i.e., apixaban, rivaroxaban, dabigatran, edoxaban) from January 2012 to December 2019 Patients with an interrupted DOAC regimen (>2 missed doses),	Transient ischemic attack (TIA) and cerebrovascular accident (CVA) were recognized as cerebral thromboembolic events. Postprocedural CVA and TIA were defined as an acute onset of a new neurological deficit up to 48	ICE imaging ruled out LAA and LA thrombi in all patients and revealed “smoke” in 1672 patients (27.03%). TIA was noted in 1 patient with long-standing persistent AF (0.016%) in the setting of a missed dose of rivaroxaban	4 weeks of OAC sufficient instead of TOE prior to catheter ablation

					secondary to either noncompliance or a planned surgical procedure, were excluded from this study	hours after the procedure	before ablation. Bias: non-randomised	

Additional Evidence Table S22 — Studies on minimally interrupted vs. interrupted oral anticoagulation

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Van Vugt, 2021	³³³	Systematic review and meta-analysis of RCTs	2168 patients, with 1233 (56.9%) on mi-DOAC and 935 (43.1%) on c-DOAC	Minimally interrupted DOAC vs. continuous DOAC in catheter ablation. DOAC strategy minimally interrupted when the morning dose was held on the day of ablation for twice-daily agents. In the	Randomized or non-randomized comparisons of a minimally interrupted vs. a continuous regimen with any DOAC (i.e. apixaban, dabigatran, rivaroxaban, edoxaban) in the setting of CA for AF. Outcome data reported both for bleeding and thrombo-	Net adverse clinical events (major bleeding, thrombo-embolic events) primary outcome	The primary endpoint occurred in 1.0% (18/1835): 1.1% (11/1005) vs. 0.8% (7/830) for the mi-DOAC and c-DOAC groups (OR=1.20; 95% CI 0.49–2.92; <i>P</i> =0.64). In the 7 studies reporting on major bleeding, the overall rate was 0.8%, without significant difference between mi-DOAC and c-DOAC: (OR=1.04 95% CI 0.43–2.51).	Overall complication rates were low, without a difference in MACE (major bleeding, thrombo-embolic events) between minimally interrupted and uninterrupted DOAC use. Despite preprocedural interruption,

				landmark trials on once-daily agents, drug intake in the evening before the day of the procedure was considered a continuous DOAC strategy. Patients using once-daily agents were considered to be on a minimally interrupted regimen	embolic events		Thrombo-embolic complications, reported in 8 studies, were observed in 0.3% of the patients (OR=1.00; 95% CI 0.59–1.69; $P=1.00$)	there were no signs of lower bleeding rates with this alternative regimen

				when the last intake was on the morning the day before the procedure				
Brunetti, 2020	334	Meta analysis of RCTs	2118 patients	Direct oral anticoagulants (DOACs) vs. vitamin K antagonists (VKAs) as uninterrupted anticoagulation in patients undergoing AF ablation to assess safety and efficacy of DOAC	Inclusion: RCTs comparing uninterrupted DOACs vs. uninterrupted VKA for CA of NVAf; and RCTs comparing the clinical outcomes of major bleeding and/or minor bleeding and/or thromboembolic events.	Thromboembolism (a stroke or transient ischemic attack) and bleeding (major and non-major bleeding events)	Compared with patients receiving VKA, patients receiving DOAC had a lower, although non-significant, risk of thromboembolic events (RR=0.40; 95% CI 0.09–1.76; <i>P</i> =0.23). MB rates in patients treated with DOACs were lower than VKA (RR=0.61; 95% CI 0.39–0.93, <i>P</i> =0.02). The incidence of NMB was not significantly	An uninterrupted DOACs strategy for CA of AF appears to be superior to uninterrupted VKA in terms of safety

					Exclusion: case reports, editorials, reviews, and expert opinions		different (RR=0.98; 95% CI 0.83–1.57; <i>P</i> =NS)	
Zhao, 2018	³³⁵	Meta analysis of RCTs	6 RCTs and 1903 patients	Efficacy and safety of uninterrupted DOACs and uninterrupted VKAs in patients undergoing AF ablation	Inclusion: RCTs comparing interrupted or uninterrupted DOACs and uninterrupted VKAs in patients undergoing ablation for AF. Exclusion: non-randomized studies; a lack of using DOAC/uninterrupted VKA as comparator; DOAC or VKAs was started only	The primary outcomes of interest were major bleeding and stroke or transient ischemic attack (TIA)	There was no significant difference between DOACs group and VKAs group in incidence of stroke or TIA (OR=1.00; 95% CI 0.23–4.40; <i>P</i> =1.00), silent cerebral thromboembolic events (OR=1.09; 95% CI 0.67–1.75; <i>P</i> =0.74) or minor bleeding (OR=1.01; 95% CI 0.78–1.31; <i>P</i> =0.93), which were consistent in subgroup analysis of	In patients undergoing AF ablation, uninterrupted DOACs was similarly effective as uninterrupted VKAs treatment

					after catheter ablation		individual DOAC vs. VKAs group. DOACs treatment was associated with reduced risk of major bleeding as compared with VKAs (OR=0.45; 95% CI 0.26–0.81; $P<0.01$)	
Romero , 2018	³³⁶	Meta analysis of RCTs	4 RCTs that enrolled a total of 1716	Uninterrupted direct oral anticoagulants (DOACs) vs. uninterrupted vitamin K antagonists (VKA) for catheter ablation (CA)	Inclusion: RCTs comparing uninterrupted DOACs vs. uninterrupted VKA for CA of NVAf that compared the clinical outcomes of major bleeding and/or minor bleeding and/or	Three primary outcomes: major bleeding, thrombo-embolic events, and minor bleeding. A secondary outcome was post-procedural silent cerebral infarction (SCI) as detected by brain magnetic	No significant benefit was seen in major bleeding events (RR=0.54; 95% CI 0.29–1.00; $P=0.05$). No significant differences were found in minor bleeding events (RR=1.11; 95% CI 0.82–1.52; $P=0.50$), thrombo-embolic events (RR=0.74; 95% CI 0.26–2.11;	Uninterrupted DOACs strategy for CA of NVAf appears to be as safe as uninterrupted VKA without a significantly increased risk of minor or major bleeding events. DOACs were favored in

					thrombo-embolic events. Exclusion: case reports, editorials, reviews, and expert opinions	resonance imaging	$P=0.57$), or post-procedural SCI (RR=1.06; 95% CI 0.74–1.53; $P=0.74$)	terms of major bleeding
Yang Q, 2022	³³⁷	Meta-analysis of RCTs	6 RCTs 2392 patients	Bleeding risks during catheter ablation, comparison between DOAC and VKA	Catheter ablation with DOAC or VKA	Bleeding post ablation	The incidence of major bleeding was lower in the DOACs group than in the VKA group (OR=0.56; 95% CI 0.34–0.93; $P=0.15$). Subgroup analyses showed that the incidence of severe puncture site complications was lower in the DOACs group than in the VKA group (OR=0.53; 95% CI	Incidence of major bleeding was lower in uninterrupted DOACs compared to VKA. Puncture site bleedings lower in uninterrupted DOAC

							0.30–0.96; $P=0.32$). Bleeding definition per ISTH – exclusion of 1 study without ISTH def no difference	
Liu, 2020	338	Systematic review and meta- analysis of RCT and observatio nal studies	23 studies involving 12 725 individuals 7 RCTs	Uninterrupted DOAC vs. VKA	Inclusion: studies performed in patients undergoing AF ablation; comparative studies between uninterrupted DOACs and uninterrupted VKA during peri- ablation period. Exclusion: interrupted DOACs or VKA; single-arm	Incidence of Stroke/TIA and major bleeding, secondary outcomes were silent cerebral embolism (SCE) on magnetic resonance imaging, minor bleeding complication, cardiac tamponade, pericardial effusion with or without	There was no difference between uninterrupted DOACs and VKA groups in incidence of Stroke/TIA (RR=0.98; 95% CI 0.54–1.77; $P=0.93$) silent cerebral embolism (RR=1.09; 95% CI 0.82–1.43; $P=0.56$) minor bleeding complication (RR=0.97; 95% CI 0.83–1.14; $P=0.73$), cardiac tamponade (RR=0.95, 95% CI	A reduced risk for bleeding was seen with uninterrupted DOAC versus warfarin

					studies; animal studies	tamponade	0.63–1.42, $P=0.80$). Uninterrupted DOACs was associated with significantly lower major bleeding incidence (RR=0.67; 95% CI 0.49–0.92; $P=0.01$)	
Sun, 2020	³³⁹	Systematic review and meta analysis of RCT and observational studies	19 studies 6827 patients	DOAC vs. VKA in catheter ablation	Inclusion: DOACs and warfarin use in Japanese patients with NVAf undergoing CA. Exclusion: studies in which DOAC treatment or warfarin treatment was started only after CA	The safety endpoints were bleeding complications; the efficacy endpoints were thromboembolic complications	Patients with DOACs had a lower risk of overall bleeding complications (OR=0.69; 95% CI 0.54–0.87; $P=0.002$), including major bleeding complications (OR=0.52; 95% CI 0.32–0.84; $P=0.007$) and minor bleeding complications (OR=0.73; 95% CI 0.56–0.94; $P=0.02$).	In Japanese NVAf patients undergoing CA, DOACs have similar effects to warfarin in the prevention of stroke and systemic embolism. Moreover, DOACs were associated with a lower incidence of

							There was no significant difference in thromboembolic complications between DOACs and warfarin after CA (OR=0.39; 95% CI 0.14–1.10; <i>P</i> =0.08)	bleeding complications
Rahman, 2019	³⁴⁰	Systematic review and meta-analysis of RCT and observational studies	4911 patients (RCTs = 1525 patients) (observational studies= 3386 patients), mean age was 61.1 ± 3.0 years, 73% were male and	DOAC vs. VKA in CA	Inclusion: RCTs and propensity score matched observational studies comparing DOACs and U-VKA in AF adult patients undergoing CA	The primary safety endpoint was major bleeding. The main efficacy outcome was thromboembolism	In RCTs restricted analysis, DOACs significantly reduced the relative risk of major bleeding by 72% compared to U-VKA (RR=0.28; 95% CI 0.14–0.58; <i>P</i> <0.001). In terms of thromboembolism, both anticoagulation strategies were equally effective in analysis of RCTs (RR=0.28; 95% CI	DOACs are safer and similarly effective

			40.5% had persistent AF				0.05–1.70; $P=0.17$) or observational studies (RR=1.43, 95% CI 0.46–4.39; $P=0.54$)	
Asad, 2021	³⁴¹	Systematic review and meta-analysis of RCT and observational studies	3595 patients	Safety of uninterrupted vs. interrupted DOAC for patients undergoing CA for AF	Inclusion: RCT and observational studies comparing uninterrupted versus interrupted DOAC for patients undergoing CA of AF	Primary outcome major bleeding. Secondary outcome minor bleeding, stroke or TIA or SEE, silent stroke, and tamponade	No difference in major bleeding (RR=0.79; 95% CI 0.35–1.79). No diff in all other secondary outcomes. Possible protective effect on silent stroke with DOAC	Similar rates of bleeding and thromboembolic outcomes associated with uninterrupted versus interrupted DOAC for CA of AF. Observational data suggests that uninterrupted DOACs are associated with protective effect against silent cerebral

								ischemic lesions
Ge, 2018	³⁴²	Systematic review and meta-analysis of RCT and observational studies	29 studies with 12 644 patients were included in the meta-analysis	Safety and efficacy of periprocedural anticoagulation with DOACs compared with VKAs in AF patients undergoing catheter ablation	Inclusion: studies comparing any of DOACs (dabigatran, apixaban, or rivaroxaban) with VKAs as periprocedural anticoagulants for AF ablation. Exclusion: use of anticoagulant edoxaban	The primary safety endpoint was major bleeding events, and the primary efficacy endpoint was thromboembolic events (a composite of systemic thromboembolism, transient ischemic attack, and stroke)	Patients on DOACs had a significantly lower risk of major bleeding compared to VKAs either in observational studies (OR=0.68; 95% CI 0.48–0.95; $P=0.022$) or in RCTs (OR=0.30; 95% CI 0.14–0.62; $P=0.001$). Uninterrupted DOACs reduced the risk of major bleeding when compared to uninterrupted VKAs (OR=0.66; 95% CI 0.45–0.96; $P=0.028$), similarly, interrupted DOACs lowered the risk of major bleeding	Use of DOACs compared to VKAs significantly reduced the risk of bleeding in patients with AF ablation. Similarly, the risk of bleeding was lower with uninterrupted DOACs than with uninterrupted VKAs, and with interrupted DOACs than with interrupted VKAs. The rate of

							compared to interrupted VKAs (OR=0.29; 95% CI: 0.13–0.66; $P=0.003$). The rate of thromboembolic complications was very low and did not significantly differ between the study groups either in observational studies (OR=0.91; 95% CI 0.49–1.67; $P=0.75$) or in RCTs (OR=0.14; 95% CI 0.01–1.30; $P=0.08$)	thromboembolic complications was extremely low in both study groups without any differences
Ha, 2018	³⁴³	Systematic review and meta-analysis of RCT and observational	Thirteen studies (4 randomized, 9 observational) with	DOACs compared to VKAs	Inclusion: patients who underwent CA for AF and were receiving either a DOAC or	The primary endpoint was major bleeding. Secondary endpoints were total bleeding	DOAC was associated with less major bleeding compared with VKA in pooled randomized studies (OR=0.27;	Continuous and minimally interrupted DOAC are both safe and not-different in peri-

		nal studies	5463 patients were included in final analysis (45% on DOAC)		uninterrupted VKA Exclusion: prospective studies if groups were not matched for age and sex (<i>P</i> -value for between-group difference > 0.05)	(composite of major and minor bleeding) and symptomatic thromboembolism	95% CI 0.09–0.80; <i>P</i> =0.03) however there was no difference on overall analyses (OR=0.70; 95% CI 0.39–1.24; <i>P</i> =0.22). When stratified by DOAC dose schedule, there was no difference in major bleeding for continuous DOAC (OR=0.48; 95% CI 0.21–1.11; <i>P</i> =0.09) or minimally interrupted DOAC (OR=0.81; 95% CI 0.37–1.76; <i>P</i> =0.60) compared with VKA. There was no difference between DOAC and VKA for risk of total bleeding (<i>P</i> =0.20) or	procedural anticoagulation strategies compared with uninterrupted VKA for AF ablation. DOAC in general is associated with reduced major bleeding as demonstrated in pooled randomized studies

							symptomatic thromboembolism ($P=0.78$)	
Mao, 2021	³⁴⁴	Systematic review and meta-analysis of RCT and observational studies	6203 patients (47% minimally interrupted DOAC)	Safety and efficacy of minimally interrupted DOACs in ablation for AF vs. uninterrupted DOAC/VKA	Inclusion: RCT or prospective observational studies that compared a minimally interrupted DOAC strategy with an uninterrupted DOAC or VKA strategy from the time of database establishment up to December 2019	Primary endpoint major bleeding, minor bleeding and symptomatic stroke. 2 nd silent stroke on MRI	No significant difference in treatment groups regarding risk for major bleeding, nor minor bleeding or stroke. Brain MRI showed that uninterrupted DOAC (OR=0.44) and uninterrupted VKA (OR=0.48) produced a sign reduction in silent infarction compared with minimally interrupted	A periprocedural anticoagulation strategy of minimally interrupted DOAC is not superior to uninterrupted DOAC of VKA in AF ablation. No benefit on bleeding with minimally interrupted, but increased risk of silent stroke
Mao, 2020	³⁴⁵	Systematic review and meta-	2578 patients (55%	Uninterrupted DOAC vs. minimally	Inclusion: prospective observational	Bleeding events	No significant difference was found regarding the risk of	UI-DOAC, as a peri-procedural anticoagulation

		analysis of RCT and observational studies	minimally interrupted)	interrupted DOAC	studies or RCTs comparing UI-DOAC versus MI-DOAC from their establishment to January 2020		major bleeding (OR=0.92; 95% CI 0.43–2.00; $P=0.84$). The risk of minor bleeding ($P=0.88$) or stroke ($P=0.69$) was comparable between the groups. UI-DOAC resulted in a significant reduction in silent stroke (SS) (OR=0.44; 95% CI 0.23–0.83, $P=0.01$)	strategy for catheter ablation in AF, had similar safety compared with MI-DOAC, but was advantageous in terms of SS
Basu-Ray, 2021	³⁴⁶	Systematic review and meta-analysis of observational studies	840 patients with uninterrupted anticoagulation and 938 patients with IA	Compares interrupted and uninterrupted direct oral anticoagulation during catheter ablation of AF	Inclusion: studies that directly compared uninterrupted anticoagulation vs. interrupted anticoagulation with a DOAC regimen before	Major adverse cerebro-cardiovascular events which was a composite of stroke or TIA and major bleeding, total bleeding	Silent cerebral events (SCEs) were significantly more frequent with IA (OR=−0.90; 95% CI -1.59 to -0.22; $P<0.01$). Rates of major bleeding, minor bleeding, pericardial effusion, cardiac	Silent strokes more common in interrupted DOACs

					CA of AF and provided procedural outcomes and embolic and bleeding events. Exclusion: anticoagulation with DOACs without reporting comparative outcome data for each regimen	(composite of major and minor bleedings), and SCE	tamponade, and puncture complications were similar between groups	

Additional Evidence Table S23 — Discontinuing oral anticoagulation post-ablation

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Zhao, 2018	³³⁵	Systematic review and meta-analysis of RCT studies	1903 patients	Efficacy and safety of uninterrupted DOACs and uninterrupted VKAs in patients undergoing AF ablation	Inclusion: RCTs published up to 20 March 2018	This meta-analysis aimed to compare the efficacy and safety of uninterrupted DOACs and uninterrupted VKAs in patients undergoing AF ablation	There was no significant difference between DOACs group and VKAs group in incidence of stroke or TIA (OR=1.00; 95% CI=0.23–4.40; <i>P</i> =1.00), silent cerebral thromboembolic events (OR=1.09; 95% CI=0.67–1.75; <i>P</i> =0.74) or	In patients undergoing AF ablation, uninterrupted DOACs is similarly effective as uninterrupted VKAs treatment. Uninterrupted dabigatran (150 mg twice daily) may be superior to other uninterrupted OACs strategies

							minor bleeding (OR=1.01; 95% CI=0.78–1.31; $P=0.93$), which were consistent in subgroup analysis of individual DOAC vs. VKAs group. DOACs treatment was associated with reduced risk of major bleeding as compared with VKAs (OR=0.45; 95% CI=0.26–0.81; $P<0.01$)	
Toso, 2018	³⁴⁷	Systematic review and meta-	50 973 patients in the	VKA vs. DOAC	Inclusion: studies with >500 patients	The aim of the present study is to compare the long-	After a mean follow-up of 2.4 (1.5–3.8) years,	AF catheter ablation was associated with a

		analysis of RCT and observational studies	AF catheter ablation group; 281 595 patients in the VKA group; 54 811 patients in the DOAC group		evaluating AF patients treated with OAT (VKA: vitamin K antagonist or DOAC (direct oral anticoagulants)) and/or AF ablation	term risk of thromboembolic events and treatment-related complications in patients with AF treated by OAT strategies and catheter ablation	the overall incidence of stroke and thromboembolic events was 0.63 per 100 patients/year in AF ablation group, 2.09 per 100 patients/year in VKA group and 1.24 per 100 patients/year in DOAC group ($P<0.001$). After stratification in 4 groups according to CHADS ₂ score, the incidence of thromboemboli	reduction in the incidence of long-term thromboembolic events compared to both VKA and DOAC. This reduction is maintained in all CHADS ₂ score clusters and is strengthened by the concomitant reduction in hemorrhagic complications provided by AF ablation

							c events remained lower in patients included in the AF ablation, followed by DOAC and VKA respectively ($P<0.001$), for each CHADS ₂ cluster. Both the incidence of all cause bleedings and major bleedings resulted lower in AF ablation group ($P<0.001$)	
Liu, 2020	³³⁸	Systematic review and meta-	11 148 patients (7160	Discontinuing OAC after AF ablation	Until Oct 2020	Incidence of TE events	No sign difference in TE (OR=0.73; 95%	Uninterrupted DOACs was associated with

		analysis of RCT and observational studies	off-OAC, 3988 in the on-OAC) 2006–2020				CI 0.51–1.05). Risk of major bleeding sign lower in the off OAC-group (OR=0.18; 95% CI 0.07–0.51). Bias: sign heterogeneity	more effectiveness than uninterrupted VKA in reducing major bleeding and pericardial effusion risk without increasing thromboembolism risk, and the benefits of uninterrupted DOACs on major bleeding complication could be more pronounced if CHA ₂ DS ₂ -VASc score ≥ 2 or target ACT >300 s

Maduray , 2022	³⁴⁸	Systematic review and meta- analysis of observational studies	22 429 patients (13 505 off-OAC) were analysed – from 2006– 2020	Continuation versus discontinuation of OACs post- ablation	AF patients following a successful CA reflected population, discontinuation of OAC as intervention, continuation of OAC as a comparison	Thromboembolism and bleeding events as the outcome	Compared to the off-OAC group, patients on-OAC were 0.50% more likely to suffer from TE (OR=0.65; 95% CI 0.44–0.94; <i>P</i> =0.02). The incidence of total TE was analysed by stratification for the CHA ₂ DS ₂ - VASc<2 group (OR=0.61; 95% CI 0.15–2.42; <i>P</i> =0.48). Bias: nonrandomized ; the inclusion of 13 retrospective	Discontinuation could be beneficial in CHA ₂ DS ₂ - VASc < 2 group given risk of major bleeding (MB). MB events were associated with increased rates in the long- term anticoagulated group, supporting discontinuation

							studies raises the risk of confounding and reporting bias	
Romero, 2019	³⁴⁹	Systematic review and meta-analysis of observational studies	3956 patients were included	Continuation of OAC after catheter ablation (CA) for AF is associated with improved outcomes	CHA ₂ DS ₂ -VASc score had to be available for the classification of patients into high- or low-risk cohorts (CHA ₂ DS ₂ -VASc ≥ 2 and ≤ 1)	The primary efficacy outcome was thromboembolic events (TE). Intracranial hemorrhage (ICH) was the primary safety outcome	OAC-continuation was associated with a significant decrease in risk of TE in the high-risk cohort (CHA ₂ DS ₂ -VASc ≥ 2) (RR=0.41; 95% CI=0.21–0.82; <i>P</i> =0.01) with a RR reduction of 59%. ICH was significantly higher in the ON-OAC group	Continuation of OAC after CA of AF with CHA ₂ DS ₂ -VASc ≥ 2 is associated with a significant decreased TE risk and a favourable net clinical benefit in spite of ICH being significantly increased in the ON-OAC group. Continued OAC offers no benefit with CHA ₂ DS ₂ -

							(RR= 5.78; 95% CI 1.33–25.08; $P=0.02$). No significant benefit was observed in the low-risk cohort ON-OAC after the blanking period	VASC $\leq$ 1
Proietti, 2019	³⁵⁰	Systematic review and meta-analysis of observational studies	25 177 patients (13 166 off-OAC and 12 011 on-OAC)	CVE after catheter ablation of AF and compared patients on or off OAC	Inclusion: a systematic literature review of all studies published up to 31 July 2018, that reported CVE after catheter ablation of AF and compared patients on or off OAC	The risk of CVE and major bleeding in on-OAC vs. off-OAC patients	No significant difference in the incidence of CVE emerged between on-OAC and off-OAC patients after AF ablation (RR=0.66; 95% CI 0.38–1.15). Similar results were found	The risk-benefit ratio favoured the suspension of OAT after successful AF ablation even in patients at moderate-high risk. Whether the reported results can be extended also to DOAC warrants further

							after stratification by CHADS ₂ and CHA ₂ DS ₂ -VASc score. Off-OAC patients suffered significantly less bleeding than those on OAC (RR=0.17; 95% CI 0.09–0.34). Of note, the percentage of patients with AF recurrence impacts the treatment effect in the two groups (<i>P</i> =0.001)	investigations
Deng, 2018	³⁵¹	Systematic review and	Total of 7612	Stopping OAC post ablation	Inclusion: clinical trials which	TE and hemorrhage risk	The results showed no	The withdrawal of OACs 3 months

		meta-analysis of observational studies	patients	differences between thromboembolism (TE) and hemorrhage in an off-oral anticoagulants (OACs) treatment group (the observation group) and an on-OACs treatment group (the control group), at 3 months after successful radiofrequency catheter ablation (RFCA)	evaluated the differences between TE and hemorrhage in an off-OACs treatment group (the observation group) and an on-OACs treatment group (the control group), at 3 months after successful RFCA		significant differences between two groups in TE (RR=0.82; 95% CI 0.51–1.33; $P=0.42$), and only mild heterogeneity ($P=0.22$). No significant differences in TE between two subgroups were found according to <3 years and ≥3years follow-up analyses (RR=0.58; 95% CI 0.26–1.28; $P=0.18$; RR 1.00; 95% CI	after successful radiofrequency catheter ablation for patients with AF may be safe and feasible. It needs to be tested by randomized controlled trial

							0.54–1.85; <i>P</i> =1.00). The risk of hemorrhage in the observation group was significantly lower compared to the control group (RR=0.05; 95% CI 0.02–0.14; <i>P</i> <0.001)	

Evidence Table 21 for Recommendation Table 21 (Sec. 7) — Recommendations for endoscopic and hybrid atrial fibrillation ablation

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Boersma , 2012 (FAST)	352	RCT	124 (paroxysmal in 67% and persistent in 33%)	Randomized to catheter ablation (63 patients) or surgical ablation (61 patients)	Inclusion: documented, symptomatic paroxysmal and/or persistent AF for at least 12 months that was refractory to or intolerant of at least 1 AAD, age between 30 and 70 years, and mentally able and willing to give informed	Freedom from any LA arrhythmia of >30 seconds in the absence of AADs after 12 months was 36.5% in the CA group and 65.6% in the SA group ($P=0.02$); allowing for AAD use, CA efficacy was 42.9% and	In AF patients with dilated left atrium and hypertension or failed prior AF CA, surgical ablation is superior to CA in achieving freedom from left atrial arrhythmias after 12 months of follow-up, although the procedural adverse event rate is significantly higher for surgical ablation than for CA	Minimally invasive SA is superior to CA in achieving freedom from LA arrhythmias after 1 year of follow-up. Procedural adverse event rate, however, is significantly higher for SA than for CA

					consent, LA diameter of 40–44 mm with hypertension, LAd≥45 mm, or failure of a prior CA for AF. Exclusion: longstanding AF >1 year, cardiac CA or a surgical cardiac procedure in the last 3 months, previous stroke or transient ischemic attack, LA	SA efficacy was 78.7% ($P<0.0001$); primary safety end point of all SAEs during 12-month follow-up was 34.4% in the SA group versus 15.9% in the CA group ($P=0.027$)		

					thrombus, LA size >65 mm, LVEF <45%			
Doll, 2023	353	RCT	154	Hybrid epicardial-endocardial ablation vs. Endocardial catheter ablation	Participants with symptomatic, drug refractory persistent AF and left atrial diameter (LAD) >4.0 cm or LSPAF	Primary effectiveness was freedom from AF/atrial flutter/atrial tachycardia >30-s through 12-months absent class I/III anti-arrhythmic drugs except those not exceeding previously failed doses. Major complication	Primary effectiveness was 71.6% (68/95) in Hybrid ablation versus 39.2% (20/51) in Endocardial catheter ablation (absolute benefit increase: 32.4% [95% CI 14.3–48.0%], <i>P</i> <0.001). Major complications through 30-days after index procedures plus 30-days after second stage/repeat Endocardial catheter ablation were similar	Hybrid ablation had superior effectiveness compared to Endocardial catheter ablation/ repeat Endocardial catheter ablation patients with persistent/ longstanding persistent AF without significant procedural risk increase

						s	(hybrid ablation: 7.8% [8/102] versus catheter ablation: 5.8% [3/52], $P=0.75$)	
Delurgio, 2020	³⁵⁴	RCT	153 (convergent 102/CA 51)	Hybrid Convergent procedure vs. CA	Eligible patients were between 18 and 80 years of age, with symptomatic persistent AF that was refractory or intolerant to at least one class I/III antiarrhythmic drug (AAD) and had a left atrium size of ≤ 6.0 cm. There was no limitation on	Freedom from AF/atrial flutter (AFL)/atrial tachycardia (AT) absent of class I/III AADs, except previously failed or intolerant AADs with no increase in dosage was achieved in 67.7%	The Hybrid Convergent procedure has superior effectiveness compared to the CA for the treatment of persistent and long-standing persistent AF.	Improved outcomes with a hybrid epicardial/endocardial ablation approach compared with an endocardial-only ablation

					duration of AF	(67/99) patients in Hybrid Convergent compared to 50% (25/50) in the catheter ablation group. Freedom from AF/atrial flutter (AFL)/atrial tachycardia (AT) absent class I/III AAD was 53.5% (53/99) in the Hybrid Convergent		

						compared to 32.0% (16/50) in the catheter ablation group. Total of 80% (60/75) subjects in the Hybrid Convergent group achieved at least 90% AF burden reduction at 12 months (24-hour Holter), compared with 56.8% (25/44) in the catheter		

						ablation group. A total of 2.9% (3/102) subjects reported MAE within 7 days post-procedure, not reported in the catheter ablation arm (0% versus 7.8%; $P=0.05$)		
Castella, 2019 (FAST – long follow up)	³⁵⁵	RCT	124 (paroxysmal in 67% and persistent in 33%)	Randomized to CA (63 patients) or surgical ablation (61 patients)	Inclusion: documented, symptomatic paroxysmal and/or persistent AF for at least 12	Meta-analysis combining the long-term study with 12-month data from	Long term follow-up (7 years): patients randomized to thoracoscopic ablation had lower recurrence rates during extended	Thoracoscopic AF ablation demonstrated more consistent maintenance of sinus rhythm than catheter ablation,

					months that was refractory to or intolerant of at least 1 AAD, age between 30 and 70 years, and mentally able and willing to give informed consent, LA diameter of 40 to 44 mm with hypertension, LA diameter ≥ 45 mm, or failure of a prior CA for AF Exclusion: longstanding AF >1 year, cardiac CA or	two other prospective randomized trials confirmed a lower rate of incident atrial arrhythmia recurrence after thoracoscopic vs. catheter ablation. The pooled incidence RR=0.55; 95% CI 0.38–0.78; $P=0.001$, no heterogeneity between trials	follow-up; 34/61 (56%) compared with 55/63 (87%) with catheter ablation (HR=0.40; 95% CI 0.25–0.64; $P<0.001$). There was no difference in the composite clinical outcome: 9 patients (15%) in the thoracoscopy arm vs. 10 patients (16%) with catheter ablation (HR 1.11, 95% CI 0.40–3.10; $P=0.84$)	with similar long-term clinical event rates

					a surgical cardiac procedure in the last 3 months, previous stroke or transient ischemic attack, LA thrombus, LA size>65 mm, LVEF<45%	($P=0.43$), but variable risk of bias. Composite of death, MI, or cerebrovascular event (transient ischaemic attack, ischaemic or haemorrhagic stroke) occurred in 9/61 patients (15%) assigned to thoracoscopy and 10/63 (16%) to catheter ablation. For time to first		

						event HR=1.11; 95% CI 0.40–3.10; <i>P</i> =0.84		
Van der Heijden, 2023	³⁵⁶	RCT	41	Hybrid ablation vs. catheter ablation	Ablation-naïve patients with (long-standing)-persistent AF	Primary efficacy endpoint: freedom from any atrial tachyarrhythmia >5 minutes off antiarrhythmic drugs after 12 months. Primary and secondary safety endpoints: major and minor	Freedom of atrial tachyarrhythmias off antiarrhythmic drugs was higher in the hybrid ablation group versus the catheter ablation group (89% vs. 41%, <i>P</i> =0.002). There was 1 pericarditis requiring pericardiocentesis and 1 femoral arteriovenous-fistula in the hybrid ablation group versus 1 bleeding from the femoral artery in the catheter ablation	Hybrid AF ablation is an efficacious and safe procedure and results in better outcomes than catheter ablation for the treatment of patients with persistent AF

						complications and the total number of serious adverse events	group. The number of (serious) adverse events was comparable between groups (21% vs. 14%, $P=0.685$)	
Van der Heijden, 2019	357	Systematic review and meta-analysis of RCT and observational studies	3865	Catheter vs. hybrid ablation in maintaining the sinus rhythm (SR) in patients with persistent AF or LSPAF after at least 12 months of follow-up	Inclusion: studies reporting on catheter and hybrid ablation of persistent or longstanding persistent AF Exclusion: different patient population (paroxysmal AF), focus on different outcome measures and	Hybrid ablation was more effective in maintaining SR than a single catheter ablation (70.7% vs. 49.9%; $P=0.001$). Complications that were significantly higher among	Hybrid ablation resulted in higher freedom of atrial arrhythmias in patients with persistent and longstanding-persistent AF than catheter ablation (70.7% vs. 49.9%, $P<0.001$). Although hybrid ablation had a slightly higher complication rate than catheter ablation, overall morbidity and	Hybrid ablation is associated with higher success rates in maintaining SR compared to catheter ablation. Although over-all mortality and morbidity of both techniques is low, hybrid ablation has a slightly higher complication rate than catheter ablation

					performance of catheter ablation only after surgical ablation in case of a recurrence	hybrid studies include: bleeding requiring transfusion (1.6% vs. 0.4%, $P=0.000$), conversion to sternotomy (1.1% vs. 0.4%; $P=0.010$), cardiac tamponade (1.7% vs. 0.7%; $P=0.05$), hospital mortality (1.1% vs.	mortality were low	

						0.5%; <i>P</i> =0.007), pace-maker implantation (1.0% vs. 0.4%; <i>P</i> =0.04), phrenic nerve injury (1.2% vs. 0.4%; <i>P</i> =0.002), pneumothora x (1.0% vs. 0.4%; <i>P</i> =0.033) and PV stenosis not requiring stenting (1.0% vs. 0.4%; <i>P</i> =0.007)		

Additional Evidence Table S24 — Rhythm control: Endoscopic and hybrid atrial fibrillation ablation

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
DeLurgio, 2020	354	RCT	153	Hybrid convergent vs. endocardial ablation	Inclusion: persistent AF Exclusion: LA >60 mm, LVEF <40%, need for concomitant surgery	Efficacy (freedom from AF) and safety events (cardiac tamponade; severe PV stenosis; excessive bleeding; myocardial infarction; stroke; transient ischemic attack; atrio-esophageal	Key findings: 68% success hybrid vs. 50% endo (on drugs); greater AF burden reduction ($P=0.04$). Bias: dissimilar ablation strategies in both arms	The Hybrid Convergent procedure has superior effectiveness compared to the CA for the treatment of persistent and long-standing persistent AF

						fistula; phrenic nerve injury; death)		
Haldar, 2019 (CASA-AF)	³⁵⁸	RCT	120 long- standing persistent AF (LSPAF) patients to surgical ablation (SA) or CA	Surgical ablation vs. CA as the first interventional strategy in de novo LSPAF	Inclusion: adults with symptomatic LSPAF, EHRA symptom score >2, LVEF ≥40%, referred for treatment and suitable for both procedures. Exclusion: included heart disease (severity greater than mild) and previous cardiothoracic surgery (including surgical AF interventions)	Primary outcome was single procedure freedom from AF/atrial tachycardia (AT) ≥30 s without anti- arrhythmic drugs at 12 months. At 12 months, freedom from AF/AT was recorded in 26% (14/54) of patients in SA vs. 28% (17/60) in the	Freedom from AF/AT ≥30 s was recorded in 26% of patients in SA and 28% in the CA group following a single procedure and without AADs (OR=1.13; 95% CI 0.46–2.82; P=0.84)	Single procedure thoracoscopic SA is not superior to CA in treating LSPAF

						CA group (OR=1.13; 95% CI 0.46–2.83; $P=0.83$). Reduction in AF/AT burden $\geq 75\%$ was recorded in 67% vs. 77% (OR=1.1; 95% CI 0.67–4.08; $P=0.3$) in SA and CA groups, respectively		
Van der Heijden, 2019	³⁵⁷	Systematic review and meta-analysis of RCT and observational studies	3865	Catheter vs. hybrid ablation in maintaining the sinus rhythm (SR) in patients	Inclusion: studies reporting on catheter and hybrid ablation of persistent or longstanding persistent AF	Hybrid ablation was more effective in maintaining SR than a single	Hybrid ablation resulted in higher freedom of atrial arrhythmias in patients with persistent and longstanding-	Hybrid ablation is associated with higher success rates in maintaining SR compared to catheter

				with persistent AF or LSPAF after at least 12 months of follow-up	Exclusion: different patient population (paroxysmal AF), focus on different outcome measures and performance of catheter ablation only after surgical ablation in case of a recurrence	catheter ablation (70.7% vs. 49.9%; $P=0.001$). Complications that were significantly higher among hybrid studies include: bleeding requiring transfusion (1.6% vs. 0.4%, $P=0.000$), conversion to sternotomy (1.1% vs. 0.4%; $P=0.010$), cardiac	persistent AF than catheter ablation (70.7% vs. 49.9%, $P<0.001$). Although hybrid ablation had a slightly higher complication rate than catheter ablation, overall morbidity and mortality were low	ablation. Although overall mortality and morbidity of both techniques is low, hybrid ablation has a slightly higher complication rate than catheter ablation

						tamponade (1.7% vs. 0.7%; $P=0.05$), hospital mortality (1.1% vs. 0.5%; $P=0.007$), pace-maker implantation (1.0% vs. 0.4%; $P=0.04$), phrenic nerve injury (1.2% vs. 0.4%; $P=0.002$), pneumothora x (1.0% vs. 0.4%; $P=0.033$) and PV stenosis		

						not requiring stenting (1.0% vs. 0.4%; $P=0.007$)		
Mhanna, 2021	³⁵⁹	Systematic review and meta-analysis of RCT and observational studies	797 (366 Hybrid Vs. 431 Endo)	Hybrid convergent ablation and endocardial ablation Hybrid: time: 3 staged, 5 concomitant; access: 5 subxiphoid, 2 thoracoscopy, 1 mini-thoracotomy)	Mostly (93%) persistent, longstanding, permanent AF (the minority had a prior ablation for AF, 18.7%)	Freedom from atrial arrhythmia higher in hybrid Vs Endo ($P=0.004$; $RR=1.48$; 95% CI 1.13–1.94). Periprocedural complication rate higher in hybrid Vs. endo ($RR=3.64$; 95% CI 2.06–	Key findings: hybrid success higher than endo; hybrid complication rate higher than endo, longer procedure time and hospital stay; better safety profile for thoracoscopy group. Bias: ablation procedure not standardized among the included studies. Success rate assessed with	Hybrid ablation was associated with a higher success rate but also higher periprocedural adverse events and extended hospital stay

						6.43; $P=0.001$), mostly pericardial effusion, but also 5 deaths	different approaches (ECG/Holter/ILR/only symptomatic). Investigator bias (single-blinded design) and publication bias (small number of studies) cannot be excluded	
Eranki, 2022	³⁶⁰	Systematic review and meta-analysis of RCT and observational studies	422 (283 Hybrid VS. 189 Endo)	Hybrid convergent ablation (all subxiphoid approach) and endocardial ablation	Inclusion: comparative HCA procedures to ECA only; freedom from AF; RCT or PSM analysis	Freedom from AF 73% Hybrid Vs 49% ablation (OR=2.78; 95% CI 1.82–4.24), 50% Vs. 26% off AADs in 3 studies (OR=2.75; 95% CI 1.63–	Key findings: hybrid higher success rate; hybrid higher complication rate. Bias: significant degree of heterogeneity due to the inclusion of retrospective analyses; small number of studies	Hybrid ablation is associated with a significantly higher freedom from AF than endocardial ablation, but it is associated with increased post-procedural complications

						4.65). Higher complication rate in the Hybrid group (OR=5.14; 95% CI 1.70–15.54), 1 death	included; success rate assessed with different approaches, only (ECG/Holter/ILR/only symptomatic); only freedom from AF was considered (not AT)	
Pokushalov, 2013	⁸³	Prospective cohort study	35 patients with first diagnosed PAF and indication for CABG	First diagnosed AF submitted to CABG and treated with vs. without epicardial pulmonary vein isolation (PVI)	Inclusion: first diagnosed PAF; indication for CABG according to the American College of Cardiology/American Heart Association (ACC/AHA) guidelines for CABG surgery. Exclusion:	The primary endpoint was AF-free survival (AF burden <0.5%) between the two groups at 18-month follow-up	At the end of follow-up, the mean AF burden in the CABG and the CABG + PVI group was 7.8 ± 5.1 and $1.6 \pm 1.8\%$, respectively ($P<0.001$)	Patients with recent-onset AF submitted to CABG may benefit of concomitant ablation of the arrhythmia for preventing recurrences

					previous treatment with IC or class III antiarrhythmic drugs (AAD); previous heart surgery and AF ablation procedure; requiring concomitant valve surgery; LVEF <35%; left atrial diameter >55 mm			
Wang, 2014	³⁶¹	Prospective cohort study	103 long-standing persistent AF (LSPAF) patients were treated with the Dallas lesion set	Patients who underwent video-assisted thoracoscopic surgical ablation for LSPAF	Inclusion: patients with LSPAF, who underwent video-assisted thoracoscopic surgical ablation between January 2009 and April 2011. Exclusion: patients with a prior	At the 24-month follow-up, 83 of 103 (80.6%) patients were free of any atrial arrhythmia lasting >30 s, with 77 patients	After 6 months, a significant reduction in LA volume and improvement in LA function was noted in patients without recurrence ($P<0.05$)	The Dallas lesion set is an effective treatment in patients with LSPAF. It resulted in significant improvement in LA volume and function after

					catheter ablation, severe structural heart disease, an LA diameter of ≥65 mm or LVEF≤40%	(74.8%) off antiarrhythmi c drugs (AADs)		restoration of sinus rhythm

Evidence Table 22 for Recommendation Table 22 (Sec. 7) — Recommendations for atrial fibrillation ablation during cardiac surgery

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Huffman, 2016	362	Systematic review and meta-analysis of RCT studies	1899 participants	Concomitant AF surgery among people with AF who are undergoing cardiac surgery on short-term and long-term (12 months or greater) health-related outcomes, health-	Inclusion: RCTs evaluating the effect of any concomitant AF surgery compared with no AF surgery among adults with preoperative AF, regardless of symptoms, who were undergoing	The effect of concomitant AF surgery on all-cause mortality was uncertain when compared with no concomitant AF surgery (7.0% versus 6.6%, RR=1.14; 95% CI 0.81–1.59, I ² = 0%), 20 trials, 1829 participants, low-quality	The effect of concomitant AF surgery on all-cause mortality was uncertain when compared with no concomitant AF surgery (7.0% versus 6.6%, RR=1.14; 95% CI 0.81–1.59, I ² = 0%, 20 trials, 1829 participants, low-quality	For patients with AF undergoing cardiac surgery, there is moderate-quality evidence that concomitant AF surgery approximately doubles the risk of freedom from AF, atrial flutter, or atrial tachycardia off anti-arrhythmic drugs while increasing the risk of permanent pacemaker

				related quality of life, and costs	cardiac surgery for another indication	evidence), but the intervention increased freedom from AF, atrial flutter, or atrial tachycardia off antiarrhythmic medications > three months (51.0% versus 24.1%, RR=2.04,;95% CI 1.63–2.55, I ² =0%), eight trials, 649 participants, moderate- quality evidence	evidence), but the intervention increased freedom from AF, atrial flutter, or atrial tachycardia off antiarrhythmic medications > three months (51.0% versus 24.1%, RR=2.04, 95% CI 1.63 -2.55, I ² = 0%, eight trials, 649 participants, moderate- quality evidence)	implantation

Phan, 2014	³⁶³	Systematic review and meta-analysis of RCTs	1082	Clinical outcomes of surgical ablation versus no ablative treatment in all patients with cardiac surgery	All types of cardiosurgical procedures with concomitant ablation vs. no ablation	There were no significant differences between surgical ablation versus no ablation in terms of mortality (OR=1.05; 95% CI 0.66–1.68; <i>P</i> =0.83), pacemaker implantations (OR=0.88; 95% CI 0.51–1.51; <i>P</i> =0.64), and neurological events (OR=0.86; 95% CI 0.37–2.04; <i>P</i> =0.74)	Higher prevalence of sinus rhythm in the surgical ablation group was evident at all ≥12-month follow-up (OR=6.72; 95% CI 4.88–9.25; <i>P</i> <0.001)	Concomitant surgical ablation and cardiac surgery is safe and effective at restoring sinus rhythm

McClure, 2018	³⁶⁴	Systematic review and meta-analysis of RCTs	1965	Surgical AF ablation using any lesion set vs. no surgical AF ablation in adults with AF undergoing cardiac surgery	Inclusion: adult patients undergoing any type of cardiac surgery with a documented history of AF of any type; any surgical AF ablation during cardiac surgery, regardless of lesion set	Freedom from AF at 12 months, higher in the surgical ablation group (RR=2.32; 95% CI 1.92–2.80; $P<0.001$). Batrial procedures led to more freedom from AF compared to left-sided lesions ($P=0.04$)	Only one study out of 23 was considered at low risk of bias by the researchers	Concomitant surgical ablation is effective in restoring sinus rhythm
Pokushalov, 2012	³⁶⁵	RCT	35	Concomitant ablation vs. no ablation in CABG patients	New diagnosed paroxysmal AF in patients qualified for CABG	At 18-month follow-up after surgery, 16 (89%) patients in the CABG + PVI group were AF-free (i.e.	RCT, Small, focused on paroxysmal AF, AF burden and symptoms assessed in FU	Benefit of concomitant ablation of the arrhythmia for preventing recurrences and symptoms

						AF%<0.5%) vs. 8 (47%) in the CABG only group (log-rank test, $P=0.007$). At the end of follow-up, the mean AF burden in the CABG and the CABG + PVI group was 7.8 ± 5.1 and $1.6 \pm 1.8\%$ ($P<0.001$). Two (18.2%) of the 11 patients with AF recurrences were completely asymptomatic		
Cheng,	³⁶⁶	Systematic	4647	Surgical	Inclusion:	N patients with	Concomitant	Concomitant

2010		review and meta-analysis of RCT and observational studies		ablation vs. no ablation in patients undergoing cardiac surgery	RCTs or non-RCTs comparing surgical AF ablation performed during valvular or bypass surgery. All surgical AF ablation techniques	sinus rhythm on discharge: 68.6% in the surgical ablation group vs. 23.0% in the surgery alone group. This effect on sinus rhythm (74.6% vs. 18.4%) remained significant at follow-up of 1 to 5 years. The effect was significant in both RCT and non-RCT sub-analysis	surgical ablation is effective in restoring sinus rhythm. No reporting of LAAO, surgeon's expertise	surgical ablation is effective in restoring sinus rhythm
Yoo, 2014	³⁶⁷	Retrospective cohort study	124	Patients with AF	Inclusion: patients who	No significant differences in	Small group, non-	Concomitant AF ablation in patients

				undergoing aortic valve replacement with or without concomitant Maze procedure	underwent concomitant CABG, tricuspid annuloplasty, and ascending aorta replacement (ie, not requiring additional left atriotomy) Exclusion: patients who underwent concomitant MV surgery, tricuspid valve replacement, and ventricular septal defect	early postoperative outcomes Major event-free survival at 5 years was $60.9 \pm 9.9\%$ in the maze group vs. $57.0 \pm 10.3\%$ ($P=0.41$) in control. Risk of major adverse cardiac events (HR=1.18; 95% CI 0.56–2.49; $P=0.67$) was similar. The rate of sinus rhythm restoration at 4 years was significantly	randomized, although adjusted. Significantly more patients in non-maze group received mechanical prosthesis, although in the bioprosthesis subgroup significantly less patients in the Maze group required anticoagulation (14.3% vs. 80%). Significantly more patients in maze group had LAA	undergoing AVR resulted in increased sinus rhythm restoration, better echocardiographic results, and decreased anticoagulation requirement, without increasing surgical morbidity or mortality

					closure; patients who underwent AVR using minimally invasive approaches, such as upper sternotomy or mini thoracotomy	higher in the maze group (80.6% vs. 3.6%, $P<0.001$), so was left atrial dimension (46.9 vs. 50.4 mm, $P=0.017$), and the ejection fraction was higher (60.6% vs. 58.0%, $P=0.06$). The rate of postoperative anticoagulation was also lower in the maze group (53.1% vs. 89.2%, $P<0.001$)	occluded	

Malaisrie, 2012	³⁶⁸	Retrospective cohort study	124	Patients with AF undergoing aortic valve replacement with or without concomitant SA	Inclusion: with or without CABG. All AF types. Exclusion: mitral, tricuspid, other aortic surgeries	Freedom from AF when not receiving anti-arrhythmic drugs occurred in 58 patients (82%) in the ablation group, compared to eight (36%) in the non-ablation group ($P<0.001$). Fifty patients (70%) were free from warfarin in the ablation group, compared to six (27%) in the non-ablation group ($P<0.001$). No differences	Non-randomized, although adjusted with propensity scores. 42 (95%) patients in non-SA group had either previous sternotomy, mini-AVR or paroxysmal AF. No standardized SA technique	Surgical AF ablation is associated with an improved restoration of sinus rhythm in patients with AF requiring AVR

						were identified in freedom from AF between the surgical AF lesion sets		
Schill, 2017	³⁶⁹	Retrospective cohort study	135	CABG with and without CMIV	Emergent, preoperative, or off-pump procedures	Operative mortality was 3%. Freedom from ATAs at 1 year in the CMIV group was 98%, with 88% off antiarrhythmic drugs. Freedom from ATAs and antiarrhythmic drugs was 70% at 5 years	The short-term outcomes of CMIV and CABG reflect the fact that a relatively high-risk group of patients underwent an extensive operation	The addition of CMIV to CABG resulted in excellent freedom from ATAs at 1 to 5 years. These patients are at increased risk for nonfatal complications compared with others undergoing concomitant surgical ablation
Rankin, 2017	³⁷⁰	Retrospective registry	3745	Surgical ablation	AF patients undergoing	SA was performed in	Validated data, SA in CABG-	Potentially improved late

				concomitant to CABG vs. no surgical ablation	CABG	17% of CABG-AF patients. Operative risks for mortality and stroke did not increase with SA; in hospital but equalled in FU. Patients receiving SA, however, had significantly better risk-adjusted late survival	AF is associated with improved survival; 1 year FU	survival with SA concomitant to CABG

Additional Evidence Table S25 — Atrial fibrillation ablation during cardiac surgery

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Cherniavsk y, 2014	³⁷¹	RCT	95	3 groups: CABG + PVI, CABG + modified Maze, CABG alone	Persistent AF and coronary heart disease, open heart surgery combined with intraoperative irrigated radiofrequency ablation	The implantable loop recorder-determined freedom from AF was 80% in the CABG+PVI group, 86.2% in the CABG+MM group and 44.1% in the CABG alone group. None of the patients in sinus rhythm was treated with anti-arrhythmic medications for longer than 3 months	Small group. A strength is the employment of implantable loop recorders, more accurate than Holter recordings	Patients with concomitant AF and coronary heart disease may benefit from concomitant surgical ablation

						postoperatively		
Cherniavsk y, 2014	³⁷¹	RCT	95	3 groups: CABG + PVI, CABG + modified Maze, CABG alone	Persistent AF and coronary heart disease, open heart surgery combined with intraoperativ e irrigated radiofrequen cy ablation	The implantable loop recorder- determined freedom from AF was 80% in the CABG+PVI group, 86.2% in the CABG+MM group and 44.1% in the CABG alone group. None of the patients in sinus rhythm was treated with anti-arrhythmic medications for longer than 3 months postoperatively	Small group. A strength is the employment of implantable loop recorders, more accurate than Holter recordings	Patients with concomitant AF and coronary heart disease may benefit from concomitant surgical ablation
Maesen, 2022	³⁷²	Systematic review and meta- analysis of	45 patients	Studies specifically evaluating the effect of	Evidence of QOL following concomitant	QOL scores improved 1 year after surgical ablation for AF	QOL scores improved 1 year after surgical ablation for AF	In patients with AF, QOL improves after both stand-

		RCT and observational studies		arrhythmia surgery on QOL	and stand-alone arrhythmia surgery for AF	evaluated by several questionnaires	evaluated by several questionnaires. In stand-alone arrhythmia procedures, meta-regression was associated with improvements in those who were in sinus rhythm compared to those in AF after 1 year	alone and concomitant arrhythmia surgery. In the concomitant group, this improvement can be attributed to both the cardiac procedure itself as well as the add-on arrhythmia surgery
Maesen, 2022	³⁷²	Systematic review and meta-analysis of RCT and observational studies	45 patients	Studies specifically evaluating the effect of arrhythmia surgery on QOL	Evidence of QOL following concomitant and stand-alone arrhythmia	QOL scores improved 1 year after surgical ablation for AF evaluated by several questionnaires	QOL scores improved 1 year after surgical ablation for AF evaluated by several questionnaires. In	In patients with AF, QOL improves after both stand-alone and concomitant arrhythmia

					surgery for AF		stand-alone arrhythmia procedures, meta-regression was associated with improvements in those who were in sinus rhythm compared to those in AF after 1 year	surgery. In the concomitant group, this improvement can be attributed to both the cardiac procedure itself as well as the add-on arrhythmia surgery
Musharbas h, 2018	³⁷³	Retrospecti ve cohort study	2001 to 2016 (n= 10 859)	CMIV vs. no SA in concomitant surgery	General group of elective cardiac surgery. Patients were stratified into 3 groups: patients with	Thirty-day mortality was similar between the matched groups. Kaplan-Meier analysis showed greater survival for CM4 compared to Untreated AF (P=0.004). Ten-	Large cohort, 12 years FU; No added mortality perioperative and long-term survival benefit; survival similar to those with no AF history	No added mortality perioperative and long-term survival benefit; survival similar to those with no AF history. Performance of the Cox-maze

					a history of AF receiving a concomitant CM4 (CM4; n=438), patients with a history of AF unaddressed during surgery (Untreated AF; n=1510), and patients without AF history (No AF; n=8911)	year survival was 62% for CM4 and 42% for Untreated AF. HR=0.47; 95% CI 0.26–0.86; <i>P</i> =0.014). No difference in survival was found between CM4 and No AF groups with the Kaplan-Meier analysis (<i>P</i> =0.84). Ten-year survival was 63% for CM4 and 55% for No AF. HR=1.03; 95% CI 0.51–2.11; <i>P</i> =0.92)		IV procedure is associated with improved long-term survival in patients with AF undergoing cardiac surgery
Melo, 2008	³⁷⁴	Retrospective cohort study	1723	Surgical ablation concomitant to mitral valve surgery.	Patients with mitral valve surgery and concomitant surgical	Smaller left atrial dimension and absence of CABG were predictors of sinus rhythm. At 48	At 1 year, 63.4% patients were in stable SR. SR was associated with improved early and	The achievement of stable SR after concomitant SA is a

				Analysis of safety, efficacy and comparison of the outcomes between patients in sinus rhythm (SR) vs. in AF post-surgery	ablation	months' follow-up, predictors for stable SR were biatrial surgical approach and absence of preoperative permanent AF (OR=3.56; 95% CI 1.62–7.83; $P<0.002$)	late survival ($P=0.01$). Thromboembolic events were found to be associated with absence of stable SR ($P=0.010$)/Limitations: a significant N patients was lost to follow-up after 1 year, no standardized SA protocol, no adjustment for cofactors in mortality analysis	predictor of better survival and lower incidence of thromboembolic events
Almoussa, 2022	³⁷⁵	Retrospective cohort study	135, prospective 4y FU	Robotic SA, stand-alone maze performed in 25.2%, whereas	Mainly concomitant SA in persistent AF, (valvular, CABG	For persistent AF, robotic biatrial cryothermic Cox maze offered greater than 90% 1-year longitudinal	Good prospective FU, single institution	After SA, over 90% 1-year longitudinal freedom from stroke, oral anticoagulation

				61.4% underwent concomitant robotic mitral valve surgery, 7.4% tricuspid valve repair, and 4.4% aortic valve replacement	surgery)	freedom from stroke, oral anticoagulation, repeat ablation, and recurrent AF without the need for antiarrhythmic drugs		, repeat ablation, and recurrent AF without the need for antiarrhythmic drugs
Lauritzen, 2022	³⁷⁶	Retrospective cohort study	494 patients underwent PVI concomitantly with other cardiac surgery (337 patients eligible for	Comparison APPLE, CHA2DS2-VASc, and CHADS2 in predicting AF recurrence following surgical ablation	Inclusion: all patients undergoing concomitant pulmonary vein ablation during cardiac surgery. APPLE-, CHA2 DS2 - VASc-, and	Using logistic regression analyses, APPLE and CHA2DS2 - VASc were predictors of AF recurrence between 3- and 12 months after surgical ablation (OR=1.93, 95% CI 1.39–2.67, <i>P</i> <0.01	Receiver operating characteristic curves showed the superiority of the APPLE scoring system with an AUC 0.690 compared to 0.571 for CHA2DS2-VASc and 0.569 for CHADS2, <i>P</i> =0.01.	The APPLE scoring system is superior to CHA2DS2-VASc and CHADS2 in predicting AF recurrence after surgical ablation

			analyses)		CHADS2 scores were calculated for each patient	and OR=1.17, 95% CI 1.01–1.36, $P=0.04$, respectively)	Limitations: retrospective, single institution	
Kowalewski, 2022	³⁷⁷	Prospective registry	20 765	General cardiac surgery procedures with or without concomitant surgical ablation	AF patients undergoing general cardiac surgery	The highest rates of SA were observed for mitral interventions (mitral valve repair or replacement and tricuspid intervention, 25.2%), lowest for isolated coronary artery bypass grafting (6.2%). SA was associated with 16% mortality decline, regardless of baseline risk as assessed by EuroSCORE II	Big validated national registry data; survival benefit in long-term (12 years); No data on rhythm maintenance	SA concomitant with other cardiac surgery was associated with improved long-term survival regardless of baseline surgical risk
Kowalewski	³⁷⁸	Prospective	11 949	Patients	AF patients	PPM implantation	Time to PPM not	In patients with

i, 2022		e registry		undergoing valvular (aortic, mitral, or tricuspid valve replacement or repair) surgery and/or surgical ablation (SA) and were stratified according to postoperative PPM status		after surgery was necessary in 2.5% of patients, with significant variation depending on the type of surgery (from 1.1% in mitral valve repair to 3.3% in combined mitral and tricuspid valve surgery). Over long-term follow-up, PPM was not associated with increased mortality compared to no PPM. Surgical ablation was not associated with PPM implantation. However, SA improved survival regardless of PPM	defined	preoperative AF, the need for PPM implantation after valve surgery or SA is not an infrequent outcome, with SA not affecting its prevalence but actually improving long- term survival

						status		
Wehbe, 2022	³⁷⁹	Prospective registry	1000	1-year outcomes of patients undergoing ablative procedures for AF in a cardiosurgical setting	Concomitant or stand-alone ablation for AF	At 1-year follow-up significant improvement ($P<0.001$) in baseline modified EHRA Class I was reported in both concomitant and stand-alone patients. All-cause mortality at 1 year was 1% (n=1) in stand-alone patients and 6.7% (n=58) in concomitant patients	1-year follow-up	Surgical ablation of AF is safe and provides satisfactory results at short-term follow-up, with significant improvement in patient symptoms
Suwalski, 2019	³⁸⁰	Prospective registry	11 381	Mitral valve surgery+ ablation versus mitral valve surgery	AF patients undergoing isolated or combined mitral valve	Surgical ablation was associated with nearly 20% improved survival (HR=0.82; 95% CI	Big validated national registry data; survival benefit in long-term (12 years);	Concomitant surgical ablation for AF in patients undergoing

				alone	interventions	0.70–0.96; $P=0.011$). Benefit of surgical ablation was maintained in subgroup analyses, yet most benefit was appraised in low-risk patients such as those with EuroSCORE: 2–5 or age<50 years	No data on rhythm maintenance retrospective	mitral valve procedures is associated with improved survival
Suwalski, 2020	³⁸¹	Prospective registry	7879	CABG with or without surgical ablation	Isolated CABG included only	Surgical ablation was associated with a lower 30-day risk of death (RR=0.37; 95% CI 0.15–0.91; $P=0.032$) and multiorgan failure (RR=0.29; 95% CI 0.10–0.94; $P=0.029$). In the long term, surgical	Big national registry cohort, validated survival benefit in long-term FU in CABG AF patients; retrospective	Surgical ablation for AF in patients undergoing isolated CABG is safe and associated with significantly improved long-term survival. Surgical ablation for AF

						ablation was associated with a significant 33% improved overall survival rate		during isolated coronary artery bypass surgery
Wehbe, 2022	³⁸²	Prospective registry	1000	1-year outcomes of patients undergoing ablative procedures for AF in a cardiosurgical setting	Concomitant or stand-alone ablation for AF	At 1-year follow-up significant improvement ($P<0.001$) in baseline modified EHRA Class I was reported in both concomitant and stand-alone patients. All-cause mortality at 1 year was 1% (n=1) in stand-alone patients and 6.7% (n=58) in concomitant patients	1-year follow-up	Surgical ablation of AF is safe and provides satisfactory results at short-term follow-up, with significant improvement in patient symptoms
Kim, 2022	³⁸³	Prospective	17 247	Patients with	Surgical	During a median	Nationwide registry	SA carries

		e registry		AF and surgical concomitant ablation to mitral/aortic valve surgery	concomitant ablation to mitral/aortic valve surgery	follow-up of 6.7 years (124 842.2 patient-years), death was less in the ablation group than in the no-ablation group (2.7 vs. 4.1 patient-years; $P<0.001$). The incidence of ischemic stroke or systemic embolization was also lower in the ablation group (0.9 vs. 1.3 patient-years; $P<0.001$). After adjustment with inverse probability of treatment weighting, surgical ablation was	from South Korea, adjusted	short and very long-term benefits in: survival, ischemic stroke rate, peripheral embolism rate, number of hospitalisations for HF

						associated with decreased risks of all-cause death (HR=0.86; 95% CI 0.80–0.92), ischemic stroke or systemic embolization (HR=0.62; 95% CI 0.55–0.71), and hospitalization from HF (HR=0.87; 95% CI 0.79–0.96)		
Rankin, 2020	³⁸⁴	Retrospective registry	3745	Surgical ablation concomitant to CABG vs. no surgical ablation	AF patients undergoing CABG	Risk-adjusted index admission costs were higher with SA as were readmissions for AF and pacemaker/defibrillator implantation. Risk-adjusted inpatient days and	Validated data, SA in CABG-AF improves survival and is cost-effective. 2 year FU retrospective	In patients with AF requiring CABG, SA was associated with a 29% lower risk-adjusted hazard for late mortality. Surgical ablation of AF

						inpatient costs were similar after 2 years, however, the risk-adjusted hazard for late mortality was significantly lower with SA		concomitant to coronary-artery bypass grafting provides cost-effective mortality reduction
Badhwar, 2017	³⁸⁵	Retrospective registry	86 941	Surgical ablation concomitant to other cardiac surgery procedure vs. no surgical ablation	Exclusion: AF patients undergoing heart surgery, endocarditis	SA was associated with a reduction in relative risk (RR) of 30-day mortality (RR=0.92; 95% CI 0.85–0.99) and stroke (RR=0.84; 95% CI: 0.74–0.94), but an increase in renal failure (RR=1.12; 95% CI 1.03–1.22) and pacemaker implantation (RR=1.33; 95% CI	SA was associated with lower 30-day mortality rates; retrospective	SA use was associated with an increase across all operative categories. Performance of SA was associated with a 30-day reduction in mortality and stroke

						1.24–1.43)		

Evidence Table 23 for Recommendation Table 23 (Sec. 8) — Recommendations to measure and improve patient quality of life

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Mantovan, 2013 (STAR-AF)	¹²	RCT	100 AF patients	Compared 3 strategies for ablation of high-burden paroxysmal/persistent AF: complex fractionated electrogram ablation (CFE), pulmonary vein isolation (PVI), or a combined approach (PVI with CFE)	The STAR AF study found 88%, 68%, and 38% freedom from AF >30 seconds at 12 months for PVI with CFE, PVI, and CFE approaches, respectively ($P=0.001$)	There was a significant improvement in physical health (24%) and mental health (19%) component scores from baseline to 12 months after ablation ($P<0.05$ for both). Significant QOL improvements were seen for all 3 ablation strategies	QOL was measured before ablation and at 12 months after ablation using the Short-Form Health Survey (SF-36) scale. Transformed scores were calculated for each of the 8 subscales of the SF-36, and also converted to physical health and mental	QOL after AF ablation improves regardless of procedural outcome. QOL scores were only negatively affected in patients with a high symptomatic burden of arrhythmia recurrence suggesting that significant reduction in AF

						despite differences in outcome. QOL measurements also improved regardless of AF recurrence, except in patients with an AF burden in the highest quartile (median 27.2 hours per month). AF recurrence independently predicted aggregate QOL score	health component scores	burden can improve QOL without total elimination of AF
Samuel, 2021 (CIRCA-DOSE)	¹³	RCT	346 patients >18 years were randomized	A secondary analysis of a prospective, parallel-group,	The exposure in the present analysis is the absolute	At 12 months, a 1-point improvement in AFEQT score	To determine the association between change in AF burden	In patients with primarily low-burden paroxysmal AF,

			1:1:1 to contact force-guided radiofrequency ablation, 4-minute cryoballoon ablation, or 2-minute cryoballoon ablation	multicenter, single-masked randomized clinical trial (Cryoballoon vs. Irrigated Radiofrequency Catheter Ablation: Double Short vs. Standard Exposure Duration [CIRCA-DOSE] study)	difference in AF burden prior to ablation and 12 months following ablation, as evaluated by the AFEQT Score	was observed for every absolute reduction in daily AF burden of 15.8 minutes (95% CI 7.2–24.4; $P<0.001$), or every 0.63% (95% CI 0.30–0.95; $P<0.001$) reduction in relative AF burden from baseline	and quality of life in the year following ablation	the reduction in AF burden following ablation may be associated with a clinically meaningful improvement in quality of life
Terricabras, 2020 (STAR-AF II)	¹⁴	RCT	549 patients enrolled in the trial who underwent ablation. Patients underwent AF ablation	Patients underwent AF ablation with 1 of 3 ablation strategies: (1) pulmonary vein isolation (PVI), (2) PVI plus complex fractionated	Inclusion: symptomatic persistent AF (<3 years) refractory to at least 1 antiarrhythmic agent and no	The primary endpoint for the original trial and for this analysis was freedom from documented episodes of AF	Significant QOL improvement occurred in all 3 study arms and regardless of AF recurrence, defined as AF episodes lasting	In this secondary analysis, decreases in AF burden after ablation for AF were significantly

			with 1 of 3 ablation strategies: (1) pulmonary vein isolation (PVI), (2) PVI plus complex fractionated electrograms, or (3) PVI plus linear lesions	electrograms, or (3) PVI plus linear lesions	previous ablations	lasting longer than 30 seconds after an initial 3-month blanking period in the presence or absence of antiarrhythmic treatment after a single procedure. Significant improvements in mean (SD) PCS (68.3 [20.7] to 82.5 [18.6]) and MCS (35.3 [8.6] to 37.5 [7.6]) occurred 18 months after ablation ($P<0.05$ for both)	more than 30 seconds: for no recurrence, mean (SD) PCS increased from 66.5 (20.9) to 79.1 (19.4) and MCS from 35.3 (8.7) to 37.7 (7.7)	associated with improvements in QOL. Quality of life changes were significantly associated with the percentage of AF burden reduction after ablation
Kotecha,	¹⁶	Syste	Screened	A systematic review	Articles	Good reliability	Responsiveness	Given the low

2016		matic review of RCT and observational studies	2216 articles, of which eight articles describing five questionnaires were eligible for inclusion	of the measurement properties of AF - specific health-related quality of life questionnaires	describing five questionnaires were eligible for inclusion: AF6, AFEQT, AFQLQ, Atrial Fibrillation Quality of Life (AFQoL), and QLAF.	(internal consistency and test-retest reliability) was demonstrated for AF6, AFEQT, AFQLQ and AFQoL. Content, construct and criterion validity were positively rated only in AFEQT	was positively rated only in AFEQT, but with limited evidence. Overall, AFEQT showed strong positive evidence for 2 of 9 measurement properties, compared to one for AFQoL and none for the remaining questionnaires	ratings for many measurement properties, no single questionnaire can be recommended, although AFEQT performed strongest
Zenger, 2020	¹⁹	Prospective cohort study	1338 patients completed the AFSS symptom score	The Utah My Evaluation (mEVAL) program collects the Toronto AFSS in AF outpatients at the University of Utah	Younger age (mean difference 2.92 for <65 vs. ≥75; <i>P</i> <.001), female sex (mean	At 6-months, worse baseline symptom score was associated with the use of rhythm control	Compared subsequent clinical management at 6 months between	AF Patient-reported outcomes (PROs) in clinical practice identify highly-

					difference 2.57; $P<.001$), pulmonary disease (mean difference 1.88; $P<.001$), and depression (mean difference 2.46; $P<.001$) were associated with higher scores	(37.1% vs. 24.5%; $P<0.001$)	patients with better versus worse AF HRQoL	symptomatic patients, corroborating findings in more controlled, clinical trials. Increased AFSS score correlates with more aggressive clinical management, supporting the utility of disease-specific PROs guiding clinical practice
Sandhu, 2017	¹⁸	Prospective cohort	100 patients underwent electrical	A prospective cohort study of consecutive patients with AF	The overall mean AFEQT score was 55.6	There were significant improvements in	Patients who were in AF by 3 months	There are significant QoL benefits for

		t study	cardioversion and completed follow-up	referred for outpatient electrical cardioversion at 2 hospitals in Edmonton from 2013–2014	± 24.4 , and the domain-specific scores were as follows: symptoms, 66.2 ± 26.6 ; daily activities, 48.5 ± 29.5 ; treatment concerns, 57.6 ± 25.8 ; and treatment satisfaction, 56.7 ± 26.1	the vast majority of the SF-36 and AFEQT domains for the 51 patients who maintained sinus rhythm at 3 months	demonstrated improvements in the AFEQT treatment concern score ($P=0.02$) and SF-36 emotional role value ($P<0.01$) compared with baseline values, which may be the result of treatment expectations related to cardioversion	patients who maintain sinus rhythm after electrical cardioversion
Arbelo, 2021	²¹	Guideline	Patients with AF	The construction of candidate QIs (including a systematic review of the literature) and the selection of the	N/a	Quality indicator development	Six domains of AF care (patient assessment, anticoagulation, rate control, rhythm control,	It is anticipated that implementation of these Quality Indicators will improve the

				final set of QIs (using a modified Delphi method)			risk factor management, and outcomes), and provides 17 main and 17 secondary QIs for the diagnosis and management of AF	quality of AF care

Additional Evidence Table S26 — Recommendations to measure and improve patient quality of life

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Jones, 2020 (RATE-AF)	¹⁵	RCT	160 patients	Focus groups of patients with symptomatic permanent AF in a trial of heart rate control	The RATE-AF trial randomised 160 patients aged ≥60 years with permanent AF and at least NYHA class II dyspnoea to either digoxin or beta-blockers	Substantial impairment of health-related QoL was noted in 160 trial patients, with impact on all domains apart from mental health	There was marked variability in symptoms in individual patients, with some describing severe impact on activities of daily living, and profound interaction with comorbidities such as arthritis	The impact of comorbidities is poorly appreciated in the context of AF, with considerable variability in QoL that requires both generic and AF-specific assessment

Evidence Table 24 for Recommendation Table 24 (Sec. 9) — Recommendations for patients with an acute coronary syndromes or undergoing percutaneous intervention

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Cannon, 2017 (RE-DUAL PCI)	³⁸⁶	RCT	2725 patients	Warfarin plus a P2Y12 inhibitor (clopidogrel or Ticagrelor) and aspirin (for 1 to 3 months) (triple-therapy group) versus dual therapy with dabigatran (110 mg or 150 mg twice daily) plus a	Inclusion: AF patients who had undergone PCI to triple therapy with warfarin plus a P2Y12 inhibitor (clopidogrel or ticagrelor) and aspirin (for 1 to 3 months) (triple-therapy group) or dual therapy with dabigatran (110 mg or 150 mg twice daily) plus a P2Y12 inhibitor	The primary end point was a major or clinically relevant nonmajor bleeding event during follow-up (mean follow-up, 14 months). The incidence of the primary end point was 15.4% in the 110-mg dual-therapy group as compared with 26.9% in the triple-therapy	The incidence of the composite efficacy end point was 13.7% in the two dual-therapy groups combined as compared with 13.4% in the triple-therapy group (HR=1.04; 95% CI 0.84–1.29; P=0.005	Among patients with AF who had undergone PCI, the risk of bleeding was lower among those who received dual therapy with dabigatran and a P2Y12 inhibitor than among those who received triple therapy with warfarin, a P2Y12 inhibitor,

				P2Y12 inhibitor (clopidogrel or Ticagrelor) and no aspirin (110-mg and 150-mg dual-therapy groups)	(clopidogrel or ticagrelor) and no aspirin (110-mg and 150-mg dual-therapy groups)	group (HR=0.52; 95% CI 0.42–0.63; $P<0.001$ for noninferiority; $P<0.001$ for superiority) and 20.2% in the 150-mg dual-therapy group as compared with 25.7% in the corresponding triple-therapy group, which did not include elderly patients outside the United States (HR=0.72; 95% CI 0.58–0.88; $P<0.001$ for noninferiority)	for noninferiority)	and aspirin. Dual therapy was noninferior to triple therapy with respect to the risk of thromboembolic events
Vranckx,	³⁸⁷	RCT	1506 patients	Edoxaban	Patients with AF	Primary endpoint	Major or	In Patients with

2019			were enrolled and randomly assigned to the edoxaban regimen (n=751) or VKA regimen (n=755)	(60 mg once daily) plus a P2Y12 inhibitor for 12 months or a vitamin K antagonist (VKA) in combination with a P2Y12 inhibitor and aspirin (100 mg once daily, for 1–12 months)	requiring oral anticoagulation, were aged at least 18 years, and had a successful PCI for stable coronary artery disease or acute coronary syndrome	was a composite of major or clinically relevant non-major (CRNM) bleeding within 12 months. The main efficacy outcome (the composite of cardiovascular death, stroke, SEE, myocardial infarction, and definite stent thrombosis)	CRNM bleeding events occurred in 17% patients in edoxaban arm regimen and 20% in VKA arm; hazard ratio 0.83 (95% CI 0.65–1.05; $P=0.0010$ for non-inferiority, margin hazard ratio 1.20; $P=0.1154$ for superiority). For the main efficacy outcome: 7% in edoxaban arm versus	AF who had undergone PCI, the edoxaban-based regimen was non-inferior for bleeding compared with the VKA-based regimen, without significant differences in ischaemic events

							6%in VKA arm; HR for edoxaban 1.06 [95% CI 0.71–1.69]	
Gibson, 2016	³⁸⁸	RCT	2124 participants with nonvalvular AF who had undergone PCI with stenting	Group 1: low-dose rivaroxaban (15 mg once daily) plus a P2Y12 inhibitor for 12 months Group 2: very-low-dose rivaroxaban (2.5 mg twice daily) plus DAPT for 1, 6, or 12 months Group 3:	≥18 years of age who had paroxysmal, persistent, or permanent nonvalvular AF and who had just undergone PCI with stent placement. Exclusion: a history of stroke or transient ischemic attack, clinically significant gastrointestinal bleeding within 12 months before	Primary safety outcome: was clinically significant bleeding (a composite of major bleeding or minor bleeding according to Thrombolysis in Myocardial Infarction [TIMI] criteria or bleeding requiring medical attention)	The rates of clinically significant bleeding were lower in groups 1 and 2 than in group 3 (16.8% & 18.0% versus 26.7%;; hazard ratio (HR) for group 1 vs. group 3: 0.59; 95% CI, 0.47 to 0.76; <i>P</i> <0.001; HR for group 2 vs.	In patients with AF undergoing PCI with stents, the administration of either low-dose rivaroxaban plus a P2Y12 inhibitor for 12 months or very-low-dose rivaroxaban plus DAPT for 1, 6, or 12 months was associated with a lower rate of

				standard therapy with a dose-adjusted vitamin K antagonist (once daily) plus DAPT for 1, 6, or 12 months (group 3)	randomization, a calculated creatinine clearance of less than 30 mL per minute, anemia of an unknown cause with a haemoglobin concentration of less than 10 g per decilitre, or any other condition known to increase the risk of bleeding		group 3, 0.63; 95% CI, 0.50 to 0.80; $P<0.001$). The rates of death from cardiovascular causes, myocardial infarction, or stroke were similar in the three groups (Kaplan-Meier estimates, 6.5% in group 1, 5.6% in group 2, and 6.0% in group 3)	clinically significant bleeding than standard therapy with a vitamin K antagonist plus DAPT for 1, 6, or 12 months
Dewilde, 2013	³⁸⁹	RCT	573 adults receiving oral anticoagulants	Clopidogrel alone (double therapy)	Patients with long-term indication for oral	Primary outcome was any bleeding episode within 1	Bleeding episodes were seen in 54	In patients undergoing PCI receiving oral

			and undergoing PCI	versus clopidogrel plus aspirin (triple therapy)	anticoagulation treatment, a severe coronary lesion with indication for PCI; and age 18–80 years. Exclusion criteria: history of intracranial bleeding; cardiogenic shock; contraindication to use of aspirin, clopidogrel, or both; peptic ulcer in the previous 6 months; thrombocytopenia; major bleeding in the past 12 months; and pregnancy	year of PCI	(19.4%) patients receiving double therapy and in 126 (44.4%) receiving triple therapy (hazard ratio [HR] 0.36, 95% CI 0.26– 0.50, <i>P</i> <0.0001). In the double- therapy group, six (2.2%) patients had multiple bleeding events, compared with 34 (12.0%) in the triple-	anticoagulants u of clopiogrel without aspirin was associated with a significant reduction in bleeding complications and no increase in the rate of thrombotic events

							therapy group. 11 (3.9%) patients receiving double therapy required at least one blood transfusion, compared with 27 (9.5%) patients in the triple-therapy group (odds ratio from Kaplan-Meier curve 0.39, 95% CI 0.17– 0.84, <i>P</i> =0.011)	
Yasuda, 2019 (AFIRE)	¹⁶²	RCT	2236 AF patients	Intervention: rivaroxaban.	Inclusion: ≥20 years with AF and	The primary efficacy end point	Rivaroxaban monotherapy	As antithrombotic

				Control: combination therapy with rivaroxaban plus a single antiplatelet agent	stable CAD in Japan; CHADS ₂ ≥1; a history of PCI, including angioplasty ± stenting at ≥1 year before enrollment; a history of angiographically confirmed CAD (with stenosis of ≥50%) not requiring revascularization; or a history of CABG at ≥1 year before enrolment. Exclusion: a history of stent thrombosis, coexisting active tumor, and poorly	was a composite of stroke, systemic embolism, myocardial infarction, unstable angina requiring revascularization, or death from any cause; this end point was analyzed for noninferiority with a noninferiority margin of 1.46. The primary safety end point was major bleeding, according to the criteria of the International	was noninferior to combination therapy for the primary efficacy end point, with event rates of 4.14% and 5.75% per patient-year, respectively (HR=0.72; 95% CI 0.55–0.95; <i>P</i> <0.001 for noninferiority). Rivaroxaban monotherapy was superior to combination therapy for the primary safety	therapy, rivaroxaban monotherapy was noninferior to combination therapy for efficacy and superior for safety in AF patients and stable coronary artery disease

					controlled hypertension	Society on Thrombosis and Hemostasis; this end point was analyzed for superiority	end point, with event rates of 1.62% and 2.76% per patient-year, respectively (HR=0.59; 95% CI 0.39–0.89; $P=0.01$ for superiority). Limitations: The choice of antiplatelet regimen (aspirin/P2Y12 inhibitor) was at the discretion of the treating physicians, a factor that makes it	

							uncertain whether the benefit of rivaroxaban monotherapy applies equally to the two combination regimens. The early termination of the trial because of an increased risk of death from any cause in the combination-therapy group may overestimate the efficacy	

							data	
Lopes, 2019 (AUGUSTUS)	³⁹⁰	RCT	4614 patients from 33 countries	P2Y12 inhibitor to receive apixaban versus a vitamin K antagonist and to receive aspirin or matching placebo	Inclusion: AF patients who had an acute coronary syndrome or had undergone PCI and were planning to take a P2Y12 inhibitor to receive apixaban or a vitamin K antagonist and to receive aspirin or matching placebo for 6 months	The primary outcome was major or clinically relevant nonmajor bleeding. Secondary outcomes included death or hospitalization and a composite of ischemic events. Major or clinically relevant nonmajor bleeding was noted in 10.5% of the patients receiving apixaban, as compared with 14.7% of those	Patients in the apixaban group had a lower incidence of death or hospitalization than those in the vitamin K antagonist group (23.5% vs. 27.4%; HR=0.83; 95% CI 0.74–0.93; <i>P</i> =0.002) and a similar incidence of ischemic events. Patients in the aspirin group had an	In AF patients with a recent acute coronary syndrome or PCI treated with a P2Y12 inhibitor, an antithrombotic regimen that included apixaban, without aspirin, resulted in less bleeding and fewer hospitalizations without significant differences in the incidence of ischemic events than regimens

						receiving a vitamin K antagonist (HR=0.69; 95% CI 0.58–0.81; $P<0.001$ for both noninferiority and superiority), and in 16.1% of the patients receiving aspirin, as compared with 9.0% of those receiving placebo (HR=1.89; 95% CI 1.59–2.24; $P<0.001$)	incidence of death or hospitalization and of ischemic events that was similar to that in the placebo group	that included a vitamin K antagonist, aspirin, or both
Fiedler, 2015	³⁹¹	RCT	614 patients receiving concomitant aspirin and OAC	6-week clopidogrel therapy (n=307) versus 6-month	Patients receiving OAC who underwent drug-eluting stent implantation Major exclusion	Composite of death, myocardial infarction (MI), definite stent thrombosis,	The primary endpoint occurred in 30 patients (9.8%) in the 6-week group	In patients taking OAC who had undergone drug-eluting stent

				clopidogrel therapy (n=307)	criteria: age ≤18 years, previous stent thrombosis, drug-eluting stent implantation in the left main stem, active bleeding or bleeding diathesis, or a history of intracranial bleeding	stroke, or Thrombolysis In Myocardial Infarction (TIMI) major bleeding at 9 months. Secondary combined ischemic endpoint of cardiac death, MI, definite stent thrombosis, and ischemic stroke. Secondary bleeding endpoint of TIMI major bleeding	compared with 27 patients (8.8%) in the 6-month group (hazard ratio [HR]: 1.14; 95% CI: 0.68 to 1.91; <i>P</i>=0.63). There were no significant differences for the secondary combined ischemic endpoints (12 [4.0%] vs. 13 [4.3%]; HR: 0.93; 95% CI: 0.43 to 2.05; <i>P</i>=0.87) or the secondary bleeding	implantation there was no difference in net clinical outcomes between six weeks of triple therapy versus 6 months. Physicians should weigh the trade-off between ischemic and bleeding risk when choosing the shorter or longer duration of triple therapy

							endpoint (16 [5.3%] vs. 12 [4.0%]; HR: 1.35; 95% CI: 0.64 to 2.84; <i>P</i> =0.44)	
Matsumura-Nakano, 2019	392	RCT	696 patients	OAC alone to combined OAC and single antiplatelet therapy	Patients who were treated with a combination of an oral anticoagulant and a single antiplatelet agent	Primary end point: composite of all-cause death, myocardial infarction, stroke, or systemic embolism. Major secondary end point: composite of the primary end point or major bleeding according to the International Society on Thrombosis and	Primary end point occurred in 54 patients (15.7%) in the OAC-alone group and in 47 patients (13.6%) in the combined OAC and APT group (HR, 1.16; 95% CI, 0.79–1.72; <i>P</i> =0.20 for noninferiority, <i>P</i> =0.45 for superiority).	Trial prematurely terminated. In patients with AF and stable coronary artery disease beyond 1 year after stenting, there was no noninferiority of OAC alone to combined OAC and antiplatelet therapy

						Haemostasis classification	The major secondary end point occurred in 67 patients (19.5%) in the OAC-alone group and in 67 patients (19.4%) in the combined OAC and APT group (HR, 0.99; 95% CI, 0.71–1.39; <i>P</i>=0.016 for noninferiority, <i>P</i>=0.96 for superiority). Myocardial infarction occurred in 8 (2.3%) and 4 (1.2%)	

							patients, whereas stroke or systemic embolism occurred in 13 (3.8%) and 19 (5.5%) patients, respectively. Major bleeding occurred in 27 (7.8%) and 36 (10.4%) patients, respectively	
Alexander, 2020	³⁹³	Post-hoc analysis of RCT (AUGUSTUS Trial)	4614 patients with AF and recent acute coronary syndrome or percutaneous coronary	Aspirin or placebo and to open-label apixaban or VKA for 6 months	Patients with AF and recent ACS or PCI who were planning to take a P2Y12 inhibitor for 6 months	3 composite bleeding outcomes and 3 composite ischemic outcomes	Compared with VKA, apixaban had either a lower or a similar risk of bleeding and	In patients with AF and recent acute coronary syndrome or percutaneous coronary intervention

			intervention on a P2Y12 inhibitor				ischemic outcomes. Aspirin caused more severe bleeding (absolute risk difference, 0.97% [95% CI, 0.23– 1.70]) and fewer severe ischemic events (absolute risk difference, - 0.91% [95% CI, -1.74 to - 0.08]) than placebo. From 30 days to 6 months, the risk of severe bleeding was	receiving a P2Y12 inhibitor, apixaban is preferred over VKA. Use of aspirin immediately and for up to 30 days results in an equal trade off between an increase in severe bleeding and a reduction in severe ischemic events. After 30 days, aspirin continues to increase bleeding without significantly

							higher with aspirin than placebo (absolute risk difference, 1.25% [95% CI, 0.23–2.27]), whereas the risk of severe ischemic events was similar (absolute risk difference, -0.17% [95% CI, -1.33 to 0.98])	reducing ischemic events
Jensen, 2023	³⁹⁴	Prospective registry	Monotherapy vs. dual therapy included 3331 patients.	Monotherapy vs. dual therapy. Among patients	All patients with AF undergoing first-time PCI between 2003 and 2017 from the	Hospitalization for bleeding and major adverse cardiac events (MACE)	Risks of hospitalization for bleeding (HRw 0.90, 95% CI 0.75–	In patients with AF undergoing PCI long-term OAC monotherapy

			DOAC vs. VKA monotherapy included 1275 patients	treated with monotherapy, we compared DOAC therapy and VKA therapy	Western Denmark Heart Registry		1.09) and MACE (HRw 1.04, 95% CI 0.90–1.19) were similar with monotherapy and dual therapy. Similarly, risks of hospitalization for bleeding (HRw 1.27, 95% CI 0.84–1.92) and MACE (HRw 1.15, 95% CI 0.87–1.50) were equal with DOAC and VKA monotherapy	and dual therapy have the same risk of bleeding and MACE. DOAC monotherapy is as safe and effective as VKA monotherapy

Additional Evidence Table S27 — Acute and chronic coronary syndromes in patients with atrial fibrillation

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Saglietto, 2020	³⁹⁵	Systematic review and meta-analysis of RCTs	10 797	OAC type (vitamin K antagonist-based [VKA]; non-VKA OAT [DOAC]) and antiplatelet agents (P2Y inhibitor only: dual therapy [DAT]; P2Y plus aspirin: triple therapy	ACS or undergoing PCI requiring OAT	Safety: thrombolysis in Myocardial Infarction (TIMI) major bleeding and intracranial hemorrhage (ICH). Efficacy outcomes were cardiovascular death, myocardial infarction, stroke and stent-thrombosis (ST)	VKA and DOAC-based DAT regimens reduced the occurrence of TIMI major bleeding; numerically, potentially clinically important, higher ST occurrence in DOAC DAT vs. VKA TAT (HR=1.50; 95% CI= 0.96–2.33) and DOAC TAT (HR=1.86; 95%	DAT regimens highest safety among antithrombotic strategies, (a DOAC-specific impact on ICH reduction) DOAC DAT clinically important higher ST occurrence, warranting a case-by-case comprehensive evaluation that integrates patient- and procedure-

				[TAT])			CI 0.93–3.73)	related residual ischemic/bleeding risk
Jeridi, 2022	³⁹⁶	Systematic review and meta-analysis of RCTs	10 studies, 53 302 patients	RCTs that included post hoc analyses or prospective observational studies on clinical cardiovascular outcomes associated with proton pump inhibitor (PPI) use for 6+ months in cardiovascular disease	Cardiovascular disease patients requiring antiplatelet agent therapy and/or coronary angioplasty	Primary analysis showed no significant differences between the PPI group and the control group for the risks of major adverse cardiovascular events (MACEs), all-cause death (ACD), or target vessel revascularization (TVR) using a random-effects model	Large heterogeneity	Long-term PPI use not associated with risk of adverse cardiovascular events; inconsistent results for combined PPI/clopidogrel therapy

				patients requiring antiplatelet agent therapy and/or coronary angioplasty				
Liao, 2020	³⁹⁷	Systematic review and meta-analysis of RCTs	10 643	Dual vs. TAT and DOACs versus VKA regimens	Long-term indication for OAC and ACS or PCI	Dual antithrombotic regimens were associated with significantly less thrombolysis in myocardial infarction major and minor bleeding (OR=0.53; 95% CI 0.40–0.71), with no significant difference in major adverse	DOAC regimens had significantly lower TIMI major and minor bleeding (OR=0.58; 95% CI 0.43–0.78) and intracranial bleeding (OR=0.33; 95% CI 0.16–0.66), with similar rates of major adverse cardiovascular events	Dual antithrombotic & DOAC regimens have reduced bleeding without compromising the risk of CV or mortality

						cardiovascular events (OR=0.93; 95% CI 0.72–1.22) or all-cause mortality (OR 0.89; 95% CI 0.61–1.19)	(OR=1.00; 95% CI 0.86–1.16) and all-cause mortality (OR=1.01; 95% CI 0.81–1.26)	
Haller, 2019	³⁹⁸	Systematic review and meta-analysis of RCTs	9317 patients (5039 DAT, 4278 TAT)	DAT vs. triple antithrombotic therapy (TAT) in patients with AF following PCI and/or ACS	Indication for OAC and ACS or PCI	TIMI bleeding	Substantial heterogeneity regarding primary ischaemic endpoint definition, duration of follow-up, as well as type, dose and duration of antithrombotic therapy	DAT reduces bleedings compared with TAT, similar effect in preventing ischaemic endpoints in AF post-PCI or ACS
Park, 2022	³⁹⁹	Systematic review and meta-	25 907	1 to 3 months of DAPT in	PCI in ACS	NACE, MACE, bleeding	No difference in the hazard of net adverse clinical	1 to 3 months of DAPT has similar efficacy for

		analysis of RCTs		patients who underwent PCI for ACS vs. 6 to 12 months of DAPT after PCI for ACS			events, MACE, lower bleeding, nonsignificant but increasing trend of both NACE and MACE with greater proportion of left main and left anterior descending coronary artery lesions and greater proportion of STEMI included in the trials; bias? successful procedures/trial patient selection APT only	preventing ischemic events with reduced bleeding risk compared with 6 to 12 months of DAPT
Watanabe,	⁴⁰⁰	RCT	4169	1 to 2	4169 patients	Composite of	1 to 2 months of	Clopidogrel

2022 (STOPDAPT-2 ACS)				months of DAPT compared with 12 months of DAPT for a composite end point of cardiovascular and bleeding events in patients with ACS	with ACS who underwent successful PCI using cobalt-chromium everolimus-eluting stents at 96 centres in Japan	cardiovascular (CV death, MI, any stroke, or definite stent thrombosis) or bleeding (thrombolysis in MI major or minor bleeding) events at 12 months; major secondary end points were cardiovascular and bleeding components of the primary end point	DAPT was not noninferior to 12 months of DAPT for the primary end point (3.2 vs. 2.8% in the 12-month DAPT group) (absolute difference=0.37%; 95% CI -0.68% to 1.42%; HR=1.14; 95% CI 0.80–1.62; <i>P</i> for noninferiority=0.06) APT only	monotherapy after 1 to 2 months of DAPT failed to attest noninferiority to standard 12 months of DAPT for the net clinical benefit with a numerical increase in cardiovascular events despite reduction in bleeding events
Bahit, 2022 (AUGUSTUS)	⁴⁰¹	RCT	633 out of 4581	Apixaban (5 mg or 2.5 mg twice daily) or VKA and aspirin or	AF, ACS and/or PCI, indication for OAC, prior stroke/TIA/TE	Major or clinically relevant nonmajor (CRNM) bleeding	Aspirin vs. placebo higher rates of bleeding, interaction by prior	Aspirin may have some benefit in patients with prior stroke, these findings support the use of

				placebo			stroke/TIA/TE (less in prior stroke/TIA/TE), aspirin associated with numerically lower rates of death or ischemic events than placebo	apixaban and a P2Y12 inhibitor without aspirin for the majority of patients with AF and ACS and/or PCI, regardless of prior stroke/TIA/TE status
Bor, 2022 (WOEST 2)	⁴⁰²	Prospective registry	1075	DAT (P2Y12 inhibitor and OAC) vs. TAT: aspirin, P2Y12 inhibitor, and OAC)	PCI in patients with an indication for OAC; VKA/mechanic heart valves included	Thrombotic and bleeding outcomes after one year, BARC & MACE	DAT less clinically relevant & similar major bleeding (16.8% vs. 23.4%; $P<0.01$ and 7.6% vs. 7.7%, not significant); MACCE 12.4% vs. 9.7%; $P=0.17$	DAT was associated with lower risk of clinically relevant bleeding without a penalty in ischaemic events

Additional Evidence Table S28 — Acute stroke or intracranial haemorrhage in patients with atrial fibrillation

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Oldgren, 2022 (TIMING)	⁴⁰³	RCT	888 patients were randomized to either early (n=450) or delayed (n=438) initiation of DOAC	To investigate the efficacy and safety of early versus delayed initiation of DOAC in these patients after acute stroke	Patients were randomized to early (≤ 4 days) or delayed (5–10 days) DOAC initiation, with choice of DOAC at the investigators' discretion with 72 hours from stroke onset. The primary outcome was the composite of recurrent ischemic stroke, symptomatic intracerebral haemorrhage, or	Early initiation was noninferior to delayed start of DOAC after acute ischemic stroke in patients with AF	Low NIHSS-score Stopped prematurely “Cherry picking patients?”	Early initiation was noninferior to delayed start of DOAC after acute ischemic stroke in AF patients

					all-cause mortality at 90 days. The prespecified noninferiority margin was 3%. Secondary outcomes included the individual components of the primary outcome			
Schreuder , 2021 (APACHE AF)	404	RCT	101	To assess whether apixaban (2x5mg) compared to antithrombotics/none reduces the risk of stroke in high-risk AF with previous intracranial	Inclusion: previous intracerebral, non-traumatic hemorrhage (ICH) between 7–90 days old; >45y & AF with CHA ₂ DS ₂ -VASc ≥ 2; CrCl >15 mL/min	Primary outcome measures: 1. vascular death + non-fatal stroke (FU 12–72months)	Low number of patients, long recruitment time	Patients with AF who had an ICH while taking anticoagulants have a high subsequent annual risk of non-fatal stroke or vascular death, whether allocated to apixaban or to

				hemorrhage				avoid anticoagulation
Al-Shahi, 2021 (SoSTAR T)	⁴⁰⁵	RCT	203	Randomised, open-label, assessor-masked, Pilot-phase, non-inferiority trial	To assess in adults surviving spontaneous (non-traumatic) symptomatic intracranial haemorrhage with persistent/paroxysmal AF/flutter, if starting full treatment dose oral anticoagulation (OAC) result in a beneficial net reduction of all serious vascular events compared with not starting OAC	Recurrent symptomatic spontaneous intracranial haemorrhage (in the safety phase of the trial)	Preliminary Results	Starting oral anticoagulation was non-inferior to avoiding it for people with AF after ICH was inconclusive, although rates of recurrent ICH were lower than expected
Shahjouei,	⁴⁰⁶	Systemati	52 823	Patients pre-	Meta-analysis was	Symptomatic	Non RCTs	Prior intake of

2020		c review and meta-analysis of RCT and observational studies	acute ischemic stroke patients	treated with DOAC who received IVT for acute ischemic stroke were recorded with international normalized ratio <1.7	performed by comparing the rate of symptomatic intracerebral haemorrhage in these patients with: stroke patients without prior anticoagulation therapy; and patients on warfarin	intracerebral haemorrhage outcome according to the National Institute of Neurological Disorders (NINDS) versus the European Cooperative Acute Stroke Study II (ECASS-II) criteria	included	DOAC did not increase the risk of symptomatic intracerebral haemorrhage in selected AIS patients treated with IVT
Kermer, 2020	⁴⁰⁷	Retrospective cohort study	80 ischemic stroke patients, 40 ICH	80 patients treated with dabigatran presented with ischemic stroke and 40 patients suffered intracranial bleeding	61 German stroke centres, retrospective data collected from German neurological/neuro surgical departments administering idarucizumab	Safety of thrombolysis, hematoma expansion. In patients receiving intravenous thrombolysis with rt-PA following idarucizumab, 78% showed a median	Retrospective study design 80 patients treated with dabigatran presented with ischemic stroke and 40 patients suffered	Administration of rt-PA after reversal of dabigatran activity with idarucizumab in case of acute ischemic stroke seems feasible,

				(intracerebral haemorrhage (ICH))	following product launch from January 2016 to August 2018	improvement of 7 points in NIHSS. No bleeding complications were reported. Hematoma growth was observed in 3/27 patients with ICH. Outcome was favourable with a median NIHSS improvement of 4 points and modified Rankin score 0–3 in 61%	intracranial bleeding (intracerebral haemorrhage (ICH)). In patients receiving intravenous thrombolysis with rt-PA following idarucizumab , 78% showed a median improvement of 7 points in NIHSS. No bleeding complications were reported. Hematoma	effective, and safe. In dabigatran-associated intracranial haemorrhage, idarucizumab appears to prevent hematoma growth and to improve outcome

							growth was observed in 3/27 patients with ICH. Outcome was favourable with a modified Rankin score 0–3 in 61%	

Evidence Table 25 for Recommendation Table 25 (Sec. 9) — Recommendations for triggered atrial fibrillation

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Corica, 2022	408	Systematic review and meta-analysis of RCT and observational studies	207 847 individuals with sepsis from 22 articles	Intervention: sepsis, and its impact on in-hospital mortality and intensive care unit (ICU) mortality	Inclusion: studies reporting on the prevalence of new-onset AF and/or its impact on in-hospital mortality or ICU mortality in patients with sepsis or septic shock	Across 207 847 patients with sepsis, new onset AF was found in 13.5% (95% CI: 8.9–20.1%), with high heterogeneity between studies; significant subgroup differences were observed, according to the geographical	Newonset AF patients showed an increased risk of both in-hospital mortality (RR=1.69, 95% CI 1.47–1.96) and ICU mortality (RR=2.12, 95% CI 1.86–2.43), with moderate to no heterogeneity between the included studies	New-onset AF is a common complication during sepsis, being present in one out of seven individuals. Patients with new-onset AF are at a higher risk of adverse events during sepsis, and may need specific therapeutical interventions

						location, study design and sample size of the included studies		
McIntyre, 2019	⁴⁰⁹	Systematic review and meta-analysis of RCT and observational studies	36 studies (10 prospective)	Intervention: ECG for AF detection	Inclusion: patients hospitalised for medical (i.e. non-surgical) illness who developed newly diagnosed AF. Studies with data on AF with stress patients following hospital discharge	AF incidence ranged from 1% to 44%, which was too heterogeneous to justify meta-analysis (I2=99%)	The use of continuous ECG monitoring explained 13% of the variance in AF incidence, while care in an intensive care unit explained none. Two studies reported the long-term rate of AF recurrence following AF occurring transiently with stress.	The incidence of AF with medical illness may be as high as 44%, with higher estimates in reports using continuous ECG monitoring. Within 5 years following hospital discharge, AF recurrence is documented in approximately half of patients; however, the

							Recurrence rates at 5 years ranged from 42% to 68%	true rate may be higher
Quon, 2018	410	Retrospective cohort study	2304 patients	Intervention: anticoagulation	Inclusion: hospitalized patients with a primary diagnosis of acute coronary syndrome (ACS), acute pulmonary disease or sepsis, and a complication of new-onset AF during admission from 1999 to 2015	The study did not identify any association between anticoagulation and a lower incidence of ischemic stroke in patients with new-onset AF occurring with ACS, acute pulmonary disease, or sepsis (OR=1.22, 95% CI 0.65–2.27, OR=0.97, 95% CI: 0.53–1.77,	Anticoagulation was associated with a higher risk of bleeding in patients with AF associated with acute pulmonary disease (OR=1.72, 95% CI: 1.23 to 2.39), but not in ACS or sepsis (OR=1.42, 95% CI: 0.94–2.14, OR=0.96, 95% CI: 0.29–3.21)	The benefit of anticoagulation in secondary AF is not strong and can be associated with a higher risk of bleeding. Careful individual assessment regarding decisions on anticoagulation is warranted in these patients

						and OR=1.98, 95% CI: 0.29–13.47), after adjusting for confounders		
Walkey, 2015	⁴¹¹	Prospective registry	138 722 sepsis survivors	95 536 (69%) had no AF during sepsis, 33 646 (24%) had prior AF, and 9 540 (7%) had new-onset AF during sepsis	A Medicare 5% sample to identify patients who survived hospitalization with sepsis between 1999 and 2010	AF occurrence following sepsis hospitalization was more common among patients with new-onset AF during sepsis (54.9%) than in patients with no AF during sepsis (15.5%). Compared with patients with no AF during sepsis, those with new-onset AF during sepsis	AF occurrence following sepsis hospitalization was more common among patients with new-onset AF during sepsis (54.9%) than in patients with no AF during sepsis (15.5%). Compared with patients with no AF during sepsis, those with new-onset AF during sepsis	Most sepsis survivors with new-onset AF during sepsis have AF occur after discharge from the sepsis hospitalization and have increased long-term risks of heart failure, ischemic stroke, and death

						had greater 5-year risks of hospitalization HF, ischemic stroke and death	had greater 5-year risks of hospitalization for heart failure (11.2% vs. 8.2%; HR=1.25; 95% CI 1.16–1.34), ischemic stroke (5.3% vs. 4.7%; HR=1.22; 95% CI 1.10–1.36), and death (74.8% vs. 72.1%; HR=1.04; 95% CI 1.01–1.07)	
Søgaard, 2022	⁴¹²	Prospective registry	274 196 patients hospitalized for community-acquired pneumonia	The primary outcome was a record of arterial thromboembolic event defined as ischemic stroke and/or systemic	Inclusion: patients hospitalized with incident community-acquired pneumonia in	1-year risk of thromboembolism was 0.8% (95% CI 0.8–0.8%) in patients without AF vs. 2.1% (95% CI	Baseline stroke risk according to CHA ₂ DS ₂ -VASc score was categorized on the basis of assigned points:	Patients hospitalized with pneumonia with new-onset AF have a higher risk of thromboembolism

			, 6553 patients (mean age 79.1 ± 11.0 years; 3405 women 52.0%) developed new-onset AF	arterial embolism. Given the severity of the diagnosis of thromboembolism, there were considered events where thromboembolism was the reason for hospital admission. Exposure: new-onset AF. Intervention: initiation of anticoagulation therapy	Denmark from 1998 to 2018. Exclusion: all patients with hospital contact (inpatient or ambulatory) within the 30 days before pneumonia admission; patients with prior AF diagnoses and patients with prior experience of any OAC treatment within 180 days before index date	1.8–2.5%) in patients with new-onset AF without anticoagulation The risk of stroke was higher in patients at high risk of stroke without anticoagulation and with incident AF. Among patients with new-onset AF, 32.9% (95% CI, 31.8–34.1%) had a new hospital contact with AF, and 14.0% (95% CI 13.2–14.9%) initiated	low risk (0, no risk factors when disregarding female sex as a lone risk factor), intermediate risk (1–2 risk factors), and high risk (3 risk factors) where points for female sex were not considered	m during 3-y follow-up and a high risk of recurrent AF

						anticoagulation therapy during the 3 years after incident AF diagnosis		
Wang, 2020	⁴¹³	Prospective registry	10 723 individuals with newly diagnosed AF in the overall sample of 921 733 patients, pneumonia (n=415; 20%)	Acute precipitants of AF and long-term recurrence of AF in a clinical setting	AF precipitants included surgery (classified as cardiac, thoracic noncardiac, and non-cardiothoracic), acute MI, sepsis, pneumonia, pulmonary embolism, pneumothorax, respiratory failure due to	Among 10 723 patients with newly diagnosed AF (67.9 ± 9.9 years, 41% women), 19% had an acute AF precipitant, the most common of which were cardiac surgery (22%), pneumonia (20%). AF recurrence rates were substantial after newly diagnosed AF	Reliance solely on AF episodes captured by ECG or leading to cardioversion likely leads to underestimation of recurrent AF, as episodes may be asymptomatic or undetected, both before and following AF diagnosis. A causal relation between recurrent AF and outcomes after	AF after an acute precipitant frequently recurs, although the risk of recurrence was associated with lower rates than among individuals without an acute precipitant. Recurrence is associated with substantial long-term morbidity and mortality

					other causes, acute alcohol consumption, thyrotoxicosis, pericardial disease (pericarditis and tamponade), and myocarditis	with and without an acute precipitant, with a 5-year cumulative incidence of 41% and 52%, respectively	AF cannot be established	
Gundlund , 2021	414	Prospective registry	30 307 patients with infection-related AF and 90 912 patients with infection without AF	Patients with infection-related AF and infection without AF	Inclusion: All Danish residents admitted to a Danish hospital with an infection [including gastrointestinal (GI) infections, pneumonia,	The 1-year absolute risk of AF and thromboembolic events were 36.4% and 7.6%, respectively (infection-related AF) and 1.9% and 4.4%, respectively	Some degree of misclassification bias regarding diagnosis coding	During the first year after discharge, 36% of patients with infection-related AF had a new hospital contact with AF. Infection-related AF was associated with increased risk of

					sepsis, urinary tract infections, and other infections]. Exclusion: previous diagnosis of AF or previous AF treatment (amiodarone, flecainide, dronedarone, sotalol, propafenone, or digoxin at any time before the infection or OAC therapy 180 days prior to the	(infection without AF). In the multivariable analyses, infection-related AF was associated with an increased long-term risk of AF and thromboembolic events compared with infection without AF: HR=25.98; 95% CI 24.64–27.39 for AF and HR=2.10; 95% CI 1.98–2.22 for thromboembolic events	thromboembolic events compared with infection without AF

					infection)			

Evidence Table 26 for Recommendation Table 26 (Sec. 9) — Recommendations for prevention of postoperative atrial fibrillation

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Ziff, 2020	⁴¹⁵	Systematic review and meta-analysis of RCTs	89 RCTs, 19 211 patients	Beta-blockers versus control	Meta-analyses of RCTs that looked at the clinical effects of beta-blockers on adults in four cardiovascular indications	All-cause mortality, myocardial infarction (MI), incident HF or stroke	Beta-blockers versus control: all large meta-analyses with low risk of bias in non-cardiac surgery suggested that beta-blockers increased mortality, (RR 1.03 to 1.31); reduced risk of incident MI after non-cardiac surgery (RR range 0.08 to 0.92); but	Beta-blockers had no effect on mortality for cardiac surgery, but increased mortality in non-cardiac surgery. In non-cardiac surgery, beta-blockers reduced MI after surgery but increased the risk of stroke

							increased risk of stroke (RR range 1.33 to 7.72)	
Abdelaziz, 2023	⁴¹⁶	Systematic review and meta-analysis of RCTs	25 RCTs (4467 patients)	Posterior pericardiotomy versus control	RCTs that compared posterior pericardiotomy versus control in patients undergoing cardiac surgery	Primary endpoint was the incidence of POAF after cardiac surgery. The secondary endpoints were supraventricular arrhythmias, early/late pericardial effusion, pericardial tamponade, pleural effusion, length of hospital/intensive care unit stay, intra-aortic	The overall incidence rate of POAF was 11.7% in the posterior pericardiotomy group versus 23.67% in the control group, (odds ratio [OR] 0.49, 95% confidence interval [CI]: 0.38–0.61). Compared with the control group, the risk of supraventricula	Posterior pericardiotomy is an effective intervention for reducing the risk of POAF after cardiac surgery. Also, Posterior pericardiotomy is economically efficient in terms of decreasing the length of hospital stay

						balloon pump use, revision surgery for bleeding, and mortality	r tachycardia (OR 0.66, 95% CI: 0.43–0.89), early pericardial effusion (OR 0.32, 95% CI: 0.22–0.46), late pericardial effusion (OR 0.15, 95% CI: 0.09–0.25), and pericardiac tamponade (OR 0.18, 95% CI: 0.10–0.33) were lower in the posterior pericardiotomy group	
Soletti, 2022	⁴¹⁷	Systematic review and meta-	18 RCTs (3531 patients)	Posterior pericardiotomy versus no	RCTs reporting outcomes of patients that	Primary outcome was the incidence of	Posterior pericardiotomy was associated	Posterior pericardiotomy is a safe and

		analysis of RCTs		intervention	received a posterior pericardiotomy or no intervention after cardiac surgery	POAF. Key secondary outcomes were operative mortality, incidence of pericardial and pleural effusion, cardiac tamponade, length of stay, pulmonary complications, amount of chest drainage, need for intra-aortic balloon pump, and re-exploration for bleeding	with a significantly lower incidence of POAF (OR 0.45, 95% CI 0.32–0.64, $P<0.0001$), early (OR 0.18, 95% CI 0.10–0.34, $P<0.0001$) and late pericardial effusion (incidence rate ratio 0.13, 95% CI 0.06–0.29, $P<0.0001$), and cardiac tamponade (risk difference -0.02, 95% CI -0.04 to -0.01,	effective intervention that significantly decreases the incidence of POAF and pericardial effusion following cardiac surgery

							$P=0.001$). PP was associated with a higher incidence of pleural effusion (OR 1.42, 95% CI 1.06–1.90, $P=0.02$), but not pulmonary complications (OR 0.82, 95% CI 0.56–1.19; $P=0.38$). No differences in other outcomes were found	
Buckley, 2007	418	Systematic review and meta-analysis of RCTs	14 studies; 2864 patients	Amiodarone versus placebo	RCTS, reporting incidence of AF data regarding amiodarone dose and timing of initiation of	Incidence of AF	The incidence of postoperative AF was significantly reduced by	Total amiodarone doses of 3000 mg or higher may be more effective

					therapy		amiodarone compared with placebo ($P<0.001$). No significant differences were noted in the odds ratios (ORs) of developing AF among the low-, medium-, and high-dose groups: OR 0.58, 95% confidence interval (CI) 0.44–0.77; OR 0.45, 95% CI 0.30–0.69; and OR 0.44, 95% CI 0.33–0.58; respectively	than lower doses in reducing the rate of postoperative AF after cardiac surgery. Preoperative initiation of amiodarone appears to be unnecessary

							($P=0.238$). In addition, the ORs for AF development associated with preoperative and postoperative initiation of amiodarone were not significantly different (OR 0.50, 95% CI 0.39–0.63; and OR 0.48, 95% CI 0.37–0.63; respectively, $P=0.862$)	
Auer, 2004 (SPPAF)	⁴¹⁹	RCT	253 patients	Oral amiodarone plus metoprolol;	Inclusion: patients undergoing cardiac surgery	Patients receiving combination therapy	Patients in the placebo group had a non-significantly	Oral active prophylaxis with either sotalol or amiodarone plus

				metoprolol alone; sotalol versus placebo	in the absence of heart failure and without significant left ventricular dysfunction	(amiodarone plus metoprolol) and those receiving sotalol had a significantly lower frequency of AF (30.2% and 31.7%; absolute difference, 23.6% and 22.1%; OR=0.37; 95% CI 0.18–0.77, $P<0.01$ vs. placebo] and 0.40; 95% CI 0.19–0.82, $P=0.01$ vs. placebo]) compared with patients	longer length of hospital stay as compared with the active treatment groups (13.1 ± 8.9 days vs. 11.3 ± 7 ; $P=0.10$), with no significant difference between the active treatment groups	metoprolol may reduce the rate of AF after cardiac surgery in a population at high risk for postoperative AF. Treatment with metoprolol alone resulted in a trend to a lower risk for postoperative AF

						receiving placebo (53.8%). Treatment with metoprolol was associated with a 13.5% absolute reduction of AF ($P=0.16$; OR=0.58; 95% CI 0.29–0.17)		
Yagdi, 2003	420	RCT	157	Intravenous amiodarone in a dose of 10 mg/kg/d for postoperative 48 hours. On postoperative day 2 oral amiodarone was started with a dose of 600 mg/d for	Patients who underwent elective Coronary Artery Bypass Graft (CABG) surgery. Exclusion: t preoperative chronic/ paroxysmal AF; myocardial infarction less than 3 weeks	Incidence of new-onset AF; Maximum ventricular rate; Duration of AF; Length of in-hospital stay for patients	Postoperative AF occurred in 10.4% receiving amiodarone and in 25.0% patients receiving placebo ($P=.017$). Duration of AF was 12.8 +/- 4.8 hours for	Postoperative intravenous amiodarone, followed by oral amiodarone reduces new-onset postoperative AF, reduces ventricular rate and duration of AF after coronary artery

				5 days, 400 mg/d for the following 5 days, and 200 mg/d for 20 days versus placebo (control group)	before surgery; second- or third-degree atrioventricular block; sick sinus syndrome; need for temporary or permanent pacemaker; preoperative use of certain interacting drugs; amiodarone side effects; use of amiodarone in the year preceding the operation; heart rate less than 60 beats/min at rest; an initial systolic blood		the amiodarone group compared with 34.7 +/- 28.7 hours for the control group ($P = .003$). The maximum ventricular rate during AF was slower in the amiodarone group than in the control group (105.9 +/- 19.1 beats per minute and 126.0 +/- 18.5 beats per minute, respectively, $P = .016$). The	bypass grafting. It is also well tolerated and decreases the length of hospital stay

					pressure of less than 100 mm Hg; redo coronary artery bypass surgery; concomitant operations; thyroid disease; asthma; chronic obstructive pulmonary disease; chronic renal failure; or liver function test results greater than 2 times normal		two groups had a similar incidence of complication other than rhythm disturbances (20.8% vs. 20.0%, $P = .904$). Amiodarone group patients had shorter hospital stays than that of control group patients (6.8 +/- 1.7 days vs. 7.8 +/- 2.9 days, $P = .014$). The in-hospital mortality was not different	

							between two groups (1.3% vs. 3.8, $P = .620$)	
Devereaux , 2008	⁴²¹	RCT	8351	Extended-release metoprolol succinate (n=4174) or placebo (n=4177)	Patients with, or at risk of, atherosclerotic disease who were undergoing non-cardiac surgery	Primary endpoint was a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal cardiac arrest	Fewer patients in the metoprolol group (5.8%) than in the placebo group (6.9%) reached the primary endpoint (HR 0.84, 95% CI 0.70–0.99; $P=0.0399$). Fewer patients in the metoprolol (4.2%) versus placebo group (5.7%) had a myocardial	In patients undergoing noncardiac surgery, beta-blockers reduce the risk of myocardial infarctions but increase the risk of deaths and stroke

							infarction (HR 0.73, 0.60–0.89; $P=0.0017$). However, there were more deaths in the metoprolol group (3.1%) versus placebo (2.3%)(HR 1.33, 1.03–1.74; $P=0.0317$). More patients in the metoprolol group (1.0%) versus placebo group (0.5%) had a stroke (HR= 2.17, 1.26–3.74;	

							<i>P</i> =0.0053)	
Daoud, 1997	⁴²²	RCT	124 (64 assigned to amiodarone and 60 to placebo)	Oral amiodarone versus placebo	Patients for whom cardiac surgery was scheduled and with sinus rhythm. Exclusion: allergic to amiodarone; had used amiodarone within four months of enrollment; had a history of amiodarone toxicity; had participated in another investigational protocol; required the use	Free from AF	Postoperative AF occurred in 25% of the amiodarone group 53% in the placebo group (<i>P</i> =0.003). Patients in the amiodarone group were hospitalized for significantly fewer days (6.5+/-2.6 vs. 7.9+/-4.3 days, <i>P</i> =0.04). Nonfatal postoperative complications occurred in 12% of	Preoperative oral amiodarone in patients undergoing complex cardiac surgery is well tolerated and significantly reduces the incidence of postoperative AF and the duration and cost of hospitalization

					of antiarrhythmic therapy other than beta-receptor antagonists, calcium-channel antagonists, or digitalis; had untreated thyroid disease; had serum aspartate aminotransferase or alanine aminotransferase concentrations four times the upper limit of normal; were pregnant; had a resting heart rate of less than 50 beats per		amiodarone-treated patients and in 10% of patients receiving placebo ($P=0.78$). Fatal postoperative complications occurred in 5% of patients who received amiodarone and in 3% of patients who received placebo ($P=1.00$). Total hospitalization costs were significantly less for the	

					minute in the absence of medical therapy known to slow the sinus rate; or had uncontrolled heart failure		amiodarone group than for the placebo group (\$18 375+/- \$13 863 vs. \$26 491+/- \$23 837, <i>P</i> =0.03)	
Butt, 2018	⁴²³	Prospective cohort study	A total of 3830 patients with post-operative AF (POAF) were matched with 15 320 patients with NVAF	Exposure: OAC	Inclusion: Danish residents ≥ 30 years of age undergoing first-time surgery who underwent noncardiac, nonobstetrical surgery; had no history of AF; developed postoperative AF (POAF); were not	The primary outcome was thromboembolism (a composite of ischemic stroke, transient cerebral ischemia, and thrombosis or embolism in peripheral arteries). The long-term risk of thromboembolism	Anticoagulation therapy during follow-up was associated with a comparably lowered risk of thromboembolic events in patients with POAF (HR=0.52; 95% CI 0.40–0.67) as well as NVAF	New-onset POAF following noncardiac surgery was associated with a long-term risk of thromboembolism similar to NVAF

					diagnosed with cancer within 1 year prior to admission or during admission; had not redeemed any OAC prescriptions 6 months prior to surgery; and were alive at discharge	m was similar in patients with POAF and NVAf (31.7 events vs. 29.9 events per 1000 person years; HR=0.95; 95% CI 0.85–1.07)	(HR=0.56; 95% CI 0.51–0.62) compared with no anticoagulation therapy	
Gialdini, 2014	⁴²⁴	Retrospective cohort study	1 729 360 eligible patients	Perioperative AF and the long-term risk of stroke	Inclusion: adult patients who underwent inpatient surgery. Exclusion: patients who did not undergo any inpatient surgery; patients	Of 1729 360 eligible patients, 24 711 (1.43%; 95% CI, 1.41–1.45%) had new-onset perioperative AF during the index hospitalization and 13 952	At 1 year after noncardiac surgery, cumulative rates of stroke were 1.47% (95% CI 1.24–1.75%) in those with perioperative	Among patients hospitalized for surgery, perioperative AF was associated with an increased long-term risk of ischemic stroke, especially

					with any AF diagnoses recorded during encounters prior to the index hospitalization for surgery, or with AF labelled as present on admission during the index hospitalization for surgery; patients with documented cerebrovascular disease	(0.81%; 95% CI 0.79–0.82%) experienced a stroke after discharge. At 1 year after hospitalization for cardiac surgery, cumulative rates of stroke were 0.99% (95% CI 0.81–1.20%) in those with perioperative AF and 0.83% (95% CI 0.76–0.91%) in those without AF	AF and 0.36% (95% CI 0.35–0.37%) in those without AF. In a Cox proportional hazards analysis accounting for potential confounders, perioperative AF was associated with subsequent stroke both after cardiac surgery (HR=1.3; 95% CI 1.1–1.6) and noncardiac surgery (HR=2.0; 95%	following noncardiac surgery

							CI 1.7–2.3). The association was significantly stronger for perioperative AF after noncardiac vs. cardiac surgery ($P<0.001$ for interaction)	
Horwich, 2013	⁴²⁵	Retrospective cohort study	8058 patients	Long-term impact of post-cardiac surgery AF on the risk of stroke and survival	Inclusion: patients undergoing isolated CABG surgery	Overall, in-hospital mortality was 2.4% and was not different between groups. Unadjusted in-hospital outcomes suggest patients with new AF were more likely	Stroke was reported in 268 (12.1%) patients in the new AF group compared to others (8.4%). After adjustment new AF was independently	Patients with new AF perioperatively have increased risk of stroke and early death after discharge independent of other clinical risk factors

						to suffer a permanent stroke (1% vs. 2.5%; $P<0.001$) require prolonged mechanical ventilation ($P<0.001$) and prolonged stay in hospital ($P<0.001$). After discharge patients were followed for a mean of 5.7 years	associated with a higher risk for stroke with a HR=1.26; 95% CI 1.08–1.47; $P=0.003$) and a higher risk of death with HR=1.2; 95% CI 1.08–1.32; $P=0.0007$)	

Evidence Table 27 for Recommendation Table 27 (Sec. 9) — Recommendations for patients with embolic stroke of unknown source

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Buck, 2021 (PER DIEM)	426	RCT	300 patients	Participants were randomly assigned 1:1 to prolonged electrocardiographic monitoring with either an implantable loop recorder (n = 150) or an external loop recorder (n = 150) with follow-up visits at 30 days, 6 months, and 12 months	Inclusion: patients within 6 months of ischemic stroke and without known AF	The primary outcome was the development of definite AF or highly probable AF (adjudicated new AF lasting ≥2 minutes within 12 months of randomization). The primary outcome was observed in 15.3% (23/150) of patients in	There were 5 patients (3.3%) in the implantable loop recorder group who had recurrent ischemic stroke vs. 8 patients (5.3%) in the external loop recorder group (between-group difference, -2.0%; 95% CI, -6.6–2.6%), 1	Among patients with ischemic stroke and no prior evidence of AF, implantable electrocardiographic monitoring for 12 months, compared with prolonged external monitoring for 30 days, resulted in a significantly greater proportion of patients with AF detected over 12 months

						the implantable loop recorder group and 4.7% (7/150) of patients in the external loop recorder group (between-group difference, 10.7% [95% CI 4.0–17.3%]; RR= 3.29; 95% CI, 1.45–7.42; <i>P</i>=0.003)	(0.7%) vs. 1 (0.7%), respectively, who had intracerebral haemorrhage (between-group difference, 0%; 95% CI -1.8–1.8%); 3 (2.0%) vs. 3 (2.0%) who died (between-group difference, 0%; 95% CI -3.2–3.2%), and 1 (0.7%) vs. 0 (0%) who had device-related serious adverse events	

Bernstein, 2021 (STROKE-AF)	⁴²⁷	RCT	492 patients	Patients randomized to the intervention group (n = 242) received ICM insertion within 10 days of the index stroke; patients in the control group (n = 250) received site-specific usual care consisting of external cardiac monitoring, such as 12-lead electrocardiograms, Holter monitoring, telemetry, or event recorders	Inclusion: ≥60 years or aged 50 to 59 years with at least 1 additional stroke risk factor and had an index stroke attributed to large- or small-vessel disease within 10 days prior to insertable cardiac monitor (ICM) insertion	Incident AF lasting more than 30 seconds through 12 months. AF detection at 12 months was significantly higher in the ICM group vs. the control group (27 patients [12.1%] vs. 4 patients [1.8%]; HR=7.4; 95% CI 2.6–21.3; <i>P</i> <0.001)	Among the 221 patients in the ICM group who received an ICM, 4 (1.8%) had ICM procedure-related adverse events (1 site infection, 2 incision site haemorrhages, and 1 implant site pain)	Among patients with stroke attributed to large- or small-vessel disease, monitoring with an ICM compared with usual care detected significantly more AF over 12 months
Wachter, 2017 (Find-AF)	⁴²⁸	RCT	398 patients (200 patients)	Enhanced and prolonged monitoring versus the standard care	Inclusion: patients with acute ischaemic	The primary endpoint was the occurrence of AF or atrial	After 6 months, we detected AF in 14% of 200 patients in	Enhanced and prolonged monitoring initiated early in patients with

			were randomly assigned to the enhanced and prolonged monitoring group and 198 to the standard care group)		stroke (symptoms for 7 days or less) aged 60 years or older presenting with sinus rhythm and without history of AF. Exclusion: a severe ipsilateral carotid or intracranial artery stenosis	flutter (30 sec or longer) within 6 months after randomisation and before stroke recurrence. Because Holter ECG is a widely used procedure and not known to harm patients, we chose not to assess safety in detail. Analysis was by intention to treat	the enhanced and prolonged monitoring group (27 patients) versus 5% in the control group (nine of 198 patients, absolute difference 9.0%; 95% CI 3.4–14.5, $P=0.002$; number needed to screen 11)	acute ischaemic stroke aged 60 years or older was better than standard care for the detection of AF
Hart, 2018 (NAVIGATE ESUS)	⁴²⁹	RCT	7213	Intervention: rivaroxaban versus aspirin	Inclusion: Patients who had ischemic	The primary efficacy outcome: first	The primary efficacy outcome	Rivaroxaban was not superior to aspirin with regard

					stroke, as identified on cerebral imaging, that had occurred between 7 days and 6 months before screening. Exclusion: lacunar stroke and associated with extracranial vessel atherosclerosis causing more than 50% luminal stenosis in arteries supplying the area of	recurrence of ischemic or hemorrhagic stroke or systemic embolism in a time-to-event analysis; the primary safety outcome: rate of major bleeding	occurred in 172 patients in the rivaroxaban group and in 160; HR=1.07; 95% CI 0.87 to 1.33; <i>P</i> =0.52. Recurrent ischemic stroke occurred in 158 patients in the rivaroxaban group and in 156 in the aspirin group. Major bleeding occurred in 62 patients in the rivaroxaban group and in	to the prevention of recurrent stroke after an initial embolic stroke of undetermined source and was associated with a higher risk of bleeding

					ischemia or with identified risk factors for a cardiac source of embolism		23 in the aspirin group, HR= 2.72; 95% CI, 1.68 to 4.39; $P<0.001$	
Diener, 2019 (RE-SPECT ESUS)	430	RCT	5390	Intervention: dabigatran at a dose of 150 mg or 110 mg twice daily as compared with aspirin at a dose of 100 mg once daily	Patients 60 years of age or older who had had an embolic stroke of undetermined source within the previous 3 months Exclusion: modified Rankin Scale score of ≥ 4; Major-risk cardioembolic source of embolism;	The primary outcome was recurrent stroke. The primary safety outcome was major bleeding	Recurrent strokes occurred in 177 patients in the dabigatran group and in 207 patients in the aspirin group, HR= 0.85; 95% CI 0.69 to 1.03; $P=0.10$. Ischemic strokes occurred in 172 patients and 203	In patients with ESUS dabigatran was not superior to aspirin in preventing recurrent stroke. The incidence of major bleeding was not greater in the dabigatran group than in the aspirin group, but there were more clinically relevant nonmajor bleeding events in the dabigatran group.

					Other specific stroke etiology; Intracerebral hemorrhage; Increased risk of bleeding; Estimated creatinine clearance <30 mL per min; Indication for antiplatelet therapy; label aspirin at a dose of 100 mg once daily could be assigned, in addition to the blinded aspirin regimen, at the discretion of the		patients HR=0.84; 95% CI, 0.68 to 1.03. Major bleeding occurred in 77 patients in the dabigatran group and in 64 patients in the aspirin group, HR= 1.19; 95% CI, 0.85 to 1.66	

					investigator)			

Additional Evidence Table S29 — Patients with embolic stroke of unknown source (ESUS)

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Geisler, 2023	⁴³¹	RCT	352 screened 178 were allocated to apixaban and 174 to aspirin	Superiority of apixaban against the current standard of treatment (aspirin) for the long-term treatment after ESUS	ESUS must be defined as: stroke detected by CT or MRI that is not lacunar. Absence of extracranial or intracranial atherosclerosis causing $\geq 50\%$ luminal stenosis in arteries supplying the area of ischaemia No major-risk	Occurrence of at least one new ischemic lesion at 12 months after study drug initiation when compared to baseline MRI before study drug initiation	Surrogate endpoint	No difference in endpoint between apixaban/aspirin

					cardioembolic source of embolism			
Buck, 2021 (PER DIEM)	⁴²⁶	RCT	300	Participants were randomly assigned 1:1 to prolonged electrocardiographi c monitoring with either an implantable loop recorder (n=150) or an external loop recorder (n=150) with follow-up visits at 30 days, 6 months, and 12 months	ESUS stroke patients	AF-detection	8.6% of study participants did not complete the prescribed monitoring, which may underestimat e the underlying rate of AF. Phone assessments at 12 and 24 months did not use a validated questionnaire to assess for new stroke	Implantable electrocardiographi c monitoring for 12 months, compared with prolonged external monitoring for 30 days, resulted in a significantly greater proportion of patients with AF detected over 12 months

							events, or TIA	
Bernstein, 2021 (STROKE -AF)	⁴²⁷	RCT	496	Patients randomized to the intervention group (n=242) received ICM insertion within 10 days of the index stroke; patients in the control group (n=250) received site-specific usual care consisting of external cardiac monitoring, such as 12-lead electrocardiograms, Holter monitoring, telemetry, or event recorders	Eligible patients were aged 60 years or older or aged 50 to 59 years with at least 1 additional stroke risk factor and had an index stroke attributed to large- or small-vessel disease within 10 days prior to insertable cardiac monitor (ICM) insertion	Incident AF lasting more than 30 seconds through 12 months	Adjudication Committee was non blind	Among patients with stroke attributed to large- or small-vessel disease, monitoring with an ICM compared with usual care detected significantly more AF over 12 months

Tsivgoulis , 2019	⁴³²	Systematic review and meta- analysis of RCT and observational studies	4531 patients (28 studies)	To investigate the association of ICM duration with the yield of AF detection in ischaemic stroke patients	Inclusion: studies reporting AF detection rates by ICM in ischaemic stroke patients with negative initial AF screening. Exclusion: studies reporting prolonged cardiac monitoring with devices other than ICM, not providing AF detection rates or monitoring duration, and	Cumulative AF detection rate	The proportion of AF detection by ICM was independently associated with monitoring duration (coefficient=0 .015; 95% confidence interval [CI], 0.005 to 0.024) and mean patient age (coefficient=0 .009; 95% CI, 0.003 to 0.015)	Extended duration of ICM monitoring and increased patient age are factors that substantially increase AF detection in ischaemic stroke patients with initial negative AF screening

					reporting overlapping data for the same population			

Evidence Table 28 for Recommendation Table 28 (Sec. 9) — Recommendations for patients with atrial fibrillation during pregnancy

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Bateman, 2018	433	Prospective cohort study	2350 hypertensive pregnant women were exposed to β -blocker	Intervention: β -blockers	Inclusion: pregnant women with a diagnosis of hypertension and their offspring	First-trimester exposure to β -blockers was assessed. Outcomes were any major congenital malformation, cardiac malformations, cleft lip or palate, and central nervous system	The pooled adjusted RR=1.07, 95% CI 0.89–1.30 and risk difference per 1000 persons exposed (RD1000) =3.0, 95% CI, -6.6–12.6 associated with β -blockers for any major malformation; RR=1.12, 95% CI 0.83–1.51; and RD1000=2.1, 95% CI -4.3–8.4 for any cardiac	The results suggest that maternal use of β -blockers in the first trimester is not associated with a large increase in the risk for overall malformations or cardiac malformations, independent of measured confounders

						malformatio ns	malformation; and RR=1.97, 95% CI 0.74 - 5.25) and RD1000=1.0, 95% CI -0.9–3.0 for cleft lip or palate. For central nervous system malformations, the adjusted RR=1.37, 95% CI 0.58–3.25 and RD1000=1.0, 95% CI -2.0–4.0. Limitations: analysis was restricted to live births, exposure was based on dispensed medication, and	

							cleft lip or palate and central nervous system malformations had few outcomes	
Camm, 2010	⁴³⁴	Practice Guidelines	N/A	Intervention: electrical cardioversion	Inclusion: studies using cardioversion in pregnant women with AF	Electrical cardioversion can be performed in pregnancy	Several case reports have demonstrated successful cardioversion of maternal AF, without harm to the foetus. Energy requirements in pregnant and non-pregnant women are similar	Electrical cardioversion in AF pregnant women improves maternal and foetal outcomes
Regitz-Zagrosek, 2018	⁴³⁵	Practice guidelines	N/A	Intervention: electrical cardioversion	Inclusion: available data on management	Cardioversion seems safe in all	Electrical cardioversion is recommended	Cardioversion should be considered for

					of arrhythmias in pregnancy	phases of pregnancy as it does not compromise foetal blood flow and the risk of inducing foetal arrhythmias or initiating pre-term labour seems small. The foetal heart rate should routinely be controlled after cardioversion	whenever ongoing AF is haemodynamically unstable or a considerable risk for the mother or the foetus. The choice between cardioversion and rate control using digoxin or beta-blockers depends on the severity of the underlying valve disease and the tolerance	poorly tolerated persistent AF. Digoxin can be used for heart rate control of AF in pregnancy to reduce symptoms and improve maternal and foetal outcomes

Katrakis, 2016	⁴³⁶	Practice Guidelines	N/A	Intervention: electrical cardioversion Control: vagal manoeuvres, antiarrhythmic drugs	Inclusion: available data on management of supraventricular tachyarrhythmias in pregnancy	Direct current cardioversion can be performed at all stages of pregnancy	The current reaching the fetus is insignificant and furthermore the fetus has been shown to have a high fibrillation threshold. However, since transient foetal arrhythmias have been reported, foetal rhythm monitoring is recommended	Direct current cardioversion should be performed in all forms of sustained tachycardia causing severe haemodynamic effects, and can be used as a second line option in well tolerated SVT where drug therapy fails
Moore, 2012	⁴³⁷	Review	N/A	Intervention: electrical cardioversion Control: antiarrhythmic medications	Inclusion: studies describing treatment of maternal arrhythmias and their potential	Treatment of maternal arrhythmias and their potential adverse fetal and	Treatments include antiarrhythmic medications, electrical cardioversion, and	The decision of what therapy to use must be addressed on a case-by-case basis

					adverse fetal and maternal outcomes	maternal outcomes	radiofrequency ablation. Antepartum and intrapartum monitoring will also be addressed along with delivery planning and postpartum considerations	
Georgiopoulos, 2019	⁴³⁸	Review	N/A	Intervention: direct cardioversion Control: antiarrhythmic drugs	Inclusion: AF pregnant women	Direct cardioversion of AF is effective, safe, and preferred over pharmacologic cardioversion in pregnancy	Direct cardioversion is highly effective and safe in pregnant women and should be prioritized over pharmacologic cardioversion with intravenous ibutilide or flecainide	Although direct cardioversion is effective and safe during pregnancy, intravenous ibutilide or flecainide may be used for termination of AF in stable pregnant patients to improve

								maternal and foetal outcomes
Wang, 2006	⁴³⁹	Case report	N/A	Intervention: electrical cardioversion	Inclusion: Cardioversion used in cardiopulmonary resuscitation and in the treatment of intractable arrhythmia	The impact of cardioversion on fetal haemodynamics	By measuring umbilical artery flow immediately between each cardioversion, indicates that cardioversion is reassured during pregnancy without compromising fetal haemodynamics	Cardioversion is reassured during pregnancy without compromising fetal haemodynamics
Kockova, 2007	⁴⁴⁰	Case report	2 cases of successful cardioversion of AF using intravenous ibutilide during	Intervention: intravenous ibutilide	Inclusion: one patient had AF complicating the Wolff-Parkinson-White syndrome and the other had a history of	No adverse maternal or fetal effects were observed during or after pregnancy	No further arrhythmias occurred during the pregnancy after intravenous ibutilide administration a healthy baby was	Intravenous ibutilide may be considered for termination of AF in stable pregnant women with a structurally normal heart or

			pregnancy		nonobstructive hypertrophic cardiomyopathy	in either case with ibutilide-induced cardioversion of AF during pregnancy	delivered normally at term	with a hypertrophic nonobstructive cardiomyopathy to improve maternal and foetal outcomes

Evidence Table 29 for Recommendation Table 29 (Sec. 9) — Recommendations for patients with AF and congenital heart disease

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Jensen, 2015	⁴⁴¹	Review	N/A	Intervention: oral anticoagulation	Inclusion: current literature pertaining to anticoagulation in adults with congenital heart disease	Despite relatively young age and no typical cardiovascular risk factors, adult congenital heart disease patients have a high prevalence of thrombotic events	It is a heterogeneous population due to special conditions such as myocardial scarring after previous surgery, atypical atrial flutter, prothrombotic conditions and the presence of interatrial shunts	Oral anticoagulation should be considered in AF/AFL adult congenital heart disease patients to prevent ischaemic stroke and thromboembolism, regardless of other risk factors

Additional Evidence Table S30 — Congenital heart diseases and AF

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Guarguagli, 2019	⁴⁴²	Retrospective cohort study	58	AF catheter ablation (remote navigation was used in some patients. As mapping system they used CARTO, Rhythmia and simultaneous mapping. 25–35 W in manual procedures and 45–50 in remote magnetic navigation.	Inclusion: consecutive patients with CHD undergone ablation of AF between Jan 2008 and April 2018 in a tertiary care centre	All procedures were acutely successful in restoring SR, except for one patient (27 y/o with an anomalous left coronary artery from the pulmonary artery and mitral valve stenosis, persistent AF, and a massively dilated left	AF ablation is feasible and acutely successful in CHD patients, but recurrence rates are higher and multiple procedures may be required to control AF/AT. Persistent AF, complex anatomy, and left atrial size were independently	Ablation may be a valid option for the treatment of AF in CHD patients, but multiple procedures are likely to be required. Early referral and careful patient selection are essential to optimize the results of AF ablation. Further studies are needed to

				Techniques included PVI, focal activity ablations, and atrial substrate modification)		atrium, 170 mL/m ²). No major complications occurred. At 1 year after the index ablation, 32.8% of patients had remained in SR. Multiple procedures were required to control atrial arrhythmias in 35 (60%) patients. Freedom from AF/AT at 1 year after the 2nd and 3rd	associated with higher recurrence rates. AF ablation appears safe even in patient with complex anatomy but may necessitate special techniques such as remote magnetic navigation and more extensive ablation strategies and/or novel mapping tools like high-density	validate the results and the proposed risk model

						ablation was 40.9% and 36.5%, respectively. Severe anatomy complexity, persistent AF and LA area index were independent predictor of recurrence	mapping or simultaneous AF mapping. Bias: small sample size and the retrospective design. Heterogeneous group of CHD patients with different anatomical, clinical, and procedural characteristics	
Giamberti, 2017	⁴⁴³	Retrospective cohort study	80	Intraoperative ablation with monopolar irrigated radiofrequency during cardiac surgery	Adult patients with CHD and supraventricular arrhythmias undergoing open heart surgery for	Freedom from recurrence arrhythmias off of antiarrhythmic medications was 85% at 1	The approach to combine elective cardiac surgery and arrhythmia surgery may potentially	Surgical treatment of adults with CHD combined with supraventricular tachycardia ablation may

				procedures (Cox-Maze III procedure in the presence of preoperative AF and right-sided Maze ablation for patients with preoperative episodes of atrial flutter and/or supraventricular tachycardia)	other indications (none of the patients had arrhythmias as main indication for surgery)	year and 76% at 5 years of follow-up. Preoperative arrhythmia length ≥ 3 years, Tetralogy of Fallot and preoperative AF were associated with recurrence arrhythmia. Conversely, NYHA class, 3 was associated with a lower risk of recurrence	reduce the risk of developing late arrhythmia by means of prophylactic lesions in the atria; preoperative arrhythmia length ≥ 3 years, Tetralogy of Fallot and preoperative AF were associated with recurrence arrhythmia. NYHA class 3 was associated with a lower risk of recurrence.	represent a useful therapeutic approach

							Bias: small sample size and retrospective design	

Additional Evidence Table S31 — AF in inherited cardiomyopathies and primary arrhythmia syndromes

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Lozier, 2019	¹¹⁸	Systematic review and meta-analysis of RCT and observational studies	8479 participants with concomitant HCM and AF	Use of anticoagulation	Inclusion: observational studies ≥ 18 years old, reported data on thromboembolic events in patients with concomitant HCM and AF receiving AC versus no AC or DOACs versus VKAs. Exclusion: AF related to valve disease	Primary: incidence of thromboembolic events Secondary: incidence of thromboembolic events in patients with concomitant HCM and AF who received DOACs versus VKAs	Anticoagulation was associated with a lower pooled incidence rate of total thromboembolic events at 9.5% (112 events in 1175 patients) compared to 22.1% with no AC (108 events in 489 patients). The use of DOACs was associated with a lower pooled	Anticoagulation of patients with concomitant HCM and AF was associated with a lower incidence of thromboembolic events when compared to antiplatelet therapy or no treatment

							incidence rate of thromboembolic events at 4.7% (169 events in 3576 patients) compared to 8.7% with VKAs (281 events in 3239 patients)	
Guttmann, 2013	¹¹⁹	Systematic review and meta-analysis of RCT and observational studies	7381 HCM patients	AF prevalence and risk of thromboembolism in patients with HCM	Inclusion: AF and/or stroke or thromboembolism as primary or secondary outcome in a prospective or retrospective study	Prevalence and incidence of thromboembolism in patients with HCM and AF	Overall prevalence of thromboembolism in HCM patients with AF was 27.09% (95% CI 20.94% to 33.25%), I ² =61.4% (<i>P</i> <0.01). Overall AF incidence was 3.08% per 100 patients per year (95% CI	AF is common in HCM and associated with high thromboembolic risk. Most data suggest that AF patients should be anticoagulated

							2.63% to 3.54%, I²=86.5%, <i>P</i><0.001) and incidence of thromboembolis m in HCM patients with AF was 3.75% per 100 patients per year (95% CI 2.88% to 4.61%), I²=37.9% (<i>P</i>=0.1). Anticoagulation was associated with lower stroke incidence. There were no randomised controlled trials of therapy	

Hirota, 2019	¹²⁹	Prospective cohort study	305 patients with an HCM diagnosis; 86 patients (29%) had documented AF	The occurrence and clinical profile of thromboembolism in patients with HCM with a focus on the presence of AF	Inclusion: patients with HCM Exclusion: patients with no follow-up data	Thromboembolic events	The 5-year embolic event rate in those 117 patients with AF was 12.3%. Of the 23 patients with embolic events, 12 had AF prior to the embolic complications and another 6 had documented AF after thromboembolism. AF was not detected in the remaining 5 patients. The CHADS ₂ score did not correlate with the embolic	In this community-based registry, thromboembolic events were not rare in patients with HCM. All patients with HCM in whom AF develops should be given anticoagulation therapy regardless of their CHADS ₂ score

							outcome in HCM patients	
Guttmann, 2015	¹²³	Retrospective cohort study	4821 HCM patients (600 with AF)	Exploratory analyses were performed to determine predictors of TE, the performance of the CHA ₂ DS ₂ -VASc score, and outcome with vitamin K antagonists (VKAs)	Inclusion: adult HCM patients Exclusion: known inherited metabolic diseases or syndromic causes of HCM; Patients with a history of AF that had experienced TE prior to first evaluation	Primary: thrombo-embolic event	Patients with AF had a relative risk reduction of 54.8% (95% CI 0.31–0.97, <i>P</i> =0.037) with VKA treatment. Small number of patients	VKA treatment is associated with reduced thromboembolism. The CHA ₂ DS ₂ -VASc score does not correlate well with thromboembolism outcomes
Vilches, 2022	¹²¹	Retrospective cohort study	1191 amyloid transthyretin cardiomyopathy (ATTR-CM) patients (625 with AF)	The incidence, prevalence and factors associated with embolic events in ATTR-CM. Additionally, we	Inclusion: adult ATTR-CM patients Exclusion: incomplete information on AF and embolic	Embolic events	Incidence rate (per 100 patient-years) was 1.7 in AF with OAC, and 4.8 in AF without OAC. CHA ₂ DS ₂ -VASc	This study shows that embolic events are a frequent complication in ATTR-CM. The CHA ₂ DS ₂ -VASc

				evaluated embolic events according to the type of oral anticoagulation (OAC) and the performance of the CHA ₂ DS ₂ -VASc score in this setting	events		only predicted embolic events in patients with AF with a score ≥4	score does not appear to correlate well with clinical outcome
Lee, 2017	¹²²	Retrospective cohort study	306 apical HCM (ApHCM) patients (77 with AF)	The occurrence of AF	Inclusion: patients with AF and ApHCM Exclusion: follow-up duration was less than a year or initial ECG at the time of diagnostic TTE was not available	AF occurrence All-cause death, cardiovascular death and strokes	AF prevalence, 25.2%. 53/70 patients (76%) received warfarin. During a follow-up of 5.5 ± 2.0 years, the patients with AF had a higher incidence of all-cause death, cardiovascular death and	In patients with ApHCM, AF was common and was associated with a substantial risk for strokes and mortality suggesting that AF should be carefully managed in ApHCM

							strokes (11.7% vs. 1.3%, 6.5% vs. 0.9% and 19.5% vs. 2.6%, respectively, all $P<0.05$) than those without AF. The cause of death was a stroke in three (33%) out of nine patients with AF	
Hsu, 2020	¹²⁴	Retrospective cohort study	18 724 HCM patients (598 with AF)	To determine the characteristics of patients who experienced a stroke during a long follow-up period	Exclusion: AF diagnosed before the index date, AF associated with valvular conditions (mitral valve stenosis or prosthetic valve	TIA/ ischaemic stroke	The AF incidence in HCM patients was 5.83 per 1000 person-years, and the overall incidence of AF-associated stroke was	Taiwanese patients with concomitant HCM and AF have a high stroke risk regardless of the CHA ₂ DS ₂ -VASc score

					replacement),A F was not diagnosed		24.14 per 1000 person-years. The incidence of transient ischemic attack (TIA)/ischemic stroke varied from 20.41 to 60.55 per 1000 person-years, without proportionality to CHA ₂ DS ₂ - VASc score increase	

Evidence Table 30 for Recommendation Table 30 (Sec. 9) — Recommendations for prevention of thromboembolism in AF

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Vadmann, 2015	444	Systematic review and meta-analysis of RCT and observational studies	Aggregate population 715 741, with 17 804 AFL cases	AFL vs. population controls	Inclusion: original research papers published between 1964 and October 2014 and indexed with MeSH terms 'atrial flutter' and 'stroke' in MEDLINE and/or EMBASE	Stroke	Stroke risk ranged from (RR=1.4; 95% CI 1.35–1.46) to (HR=2.6; 95% CI 1.2–5.3)	Significantly increased risk of stroke in AFL compared with population controls
Rahman, 2016	445	Prospective cohort study	112 AFL	AFL vs. AF vs. matched controls (For each flutter case, up to 5 AF and 5 referent cases were matched by	Inclusion: typical flutter was defined by discrete, organized atrial activity defined by the presence of sawtooth pattern F waves at a rate of 240 to 340 b.p.m.;	AF, myocardial infarction, heart failure, stroke, all-cause mortality	AFL patients 10-year hazard ratios (95% CI): AF HR=5.0; 95% CI 3.1–8.0; myocardial infarction HR=3.1; 95% CI 1.4–6.6; heart	Significantly increased risks for AF, myocardial infarction, heart failure, stroke, and mortality in participants

				age (± 2 years) and sex at the same baseline examination in a nested case referent design)	AF: was defined by the absence of regular, organized atrial activity and an irregular ventricular response. Exclusion: possible atypical flutter		failure HR=4.1; 95% CI 1.9–9.0; stroke HR=2.2; 95% CI 1.1–4.2; death HR=2.0; 95% CI 1.4–2.8	who developed AFL compared to referents. No difference in the risk of HF, stroke, and mortality were found comparing AFL with AF

Evidence Table 31 for Recommendation Table 31 (Sec. 10) — Recommendations for screening for atrial fibrillation

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
McIntyre, 2022	⁴⁴⁶	Systematic review and meta-analysis of RCTs	35 836 patients	AF screening versus no-screening	Inclusion: RCTs that enrolled patients without known AF, screened for AF using electrocardiogram-based methods, and reported stroke outcomes. Exclusion: studies that focused on post-stroke populations	Stroke outcome based on intention-to-treat	The point estimate (RR=0.91; 95% CI 0.84–0.99) is modestly in favour of AF screening	The point estimate is in favour of screening, but heterogeneity in studies, and concludes that is the optimal sample size of a total of 103 454 participants randomized, indicating that further trials should be performed

Elbadawi, 2022	⁴⁴⁷	Systematic review and meta-analysis of RCTs	85 209 pts	The comparative efficacy of different AF screening strategies in older adults	Non-invasive screening for AF >65 y	All-cause mortality; stroke newly detected AF; initiation of OAC	AF screening (either systematic or opportunistic) was associated with higher AF detection (1.8% vs. 1.3%; RR=2.10; 95% CI 1.20–3.65) and initiation of oral anticoagulation (RR=3.26; 95% CI 1.15–9.23), compared with no screening. There was no	Systematic AF screening using non-invasive tools was associated with higher rate of new AF detection and initiation of OAC, but opportunistic screening was not associated with higher detection rates. There were no significant differences between the various AF screening approaches with respect to

							significant difference between any AF screening versus no screening in all-cause mortality (RR=0.97; 95% CI 0.93–1.01) or acute cerebrovascular accident (CVA) (RR=0.92; 95% CI 0.84–1.01). On network meta-analysis, only systematic screening	rates of all-cause mortality or cerebrovascular accident events

							was associated with higher AF detection (RR=2.73; 95% CI 1.62–4.59) and initiation of oral anticoagulation (RR=5.67; 95% CI 2.68–11.99), but not with the opportunistic screening, compared with no screening Underpowered for stroke	
Lyth, 2022 (STROKE-	⁴⁴⁸	RCT	27 975 persons	Intervention: invited to AF	The cost-effectiveness analysis was based on	The primary outcome was a	In the base-case	AF screening strategy in an

STOP)			(In the model, it was analysed 1000 hypothetical individuals who were invited to screening and 1000 individuals who were not invited to screening based on the patient characteristics in	screening compared to control group	data from the STROKESTOP study and was a pre-specified secondary outcome of the trial. These data were extrapolated to a life-time perspective using a half-year cycle length decision analytic Markov model. Such a model consists of multiple health states individuals can be in and move between based on specific transition probabilities	combined endpoint of ischaemic or haemorrhagic stroke, systemic embolism, bleeding leading to hospitalization, and all-cause death on intention-to-treat analysis. Per 1 000 individuals invited to the screening, there were 77 gained life years and 65 gained quality-adjusted life	scenario, screening of 1000 individuals resulted in 10.6 (95% CI -22.5–1.4) fewer strokes (8.4 ischaemic and 2.2 haemorrhagic strokes), 1.0 (95% CI: -1.9 to 4.1) more cases of systemic embolism, and 2.9 (95% CI: -18.2 to 13.1) fewer bleedings associated	elderly population is potentially cost-effective

			the STROKE STOP study)			years. The incremental cost was €1.77 million lower in the screening invitation group. Gained quality- adjusted life years to a lower cost means that the screening strategy was dominant. The result from 10 000 Monte Carlo simulations showed that the AF screening strategy was	with hospitalizatio n	

						cost-effective in 99.2% and cost-saving in 92.7% of the simulations		
Mant, 2007 (SAFE)	⁴⁴⁹	RCT	2553 ECGs	Gold standard was 12-lead interpretation by two cardiologists. This was compared to software AF detection (Biolog), GP and nurse interpretation of 12-lead and single-lead ECGs	Randomly selected electronically saved ECGs from the SAFE-trial	Sensitivity of software 83.3 increased with GP overreading to 91.9; specificity of software remained better at 99.1; compared to GP+ software at 91–1	Poor interpretation of ECGs with regards to AF by GPs and nurses. Biases: old study, likely that automatic interpretation has improved, but also that knowledge of AF has improved ECG reading	General practitioners did not accurately diagnose AF on ECG. Cardiologist might be needed to interpret correctly ECG data

							skills	
Svennberg, 2021 (STROKE-STOP)	⁶	RCT	28 768	Intervention: invitation to participate in screening program for AF using BID SL-ECGs for 30 sec Control: Standard of care	Inclusion: 75/76-year-old residing in Stockholm or Halland Exclusion: death or migration before study start	Combined primary outcome: Stroke, systemic embolism, bleeding leading to hospitalization, mortality	After a median follow-up of 6.9 years (IQR 6.5–7.2), significantly fewer primary endpoint events occurred in the intervention group (4456 [31.9%] of 13 979; 5.45 events per 100 years [95% CI 5.52–5.61]) than in the control group	Small benefit in favour of screening

							(4616 of 13 996; 5.68 events per 100 years (5.52–5.85; (HR=0.96 95% CI 0.92–1.00; $P=0.045$))	
Halcox, 2017 (REHEARS E-AF)	⁴⁵⁰	RCT	1004 participants 60 440 ECG	Comparison of algorithm vs. cardiology interpretation of single-lead ECG twice daily for 1 year	Inclusion: individuals >65 years with a CHA ₂ DS ₂ -VASc score ≥2. Exclusion: OAC-therapy, known AF, contraindication to OAC, PPM	All ECG deemed as normal by the automated algorithm were confirmed to be normal; only 5% of ECGs reported as AF by the device were confirmed to be AF	Low PPV in algorithm reported AF	Potential for remote interpretation of single-lead ECGs for screening
Duarte,	⁴⁵¹	Systematic	Diagnosti	Single-time	Studies that assessed	Diagnostic	The summary	The use of

2019		review and meta-analysis of RCT and observational studies	accuracy (13 publications reporting on nine studies) and clinical impact (24 publications reporting on 19 studies)	point lead-I ECG devices compared with manual pulse palpation followed by a 12-lead ECG	the diagnostic accuracy of lead-I ECG devices used at a single-time point to detect AF in an asymptomatic population	accuracy and cost-effectiveness	sensitivity of lead-I ECG devices was 93.9% (95% confidence interval [CI]: 86.2% to 97.4%) and summary specificity was 96.5% (95% CI: 90.4% to 98.8%)	single-time point lead-I ECG devices in primary care for the detection of AF in people with signs or symptoms of AF and an irregular pulse appears to be a cost-effective use of healthcare resources compared with manual pulse palpation followed by a 12-lead ECG
Svennberg, 2017	⁴⁵²	Prospective cohort study	3209 patients	Comparison of algorithm	Inclusion: 75/76-year-olds residing in	On an ECG level the	The sensitivity of	Usage of a manual

				performance in interpreting single-lead ECG as compared to manual interpretation by arrhythmia nurse/physician (gold standard)	Sweden, first consecutive participants in the STROKESTOP trial	algorithm showed a sensitivity of 97.8% for AF detection, specificity was 88.2%, PPV 2.8% and NPV 99.99%	the algorithm-based ECG interpretation was lower than trained ECG interpreters. The NPV of the algorithm was excellent, but the PPV was low, showing the need for manual interpretation of ECGs deemed as pathological by the algorithm	interpretation support reduce the need for professional (manual) ECG interpretation, but ECGs marked as positive still needs manual interpretation
Nordin, 2023	⁴⁵³	Prospective cohort study	200 ECGs	Single-lead ECGs were	Inclusion: ≥18 years old with a history of	Manual analysis of	Automatic interpretation	Physician oversight

			from 189 patients	compared to electrophysiologist interpreted 12-lead ECGs	atrial arrhythmia. Exclusion: pacemaker or implantable cardioverter-defibrillator (ICD) treatment, ongoing arrhythmia that was not AF, AFL, or AT, or unwilling or unable to provide informed consent	single-lead device ATA showed a sensitivity of 98.9% (95% CI 94.0–100) and a specificity of 100% (95% CI 96.6–100). Manual analysis for AF had a sensitivity of 100% (95% CI 95.3–100) and a specificity of 97.5% (95% CI 93.0–99.5). Automatic analysis for ATA showed a sensitivity of 93.5% (95% CI	showed poorer accuracy of AF and atrial tachyarrhythmia detection compared to manual interpretation	improved interpretation of single-lead ECGs as compared to automatic interpretation

						86.3–97.6) and a specificity of 92.6% (95% CI 85.9–96.7). Automatic analysis for AF showed a sensitivity of 97.4% (95% CI 91.0–99.7) and a specificity of 86.1% (95% CI 78.6-91.7)		

Additional Evidence Table S32 — Screening strategies for atrial fibrillation

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Mant, 2007 (SAFE)	⁴⁴⁹	RCT	2553 ECGs	Gold standard was 12-lead interpretation by two cardiologists. This was compared to software AF detection (Biolog), GP and nurse interpretation of 12-lead and single-lead ECGs	Randomly selected electronically saved ECGs from the SAFE-trial	Sensitivity of software 83.3 increased with GP overreading to 91.9; specificity of software remained better at 99.1; compared to GP+ software at 91-1	Poor interpretation of ECGs with regards to AF by GPs and nurses. Biases: old study, likely that automatic interpretation has improved, but also that knowledge of AF has improved ECG reading skills	General practitioners did not accurately diagnose AF on ECG. Cardiologist might be needed to interpret correctly ECG data
Mannhart, 2023	⁴⁵⁴	Prospective cohort study	201 patients,	Gold-standard: 12-lead ECG	Inclusion: ≥18 years	The intention-to-diagnose	Key finding: The intention to	Cardiologists' interpretation of

(BASEL Wearable study)			AF present in 31%	interpreted by cardiologist. This was compared to interpretation using AI-algorithm, and cardiologist interpretation of five different types of TCA from wristworn watches		analysis of the AI-algorithm of each device showed the highest sensitivity for the Apple Watch 6 and Samsung Galaxy Watch 3 with 85% (95% CI: 72–94%) and the lowest sensitivity for the Withings Scan Watch with 58% (95% CI: 42–72%). Specificity ranged from 79% (Fitbit	diagnose analysis revealed a vast number of ECGs with noise, and accuracy improved if these were removed. Manual interpretation by cardiologist of SL-ECG was very reliable. Bias: Not an ambulatory setting	single lead ECG showed a higher accuracy compared to interpretation by the AI-algorithms built in by the companies (at the time of the study)

						Sense) to 69% (AliveCor KardiaMobile) Sensitivity increased for the AI-algorithm to 87-95% and specificity to 93-98% if ECGs with noise were removed. Accuracy was best if a cardiologist interpreted the single lead ECGs with sensitivities at 98% and specificity at 98-99		

Healey, 2012 (ASSERT)	⁴⁵⁵	Prospective cohort study	2580	Patients with a recent PPM or ICD had the device reprogrammed to detect atrial tachycardia (HR >190 b.p.m.) and this was interrogated 3 months later	Inclusion: ≥65 y, history of hypertension requiring medical therapy, and first implantation of a St. Jude Medical dual-chamber pacemaker (or ICD in the preceding 8 weeks). Exclusion: history of AF, treatment with VKA	The primary outcome was ischemic stroke or systemic embolism	11 of the 261 patients (4.2%) in whom subclinical atrial tachyarrhythmias had been detected before 3 months had an ischemic stroke or systemic embolism (a rate of 1.69% per year), as compared with 40 of the 2319 in whom subclinical atrial tachyarrhythmias had not been detected (1.7%, a rate of 0.69% per year) (HR=2.49; 95% CI 1.28-4.85;	Subclinical AF was associated with increased risk of stroke 2.5 times

							$P=0.007)$	

Additional Evidence Table S33 — Prediction of incident atrial fibrillation

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Morseth, 2021 (MORGAN)	⁴⁵⁶	Systematic review and meta-analysis of RCT and observational studies	66 951	Observational	Prospective community-based, prevalent AF excluded	Incident AF, PAFs	European ancestry, selection bias in population-based cohort	Highest PAFs BMI, high alcohol consumption and a history MI or stroke from middle age
Magnussen, 2017 (BiomarCaRE)	⁴⁵⁷	Systematic review and meta-analysis of RCT and observational studies	79 793, 24.1-97.6 years	Observational	Prospective community-based, prevalent AF	Incident AF, PAFs, lifetime risk	European ancestry, selection bias in population-based cohort	Population-attributable risk of all risk factors combined was 41.9% in women, 46.0% in men
Staerk, 2018 (Framingham Heart)	⁴⁵⁸	Prospective cohort study	5338 index age 55 years	Observational	Inclusion: Prospective community-based,	Incident AF, lifetime risk	Participants with at least one elevated risk factor were associated with at	Lifetime risk optimal risk factor profile: lifetime risk of

Study)					Exclusion: prevalent AF		least 37.8% lifetime risk of AF. The gradient in lifetime risk across risk factor burden was similar at index ages 65 and 75 years	AF 1:5; risk >1:3 individuals with at least one elevated risk factor
Schnabel, 2015 (Framingham Heart Study)	⁴⁵⁹	Prospective cohort study	9511 participants from the Framingham Heart Study	Trends in incidence, prevalence, and risk factors for AF and its association with stroke and mortality after onset in 9511 participants enrolled in the Framingham	During 50 years of observation (202 417 person-years), 1544 cases of new-onset AF occurred	For AF diagnosed by ECG during routine Framingham examinations, age-adjusted prevalence per 1000 person-years increased (12.6 in	Multivariable-adjusted proportional hazards models revealed a 74% (95% CI 50-86%) decrease in stroke (HR=3.77; 95% CI 1.98-7.20 in 1958-1967 compared with 1998-2007; <i>P</i> trend=0.001) and a 25% (95% CI -3-46%) decrease in mortality (HR 1.34,	Trends of increased incidence and prevalence of AF in the community were probably partly due to enhanced surveillance

				Heart Study between 1958 and 2007		1958-67 to 25.7 in 1998-2007 in men, <i>P</i> trend=0.0007; 8.1-11.8 in women, <i>P</i> trend=0.009)	95% CI 0.97-1.86 in 1958-1967 compared with 1998-2007; <i>P</i> trend=0.003) in 20 years following AF onset	
Ghelani, 2022 (ARIC)	⁴⁶⁰	Prospective cohort study	15 343	Inclusion: patients aged 45 to 64 years in 1987 to 1989 without AF from 4 US communities in the ARIC cohort	The incident rates of AF in the ARIC cohort was 9.6 per 1000 person-years (6.9 in Black participants, 10.5 in White participants, 8.1 in women, and 11.6 in men)	Age-specific IR by time period did not show significant changes over time. In a model adjusted for sex, race, and age group, the rate of AF did not change	Similarly, no evidence of changes over time in AF rates were identified in men and women or White and Black participants separately	Even though incident rates of AF increase as age increases, the analysis provided evidence suggesting that the overall IRs of AF have not changed over time in a multicentre cohort of Black and White

						significantly from 1987 to 1991 compared with 2012 to 2017 (IR ratio, 1.10 [95% CI, 0.88-1.36] comparing 2012-2017 with 1987-1991)		individuals in the United States from 1987 to 2017
Huxley, 2011 (ARIC)	⁴⁶¹	Prospective cohort study	14 598 middle-aged	Cardiovascular risk factors	Population-based (unselected)	Incident AF, PAFs	Age range, US cohort of volunteers, population-based	Age-adjusted incidence rates highest in white men and lowest in black women (7.45 and 3.67 per 1000 person-years, respectively), 56.5% of AF

								cases could be explained by or elevated risk factors, blood pressure was the most important contributor
Rodriguez, 2015 (MESA)	⁴⁶²	Prospective cohort study	6721	Observational	Prospective community-based, prevalent AF excluded	Incident AF	AF incidence significantly lower among Hispanics, NHBs and Chinese compared with NHWs (all $P<0.001$), PAFs differed, AF hospitalizations only	Incidence of hospitalized AF significantly lower in Hispanics, NHBs, and Chinese than in NHWs; hypertension PAFs high in non-whites
GBD, 2019	⁴⁶³	Retrospective registry	N.n	Observational	Mutually exclusive and collectively exhaustive list	359 diseases and injuries	Country-level data, no specific diagnostic evaluation for AF.	Increasing relevance of AF at the population level worldwide,

					of diseases and injuries		AF among the leading 25 Level 3 causes of global DALYs and percentage of total DALYs, Number 16, almost 1-5-fold increase in DALYs in individuals 75 years or older worldwide	in particular in rapidly ageing global population
Roth, 2020	⁴⁶⁴	Retrospective registry	523 million CVD, 59.7 million AF/Atrial flutter	Observational	Prevalent CVD cases	DALYs, AF/Aflutter related mortality, prevalence	8.39 million (95% UI: 6.69 to 10.5 million) AF-related DALYs in 2019 m, 59.7 million AF/Atrial flutter	Most common arrhythmia, substantial impact on public health at a global level, prevalence rates are increasing, more effort is needed to improve prevention and

								health care, aggressive attention to the reduction of risk factors, better treatment of individuals with IHD and heart failure; improved access to medications for thromboembolism prophylaxis
Chung, 2021	465	Retrospective registry	7 998 501 patients in the UK	Observational	Socioeconomic and living status, comorbidities	Incident AF, mortality	Registered patients	Higher deprivation in socioeconomic and living status – higher AF incidence and fatality, elevated risk of hospitalisation for

								cardiovascular or respiratory diseases, considerable disparity in AF burden by socioeconomic deprivation
Williams, 2020	⁴⁶⁶	Retrospective registry	500 684 patients from integrated health care delivery network in Pennsylvania	Observational	No AF at baseline, healthcare delivery network member	Incident AF	Reliance on diagnostic codes	AF incidence rates increased, concurrent increases in AF risk factors & short-term ECG use
Lippi, 2021	⁴⁶⁷	Retrospective registry	3.046 million new cases of AF worldwide	Observational	New AF	New AF	New AF burden increases. Registry data of different origin/quality	AF prevalence & incidence have increased over the last 20 years, will continue to

								increase over the next 30 years, especially in countries with middle socio-demographic index
Bikkel, 2017	⁴⁶⁸	Retrospective registry	GBD data not specified	Observational	AF onset, European data origin, 1990, 2017 data	Age-adjusted incidence, mortality, and mortality-to-incidence ratios (MIRs) to approximate case fatality rate	Mortality rates were higher in wealthier countries, selection bias, incomplete information, not most current information	Sex differences in outcomes with more than twice the mortality-to-incidence ratio in women in Europe
Alonso, 2022 (All of US)	⁴⁶⁹	Retrospective registry	173 099	Observational	Prospective community-based	Prevalent, incident AF	Mean age 52 years, 18-89, non-Hispanic Whites 67%, non-Hispanic	Epidemiology of AF in the All of Us Research Program is

							Blacks, non-Hispanic Asians and Hispanics accounting for 26%, 4% and 3% of participants; 92 318 participants with available EHR data, 3885 (4.2%) AF at the time of study enrolment, 35 483 with medical history data 2084 (5.9%); 4% incidence over 16 months	similar to that reported in smaller studies
Risk factors								
Siland, 2022	⁴⁷⁰	Meta-analysis of observational studies	38 981	Observational	Genetics information, known AF information, European descent	Incident AF	AF status needed to be known-selection bias, Mendelian randomization provides evidence	Genetically determined resting heart rates <65 b.p.m. inverse causal association with

							for causal relationship	incident AF
Wang, 2022 (UK Biobank)	⁴⁷¹	Prospective cohort study	283 657 participants in paid employment or self-employed	Observational	Current and past night shift work, genetics	Incident AF	Employed participants	Current and lifetime night shift exposures associated with increased AF risk, regardless of genetic AF risk
Lu, 2022 (Rotterdam)	⁴⁷²	Prospective cohort study	7367	Observational	Obesity-related risk factor trajectories	Incident AF	European whites, selection bias in population-based cohort	Longitudinal trajectories of weight, BMI, WC, HC, SBP associated with new-onset AF, diastolic blood pressure trajectories in women only
Geurts, 2022 (Rotterdam)	⁴⁷³	Prospective cohort study	12 334	Observational	Genetics information, European	Incident AF	European whites, Mendelian randomization	Uncorrected HRV were significantly

					descent		provides evidence for causality	associated with new-onset AF
Geurts, 2022 (Rotterdam)	⁴⁷⁴	Prospective cohort study	12 840	Observational Subclinical measures of peripheral atherosclerosis	European descent, no baseline AF	Incident AF	European whites	Baseline & longitudinal subclinical measures of peripheral atherosclerosis associated with new-onset AF
Polygenic risk scores								
Roselli, 2018	⁴⁷⁵	Meta-analysis of observational studies	Ca. 500 000 controls, 65 446 AF cases, multi-ethnic	Observational	Genome-wide genetic information on common polymorphisms	Prevalent AF	Novel genetic loci in relation to AF, generalizability across ethnicities	97 loci significantly associated with AF, new loci
Boerschel, 2021 (FINRISK, PREVEND)	⁴⁷⁶	Prospective cohort study	6945	Observational	Genome-wide genetic information on common polymorphisms, no AF	Incident AF	European whites, good discriminatory ability of genetic risk score	Polygenic risk score & NT-proBNP showed comparable predictive ability, incremental

								predictive value over standard clinical variables
Choi, 2020 (UK Biobank)	⁴⁷⁷	Prospective cohort study	1546 AF cases, 41 593 controls	Observational	Subset with genome-wide genotyping and exome sequencing	AF information, focus on <i>TTN</i> (titin gene)	Comparison explanation of variability in phenotype by monogenic/polygenic risk	Monogenic & polygenic factors contribute to AF risk in the general population. the additive effect of many common variants explains a larger proportion of genetic susceptibility
Khera, 2018	⁴⁷⁸	Participant-data pooled analysis	Discovery 17 931 cases; 115 142, validation data sets	Observational	GWAS studies	AF information	6.1% ≥3-fold risk, top 1% =4.63-fold risk, observational cohorts, European ancestry	High genetic risk can be identified in substantial proportion of individuals. Focus screening

								on high risk individuals
Muse, 2018	⁴⁷⁹	Prospective cohort study	An AF event was the first diagnosis of AF by ECG, patch monitor, or long-term Holter monitor	≥40 years with 1 clinical risk factor for AF, presenting with symptoms of AF, or with a first diagnosis of AF, were enrolled for genetic testing and ambulatory cardiac rhythm monitoring with an adhesive patch monitor or a long-term	The AF genetic risk score was determined for each participant based on the weighted contribution of 12 genetic risk loci. Of 904 participants, 85 manifested AF	Participants in the highest quintile of AF GRS were more likely (OR=3.11; 95% CI 1.27-7.58; <i>P</i> =0.01) to have had an AF event than participants in the lowest quintile after adjusting for age, sex, smoking status, BMI,	Prospective assessment of a GRS for AF identified participants with elevated risk of AF beyond established clinical criteria. Accordingly, a genetic risk score for AF could be incorporated into overall risk assessment to better identify patients at the highest risk of developing AF, although further testing in larger populations is	PRS validation for ECG screening

				Holter monitor (mean wear time 10 days 21 hours and 13 days 18 hours, respectively)		hypertension , diabetes mellitus, heart failure, and prior myocardial infarction	needed to confirm these findings	

Evidence Table 32 for Recommendation Table 32 (Sec. 10) — Recommendations for prevention of atrial fibrillation

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Hypertension								
Larstorp, 2019 (LIFE)	480	RCT	8831	BP control in ISH vs. non-ISH	Inclusion: HTN patients with LVH on ECG,1248 ISH, (SBP 160-205mmHg and DBP <90mmHg), 7583 non-ISH Exclusion: History of AF or AF in ECG	Effect of in-treatment SBP reduction in preventing new onset AF is stronger in ISH (HR=0.83; 95% CI 0.73-0.95; P=0.008)	BP target of 140/90mmHg or lower with losartan 50 mg, or atenolol 50 mg, daily and matching placebo of the other agent. Open-label upward titration of Hydrochlorothi azide, CCB or additional	Lowering BP has a greater effect in those with ISH

							other medication	
Chen, 2016 (ACCORD)	481	RCT	3087	Standard BP lowering (SBP <140mmHg) vs. intensive BP lowering (SBP <120mmHg)	Inclusion: T2DM with HbA ₁ C ≥7.5%; ≥40 years with CVD or ≥55 years with high risk of CV events with on treatment SBP 130-180 mmHg. Exclusion: Prevalent AF of PWI, missing ECG, missing data on follow-up	Intensive BP lowering (SBP <120 mm Hg) reduced the rate of incident AF and P-wave indices (HR=0.87; 95% CI 0.77-0.98; <i>P</i> =0.02)	Incidence rates of AF in individuals with T2DM were low compared to other observational studies. Primary outcome was a composite of incident AF and PWI – effect of intensive therapy on the incidence of AF alone did not reach	In patients with T2DM, intensive BP lowering reduces the incidence of the composite outcome of AF and PWI

Soliman, 2020 (SPRINT)	482	RCT	8022	SBP target of <140mmHg (standard treatment arm), and 4678 participants were randomized to <120mmHg (intensive treatment arm)	Inclusion: participants from SPRINT trial; 50 years or older with SBP 130-180mmHg at screening and increased risk of CV events. Exclusion: T2DM, HF, stroke	Intensive BP lowering was associated with a 26% lower risk of developing new AF on biennial ECGs (HR=0.74; 95% CI 0.56-0.98; <i>P</i> =0.037)	AF endpoint only included AF on study ECGs. Could not examine the impact of individual BP medications	Intensive treatment to a target of SBP <120mmHg in patients with hypertension at high risk of cardiovascular disease has the potential to reduce the risk of AF
Heart failure								
Healey, 2005	483	Systematic review and meta analysis of RCTs	11 studies, which included 56 308 patients	ACE or ARB use	Inclusion: human RCT or reviews published since 1980, using the terms "angiotensin-converting	Overall, ACEis and ARBs reduced the RR of AF by 28% (95% CI 15-40%; <i>P</i> <0.002).	Analysis mixed all use of ACEi and ARB. Although data is presented for HF also	ACEi or ARB use reduced the development of incident AF in HFrEF

					enzyme inhibitor,” “angiotensin receptor blockers,” the individual names of all drugs in these classes, and “atrial fibrillation.”	Reduction in AF was similar between the two classes of drugs (ACEi:28%, $P<0.01$; ARB: 29%; $P<0.0002$) and was greatest in patients with heart failure (RR=44%; $P<0.007$)		
Kotecha, 2014	⁵⁵	Systematic review and meta analysis of RCTs	10 RCTs on in HF with 18 254 patients (of	Beta-blockers versus placebo	RCTs in HF that compared beta-blocker use to placebo	Death rates over a follow-up of 1.5 years (SD 1.1) were 16%	Dichotomy as AF or not in most studies based on baseline ECG – therefore	Beta blocker use in patients with HF in SR was associated with a reduction in all-cause mortality. This benefit was not seen

			whom 13 946 were in SR)			(2237 of 13 945) in SR and 21% (633 of 3064) in AF. Beta- blocker therapy reduced all- cause mortality in SR (HR=0.73; 95% CI 0.67-0.80; <i>P</i> <0.001), but not in AF (HR=0.97; 95% CI 0.83-1.14; <i>P</i> =0.73)	biased more to persistent AF. Retrospective analysis of a non-primary group division	in those in AF
Pandey, 2021	⁵⁶	Systemati	75 279	SGLT2i and	31 studies (in	Reduction	Serious risk of	Positive results:

		c review and meta analysis of RCTs		SGLT1/2i (sotagliflozin) on AF prespecified subgroup analyses to compare the effect of SGLT inhibitors on AF events among different patient populations (DM, HF, CKD, and high CV risk), SGLT inhibitor medications (Empagliflozin, dapagliflozin,	28 studies patients had diabetes) adults regardless of prior AF history or other comorbidities, such as DM, HF, CKD, CV disease, or multiple CV risk factors	in the risk of serious AF events in patients who received an SGLT inhibitor (1.1% vs. 1.5%; RR=0.75; 95% CI 0.66- 0.86%). SGLT inhibitors resulted in a 25% (95% CI 14-34%) relative risk reduction in serious AF events and	bias, however: a post-hoc sensitivity analysis of all other trials excluding the largest study (DECLARE- TIMI 58,21 41.4% of weight, RR=0.74; 95% CI 0.60-0.90) yielded consistent results (RR=0.76; 95% CI 0.64- 0.90; <i>P</i> =0.80)	SGLT inhibitors may reduce AF events and likely reduce heart failure hospitalization/cardio vascular death to a similar extent in patients with and without AF

				Canagliflozin, Ertugliflozin, and sotagliflozin), and SGLT inhibitor types		a similar relative reduction in total AF events. Subgroup analyses that separated trials according to the prespecified subgroups, did not result in subgroup effects		
Wang, 2022	⁴⁸⁴	Systematic review and meta analysis of RCTs	52 951	AF: SGLT2i vs. placebo	22 studies; patients with T2D and HF	SGLT2i can significantly reduce the incidence of AF/AFL by	The control groups all included placebo, some of which also	Positive results for SGLT2i; among SGLT2i types, Dapagliflozin was statistically superior

						18% (OR=0.82; 95% CI 0.73-0.93; $P=0.002$), and reduce the incidence of arrhythmia by 14% (OR=0.86; 95% CI 0.79-0.94; $P=0.006$); among them, the incidence of AF/AFL in T2D patients was reduced by 20%	included Glimepiride, Metformin, liraglutide, etc. of 2 RCTs used Ertugliflozin, 8 Canagliflozin, 5 Dapagliflozin, 7 empagliflozin	with incidence of AF reduced by 15%

						(OR=0.80; 95% CI 0.69-0.92; <i>P</i>=0.002); Dapagliflozi n reduced the incidence of AF/AFL by 15% (OR=0.85; 95% CI 0.74-0.98; <i>P</i>=0.03); the incidence of intracardiac thrombosis decreased by 69% (OR=0.31; 95% CI 0.10-0.91; <i>P</i>=0.03)		

Yin, 2022	⁴⁸⁵	Systematic review and meta analysis of RCTs	10 344	AF: SGLT2i vs. placebo	9 studies; patients with HF and with or without type 2DM	SGLT2i reduced the incidence of AF by 37% RR=0.63; 95% CI 0.45-0.87; $P<0.05$] and AF/AFL by 34% (RR=0.66; 95% CI 0.49-0.90; $P<0.05$)	No significant heterogeneity between trials ($P=0.91$); no significant heterogeneity between subgroups according to the type of HF ($P=0.31$) and SGLT2i ($P=0.22$)	Positive results: SGLT2i can reduce the risk of cardiac arrhythmias, particularly the AF
Swedberg, 2012 (EMPHASIS-HF)	¹⁰¹	RCT	1794	Eplerenone	Inclusion: NYHA class II and with LVEF $\leq$ 35%	New onset AFF was significantly reduced by eplerenone: 25 of 911 (2.7%) vs. 40 of 883 (4.5%) in	The risk of cardiovascular (CV) death or hospital admission for worsening heart failure, the primary endpoint, was	MRA was associated with a reduction in incident AF and recurrent AF

						the placebo group (HR=0.58; 95% CI: 0.35-0.96; $P=0.034$). The reduction in the primary endpoint with eplerenone was similar among patients with and without AFF at baseline (HR=0.60; 95% CI 0.46-0.79 vs. HR=0.70;	not significantly different in subjects with and without AFF at baseline (both study groups combined: HR=1.23' 95% CI 0.81-1.86; $P=0.33$)	

						95% CI 0.57-0.85; <i>P</i> =0.41)		
Diabetes mellitus								
Li, 2020	⁴⁸⁶	Systematic review and meta analysis of RCTs	38 335	AF: SGLT2i vs. placebo	16 studies Type 2DM	SGLT2i reduced AF/AFL (RR=0.76; 95% CI 0.65-0.90; <i>P</i> =0.001) and all-cause mortality (RR=0.91; 95% CI 0.83-0.99; <i>P</i> =0.03)	SGLT2i in DM reduce incident AF and all-cause mortality	SGLT2i in DM reduced incident AF
Yin 2022	⁴⁸⁵	Systematic review and meta analysis of RCTs	10 344	AF: SGLT2i vs. placebo	9 studies; patients with HF and with or without type 2DM	SGLT2i reduced incidence AF by 37% (RR=0.63;	No significant heterogeneity between trials (<i>P</i> =0.91); no significant	SGLT2i reduced incident AF

						95% CI 0.45-0.87; <i>P</i> <0.05) and AF/AFL by 34% (RR=0.66; 95% CI 0.49-0.90; <i>P</i> <0.05)	heterogeneity between subgroups according to the type of HF (<i>P</i> =0.31) and SGLT2i (<i>P</i> =0.22)	
Wang, 2022	⁴⁸⁴	Systematic review and meta analysis of RCTs	52 951	AF: SGLT2i vs. placebo	22 studies; patients with T2D and HF	SGLT2i can significantly reduce the incidence of AF/AFL by 18% (OR=0.82; 95% CI 0.73-0.93; <i>P</i> =0.002), and reduce the incidence of arrhythmia	The control groups all included placebo, some of which also included Glimepiride, Metformin, Liraglutide, etc. of 2 RCTs used Ertugliflozin, 8 Canagliflozin, 5	Positive results for SGLT2i; among SGLT2i types, Dapagliflozin was statistically superior with incidence of AF reduced by 15%

						by 14% (OR=0.86; 95% CI 0.79-0.94; <i>P</i>=0.006); among them, the incidence of AF/AFL in T2D patients was reduced by 20% (OR=0.80; 95% CI 0.69-0.92; <i>P</i>=0.002); Dapagliflozi n reduced the incidence of AF/AFL by	Dapagliflozin, 7 empagliflozin	

						15% (OR=0.85; 95% CI 0.74-0.98; <i>P</i> =0.03); the incidence of intracardiac thrombosis decreased by 69% (OR=0.31; 95% CI 0.10-0.91; <i>P</i> =0.03)		
Chang, 2014	⁴⁸⁷	Retrospec tive registry	645 710 patients with DM	Intervention: Metformin Comparator: no Metformin	Inclusion: at least one hospitalization with DM; or ≥2 outpatient visits due to DM in the same year; and the patient had not been	After adjusting for co- morbidities and medications , Metformin independent ly protected	Based on coding data	Metformin reduced incident AF in DM

					hospitalized or treated as an outpatient due to DM before 1999	the diabetic patients from new-onset AF (HR=0.81; 95% CI 0.76-0.86; <i>P</i> <0.001)		
Obesity								
Tedrow, 2010 (Women's Health Study)	488	RCT	34 309	Intervention: low dose aspirin and vitamin E Comparator: placebo	Inclusion: female health professionals without prior CVD. Exclusion: history of CVD, AF, missing BMI at baseline	834 AF events were confirmed. BMI was linearly associated with AF risk, with a 4.7% (95% CI 3.4-6.1; <i>P</i> <0.001) increase in risk with each	AF cases were self-reported and ECG screening not performed. Asymptomatic AF could be missed, AF onset could be hard to determined. Confounders self-reported and could	BMI is linearly associated with risk of incident AF in this large cohort of women, and the association is stronger among younger women. With updated measured of BMI, significant short-term elevations in AF risk persisted in both the overweight and obese ranges after

						kilogram per square meter. When updated measures of BMI were used to estimate dynamic risk, overweight (HR=1.22; 95% CI 1.02-1.45; $P=0.03$), and obesity (HR=1.65; 95% CI: 1.36-2.00; $P<0.001$) were associated	result in misclassification. Health, middle aged health professional women primarily Caucasian Not able to include echo measure in multivariable analysis as not systematically measured	controlling for these potential mediators. An estimated 18.3% of the incident AF in this cohort was attributable directly to short term elevations in BMI above the normal range. Women who remained obese had a trend toward a higher risk of AF after 60 months, whereas the women who developed new obesity had a significantly higher adjusted risk of incident AF after year 5 (HR=1.41; 95% CI 1.05-1.90; $P=0.02$) compared with those

						with adjusted short-term increases in AF risk. Participants becoming obese during the first 60 months had a 41% adjusted increase in risk of the development of AF ($P=0.02$) compared with those maintaining BMI $<30 \text{ kg/m}^2$.		who maintained a BMI $<30 \text{ kg/m}^2$ over the same period. In contrast, women who were obese at baseline, but then attained a BMI <30 by year 5, no longer had a significantly elevated risk of subsequent AF in adjusted analyses (HR 1.0; 95% CI 0.58-1.79; $P=0.96$) compared with those who maintained a BMI $<30 \text{ kg/m}^2$ over the same period

						The prevalence of overweight and obesity increased over time. The adjusted proportion of incident AF attributable to short-term elevations in BMI was substantial (18.3%)		
Chokesuwattanaskul, 2020	⁴⁸⁹	Systematic review and meta analysis	7681 patients undergoing	Incidence and risk factors of AF in patients after bariatric	Inclusion: studies that evaluated the incidence and	Overall, the pooled estimated incidence of	Observational studies. Variable detection of AF	Significant beneficial association between bariatric surgery and AF, and was

		of RCT and observational studies	bariatric surgery were enrolled	surgery	risk of AF in patients after bariatric surgery	AF following bariatric surgery was 5.3% (95% CI 1.9-13.8) at a median follow-up time of 7.9 years (IQR= 4.1-15.0 years). Compared to controls, the pooled OR=0.42 (95% CI 0.22-0.83) of AF among patients undergoing bariatric surgery at a		associated with a 0.42-fold decreased risk of AF

						median follow-up time of 7.9 years (IQR=7.2-19.0 years)		
Srivatsa, 2020	490	Prospective cohort study	1581 BAS cases and 3162 controls (undergoing other surgeries)	Bariatric surgery vs. other abdominal surgeries	Inclusion: All obese individuals. Exclusion: History of AF	Primary outcome is incident AF. Compared to controls, BAS cases had a significantly lower risk of new-onset AF (HR=0.71; 95% CI 0.54-0.93) or HF (HR=0.74; 95% CI	Observational; AF determined by coding data	Bariatric surgery and weight loss was associated with reduced risk of incident AF

						0.60-0.91)		
Lynch, 2019	⁴⁹¹	Prospective cohort study	3572 patients undergoing bariatric surgery	Bariatric surgery vs. obese controls. Primary outcome is incident AF	Exclusion: <18 years; history of AF	The incidence of AF was lower among surgical patients (0.8% vs. 2.9%; <i>P</i> =0.001)	Single centre and observational study. Propensity score matched 1:1 to a control population of obese patients with outpatient appointments (n=45 750)	Bariatric surgery to reduce weight was associated with a reduction in incident AF
Chan, 2021	¹⁰⁴	Retrospective cohort study	10 237	Incident AF	Inclusion: >20years with T2DM. Exclusion: using antidiabetic drugs, prevalent AF before T2DM diagnosis	Compared with those with a baseline BMI of <23.0 kg/m ² , AF risk significantly increased in patients	Retrospective observational so not be able to demonstrate causality. Missing important parameters including physical	A baseline BMI of ≥ 27.5 kg/m ² and a ≥5% BW loss following SGLT2i treatment are independently associated with a significantly lower risk of new-onset AF in patients with T2DM

						with baseline BMI of $\geq 27.5 \text{ kg/m}^2$ (HR=1.86; 95% CI 1.03-3.37) for BMI of 27.5–92.9 kg/m^2 (HR 2.23; 95% CI 1.24-3.98) for BMI of $\geq 30.0 \text{ kg/m}^2$; $P=0.015$). Compared with those without BW loss following SGLT2i treatment,	activity, smoking, dietary behaviour. Potentially missing confounders so unable to adjust for these; did not account for changes in medical status; comprised of Asian population only	treated with SGLT2i. The benefit of $\geq 5\%$ BW loss following SGLT2i treatment in reduction of AF risk persisted across most T2DM subgroups, irrespective of underlying comorbidities, baseline BMI, or DM status

						AF risk significantly decreased at a BW loss of $\geq$ 5.0%, (HR=0.39; 95% CI 0.22-0.68; $P=0.001$). Use of diuretics, old age, high-dose SGLT2i, higher estimated glomerular filtration rate, and baseline BMI were independent		

						factors associated with a BW loss of 5.0% following SGLT2i initiation		
Hoskuldsdottir, 2021	492	Retrospective registry	5321 undergoing bariatric surgery and 5321 matched controls	Hospitalisation for HF and/or AF	Inclusion: T2DM and obesity	73% lower risk for HF (HR=0.27; 95% CI 0.19-0.38), 41% for AF (HR=0.59; 95% CI 0.44-0.78), and 77% for concomitant AF and HF (HR=0.23; 95% CI, 0.12-0.46) in the	Registry data Endpoints determined by coding	In T2DM patients, bariatric surgery reduces incident AF

						surgically treated group		
Jamaly, 2016	⁴⁹³	Retrospective registry	4021 obese patients in SR. 2000 underwent bariatric surgery	First episode of AF	Inclusion: obesity; sinus rhythm	The risk of developing AF was 29% lower in the surgery group versus the control group (HR=0.71; 95% CI 0.60-0.83; $P<0.001$)	Registry AF detected by coding	In obese individuals, bariatric surgery reduced the risk of developing AF
Physical activity								
Mishima, 2021	⁴⁹⁴	Systematic review and meta analysis of RCT	1 464 539	None	Systematic review of prospective cohort studies reporting the	Individuals achieving guideline-recommended level of	Methodological limitations of self-reported physical Activity.	PA at guideline-recommended levels and above are associated with a significantly lower AF

		and observatio nal studies			risk of AF associated with a specific PA volume	PA had a significantly lower risk of AF (HR=0.94; 95% CI 0.90-0.97; <i>P</i> =0.001). Dose- response analysis showed that PA levels up to 1900 MET- minutes per week were associated with a lower risk of AF	Methods regarding physical activity and AF ascertainment across studies were variable. Some questionnaires have shown limited correlation with accelerometer data. Most studies use medical records and annual electrocardiogr ams to diagnose AF	risk
Elliot, 2020 (UK Biobank)	⁴⁹⁵	Prospectiv e cohort	402 406	None	The UK Biobank cohort	Incident AF risk was	Arrhythmia episodes were	The risk of AF and ventricular

		study			includes individuals, aged 40–69 years, recruited between April 2007 and December 2010	lower amongst physically active participants, with a more pronounced reduction amongst female participants, 1500 vs. 0 MET-min/wk: (HR=0.85, 95% CI 0.74-0.98); than males for 1500 vs. 0 MET-min/wk: (HR= 0.90; 95% CI	diagnosed through hospital admissions and death reports; physical activity was assessed by self-report and at baseline. Cardiovascular risk factors and prevalent heart disease, were only assessed at baseline; 'healthy volunteer bias' of the UK biobank	arrhythmias is lower amongst physically active individuals

						0.82-1.0)		
Jin, 2019	⁴⁹⁶	Prospective cohort study	501 690	None	Inclusion: >18 years receiving the Korean Screening Program in 2009	The subjects who met the recommended physical activity level (500-1000 MET minutes/week) had a 12% decreased AF risk (HR=0.88; 95% CI 0.80-0.97), but not the insufficiently 1-500 MET-minutes/week; (HR=0.94;	Physical activity was assessed by self-report and at baseline. Generalization of these results to western countries	Meeting the recommended key target range of physical activity was associated with the maximum benefit for AF risk reduction in the general population

						95% CI 0.86-1.03) and highly active subjects (≥1000 MET- minutes/we ek; (HR=0.93; 95% CI 0.85-1.03)		
Khurshid, 2021 (UK Biobank)	⁴⁹⁷	Prospectiv e cohort study	93 669	None	The UK Biobank cohort includes individuals, aged 40– 69 years, recruited between April 2007 and December 2010	Guideline- adherent activity was associated with lower risks of AF (HR=0.82; 95% CI 0.75-0.89; incidence 3.5/1000	Arrhythmia episodes were diagnosed through hospital admissions and death reports; physical activity was assessed by	Greater accelerometer- derived physical activity is associated with lower risks of AF and stroke

						person-years, 95% CI 3.3-3.8 vs. 6.5/1000 person-years, 95% CI 6.1-6.8) and stroke (HR=0.76; 95% CI 0.64-0.90; incidence 1.0/1000 person-years, 95% CI 0.9-1.1 vs. 1.8/1000 person-years, 95% CI 1.6-2.0)	self-report and at baseline. CV risk factors and prevalent heart disease, were only assessed at baseline; 'healthy volunteer bias' of the UK biobank	
Tikkanen, 2018 (UK Biobank)	⁴⁹⁸	Prospective cohort study	502 635	None	The UK Biobank cohort includes	Grip strength, physical	Arrhythmia episodes were diagnosed	Fitness and physical activity demonstrated inverse associations

					individuals, aged 40–69 years, recruited between April 2007 and December 2010	activity, and cardiorespiratory fitness showed inverse associations with AF: HR=0.75; 95% CI 0.73-0.76 vs. HR=0.93; 95% CI 0.91-0.95; and HR=0.60, 95% CI 0.56-0.65, per SD change, respectively). Higher grip	through hospital admissions and death reports; physical activity was assessed by self-report and at baseline. CV risk factors and prevalent heart disease, were only assessed at baseline; 'healthy volunteer bias' of the UK biobank	with incident cardiovascular disease, also in individuals with elevated genetic risk for these diseases

						strength and cardiorespiratory fitness were associated with lower risk of AF in each genetic risk score group ($P<0.001$ in each genetic risk category). In particular, high levels of cardiorespiratory fitness were associated with lower		

						risk for AF (HR=0.40; 95% CI 0.30-0.55), among individuals at high genetic risk for these diseases		
Morseth, 2016 (Tromsø Study)	⁴⁹⁹	Prospective cohort study	20 484	None	Repeated surveys with high attendance rates conducted within the same community	Moderately active individuals had a 19% lower risk of any AF (HR=0.81; 95% CI 0.68–0.97), whereas highly active had similar risk of AF.	Methodological limitations of self-reported physical activity. Limited with regard to ethnic diversity	Moderate physical activity was associated with a reduced risk of AF, whereas higher activity levels attenuated the benefits of moderate activity. Low RHR was a risk factor for AF

						Vigorously active individuals showed a non-significantly higher risk of AF (HR=1.37; 95% CI 0.77-2.43). Risk of AF increased with decreasing resting heart rate (RHR) (HR=0.92; 95% CI 0.86–0.98 for each 10 b.p.m.		

						increase in RHR), and RHR, 50 b.p.m. was a risk factor for AF ($P<0.05$)		
High-endurance training								
Newman, 2021	⁵⁰⁰	Systematic review and meta analysis of RCT and observational studies	70 478	6816 athletes, 63 662 controls	Studies were included if they reported the number of AF cases in athletes with non-athletes, case-control or cohort study design. Studies were excluded in the next evaluation step if they did not include a	The risk of developing AF was significantly higher in athletes than in non-athlete controls (OR=2.46; 95% CI 1.73-3.51; $P<0.001$). Mixed sport conferring a	Residual confounding; heterogeneity; publication bias; reduce number of females	Athletes have a significantly greater likelihood of developing AF compared with non-athlete controls

					control group	greater risk of AF than endurance sport. Younger (<55 years) athletes were significantly more likely to develop AF compared with older (≥55 years) athletes ($P<0.001$)		
Andersen, 2013	⁵⁰¹	Retrospective cohort study	52 755	N/A	Inclusion: completed a 90 km cross-country skiing event	HR for AF, highest number of completed races vs. 1 completed	Retrospective data. primary outcome was hospitalization for any arrhythmia.	A faster finishing time and a high number of completed races were associated with higher risk of arrhythmias

						race, 1.29 (95% CI 1.04-1.61); HR for fastest relative finishing time vs. >240% of winning time, 1.20 (95% CI 0.93-1.55)	Reduce number of females	
Baldesberger, 2008	⁵⁰²	Retrospective cohort study	196	134 cases and 62 controls	Inclusion: males who never performed professional endurance training	Paroxysmal or persistent AF or flutter was reported more often in athletes ($P= 0.028$). Sinus node disease	Small sample; no females	AF and sinus node dysfunction occurred significantly more often in athletes compared with age-matched controls

						(10 vs. 2%), atrial flutter (6 vs. 0%)		
Elosua, 2006	⁵⁰³	Retrospec tive cohort study	60	51 male sports competitors vs. 109 controls (not engaged in sports)	Inclusion: consecutive patients who attended an outpatient clinic	Practice of sport was associated with a higher prevalence of AF (OR=3.13; 95% CI 1.39-7.05)	Selection bias; small sample; no females; only symptomatic AF	Sport was associated with a higher prevalence of AF
Molina, 2008	⁵⁰⁴	Retrospec tive cohort study	557	252 marathon runners and 305 sedentary men	Inclusion: consecutive patients who attended an outpatient clinic	Endurance sport practice was associated with a higher risk of incident LAF in the multivariate	Selection bias; small sample; no females; only symptomatic AF	Long-term endurance sport practice is associated with a higher risk of symptomatic LAF in men

						age- and blood pressure-adjusted Cox regression models (HR=8.80; 95% CI 1.26-61.29). In the group of marathon runners, left atrial inferosuperior diameter and left atrial volume were both associated with a higher risk		

						of incident LAF		
Alcohol intake								
Gallagher, 2017	⁵⁰⁵	Systematic review and meta analysis of RCT and observational studies	249 496	Alcohol intake	Inclusion: prospective design; reported at least three categories of alcohol intake; published in English; included only participants who were free of AF or AFL at baseline; reported AF or a combination of AF/atrial flutter as an outcome measure.	Incident AF	High levels of alcohol intake were associated with an increased incident AF risk (HR=1.34; 95% CI 1.20-1.49; <i>P</i> =0.001). Moderate levels of alcohol intake were associated with a heightened AF risk in males (HR=1.26;	Dose dependent alcohol consumption was associated with incident AF risk. At moderate levels of consumption, a greater risk was associated with AF in men than women

					Exclusion: retrospective or case control design; described less than three levels of alcohol intake which would not allow ascertainment of a dose response; reported alcohol intake in a dichotomous fashion, i.e. yes or no response or alcohol abusers compared to non-abusers		95% CI 1.04- 1.54; $P=0.02$) but not females (HR=1.03; 95% CI 0.86- 1.25; $P=0.74$). Low alcohol intake, of up to 1 standard drink (SD) per day, was not associated with AF development (HR=0.95; 95% CI 0.85- 1.06; $P=0.37$)	
Csengeri, 2021	⁵⁰⁶	Systemati	107 845	Follow up	Community-	Incident AF	A positive	Even modest habitual

(MORGAN/Bio marCaRE)		c review and meta analysis of RCT and observatio nal studies		13.9 years Information on AF status and various risk factors including alcohol use (harmonized variable)	based (MORGAM/Bio marCaRE), 5 European cohorts, without AF at baseline		association between alcohol consumption and incident AF across different types of alcoholic beverages and drinking patterns, evident even in individuals with low alcohol consumption. Cardiac biomarkers or occurrence of HF did not fully explain the association	alcohol intake of 1.2 drinks/day was associated with an increased risk of AF
Tu, 2021 (UK Biobank)	⁵⁰⁷	Prospectiv e cohort	403 281	Follow up 11.4 years.	UK Biobank Past drinkers	Incident AF	A J-shaped association of	Low levels of alcohol consumption (<7 UK

		study		Incident AF events were assessed through hospitalization and death records. Total and beverage-specific alcohol consumption was calculated as UK standard drinks (8 g alcohol) per week	and those with a history of AF were excluded		total alcohol consumption was observed, with lowest risk of AF with fewer than 7 drinks/week. Beverage-specific analyses demonstrated harmful associations of beer/cider consumption with any consumption. In contrast, consumption of red wine, white wine, and spirits up to 10, 8, and 3	standard drinks were associated with lowest AF risk. Low consumption of red and white wine and very low consumption of spirits may not be associated with increased AF risk, whereas any consumption of beer/cider may be associated with harm

							drinks/week, respectively, was not associated with increased risk	
Leea, 2023	508	Retrospective registry	19 425	Comparing sustained heavy drinking, reduced drinking, and abstinence	Inclusion: heavy drinkers defined as with a high-risk level of alcohol consumption according to the WHO definition (>60 g/day for men and >40 g/day for women)	Incident AF	In reference to sustained heavy drinking group: abstinence group had a lower incidence of AF (treatment weighted HR 0.38, 95% CI 0.17-0.85); no difference in incident AF with reduced drinking (HR 0.94, 0.81-	Abstinence from alcohol in previous heavy drinkers can lower the risk of incident AF

							1.10)	

Additional Evidence Table S34 — Hypertension

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Okin, 2015 (LIFE)	⁵⁰⁹	RCT	8831	SBP levels	Inclusion: HTN patients with ECG LVH, without AF by history or baseline ECG. Exclusion: AF by history or AF by ECG	Patients with new-onset AF had slightly higher mean baseline SBP 177±14 mmHg. In-treatment SBP of ≤130mmHg – decreased risk of incident AF, independent of standard AF risk factors (HR=0.60; 95% CI 0.45-0.82; P=0.001)	Possible sources of confounding because of differences between the SBP groups both at baseline and during the trial	Compared with in-treatment SBP ≥142mmHg, in-treatment SBP ≤130mmHg was associated with a 40% lower risk (95% CI 18-55%) and in-treatment SBP of 131-141mmHg with a 24% lower risk (95% CI 7-

								38%) of new AF
Wachtell, 2005 (LIFE)	⁵¹⁰	RCT	8851	Losartan- or atenolol	Inclusion: previously treated or untreated hypertension and ECG signs of LVH with no prior AF. Exclusion: AF by history or by ECG	New onset AF: randomization to losartan reduced new-onset AF in multivariate analysis: (HR=0.67; 95% CI 0.54-0.82; $P<0.001$)	Bias: secondary analysis; Caucasian population; incident AF detected by annual ECG	33% reduced rate of new-onset AF with losartan compared to atenolol in patients with similar BP
Schmieder, 2008 (VALUE)	⁵¹¹	RCT	13 760	Valsartan or Amlodipine	Inclusion: treated or untreated HTN, aged >50 years and a least one predefined CV risk factor. Exclusion: prior AF	New-onset AF: Valsartan 3.67% vs. Amlodipine 4.34% (HR=0.84; 95% CI 0.71-0.99; $P=0.046$) Incidence of persistent AF: Valsartan 1.35% vs. Amlodipine	AF was a prespecified secondary endpoint of the study Study was not powered to detect incident AF	RAS blockers has the potential to reduce the incidence of new-onset AF

						1.97% (HR=0.68; 95% CI 0.53-0.89; <i>P</i> =0.005)		
Dewland, 2017 (ALLHAT)	⁵¹²	RCT	14 837	Lisinopril compared with Chlorthalidone	Inclusion: hypertensive individuals aged ≥55 years with at least one other CV risk factor Exclusion: history of HF, severe systolic dysfunction	Reduction in incident AF/AFL compared with Chlorthalidone: Lisinopril (HR=1.04; 95% CI 0.94-1.15; <i>P</i> =0.46); Amlodipine (HR=0.93, 95% CI 0.84-1.03; <i>P</i> =0.16)	AF was not primary endpoint, adjudicated ALLHAT end points, diagnosis using administrative database coding	In individuals with HTN, compared with chlorthalidone, treatment with lisinopril is not associated with a meaningful reduction in incident AF
Schaer, 2010	⁵¹³	Retrospective registry	4661 with AF and 18 642 matched control participants from 682 993 treated for HTN	ACEi, ARB, beta-blockers, Calcium channel blockers	Age 20-79 years in the study population with a recorded first diagnosis of AF between January 1998 and the spring	Current exclusive long-term therapy with ACE inhibitors (OR=0.75; 95% CI 0.65-0.87), ARBs (OR=0.71; 95% CI, 0.57-0.89), or beta-blockers (OR=0.78; 95% CI 0.67-0.92)	BP changes over time could not be assessed. Observation study so risk for bias by indication cannot be	Therapy with ACE inhibitors, ARBs, or beta-blockers reduces the risk for AF compared with calcium-channel

					of 2008. Censoring events were death, end of the study period (spring 2008), or departure from the GPRD	was associated with a lower risk for AF than current exclusive therapy with calcium- channel blockers	fully excluded	blocker therapy in hypertensive patients

Additional Evidence Table S35 — Heart failure

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Liu, 2022	⁵¹⁴	Systematic review and meta-analysis of RCTs	15 512 patients (7750 randomized to sacubitril/valsartan and 7762 to control)	The impact of sacubitril/valsartan on AF occurrence in patients with HF vs. ACEi/ARB/placebo	Inclusion: RCT; comparing sacubitril/valsartan with ACEi/ARB/placebo; enrolling patients with HF; reporting data on AF occurrence during follow-up. Exclusion: articles related to the same trial; observational studies, case reports, abstracts, and reviews	There was no significant difference in the prevention of AF occurrence between the Sacubitril/Valsartan group and the control group (enalapril or Valsartan) in patients with HF (RR=1.07; 95% CI 0.95-1.19)	Sacubitril/valsartan was similar to either enalapril or valsartan in preventing the occurrence of AF in patients with HF. Bias: AF was not a pre-specified endpoint in all included trials; high risk of bias as drug studies sponsored by manufacturing	Sacubitril/valsartan was similar to either ACEi or ARB in preventing the occurrence of AF for HF

							companies have more favourable efficacy results and conclusions than studies sponsored by other sources	
Butt, 2022 (DAPA-HF)	⁵¹⁵	RCT	4744	Dapagliflozin	Inclusions: ≥18 years; HF for at least 2 months; NYHA class II–IV; LVEF≤40% optimally treated with pharmacological and device therapy; NT-proBNP ≥600 pg/mL (≥400 pg/mL if hospitalized for HF within the	Compared with placebo, Dapagliflozin reduced the risk of worsening HF or cardiovascular death to a similar extent in patients with and without any AF (HR=0.75; 95% CI 0.62-0.92; and HR=0.74; 95%	Consistent benefits were observed for the components of the primary outcome, all-cause mortality, and improvement of Kansas City Cardiomyopathy Questionnaire total symptom score. However,	Dapagliflozin did not reduce incident AF

					previous 12months); ≥ 900 pg/mL if AF on the ECG at enrolment, irrespective of history of HF hospitalization. Exclusions: Symptoms of hypotension or systolic blood pressure < 95 mmHg; eGFR < 30 mL/min/1.73 m²; type 1 diabetes	CI 0.62-0.88; respectively; $P=0.88$). Among patients without AF at baseline, Dapagliflozin did not significantly reduce the risk of new-onset AF compared with placebo (HR=0.86; 95% CI 0.60-1.22)	patients with new-onset AF had a 5 to 6-fold higher risk of adverse outcomes when compared to those without incident AF	
Hess, 2013	⁵¹⁶	Systematic review and meta-analysis of RCT and	3529 patients	CRT	Incidence of new-onset AF, burden of recurrent paroxysmal AF, or the rate of conversion of	Although ten studies suggest that CRT favourably impacts AF, one secondary	CRT is associated with conversion of persistent or permanent AF to sinus rhythm.	Impact of CRT on incident AF is not clear

		observational studies			persistent or permanent AF to normal sinus rhythm after initiation of CRT in adults (aged ≥ 18 years) were included in the analysis	analysis of a clinical trial showed no effect of CRT on new-onset AF. In a meta-analysis of three studies examining the effect of CRT on persistent or permanent AF, the combined rate of conversion from persistent or permanent AF to sinus rhythm was 0.107 (95% CI 0.07-0.16)	Bias: most of the included studies were observational and thus were unable to establish a causal relationship between CRT placement and a reduction in AF. Most of the included studies also had small sample sizes; publication bias	

Additional Evidence Table S36 — Diabetes mellitus

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Li, 2020	⁴⁸⁶	Systematic review and meta-analysis of RCTs	38 335	AF: SGLT2i vs. placebo	16 studies Type 2DM	SGLT2i reduced AF/AFL (RR=0.76; 95% CI 0.65-0.90; <i>P</i> =0.001) and all-cause mortality (RR=0.91; 95% CI 0.83-0.99; <i>P</i> =0.03)	SGLT2i in DM reduce incident AF and all-cause mortality	SGLT2i in DM reduce incident AF
Wang, 2022	⁴⁸⁴	Systematic review and meta-analysis of RCTs	52 951	AF: SGLT2i vs. placebo	22 studies; patients with T2D and HF	SGLT2i reduce incident AF/AFL by 18% (OR=0.82;	The control groups all included placebo, some of which also included Glimepiride,	SGLT2i, particularly Dapagliflozin, significantly reduced incident AF in

						95% CI 0.73-0.93; $P=0.002$). Dapagliflozin reduced the incidence of AF/AFL by 15% (OR=0.85; 95% CI 0.74-0.98; $P=0.03$)	Metformin, Liraglutide, etc. of 2 RCTs used Ertugliflozin, 8 Canagliflozin, 5 Dapagliflozin, 7 empagliflozin	DM
Yin, 2022	485	Systematic review and meta-analysis of RCTs	10 344	AF: SGLT2i vs. placebo	9 studies; patients with HF and with or without type 2DM	SGLT2i reduced incidence AF by 37% (RR=0.63; 95% CI 0.45-0.87; $P<0.05$) and AF/AFL by 34% (RR=0.66; 95% CI 0.49-0.90; $P<0.05$)	No significant heterogeneity between trials ($P=0.91$); no significant heterogeneity between subgroups according to the type of HF ($P=0.31$) and SGLT2i ($P=0.22$)	SGLT2i reduced incident AF

Zelniker, 2020 (DECLARE-TIMI 58)	⁵¹⁷	RCT	17 160	Dapagliflozin on the first and total number of AF/AFL events	Type 2DM and either multiple risk factors for atherosclerotic cardiovascular disease (n=10 186) or known atherosclerotic cardiovascular disease (n=6974); patients with (n=1116) and without prevalent AF/AFL	Dapagliflozin reduced the risk of AF/AFL events by 19% (264 versus 325 events; 7.8 versus 9.6 events per 1000 patient-years; HR=0.81; 95% CI 0.68-0.95; <i>P</i> =0.009)	Dapagliflozin reduced incident AF and AFL. The reduction in AF/AFL events was consistent regardless of presence or absence of a history of AF/AFL at baseline (previous AF/AFL: HR=0.79; 95% CI 0.58-1.09; no AF/AFL: HR=0.81; 95% CI 0.67-0.98; <i>P</i> =0.89)	Dapagliflozin reduced incident AF and AFL
Chang, 2014	⁴⁸⁷	Retrospective registry	645 710 patients with	Intervention: Metformin Comparator: no Metformin	Inclusion: at least one hospitalization with DM; or	After adjusting for co-morbidities and	Based on coding data	Metformin reduced incident AF in DM

			DM		≥2 outpatient visits due to DM in the same year; and the patient had not been hospitalized or treated as an outpatient due to DM before 1999	medications, Metformin independently protected the diabetic patients from new-onset AF (HR=0.81; 95% CI 0.76-0.86; <i>P</i> <0.001)		
Tseng, 2021	⁵¹⁸	Retrospective registry	From an unmatched cohort of 173 398 ever users of Metformin and 21 666 never users and in a	Intervention: Metformin. Control: never used Metformin	DM	A total of 303 ever users and 86 never users in the unmatched cohort and 56 ever users and 86 never users in the matched cohort	Propensity matched;insurance registry	Metformin reduced incident AF in DM

			propensity score-matched cohort of 21 662 pairs of ever and never users			developed hospitalization for AF during follow-up. Ever vs. never users (HR=0.41; 95% CI 0.32-0.52) in the unmatched cohort and HR=0.62 (0.44–0.86) in the matched cohort. HR for the tertiles of cumulative duration of Metformin therapy vs. never users showed a dose-		

						response effect. The findings were consistent in sensitivity analyses		
Suzuki, 2022	⁵¹⁹	Retrospective registry	25 315	Comparison of cardiovascular outcomes in patients on SGLT2i	Patients with diabetes mellitus (DM) newly taking SGLT2 inhibitors (empagliflozin 5302, Dapagliflozin 4681, Canagliflozin): 4411, other SGLT2 inhibitors: 10 921) between January 2005	No significant difference on AF using the various SGLT2i	No significant difference on AF using the various SGLT2i	No significant difference on AF using the various SGLT2i

					and April 2021			
Chan, 2022	⁵²⁰	Retrospective registry	344 893, 44 370, and 393 100 diabetic patients without pre-existing AF treated with SGLT2i, GLP1-RA, and DPP4i	Comparison: SGLT2i, GLP-1RA, DPP4i regarding new-onset AF	344 893, 44 370, and 393 100 diabetic patients without pre-existing AF treated with SGLT2i, GLP1-RA, and DPP4i prescription for GLP-1RA, SGLT2i, or DPP4i after May 1, 2016; no simultaneous prescription	SGLT2i treatment was associated with lower risk of new-onset AF in participants compared with either DPP4i (HR=0.90; 95% CI 0.84-0.96; <i>P</i> =0.003) or GLP-1RA (HR=0.74; 95% CI 0.63-0.88; <i>P</i> =0.001) treatment after	SGLT2i reduced the risk of incident AF	SGLT2i reduced the risk of incident AF

						propensity score matching Dapagliflozin was specifically associated with a lower risk of new- onset AF compared with DPP4i ($P=0.02$)		

Additional Evidence Table S37 — Obesity

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Pathak, 2015 (LECACY)	53	Prospective cohort study	1415 consecutive patients with AF	355 were offered weight management Weight loss was categorized as group 1 ($\geq 10\%$), group 2 (3% to 9%), and group 3 ($<3\%$)	Inclusion: BMI ≥ 27 kg/m ² . Exclusion: permanent AF, history of MI or cardiac surgery in the previous 12 months, significant valvulopathy or ventricular dysfunction, active malignancy, autoimmune or systemic inflammatory diseases, severe	Weight loss and weight fluctuation were independent predictors of outcomes ($P<0.001$ for both). Weight loss $\geq 10\%$ resulted in a 6-fold (95% CI 3.4-10.3; $P<0.001$) greater probability of arrhythmia-free survival compared with	Sustained weight loss resulted in dose dependent reduction in AF burden and maintenance of sinus rhythm. Single centre, AF assessment on Holter, observational	Reduction in BMI was associated with a lower rate in AF burden

					renal or hepatic failure, and <24 months of follow-up	the other 2 groups		
Middeldorp, 2018 (REVERSE-AF)	⁵⁴	Prospective cohort study	1415 consecutive patients with AF	Change in AF type was determined by clinical review and 7-day Holter yearly. AF type was categorized as per the Heart Rhythm Society consensus. Weight loss was categorized as: Group 1 (<3%), Group 2 (3-9%), and Group 3 (≥10%)	Inclusion: patients with BMI ≥27 kg/m ² . Exclusion: permanent AF, history of myocardial infarction or cardiac surgery in the previous 12 months, significant valvulopathy or ventricular dysfunction, active malignancy, autoimmune or systemic	In Group 1, 41% progressed from paroxysmal to persistent and 26% from persistent to paroxysmal or no AF. In Group 2, 32% progressed from paroxysmal to persistent and 49% reversed from persistent to paroxysmal or no AF. In Group 3, 3% progressed to persistent and	Patients with >10% weight loss have greater reversal of AF type from persistent to paroxysmal or no AF. Single centre, AF assessment on Holter, observational	This study demonstrates the dynamic relationship between weight/risk factors and AF. Weight-loss management and RFM was associated with reversing the type and natural progression of AF

					inflammatory diseases, severe renal or hepatic failure, and <24 months of follow-up	88% reversed from persistent to paroxysmal or no AF ($P<0.001$). Increased weight loss was significantly associated with greater AF freedom: 39% in Group 1, 67% in Group 2, and 116 86% in Group 3 ($P\leq 0.001$)		
Di Benedetto, 2021 (EPIC-Norfolk)	¹⁰³	Prospective cohort study	21 499	Incident AF	Inclusion: 39-79 years without prior history of CVD, cancer, stroke, MI, and prevalent AF. Exclusion:	1195 (12.3%) men and 960 (8.1%) women with incident AF during average follow-up of 17.1 years.	Observational so could not eliminate reverse causality. Potential measurement	The combined impact of 3 health behaviours, although modest and potentially

					participants with incomplete data on smoking, alcohol, or BMI	Healthy behaviour score including non-smoking, no or moderate alcohol consumption and being not overweight or obese, with a weighting of overweight and obesity due to the strong association BMI>27.5 kg/m² (HR=1.58; 95% CI 1.13-1.42) and BMI 25–27.5 kg/m² (HR=1.27; 95% CI 1.13-1.42) compared with	errors in exposures AF based on ICD discharge codes which is approx. 90% accurate	achievable across all ages, sex, education levels and social classes in a free-living population, was associated with an estimated 2.8-fold reduction in risk for AF

						BMI<25 kg/m ² , respectively		
Pathak, 2014 (ARREST-AF)	52	Prospective cohort study	281 consecutive patients undergoing AF ablation; 165 had both BMI≥27 kg/m ² and ≥1 risk factor. The final cohort included 149 patients: 61 RFM patients and 88	Risk factor management (RFM) according to American Heart Association/American College of Cardiology guidelines. After AF ablation, all 61 patients had RFM and 88 were controls	BMI ≥27 kg/m ² and ≥1 cardiac risk factor (HT, glucose intolerance/DM, hyperlipidaemia, OSA, smoking, or alcohol excess) undergoing initial catheter ablation for symptomatic AF despite the use of antiarrhythmic medication Exclusion: history of MI or cardiac surgery in the previous 12 months; previous AF ablation;	RFM resulted in greater reductions in weight ($P=0.002$) and blood pressure ($P=0.006$), and better glycaemic control ($P=0.001$) and lipid profiles ($P=0.01$). At follow-up, AF frequency, duration, symptoms, and symptom severity decreased more in the RFM group compared	RFM improved single and multiple procedure outcomes ($P<0.001$). Reduction in weight, BP, glycaemic control and lipid profile. Decrease in AF frequency, duration, symptoms and severity. Single centre, observational	RFM was associated with improved outcomes of AF ablation by reducing AF burden and severity in conjunction with favourable changes in cardiac remodelling in these study patients

			control subjects		active malignancy; autoimmune or systemic inflammatory disease; severe renal or hepatic failure; and <12 months FU after their procedure	with the control group (all $P<0.001$). On multivariate analysis, type of AF ($P<0.001$) and RFM (HR=4.8; 95% CI 2.04-11.4; $P<0.001$) were independent predictors of arrhythmia-free survival		

Additional Evidence Table S38 — Sleep apnoea syndrome

Study	Ref	Details and quality of evidence					Summary of key findings		
		Study type	N patients	Intervention and control		Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Hunt, 2022	107	RCT	83 patients with AF ablation, paroxysmal AF and an apnea-hypopnea index (AHI) ≥ 15 events/h	CPAP: 37 patients vs. standard care: 46 patients	AF recurrence after PVI was defined as any episode of AF lasting >2 minutes after a 3-month blanking period	Inclusion: 18–75 years with symptomatic, documented paroxysmal AF with moderate to severe OSA, defined by an apnea-hypopnea index (AHI) ≥ 15 events/hour on the respiratory polygraph test. Exclusion: previously	AF burden after ablation was reduced in both groups, with no between-group difference ($P=0.69$)	CPAP did not reduce risk of AF recurrence after ablation, PVI reduced burden of AF in OSA without between group difference. Small study. Dubious powering of the study, difference from the A3 study registered and the current	No effect of CPAP on AF

					diagnosed OSA, unstable coronary disease, transitory ischemic attack, stroke, structural heart disease, left ventricular systolic dysfunction (ejection fraction <45%), severe obesity (body mass index >40 kg/m²), severe excessive daytime sleepiness (Epworth		report. Study does not state prior ablation as an exclusion. In the Phase 1 of the study, they included patients referred for first or second AF ablation. Marked attrition from screened to recruitment. Non standardised ablation technique. CPAP group had 20% greater use of RF. CPAP	

					sleepiness scale score ≥ 15), or present use of amiodarone		compliance only 3.9 ± 1.5 hours	
Caples, 2019	105	RCT	1757 screened; 34 had sleep studies; 25 randomized	Intervention: CPAP Control: Usual care	Inclusion: ≥ 18 years; AF recently underwent DCCV to sinus rhythm within the last 30 days. Exclusion: moderate to severe pulmonary disease; moderate to severe cardiac valvular disease; conge stive	AF recurred in 25% of patients in the CPAP and control groups, at 129.0 ± 166.5 versus 109.3 ± 73.2 days; $P=0.98$	Did not detect a difference in those treated with CPAP compared to usual care in those randomised to OSA treatment post DCCV. Very small study; significant attrition from screened to include in study	No differences in CPAP being useful in AF patients

					heart failure (LVEF<40%)			
Nalliah, 2022 (SLEEP-AF)	⁶⁷	RCT	24 patients with at least moderate OSA (AHI≥15/hr)	CPAP –12 patients vs. standard of care –12 patients	Inclusion: consecutive patients referred for AF management with modern OSA (AHI>15). Exclusions: previous ablation, LVEF <50%, greater than trivial valvular regurgitation, pulmonary artery hypertension (>30 mm Hg), refractory to electrical	Invasive EP study performed at baseline and after at least 6 months. CPAP group had faster conduction velocity (0.86 ± 0.16 m/s vs. 0.69 ± 0.12 m/s; $P=0.03$), significantly higher voltages (2.30 ± 0.57 mV vs. 1.94 ± 0.72 mV; $P<0.05$), and lower proportion of complex points ($8.87 \pm 3.61\%$ vs. $11.93 \pm$	CPAP results in atrial remodelling in AF patients. Small study, of 120 meeting pre-specified inclusion and exclusion criteria, only 24 studied. No evaluation of the impact on rhythm. Patients may represent higher motivation therefore higher CPAP compliance,	CPAP therapy results in reversal of atrial remodelling in AF and provides mechanistic evidence advocating for management of OSA in AF

					cardioversion, central sleep apnea diagnosis, past or current treatment of OSA. Excessive daytime sleepiness scores (Epworth Sleepiness Score ≥ 18) or who were considered to be at risk because of their vocation	4.94%; $P=0.01$) compared with the control group	study evaluated OSA on RA only, unable to assess LA, changes in clinical AF profile not evaluated	
Traaen, 2021 (A3)	¹⁰⁶	RCT	109 patients with AF and OSA	5-month study evaluating the impact	Inclusion: consecutive patients, 18-75 years with	The mean time in AF decreased from 5.6% at baseline to	CPAP did not significantly reduce AF burden in	CPAP therapy did not have an effect on AF burden

				of CPAP vs. no CPAP on AF burden by ILR	documented paroxysmal AF referred for their first or second AF catheter ablation or recruited from AF outpatient clinics were screened for SA; patients diagnosed with moderate to severe SA (apnea–hypopnea index [AHI] >15/h [OSA and/or central SA]) were eligible. Exclusion:	4.1% during the last 3 months of CPAP intervention and from 5.0% to 4.3% in the control group. The adjusted between-group difference at follow-up was 20.63 (95% CI 22.55-1.30) percentage points ($P=0.52$). Seven serious adverse events (13%) occurred in the CPAP group, and two (4%) occurred in the control group	patients with paroxysmal AF and OSA. Dubious powering, small series, 1093 patients screened, 109 randomised, possible underestimates of OSA severity, did not assess mild OSA, excluded patients with excessive daytime sleepiness based on questionnaire, short intervention	

					LVED<45%, BMI>40 kg/m ² , or severe excessive daytime sleepiness (Epworth Sleepiness Scale score.15); patients who were scheduled for catheter ablation had this procedure performed 5 months after randomization			
Qureshi, 2015	⁶⁸	Systematic review and meta- analysis of	8 studies on OSA (1RCT) with 698	OSA with CPAP vs. OSA without CPAP	Inclusion: studies that evaluated the efficacy of	Patients treated with CPAP had a 42% decreased risk of AF	Inverse relationship between CPAP and AF	CPAP users were associated with a

		RCT and observational studies	CPAP users and 549 non-CPAP users		CPAP in adults aged older than 18 years with a diagnosis of OSA, with a minimum AHI of >4. Patients had at least one type of arrhythmia. Excluded: Studies focused on central OSA, studies that did not report on measures of arrhythmias before and after CPAP	(RR=0.58; 95% CI 0.47-0.70; $P<0.001$)	recurrence. Low heterogeneity ($I^2=30\%$). Sample sizes of studies small, studies not blinded and low quality, heterogeneous patient population, OSA severity not able to be examined	decreased risk of AF recurrence
Li, 2014	⁷¹	Systematic review and	5 studies involving	OSA vs. no OSA risk	Inclusion: human	Patients with OSA had a 31%	OSA associated with	Patients not treated with

		meta-analysis of RCT and observational studies	3743 patients with AF		studies, >18yrs old. Exclusion: retrospective, prospective cohort or case-control studies, performance of catheter ablation for AF, patients assessed for presence of OSA, comparison of AF recurrence after single ablation in patients with and without AF, CPAP treatment for	greater risk of AF recurrence after catheter ablation than did patients without OSA (RR=1.31; $P=0.001$), and this risk increased by 57% in patients with OSA not undergoing CPAP therapy (RR=1.57; $P=0.00$)	AF recurrence after ablation, efficacy of ablation similar in those without OSA and patients with OSA on CPAP. Capacity to detect publication bias, unable to subgroup analysis due to small numbers, studies observational	CPAP were associated with a greater risk of recurrence in OSA

					patients with OSA			
Shukla, 2015	⁶⁹	Systematic review and meta-analysis of RCT and observational studies	7 studies: 5 studies on patients undergoing ablation; 2 studies non pulmonary vein isolation (PVI)	Primary endpoint: evaluation of AF recurrence in CPAP users and nonusers in patients with OSA	Inclusion: controlled study; study subjects to include patients with diagnosed OSA; study to have evaluated effect of CPAP therapy on AF recurrence; patients with OSA and symptomatic AF referred for PVI; outcome reported clinically in terms of AF	Users of CPAP had a significant reduction in AF recurrence rate compared with nonusers 33.3 vs. 58.1% (RR=0.58; 95% CI 0.51-0.67; $P<0.001$). In subgroup analysis these data were confirmed in PVI studies and in non-PVI studies	CPAP significantly reduced AF recurrence in OSA patients, this was consistent across populations irrespective of whether they have ablation. P value for chi-square heterogeneity 0.91, and $I^2 = 0\%$. Small patient numbers in the studies included. Risk	Decreased risk in CPAP users (42% relative risk reduction in AF recurrence in patients with OSA)

					recurrence; study duration of more than 6 months. Exclusion: no data provided for comparison amongst CPAP users and nonusers; no report of AF recurrence		of publication bias, CPAP adherence mostly based on self-report, not able to analyse raw data	
Naruse, 2013	⁷²	Prospective cohort study	153 patients with AF ablation 116 with OSA 82 with CPAP	OSA with CPAP vs. OSA without CPAP vs. no OSA	Inclusion: consecutive AF ablation patients. Exclusion: known OSA, unable to provide consent	Follow-up period of 18.8 ± 10.3 months, 51 (33%) patients experienced AF recurrences after ablation. Cox regression analysis: the left atrial volume (HR=1.11; 95%	Patients with untreated OSA have higher recurrence of AF after ablation, CPAP associated with lower AF recurrence. Single centre observational,	CPAP was associated with lower rates of AF recurrence

						CI 1.01-1.23; $P<0.05$), concomitant OSA (HR=2.61; 95% CI 1.12-6.09; $P<0.05$), and usage of CPAP therapy (HR=0.41; 95% CI 0.22-0.76; $P<0.01$) were associated with AF recurrences	AF recurrence based on ECG or Holter potentially missing episodes, small sample size	
Fein, 2013	⁷³	Prospective cohort study	426 patients with AF ablation, 62 OSA, 32 patients "CPAP users" 30 patients "CPAP	Selected groups	Inclusion: "CPAP users" had used CPAP daily for a minimum of 3 months prior to the index PVI and continued to use CPAP	CPAP therapy resulted in higher AF-free survival rate (71.9% vs. 36.7%; $P=0.01$) and AF-free survival off antiarrhythmic drugs or repeat ablation following	CPAP in OSA patients improves AF freedom following PVI, PVI offers limited value in OSA patients not treated with CPAP. Single	CPAP was associated with lower AF recurrence rates

			nonusers”		throughout the follow-up duration (12 months). Exclusion: insufficient data due to loss of follow-up	PVI (65.6% vs. 33.3%; $P=0.02$) AF recurrence rate of CPAP-treated patients was similar to a group of patients without OSA (HR=0.7; $P=0.46$). AF recurrence following PVI in CPAP nonuser patients was significantly higher (HR=2.4; $P<0.02$) and similar to that of OSA patients managed medically without ablation (HR=2.1;	centre observational, retrospective analysis, small number, unable to obtain data on OSA severity, unable to determine CPAP compliance	

						<i>P</i> =0.68)		
Abumuamar, 2019	¹⁰⁹	Prospective cohort study	100 patients with AF vs. 85 with OSA	OSA vs. no OSA	Inclusion: adult patients >18 years, previously documented AF (ECG or ECG Holter); clinically stable on AAD. Exclusion: a previous diagnosis and/or treatment of OSA, a sleep study within 6 months prior to recruitment, an inability to provide an informed consent	In patients with paroxysmal AF (n=29), atrial and ventricular ectopy counts/24 h significantly decreased at 3 months compared to baseline (IQR=351(2049)-57 (182); <i>P</i> =0.002; 68 (105)-16 (133), <i>P</i> =0.01 respectively)	Significant decrease in atrial and ventricular ectopy count in patients with AF and OSA at 3 and 6mths of CPAP. Possible selection bias, observational study, small cohort, CPAP compliance, study not powered to detect significant changes in HR after CPAP, 24hr Holter	CPAP was associated with reduced atrial ectopic beats in patients with paroxysmal AF

							used	
Kanagala, 2003	¹⁰⁸	Prospective cohort study	39 patients: 12 with CPAP, 27 no CPAP vs. control group 79 patients, without OSA	CPAP vs. no CPAPAF	Patients with AF/atrial flutter referred for DC cardioversion	The recurrence rate of AF at 12 months in the 27 untreated or inappropriately treated subjects with OSA was 82%, versus 42% in the treated OSA group ($P=0.013$) and 53% in the control group without known OSA ($P=0.009$)	Untreated OSA resulted in higher AF recurrence following cardioversion. Single centre, small cohort	OSA treated with CPAP was associated with reduced recurrent AF rates in
Holmqvist, 2015 (ORBIT-AF)	⁷⁶	Prospective registry	10 132 patients with AF, 1841 had OSA	CPAP treatment on CV outcomes. The prevalence of clinician	Inclusion: consecutive patients with AF meeting the inclusion criteria (>18 years, ECG	Of 10 132 patients enrolled in ORBIT-AF, 18% (n=1841) had OSA at baseline; no significant	AF patients with OSA had worse symptoms, higher hospitalisation, but similar	CPAP therapy was associated with lower AF burden:16% progressed towards non-

				defined OSA (ie, diagnosis or history of OSA) at baseline and CPAP treatment (“currently undergoing CPAP therapy”) was captured. In ORBIT-AF, follow-up data collection occurs at 6-month intervals for a minimum of 2 years	evidence of AF, providing informed consent). Exclusion: life expectancy of <6 months or AF secondary to reversible conditions; CPAP treatments were lacking (yielding a study population of 1837 patients with OSA for the analyses regarding CPAP). For the outcomes analysis for	difference in risk was observed between patients on CPAP treatment compared with those not on CPAP for most of the outcomes. As for AF: a smaller proportion of the patients on CPAP treatment progressed in their AF (16% of patients with non-permanent AF at baseline) compared with the patients not on CPAP treatment (18%; adjusted	mortality, MACE outcomes and progression rates than those without OSA. Observational study, not primary outcome of ORBIT study, selection and reporting biases, OSA diagnosis based on medical reports, sleep data not available	permanent AF vs. 18% of OSA non-CPAP treated patients ($P=0.02$). Similar mortality rates and major adverse cardiovascular events between patients with OSA treated with CPAP and those without CPAP treatment

					patients with OSA vs. patients with no OSA, patients without any follow-up data were excluded. For the outcomes analysis for CPAP treatment vs. no CPAP treatment, patients without any follow-up data (n=78) and patients from sites with less than 6 patients were excluded	HR=0.66; 95% CI 0.46-0.94; <i>P</i>=0.02)		

					(n=135)			

Additional Evidence Table S39 — Physical activity

Study	Ref	Details and quality of evidence				Summary of key findings		
		Study type	N patients	Intervention and control	Key inclusion & exclusion criteria	Relevant outcome(s)	Key findings Important biases	Conclusion(s)
Everett, 2011 (Women's Health Study)	⁵²¹	RCT	34 759 women	Aspirin and vitamin E in the prevention of cardiovascular disease and cancer Quintiles of weekly leisure time PA	Beginning in 1993, a total of 39 876 initially healthy women who were at least 45 years old enrolled in the WHS. The randomized treatment portion of the study was completed in March 2004, and participants were invited to participate in continued observational	Women who achieved the federal government's recommendation of 7.5 MET-h/wk of PA were at reduced risk of AF compared with those who did not (HR=0.86; 95% CI 0.75-0.98; <i>P</i> =0.03). This association was also attenuated by BMI (HR=0.96; 95% CI	Methodological limitations of self-reported physical activity	In middle-aged women, physical activity was associated with a modestly reduced risk of AF. However, this relationship was no longer significant after controlling for body mass index

					follow-up	0.84-1.10; <i>P</i> =0.57)		
Mozaffarian, 2008 (Cardiovascular Health Study)	⁵²²	Prospective cohort study	5446	Low- vs. moderate vs. high-intensity exercise	Inclusion: ≥65 years randomly selected and enrolled from Medicare eligibility lists in 4 US communities in 1989 to 1990; participants were only enrolled if they were ambulatory and non- institutionalized	AF incidence in a graded manner, with 25% (HR=0.75; 95% CI 0.61- 0.90), 22% (HR=0.78; 95% CI 0.65-0.95), and 36% (HR=0.64; 95% CI 0.52-0.79) lower risk in quintiles 3, 4, and 5 versus quintile 1 (<i>P</i> <0.001). Exercise intensity had a U-shaped relationship with AF (quadratic	Generalizability to younger individuals. Methodological limitations of self-reported physical activity	Reduced risk with of AF with moderate- intensity vs. no exercise (HR=0.72; 95% CI 0.58- 0.89), no effect with low- or high-intensity exercise

						$P=0.02$): Versus no exercise, AF incidence was lower with moderate-intensity exercise (HR=0.72; 95% CI 0.58-0.89) but not with high-intensity exercise (HR=0.87; 95% CI 0.64-1.19)		
Drca, 2015	523	Prospective cohort study	36 513 women	Duration of leisure-time PA	Inclusion: women who completed the 1997 questionnaire. Exclusion: women with an incorrect or a missing Swedish	Reduced risk with increasing levels of leisure-time exercise at study entry (RR=0.85; 95% CI 0.75-0.95) for ≥ 4 vs. <1 h/wk) and	Only women; methodological limitations of self-reported physical activity	Physical activity is associated with a reduced risk of AF in women. Moderate amount of physical

					Personal Identification Number, women who died before the start of follow-up, diagnosed before study entry with AF as recorded in the Swedish Inpatient Register or cancer, except non-melanoma skin cancer	walking/bicycling (RR=0.81; 95% CI 0.72-0.92; for ≥ 40 min/d vs. almost never)		activity was sufficient to significantly reduce AF risk
Azarbal, 2014 (Women's Health Initiative)	⁵²⁴	Prospective cohort study	81 317 women	MET-hours per week	Inclusion: postmenopausal, with ages 50-79 years at time of enrolment. Exclusion: Women unlikely	Participants in the highest stratum of physical activity (>9 MET-h/week) had a significantly	Only women; methodological limitations of self-reported physical activity	Participants who were normal weight and physically active had a significantly lower risk of

					to survive or remain in the vicinity of a Women's Health Initiative clinic for 3 years or had alcoholism, drug dependency, or dementia. women with baseline AF, missing data, or underweight body mass index (BMI)	lower multivariable-adjusted risk of incident AF (HR=0.90; 95% CI 0.85-0.96). Each increase in strata of physical activity was associated with a lower hazard of incident AF ($P<0.001$ for linear trend)		incident AF, compared to those who were obese and sedentary
Garnvik, 2018	⁵²⁵	Prospective cohort study	43 602 men and women	Levels of PA and obesity	All residents ≥ 18 years (93 860) were invited of whom 50 803 (54.1%) participated	Overweight and obesity were associated with an 18% (HR=1.18; 95% CI 1.03-1.35) and 59% (HR=1.59; 95%	Methodological limitations of self-reported physical activity	Overweight and obesity were associated with increased risk of AF. Physical activity offsets

						CI 1.37-1.84) increased risk of AF, respectively. High levels of physical activity attenuated some of the higher AF risk in obese individuals (HR=1.53; 95% CI 1.03-2.28) in active (HR=1.96; 95% CI 1.44- 2.67) in inactive. compared to normal weight active individuals		some, but not all, AF risk associated with obesity
Heitmann, 2022 (Tromsø)	⁵²⁶	Prospective cohort study	2479	None	Inclusion: from the Tromsø Study, men aged 55-74 years, all women aged 50-	U-shaped relationship between PA and AF, and moderately	Methodological limitations of self-reported physical activity	Moderate PA was associated with reduced AF risk, and

					74 years and 5-8% random samples of the other age groups aged <85 years were invited with extended examinations. Exclusion: previous or present documented AF, valvular heart disease, LVEF<40%, previous myocardial infarction and LA below normal Ref range at baseline	active had 32% lower AF risk than inactive (HR=0.68; 95% CI 0.50-0.93). Participants with LA enlargement had 38% higher AF risk compared with participants with normal LA size (HR=1.38; 95% CI 1.12-1.69). However, the increased AF risk with LA enlargement was attenuated by PA		PA attenuated the increased risk of AF with LA enlargement in both men and women and all age groups

References

1. Stroke Prevention in Atrial Fibrillation Study. Final results. *Circulation* 1991;**84**(2):527-39.
2. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;**361**(12):1139-51.
3. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM, ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;**365**(10):883-91.
4. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldles M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;**365**(11):981-92.
5. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Spinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Mercuri M, Antman EM, ENGAGE AF-TIMI Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;**369**(22):2093-104.
6. Svennberg E, Friberg L, Frykman V, Al-Khalili F, Engdahl J, Rosenqvist M. Clinical outcomes in systematic screening for atrial fibrillation (STROKESTOP): a multicentre, parallel group, unmasked, randomised controlled trial. *Lancet* 2021;**398**(10310):1498-1506.
7. Hohnloser SH, Crijns HJ, van Eickels M, Gaudin C, Page RL, Torp-Pedersen C, Connolly SJ, Athena Investigators. Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med* 2009;**360**(7):668-78.
8. Active I Investigators, Yusuf S, Healey JS, Pogue J, Chrolavicius S, Flather M, Hart RG, Hohnloser SH, Joyner CD, Pfeffer MA, Connolly SJ. Irbesartan in patients with atrial fibrillation. *N Engl J Med* 2011;**364**(10):928-38.
9. Svennberg E, Engdahl J, Al-Khalili F, Friberg L, Frykman V, Rosenqvist M. Mass Screening for Untreated Atrial Fibrillation: The STROKESTOP Study. *Circulation* 2015;**131**(25):2176-84.
10. Kirchhof P, Camm AJ, Goette A, Brandes A, Eckardt L, Elvan A, Fetsch T, van Gelder IC, Haase D, Haegeli LM, Hamann F, Heidbüchel H, Hindricks G, Kautzner J, Kuck KH, Mont L, Ng GA, Rekosz J, Schoen N, Schotten U, Suling A, Taggeselle J, Themistoclakis S, Vettorazzi E, Vardas P, Wegscheider K, Willems S, Crijns H, Breithardt G. Early Rhythm-Control Therapy in Patients with Atrial Fibrillation. *N Engl J Med* 2020;**383**(14):1305-1316.
11. Kotecha D, Bunting KV, Gill SK, Mehta S, Stanbury M, Jones JC, Haynes S, Calvert MJ, Deeks JJ, Steeds RP, Strauss VY, Rahimi K, Camm AJ, Griffith M, Lip GYH, Townend JN, Kirchhof P. Effect of Digoxin vs Bisoprolol for Heart Rate Control

in Atrial Fibrillation on Patient-Reported Quality of Life: The RATE-AF Randomized Clinical Trial. *JAMA* 2020;**324**(24):2497-2508.

12. Mantovan R, Macle L, De Martino G, Chen J, Morillo CA, Novak P, Calzolari V, Khaykin Y, Guerra PG, Nair G, Torrecilla EG, Verma A. Relationship of quality of life with procedural success of atrial fibrillation (AF) ablation and postablation AF burden: substudy of the STAR AF randomized trial. *Can J Cardiol* 2013;**29**(10):1211-7.

13. Samuel M, Khairy P, Champagne J, Deyell MW, Macle L, Leong-Sit P, Novak P, Badra-Verdu M, Sapp J, Tardif JC, Andrade JG. Association of Atrial Fibrillation Burden With Health-Related Quality of Life After Atrial Fibrillation Ablation: Substudy of the Cryoballoon vs Contact-Force Atrial Fibrillation Ablation (CIRCA-DOSE) Randomized Clinical Trial. *JAMA Cardiol* 2021;**6**(11):1324-1328.

14. Terricabras M, Mantovan R, Jiang CY, Betts TR, Chen J, Deisenhofer I, Macle L, Morillo CA, Haverkamp W, Weerasooriya R, Albenque JP, Nardi S, Menardi E, Novak P, Sanders P, Verma A. Association Between Quality of Life and Procedural Outcome After Catheter Ablation for Atrial Fibrillation: A Secondary Analysis of a Randomized Clinical Trial. *JAMA Netw Open* 2020;**3**(12):e2025473.

15. Jones J, Stanbury M, Haynes S, Bunting KV, Lobban T, Camm AJ, Calvert MJ, Kotecha D. Importance and Assessment of Quality of Life in Symptomatic Permanent Atrial Fibrillation: Patient Focus Groups from the RATE-AF Trial. *Cardiology* 2020;**145**(10):666-675.

16. Kotecha D, Ahmed A, Calvert M, Lencioni M, Terwee CB, Lane DA. Patient-Reported Outcomes for Quality of Life Assessment in Atrial Fibrillation: A Systematic Review of Measurement Properties. *PLoS One* 2016;**11**(11):e0165790.

17. Schnabel RB, Pecun L, Rzayeva N, Lucerna M, Purmah Y, Ojeda FM, De Caterina R, Kirchhof P. Symptom Burden of Atrial Fibrillation and Its Relation to Interventions and Outcome in Europe. *J Am Heart Assoc* 2018;**7**(11):e007559.

18. Sandhu RK, Smigorowsky M, Lockwood E, Savu A, Kaul P, McAlister FA. Impact of Electrical Cardioversion on Quality of Life for the Treatment of Atrial Fibrillation. *Can J Cardiol* 2017;**33**(4):450-455.

19. Zenger B, Zhang M, Lyons A, Bunch TJ, Fang JC, Freedman RA, Navaravong L, Piccini JP, Ranjan R, Spertus JA, Stehlik J, Turner JL, Greene T, Hess R, Steinberg BA. Patient-reported outcomes and subsequent management in atrial fibrillation clinical practice: Results from the Utah mEVAL AF program. *J Cardiovasc Electrophysiol* 2020;**31**(12):3187-3195.

20. Wynn GJ, Todd DM, Webber M, Bonnett L, McShane J, Kirchhof P, Gupta D. The European Heart Rhythm Association symptom classification for atrial fibrillation: validation and improvement through a simple modification. *Europace* 2014;**16**(7):965-72.

21. Arbelo E, Aktaa S, Bollmann A, D'Avila A, Drossart I, Dwight J, Hills MT, Hindricks G, Kusumoto FM, Lane DA, Lau DH, Lettino M, Lip GYH, Lobban T, Pak HN, Potpara T, Saenz LC, Van Gelder IC, Varosy P, Gale CP, Dagres N, Reviewers, Boveda S, Deneke T, Defaye P, Conte G, Lenarczyk R, Providencia R, Guerra JM, Takahashi Y, Pisani C, Nava S, Sarkozy A, Glotzer TV, Martins Oliveira M. Quality indicators for the care and outcomes of adults with atrial fibrillation. *Europace* 2021;**23**(4):494-495.

22. Tops LF, Schalij MJ, Bax JJ. Imaging and atrial fibrillation: the role of multimodality imaging in patient evaluation and management of atrial fibrillation. *Eur Heart J* 2010;**31**(5):542-51.
23. Roney CH, Sillett C, Whitaker J, Lemus JAS, Sim I, Kotadia I, O'Neill M, Williams SE, Niederer SA. Applications of multimodality imaging for left atrial catheter ablation. *Eur Heart J Cardiovasc Imaging* 2021;**23**(1):31-41.
24. Troughton RW, Asher CR, Klein AL. The role of echocardiography in atrial fibrillation and cardioversion. *Heart* 2003;**89**(12):1447-54.
25. Odutayo A, Wong CX, Hsiao AJ, Hopewell S, Altman DG, Emdin CA. Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis. *BMJ* 2016;**354**:i4482.
26. Rattanawong P, Upala S, Rianguiwat T, Jaruvongvanich V, Sanguankeo A, Vutthikraivit W, Chung EH. Atrial fibrillation is associated with sudden cardiac death: a systematic review and meta-analysis. *J Interv Card Electrophysiol* 2018;**51**(2):91-104.
27. Ruddox V, Sandven I, Munkhaugen J, Skattebu J, Edvardsen T, Otterstad JE. Atrial fibrillation and the risk for myocardial infarction, all-cause mortality and heart failure: A systematic review and meta-analysis. *Eur J Prev Cardiol* 2017;**24**(14):1555-1566.
28. Zuin M, Roncon L, Passaro A, Bosi C, Cervellati C, Zuliani G. Risk of dementia in patients with atrial fibrillation: Short versus long follow-up. A systematic review and meta-analysis. *Int J Geriatr Psychiatry* 2021;**36**(10):1488-1500.
29. Lin M, Han W, Zhong J, Wu L. A systematic review and meta-analysis to determine the effect of oral anticoagulants on incidence of dementia in patients with atrial fibrillation. *Int J Clin Pract* 2021;**75**(10):e14269.
30. Giannone ME, Filippini T, Whelton PK, Chiari A, Vitolo M, Boriani G, Vinceti M. Atrial Fibrillation and the Risk of Early-Onset Dementia: A Systematic Review and Meta-Analysis. *J Am Heart Assoc* 2022;**11**(14):e025653.
31. Papanastasiou CA, Theochari CA, Zareifopoulos N, Arfaras-Melainis A, Giannakoulas G, Karamitsos TD, Palaiodimos L, Ntaios G, Avgerinos KI, Kapogiannis D, Kokkinidis DG. Atrial Fibrillation Is Associated with Cognitive Impairment, All-Cause Dementia, Vascular Dementia, and Alzheimer's Disease: a Systematic Review and Meta-Analysis. *J Gen Intern Med* 2021;**36**(10):3122-3135.
32. Proietti R, Alturki A, Vio R, Licchelli L, Rivezzi F, Marafi M, Russo V, Potpara TS, Kalman JM, de Villers-Sidani E, Bunch TJ. The association between atrial fibrillation and Alzheimer's disease: fact or fallacy? A systematic review and meta-analysis. *J Cardiovasc Med (Hagerstown)* 2020;**21**(2):106-112.
33. Mongkhon P, Naser AY, Fanning L, Tse G, Lau WCY, Wong ICK, Kongkaew C. Oral anticoagulants and risk of dementia: A systematic review and meta-analysis of observational studies and randomized controlled trials. *Neurosci Biobehav Rev* 2019;**96**:1-9.
34. Bassand JP, Accetta G, Al Mahmeed W, Corbalan R, Eikelboom J, Fitzmaurice DA, Fox KAA, Gao H, Goldhaber SZ, Goto S, Haas S, Kayani G, Pieper K, Turpie AGG, van Eickels M, Verheugt FWA, Kakkar AK, Garfield-AF Investigators. Risk factors for death, stroke, and bleeding in 28,628 patients from the GARFIELD-AF

registry: Rationale for comprehensive management of atrial fibrillation. PLoS One 2018;**13**(1):e0191592.

35. Boriani G, Blomström-Lundqvist C, Hohnloser SH, Bergfeldt L, Botto GL, Capucci A, Lozano IF, Goette A, Israel CW, Merino JL, Camm AJ. Safety and efficacy of dronedarone from clinical trials to real-world evidence: implications for its use in atrial fibrillation. *Europace* 2019;**21**(12):1764-1775.

36. Dai H, Zhang Q, Much AA, Maor E, Segev A, Beinart R, Adawi S, Lu Y, Bragazzi NL, Wu J. Global, regional, and national prevalence, incidence, mortality, and risk factors for atrial fibrillation, 1990-2017: results from the Global Burden of Disease Study 2017. *Eur Heart J Qual Care Clin Outcomes* 2021;**7**(6):574-582.

37. van den Dries CJ, van Doorn S, Rutten FH, Oudega R, van de Leur S, Elvan A, Oude Grave L, Bilo HJG, Moons KGM, Hoes AW, Geersing GJ. Integrated management of atrial fibrillation in primary care: results of the ALL-IN cluster randomized trial. *Eur Heart J* 2020;**41**(30):2836-2844.

38. Vinereanu D, Lopes RD, Bahit MC, Xavier D, Jiang J, Al-Khalidi HR, He W, Xian Y, Ciobanu AO, Kamath DY, Fox KA, Rao MP, Pokorney SD, Berwanger O, Tajer C, de Barros ESPGM, Roettig ML, Huo Y, Granger CB. A multifaceted intervention to improve treatment with oral anticoagulants in atrial fibrillation (IMPACT-AF): an international, cluster-randomised trial. *Lancet* 2017;**390**(10104):1737-1746.

39. Wijtvlit E, Tieleman RG, van Gelder IC, Pluymaekers N, Rienstra M, Folkeringa RJ, Bronzwaer P, Elvan A, Elders J, Tukkie R, Luermans J, Van Asselt A, Van Kuijk SMJ, Tijssen JG, Crijns H. Nurse-led vs. usual-care for atrial fibrillation. *Eur Heart J* 2020;**41**(5):634-641.

40. Hendriks JM, de Wit R, Crijns HJ, Vrijhoef HJ, Prins MH, Pisters R, Pison LA, Blaauw Y, Tieleman RG. Nurse-led care vs. usual care for patients with atrial fibrillation: results of a randomized trial of integrated chronic care vs. routine clinical care in ambulatory patients with atrial fibrillation. *Eur Heart J* 2012;**33**(21):2692-9.

41. Hendriks JM, Vrijhoef HJ, Crijns HJ, Brunner-La Rocca HP. The effect of a nurse-led integrated chronic care approach on quality of life in patients with atrial fibrillation. *Europace* 2014;**16**(4):491-9.

42. Qvist I, Hendriks JM, Møller DS, Albertsen AE, Mogensen HM, Oddershede GD, Odgaard A, Mortensen LS, Johnsen SP, Frost L. Effectiveness of structured, hospital-based, nurse-led atrial fibrillation clinics: a comparison between a real-world population and a clinical trial population. *Open Heart* 2016;**3**(1):e000335.

43. Carter L, Gardner M, Magee K, Fearon A, Morgulis I, Doucette S, Sapp JL, Gray C, Abdelwahab A, Parkash R. An Integrated Management Approach to Atrial Fibrillation. *J Am Heart Assoc* 2016;**5**(1):e002950.

44. Yan H, Du YX, Wu FQ, Lu XY, Chen RM, Zhang Y. Effects of nurse-led multidisciplinary team management on cardiovascular hospitalization and quality of life in patients with atrial fibrillation: Randomized controlled trial. *Int J Nurs Stud* 2022;**127**:104159.

45. Guo Y, Lane DA, Wang L, Zhang H, Wang H, Zhang W, Wen J, Xing Y, Wu F, Xia Y, Liu T, Wu F, Liang Z, Liu F, Zhao Y, Li R, Li X, Zhang L, Guo J, Burnside G, Chen Y, Lip GYH, mAF-App II Trial Investigators. Mobile Health Technology to

Improve Care for Patients With Atrial Fibrillation. *J Am Coll Cardiol* 2020;**75**(13):1523-1534.

46. Cox JL, Parkash R, Foster GA, Xie F, MacKillop JH, Ciaccia A, Choudhri SH, Hamilton LM, Nemis-White JM, Thabane L. Integrated Management Program Advancing Community Treatment of Atrial Fibrillation (IMPACT-AF): A cluster randomized trial of a computerized clinical decision support tool. *Am Heart J* 2020;**224**:35-46.

47. Stewart S, Ball J, Horowitz JD, Marwick TH, Mahadevan G, Wong C, Abhayaratna WP, Chan YK, Esterman A, Thompson DR, Scuffham PA, Carrington MJ. Standard versus atrial fibrillation-specific management strategy (SAFETY) to reduce recurrent admission and prolong survival: pragmatic, multicentre, randomised controlled trial. *Lancet* 2015;**385**(9970):775-84.

48. Vanharen Y, Abugattas de Torres JP, Adriaenssens B, Convens C, Schwagten B, Tijssens M, Wolf M, Goossens E, Van Bogaert P, de Greef Y. Nurse-led care after ablation of atrial fibrillation: a randomized controlled trial. *Eur J Prev Cardiol* 2023;**30**(15):1599-1607.

49. Pinho-Gomes AC, Azevedo L, Copland E, Canoy D, Nazarzadeh M, Ramakrishnan R, Berge E, Sundstrom J, Kotecha D, Woodward M, Teo K, Davis BR, Chalmers J, Pepine CJ, Rahimi K, Blood Pressure Lowering Treatment Trialists C. Blood pressure-lowering treatment for the prevention of cardiovascular events in patients with atrial fibrillation: An individual participant data meta-analysis. *PLoS Med* 2021;**18**(6):e1003599.

50. Rienstra M, Hobbelt AH, Alings M, Tijssen JGP, Smit MD, Brugemann J, Geelhoed B, Tieleman RG, Hillege HL, Tukkier R, Van Veldhuisen DJ, Crijns H, Van Gelder IC, RACE Investigators. Targeted therapy of underlying conditions improves sinus rhythm maintenance in patients with persistent atrial fibrillation: results of the RACE 3 trial. *Eur Heart J* 2018;**39**(32):2987-2996.

51. Parkash R, Wells GA, Sapp JL, Healey JS, Tardif J-C, Greiss I, Rivard L, Roux J-F, Gula L, Nault I. Effect of aggressive blood pressure control on the recurrence of atrial fibrillation after catheter ablation: a randomized, open-label clinical trial (SMAC-AF [Substrate Modification With Aggressive Blood Pressure Control]). *Circulation* 2017;**135**(19):1788-1798.

52. Pathak RK, Middeldorp ME, Lau DH, Mehta AB, Mahajan R, Twomey D, Alasady M, Hanley L, Antic NA, McEvoy RD, Kalman JM, Abhayaratna WP, Sanders P. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. *J Am Coll Cardiol* 2014;**64**(21):2222-31.

53. Pathak RK, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Wong CX, Twomey D, Elliott AD, Kalman JM, Abhayaratna WP, Lau DH, Sanders P. Long-Term Effect of Goal-Directed Weight Management in an Atrial Fibrillation Cohort: A Long-Term Follow-Up Study (LEGACY). *J Am Coll Cardiol* 2015;**65**(20):2159-69.

54. Middeldorp ME, Pathak RK, Meredith M, Mehta AB, Elliott AD, Mahajan R, Twomey D, Gallagher C, Hendriks JML, Linz D, McEvoy RD, Abhayaratna WP, Kalman JM, Lau DH, Sanders P. PREVENTion and regReSSive Effect of weight-loss and risk factor modification on Atrial Fibrillation: the REVERSE-AF study. *Europace* 2018;**20**(12):1929-1935.

55. Kotecha D, Holmes J, Krum H, Altman DG, Manzano L, Cleland JG, Lip GY, Coats AJ, Andersson B, Kirchhof P, von Lueder TG, Wedel H, Rosano G, Shibata MC, Rigby A, Flather MD, Beta-Blockers in Heart Failure Collaborative Group. Efficacy of beta blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. *Lancet* 2014;**384**(9961):2235-43.
56. Pandey AK, Okaj I, Kaur H, Belley-Cote EP, Wang J, Oraii A, Benz AP, Johnson LSB, Young J, Wong JA, Verma S, Conen D, Gerstein H, Healey JS, McIntyre WF. Sodium-Glucose Co-Transporter Inhibitors and Atrial Fibrillation: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J Am Heart Assoc* 2021;**10**(17):e022222.
57. Olsson LG, Swedberg K, Ducharme A, Granger CB, Michelson EL, McMurray JJ, Puu M, Yusuf S, Pfeffer MA. Atrial fibrillation and risk of clinical events in chronic heart failure with and without left ventricular systolic dysfunction: results from the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) program. *J Am Coll Cardiol* 2006;**47**(10):1997-2004.
58. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, Inzucchi SE, Kosiborod MN, Lam CSP, Martinez F, Shah SJ, Desai AS, Jhund PS, Belohlavek J, Chiang CE, Borleffs CJW, Comin-Colet J, Dobreanu D, Drozd J, Fang JC, Alcocer-Gamba MA, Al Habeeb W, Han Y, Cabrera Honorio JW, Janssens SP, Katova T, Kitakaze M, Merkely B, O'Meara E, Saraiva JFK, Tereshchenko SN, Thierer J, Vaduganathan M, Vardeny O, Verma S, Pham VN, Wilderäng U, Zaozerska N, Bachus E, Lindholm D, Petersson M, Langkilde AM. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. *N Engl J Med* 2022;**387**(12):1089-1098.
59. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, PARADIGM-HF Investigators. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;**371**(11):993-1004.
60. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, Brunner-La Rocca HP, Choi DJ, Chopra V, Chuquiere-Valenzuela E, Giannetti N, Gomez-Mesa JE, Janssens S, Januzzi JL, Gonzalez-Juanatey JR, Merkely B, Nicholls SJ, Perrone SV, Piña IL, Ponikowski P, Senni M, Sim D, Spinar J, Squire I, Taddei S, Tsutsui H, Verma S, Vinereanu D, Zhang J, Carson P, Lam CSP, Marx N, Zeller C, Sattar N, Jamal W, Schnaidt S, Schnee JM, Brueckmann M, Pocock SJ, Zannad F, Packer M. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *N Engl J Med* 2021;**385**(16):1451-1461.
61. Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, Lewis JB, Riddle MC, Voors AA, Metra M, Lund LH, Komajda M, Testani JM, Wilcox CS, Ponikowski P, Lopes RD, Verma S, Lapuerta P, Pitt B. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. *N Engl J Med* 2021;**384**(2):117-128.
62. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B, Empasis-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011;**364**(1):11-21.
63. Abed HS, Wittert GA, Leong DP, Shirazi MG, Bahrami B, Middeldorp ME, Lorimer MF, Lau DH, Antic NA, Brooks AG, Abhayaratna WP, Kalman JM, Sanders P. Effect of weight reduction and cardiometabolic risk factor management on symptom

burden and severity in patients with atrial fibrillation: a randomized clinical trial. *JAMA* 2013;**310**(19):2050-60.

64. Donnellan E, Wazni OM, Kanj M, Elshazly M, Hussein AA, Patel DR, Trulock K, Wilner B, Baranowski B, Cantillon DJ, Varma N, Jaber W, Saliba WI. Impact of risk-factor modification on arrhythmia recurrence among morbidly obese patients undergoing atrial fibrillation ablation. *J Cardiovasc Electrophysiol* 2020;**31**(8):1979-1986.

65. Donnellan E, Wazni OM, Kanj M, Baranowski B, Cremer P, Harb S, McCarthy CP, McEvoy JW, Elshazly MB, Aagaard P, Tarakji KG, Jaber WA, Schauer PR, Saliba WI. Association between pre-ablation bariatric surgery and atrial fibrillation recurrence in morbidly obese patients undergoing atrial fibrillation ablation. *Europace* 2019;**21**(10):1476-1483.

66. Donnellan E, Wazni O, Kanj M, Hussein A, Baranowski B, Lindsay B, Aminian A, Jaber W, Schauer P, Saliba W. Outcomes of Atrial Fibrillation Ablation in Morbidly Obese Patients Following Bariatric Surgery Compared With a Nonobese Cohort. *Circ Arrhythm Electrophysiol* 2019;**12**(10):e007598.

67. Nalliah CJ, Wong GR, Lee G, Voskoboinik A, Kee K, Goldin J, Watts T, Linz D, Parameswaran R, Sugumar H, Prabhu S, McLellan A, Ling LH, Joseph SA, Morton JB, Kistler P, Sanders P, Kalman JM. Impact of CPAP on the Atrial Fibrillation Substrate in Obstructive Sleep Apnea: The SLEEP-AF Study. *JACC Clin Electrophysiol* 2022;**8**(7):869-877.

68. Qureshi WT, Nasir UB, Alqalyoobi S, O'Neal WT, Mawri S, Sabbagh S, Soliman EZ, Al-Mallah MH. Meta-Analysis of Continuous Positive Airway Pressure as a Therapy of Atrial Fibrillation in Obstructive Sleep Apnea. *Am J Cardiol* 2015;**116**(11):1767-73.

69. Shukla A, Aizer A, Holmes D, Fowler S, Park DS, Bernstein S, Bernstein N, Chinitz L. Effect of Obstructive Sleep Apnea Treatment on Atrial Fibrillation Recurrence: A Meta-Analysis. *JACC Clin Electrophysiol* 2015;**1**(1-2):41-51.

70. Kadhim K, Middeldorp ME, Elliott AD, Agbaedeng T, Gallagher C, Malik V, Wong CX, McEvoy RD, Kalman JM, Lau DH, Linz D, Sanders P. Prevalence and Assessment of Sleep-Disordered Breathing in Patients With Atrial Fibrillation: A Systematic Review and Meta-analysis. *Can J Cardiol* 2021;**37**(11):1846-1856.

71. Li L, Wang ZW, Li J, Ge X, Guo LZ, Wang Y, Guo WH, Jiang CX, Ma CS. Efficacy of catheter ablation of atrial fibrillation in patients with obstructive sleep apnoea with and without continuous positive airway pressure treatment: a meta-analysis of observational studies. *Europace* 2014;**16**(9):1309-14.

72. Naruse Y, Tada H, Satoh M, Yanagihara M, Tsuneoka H, Hirata Y, Ito Y, Kuroki K, Machino T, Yamasaki H, Igarashi M, Sekiguchi Y, Sato A, Aonuma K. Concomitant obstructive sleep apnea increases the recurrence of atrial fibrillation following radiofrequency catheter ablation of atrial fibrillation: clinical impact of continuous positive airway pressure therapy. *Heart Rhythm* 2013;**10**(3):331-7.

73. Fein AS, Shvilkin A, Shah D, Haffajee CI, Das S, Kumar K, Kramer DB, Zimetbaum PJ, Buxton AE, Josephson ME, Anter E. Treatment of obstructive sleep apnea reduces the risk of atrial fibrillation recurrence after catheter ablation. *J Am Coll Cardiol* 2013;**62**(4):300-5.

74. Kadhim K, Middeldorp ME, Elliott AD, Jones D, Hendriks JML, Gallagher C, Arzt M, McEvoy RD, Antic NA, Mahajan R, Lau DH, Nalliah C, Kalman JM, Sanders P, Linz D. Self-Reported Daytime Sleepiness and Sleep-Disordered Breathing in Patients With Atrial Fibrillation: SNOozE-AF. *Can J Cardiol* 2019;**35**(11):1457-1464.
75. Traaen GM, Overland B, Aakeroy L, Hunt TE, Bendz C, Sande L, Aakhus S, Zare H, Steinshamn S, Anfinson OG, Loennechen JP, Gullestad L, Akre H. Prevalence, risk factors, and type of sleep apnea in patients with paroxysmal atrial fibrillation. *Int J Cardiol Heart Vasc* 2020;**26**:100447.
76. Holmqvist F, Guan N, Zhu Z, Kowey PR, Allen LA, Fonarow GC, Hylek EM, Mahaffey KW, Freeman JV, Chang P, Holmes DN, Peterson ED, Piccini JP, Gersh BJ, Investigators O-A. Impact of obstructive sleep apnea and continuous positive airway pressure therapy on outcomes in patients with atrial fibrillation-Results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *Am Heart J* 2015;**169**(5):647-654 e2.
77. Oesterle A, Giancaterino S, Van Noord MG, Pellegrini CN, Fan D, Srivatsa UN, Amsterdam EA. Effects of Supervised Exercise Training on Atrial Fibrillation: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS. *J Cardiopulm Rehabil Prev* 2022;**42**(4):258-265.
78. Hegbom F, Stavem K, Sire S, Heldal M, Orning OM, Gjesdal K. Effects of short-term exercise training on symptoms and quality of life in patients with chronic atrial fibrillation. *Int J Cardiol* 2007;**116**(1):86-92.
79. Osbak PS, Mourier M, Kjaer A, Henriksen JH, Kofoed KF, Jensen GB. A randomized study of the effects of exercise training on patients with atrial fibrillation. *Am Heart J* 2011;**162**(6):1080-7.
80. Malmo V, Nes BM, Amundsen BH, Tjonna AE, Stoylen A, Rossvoll O, Wisloff U, Loennechen JP. Aerobic Interval Training Reduces the Burden of Atrial Fibrillation in the Short Term: A Randomized Trial. *Circulation* 2016;**133**(5):466-73.
81. Elliott AD, Verdicchio CV, Mahajan R, Middeldorp ME, Gallagher C, Mishima RS, Hendriks JML, Pathak RK, Thomas G, Lau DH, Sanders P. An Exercise and Physical Activity Program in Patients With Atrial Fibrillation: The ACTIVE-AF Randomized Controlled Trial. *JACC Clin Electrophysiol* 2023;**9**(4):455-465.
82. Voskoboinik A, Kalman JM, De Silva A, Nicholls T, Costello B, Nanayakkara S, Prabhu S, Stub D, Azzopardi S, Vizi D, Wong G, Nalliah C, Sugumar H, Wong M, Kotschet E, Kaye D, Taylor AJ, Kistler PM. Alcohol Abstinence in Drinkers with Atrial Fibrillation. *N Engl J Med* 2020;**382**(1):20-28.
83. Pokushalov E, Romanov A, Corbucci G, Artyomenko S, Baranova V, Turov A, Shirokova N, Karaskov A, Mittal S, Steinberg JS. A randomized comparison of pulmonary vein isolation with versus without concomitant renal artery denervation in patients with refractory symptomatic atrial fibrillation and resistant hypertension. *J Am Coll Cardiol* 2012;**60**(13):1163-70.
84. Steinberg JS, Shabanov V, Ponomarev D, Losik D, Ivanickiy E, Kropotkin E, Polyakov K, Ptaszynski P, Keweloh B, Yao CJ, Pokushalov EA, Romanov AB. Effect of Renal Denervation and Catheter Ablation vs Catheter Ablation Alone on Atrial Fibrillation Recurrence Among Patients With Paroxysmal Atrial Fibrillation and Hypertension: The ERADICATE-AF Randomized Clinical Trial. *JAMA* 2020;**323**(3):248-255.

85. Galzerano D, Di Michele S, Paolisso G, Tuccillo B, Lama D, Carbotta S, Cittadini A, Tedesco MA, Gaudio C. A multicentre, randomized study of telmisartan versus carvedilol for prevention of atrial fibrillation recurrence in hypertensive patients. *J Renin Angiotensin Aldosterone Syst* 2012;**13**(4):496-503.
86. Du H, Fan J, Ling Z, Woo K, Su L, Chen S, Liu Z, Lan X, Zhou B, Xu Y, Chen W, Xiao P, Yin Y. Effect of nifedipine versus telmisartan on prevention of atrial fibrillation recurrence in hypertensive patients. *Hypertension* 2013;**61**(4):786-92.
87. Giannopoulos G, Kossyvakis C, Efremidis M, Katsivas A, Panagopoulou V, Doudoumis K, Raisakis K, Letsas K, Rentoukas I, Pyrgakis V, Manolis AS, Tousoulis D, Stefanadis C, Devereux S. Central sympathetic inhibition to reduce postablation atrial fibrillation recurrences in hypertensive patients: a randomized, controlled study. *Circulation* 2014;**130**(16):1346-52.
88. Santoro F, Di Biase L, Trivedi C, Burkhardt JD, Paoletti Perini A, Sanchez J, Horton R, Mohanty P, Mohanty S, Bai R, Santangeli P, Lakkireddy D, Reddy M, Elayi CS, Hongo R, Beheiry S, Hao S, Schweikert RA, Viles-Gonzalez J, Fassini G, Casella M, Dello Russo A, Tondo C, Natale A. Impact of Uncontrolled Hypertension on Atrial Fibrillation Ablation Outcome. *JACC Clin Electrophysiol* 2015;**1**(3):164-173.
89. Berruezo A, Tamborero D, Mont L, Benito B, Tolosana JM, Sitges M, Vidal B, Arriagada G, Mendez F, Matiello M, Molina I, Brugada J. Pre-procedural predictors of atrial fibrillation recurrence after circumferential pulmonary vein ablation. *Eur Heart J* 2007;**28**(7):836-41.
90. Themistoclakis S, Schweikert RA, Saliba WI, Bonso A, Rossillo A, Bader G, Wazni O, Burkhardt DJ, Raviele A, Natale A. Clinical predictors and relationship between early and late atrial tachyarrhythmias after pulmonary vein antrum isolation. *Heart Rhythm* 2008;**5**(5):679-85.
91. Letsas KP, Weber R, Burkle G, Mihos CC, Minners J, Kalusche D, Arentz T. Pre-ablative predictors of atrial fibrillation recurrence following pulmonary vein isolation: the potential role of inflammation. *Europace* 2009;**11**(2):158-63.
92. Khaykin Y, Oosthuizen R, Zarnett L, Essebag V, Parkash R, Seabrook C, Beardsall M, Tsang B, Wulffhart Z, Verma A. Clinical predictors of arrhythmia recurrences following pulmonary vein antrum isolation for atrial fibrillation: predicting arrhythmia recurrence post-PVAI. *J Cardiovasc Electrophysiol* 2011;**22**(11):1206-14.
93. Kamioka M, Hijioka N, Matsumoto Y, Nodera M, Kaneshiro T, Suzuki H, Takeishi Y. Uncontrolled blood pressure affects atrial remodeling and adverse clinical outcome in paroxysmal atrial fibrillation. *Pacing Clin Electrophysiol* 2018;**41**(4):402-410.
94. Shah AN, Mittal S, Sichrovsky TC, Cotiga D, Arshad A, Maleki K, Pierce WJ, Steinberg JS. Long-term outcome following successful pulmonary vein isolation: pattern and prediction of very late recurrence. *J Cardiovasc Electrophysiol* 2008;**19**(7):661-7.
95. Zylla MM, Hochadel M, Andresen D, Brachmann J, Eckardt L, Hoffmann E, Kuck KH, Lewalter T, Schumacher B, Spitzer SG, Willems S, Senges J, Katus HA, Thomas D. Ablation of atrial fibrillation in patients with hypertension-an analysis from the German ablation registry. *J Clin Med* 2020;**9**(8):1-14.

96. Trines SA, Stabile G, Arbelo E, Dagres N, Brugada J, Kautzner J, Pokushalov E, Maggioni AP, Laroche C, Anselmino M, Beinart R, Traykov V, Blomstrom-Lundqvist C, investigators E-EAFAL-TR. Influence of risk factors in the ESC-EHRA EORP atrial fibrillation ablation long-term registry. *Pacing Clin Electrophysiol* 2019;**42**(10):1365-1373.
97. Martin N, Manoharan K, Davies C, Lumbers RT. Beta-blockers and inhibitors of the renin-angiotensin aldosterone system for chronic heart failure with preserved ejection fraction. *Cochrane Database Syst Rev* 2021;**5**(5):Cd012721.
98. Cleland JGF, Bunting KV, Flather MD, Altman DG, Holmes J, Coats AJS, Manzano L, McMurray JJV, Ruschitzka F, van Veldhuisen DJ, von Lueder TG, Böhm M, Andersson B, Kjekshus J, Packer M, Rigby AS, Rosano G, Wedel H, Hjalmarson Å, Wikstrand J, Kotecha D. Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials. *Eur Heart J* 2018;**39**(1):26-35.
99. Solomon SD, Claggett B, Lewis EF, Desai A, Anand I, Sweitzer NK, O'Meara E, Shah SJ, McKinlay S, Fleg JL, Sopko G, Pitt B, Pfeffer MA. Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. *Eur Heart J* 2016;**37**(5):455-62.
100. Lund LH, Claggett B, Liu J, Lam CS, Jhund PS, Rosano GM, Swedberg K, Yusuf S, Granger CB, Pfeffer MA, McMurray JJV, Solomon SD. Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum. *Eur J Heart Fail* 2018;**20**(8):1230-1239.
101. Swedberg K, Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Shi H, Vincent J, Pitt B. Eplerenone and atrial fibrillation in mild systolic heart failure: results from the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure) study. *J Am Coll Cardiol* 2012;**59**(18):1598-603.
102. Donnellan E, Aagaard P, Kanj M, Jaber W, Elshazly M, Hoosien M, Baranowski B, Hussein A, Saliba W, Wazni O. Association Between Pre-Ablation Glycemic Control and Outcomes Among Patients With Diabetes Undergoing Atrial Fibrillation Ablation. *JACC Clin Electrophysiol* 2019;**5**(8):897-903.
103. Di Benedetto L, Michels G, Luben R, Khaw KT, Pfister R. Individual and combined impact of lifestyle factors on atrial fibrillation in apparently healthy men and women: The EPIC-Norfolk prospective population study. *Eur J Prev Cardiol* 2018;**25**(13):1374-1383.
104. Chan YH, Chen SW, Chao TF, Kao YW, Huang CY, Chu PH. The impact of weight loss related to risk of new-onset atrial fibrillation in patients with type 2 diabetes mellitus treated with sodium-glucose cotransporter 2 inhibitor. *Cardiovasc Diabetol* 2021;**20**(1):93.
105. Caples SM, Mansukhani MP, Friedman PA, Somers VK. The impact of continuous positive airway pressure treatment on the recurrence of atrial fibrillation post cardioversion: A randomized controlled trial. *Int J Cardiol* 2019;**278**:133-136.
106. Traaen GM, Aakeroy L, Hunt TE, Overland B, Bendz C, Sande LO, Aakhus S, Fagerland MW, Steinshamn S, Anfinson OG, Massey RJ, Broch K, Ueland T, Akre H, Loennechen JP, Gullestad L. Effect of Continuous Positive Airway Pressure on Arrhythmia in Atrial Fibrillation and Sleep Apnea: A Randomized Controlled Trial. *Am J Respir Crit Care Med* 2021;**204**(5):573-582.

107. Hunt TE, Traaen GM, Aakeroy L, Bendz C, Overland B, Akre H, Steinshamn S, Loennechen JP, Hegbom F, Broch K, Lie OH, Lyseggen E, Haugaa KH, Gullestad L, Anfinssen OG. Effect of continuous positive airway pressure therapy on recurrence of atrial fibrillation after pulmonary vein isolation in patients with obstructive sleep apnea: A randomized controlled trial. *Heart Rhythm* 2022;**19**(9):1433-1441.
108. Kanagala R, Murali NS, Friedman PA, Ammash NM, Gersh BJ, Ballman KV, Shamsuzzaman AS, Somers VK. Obstructive sleep apnea and the recurrence of atrial fibrillation. *Circulation* 2003;**107**(20):2589-94.
109. Abumuamar AM, Newman D, Dorian P, Shapiro CM. Cardiac effects of CPAP treatment in patients with obstructive sleep apnea and atrial fibrillation. *J Interv Card Electrophysiol* 2019;**54**(3):289-297.
110. Alonso A, Bahnson JL, Gaussoin SA, Bertoni AG, Johnson KC, Lewis CE, Vetter M, Mantzoros CS, Jeffery RW, Soliman EZ. Effect of an intensive lifestyle intervention on atrial fibrillation risk in individuals with type 2 diabetes: the Look AHEAD randomized trial. *Am Heart J* 2015;**170**(4):770-777.e5.
111. Pathak RK, Elliott A, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Hendriks JM, Twomey D, Kalman JM, Abhayaratna WP, Lau DH, Sanders P. Impact of CARDIOrespiratory FITness on Arrhythmia Recurrence in Obese Individuals With Atrial Fibrillation: The CARDIO-FIT Study. *J Am Coll Cardiol* 2015;**66**(9):985-96.
112. Takahashi Y, Nitta J, Kobori A, Sakamoto Y, Nagata Y, Tanimoto K, Matsuo S, Yamane T, Morita N, Satomi K, Inaba O, Murata K, Sasaki Y, Yoshimoto D, Kaneko M, Tanimoto Y, Isogai R, Yamashita S, Sato H, Hanazawa R, Hirakawa A, Goya M, Sasano T. Alcohol Consumption Reduction and Clinical Outcomes of Catheter Ablation for Atrial Fibrillation. *Circ Arrhythm Electrophysiol* 2021;**14**(6):e009770.
113. Healey JS, Lopes RD, Granger CB, Alings M, Rivard L, McIntyre WF, Atar D, Birnie DH, Boriani G, Camm AJ, Conen D, Erath JW, Gold MR, Hohnloser SH, Ip J, Kautzner J, Kutyla V, Linde C, Mabo P, Mairesse G, Benezet Mazuecos J, Cosedis Nielsen J, Philippon F, Proietti M, Sticherling C, Wong JA, Wright DJ, Zarraga IG, Coutts SB, Kaplan A, Pombo M, Ayala-Paredes F, Xu L, Simek K, Nevills S, Mian R, Connolly SJ. Apixaban for Stroke Prevention in Subclinical Atrial Fibrillation. *N Engl J Med* 2024;**390**(2):107-117.
114. Kirchhof P, Toennis T, Goette A, Camm AJ, Diener HC, Becher N, Bertaglia E, Blomstrom Lundqvist C, Borlich M, Brandes A, Cabanelas N, Calvert M, Chlouverakis G, Dan GA, de Groot JR, Dichtl W, Kravchuk B, Lubiński A, Marijon E, Merkely B, Mont L, Ozga AK, Rajappan K, Sarkozy A, Scherr D, Sznajder R, Velchev V, Wichterle D, Sehner S, Simantirakis E, Lip GYH, Vardas P, Schotten U, Zapf A. Anticoagulation with Edoxaban in Patients with Atrial High-Rate Episodes. *N Engl J Med* 2023;**389**(13):1167-1179.
115. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;**146**(12):857-67.
116. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, Yamashita T, Antman EM. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014;**383**(9921):955-62.

117. van Walraven C, Hart RG, Singer DE, Laupacis A, Connolly S, Petersen P, Koudstaal PJ, Chang Y, Hellemons B. Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation: an individual patient meta-analysis. *JAMA* 2002;**288**(19):2441-8.
118. Lozier MR, Sanchez AM, Lee JJ, Donath EM, Font VE, Escolar E. Thromboembolic Outcomes of Different Anticoagulation Strategies for Patients with Atrial Fibrillation in the Setting of Hypertrophic Cardiomyopathy: A Systematic Review. *J Atr Fibrillation* 2019;**12**(4):2207.
119. Guttman OP, Rahman MS, O'Mahony C, Anastasakis A, Elliott PM. Atrial fibrillation and thromboembolism in patients with hypertrophic cardiomyopathy: systematic review. *Heart* 2014;**100**(6):465-72.
120. Hart RG, Pearce LA, Rothbart RM, McAnulty JH, Asinger RW, Halperin JL. Stroke with intermittent atrial fibrillation: incidence and predictors during aspirin therapy. Stroke Prevention in Atrial Fibrillation Investigators. *J Am Coll Cardiol* 2000;**35**(1):183-7.
121. Vilches S, Fontana M, Gonzalez-Lopez E, Mitrani L, Satri G, Renju M, Griffin JM, Caponetti A, Gnanasampathan S, De Los Santos J, Gagliardi C, Rivas A, Dominguez F, Longhi S, Rapezzi C, Maurer MS, Gillmore J, Garcia-Pavia P. Systemic embolism in amyloid transthyretin cardiomyopathy. *Eur J Heart Fail* 2022;**24**(8):1387-1396.
122. Lee SE, Park JK, Uhm JS, Kim JY, Pak HN, Lee MH, Joung B. Impact of atrial fibrillation on the clinical course of apical hypertrophic cardiomyopathy. *Heart* 2017;**103**(19):1496-1501.
123. Guttman OP, Pavlou M, O'Mahony C, Monserrat L, Anastasakis A, Rapezzi C, Biagini E, Gimeno JR, Limongelli G, Garcia-Pavia P, McKenna WJ, Omar RZ, Elliott PM. Prediction of thrombo-embolic risk in patients with hypertrophic cardiomyopathy (HCM Risk-CVA). *Eur J Heart Fail* 2015;**17**(8):837-45.
124. Hsu JC, Huang YT, Lin LY. Stroke risk in hypertrophic cardiomyopathy patients with atrial fibrillation: a nationwide database study. *Aging (Albany NY)* 2020;**12**(23):24219-24227.
125. Chao TF, Lip GYH, Liu CJ, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Liao JN, Chung FP, Chen TJ, Chen SA. Relationship of Aging and Incident Comorbidities to Stroke Risk in Patients With Atrial Fibrillation. *J Am Coll Cardiol* 2018;**71**(2):122-132.
126. Fauchier L, Bodin A, Bisson A, Herbert J, Spiesser P, Clementy N, Babuty D, Chao TF, Lip GYH. Incident Comorbidities, Aging and the Risk of Stroke in 608,108 Patients with Atrial Fibrillation: A Nationwide Analysis. *J Clin Med* 2020;**9**(4):1234.
127. Weijs B, Dudink E, de Vos CB, Limantoro I, Tieleman RG, Pisters R, Cheriex EC, Luermans J, Crijns H. Idiopathic atrial fibrillation patients rapidly outgrow their low thromboembolic risk: a 10-year follow-up study. *Neth Heart J* 2019;**27**(10):487-497.
128. Bezabhe WM, Bereznicki LR, Radford J, Wimmer BC, Salahudeen MS, Garrahy E, Bindoff I, Peterson GM. Stroke risk reassessment and oral anticoagulant initiation in primary care patients with atrial fibrillation: A ten-year follow-up. *Eur J Clin Invest* 2021;**51**(6):e13489.
129. Hirota T, Kubo T, Baba Y, Ochi Y, Takahashi A, Yamasaki N, Hamashige N, Yamamoto K, Kondo F, Bando K, Yamada E, Furuno T, Yabe T, Doi YL, Kitaoka H.

Clinical Profile of Thromboembolic Events in Patients With Hypertrophic Cardiomyopathy in a Regional Japanese Cohort- Results From Kochi RYOMA Study. *Circ J* 2019;**83**(8):1747-1754.

130. Nieuwlaat R, Dinh T, Olsson SB, Camm AJ, Capucci A, Tieleman RG, Lip GY, Crijns HJ. Should we abandon the common practice of withholding oral anticoagulation in paroxysmal atrial fibrillation? *Eur Heart J* 2008;**29**(7):915-22.

131. Lowenstern A, Al-Khatib SM, Sharan L, Chatterjee R, Allen LaPointe NM, Shah B, Borre ED, Raitz G, Goode A, Yapa R, Davis JK, Lallinger K, Schmidt R, Kosinski AS, Sanders GD. Interventions for Preventing Thromboembolic Events in Patients With Atrial Fibrillation: A Systematic Review. *Ann Intern Med* 2018;**169**(11):774-787.

132. Sanders GD, Lowenstern A, Borre E, Chatterjee R, Goode A, Sharan L, LaPointe NMA, Raitz G, Shah B, Yapa R, Davis JK, Lallinger K, Schmidt R, Kosinski A, Al-Khatib S. AHRQ Comparative Effectiveness Reviews. In. *Stroke Prevention in Patients With Atrial Fibrillation: A Systematic Review Update*. Rockville (MD): Agency for Healthcare Research and Quality (US); 2018.

133. Tomita H, Okumura K, Inoue H, Atarashi H, Yamashita T, Origasa H, Tsushima E. Validation of Risk Scoring System Excluding Female Sex From CHA₂DS₂-VASc in Japanese Patients With Nonvalvular Atrial Fibrillation – Subanalysis of the J-RHYTHM Registry. *Circ J* 2015;**79**(8):1719-26.

134. Cardoso R, Ternes CMP, Justino GB, Fernandes A, Rocha AV, Knijnik L, d'Avila A, Lopes RD. Non-Vitamin K Antagonists Versus Warfarin in Patients with Atrial Fibrillation and Bioprosthetic Valves: A Systematic Review and Meta-Analysis. *Am J Med* 2022;**135**(2):228-234 e1.

135. Kotecha D, Pollack CV, Jr., De Caterina R, Renda G, Kirchhof P. Direct Oral Anticoagulants Halve Thromboembolic Events After Cardioversion of AF Compared With Warfarin. *J Am Coll Cardiol* 2018;**72**(16):1984-1986.

136. Carnicelli AP, Hong H, Connolly SJ, Eikelboom J, Giugliano RP, Morrow DA, Patel MR, Wallentin L, Alexander JH, Cecilia Bahit M, Benz AP, Bohula EA, Chao TF, Dyal L, Ezekowitz M, K AAF, Gencer B, Halperin JL, Hijazi Z, Hohnloser SH, Hua K, Hylek E, Toda Kato E, Kuder J, Lopes RD, Mahaffey KW, Oldgren J, Piccini JP, Ruff CT, Steffel J, Wojdyla D, Granger CB. Direct Oral Anticoagulants Versus Warfarin in Patients With Atrial Fibrillation: Patient-Level Network Meta-Analyses of Randomized Clinical Trials With Interaction Testing by Age and Sex. *Circulation* 2022;**145**(4):242-255.

137. Heneghan C, Ward A, Perera R, Bankhead C, Fuller A, Stevens R, Bradford K, Tyndel S, Alonso-Coello P, Ansell J, Beyth R, Bernardo A, Christensen TD, Cromheecke ME, Edson RG, Fitzmaurice D, Gadisseur AP, Garcia-Alamino JM, Gardiner C, Hasenkam JM, Jacobson A, Kaatz S, Kamali F, Khan TI, Knight E, Körtke H, Levi M, Matchar D, Menéndez-Jándula B, Rakovac I, Schaefer C, Siebenhofer A, Souto JC, Sunderji R, Gin K, Shalansky K, Völler H, Wagner O, Zittermann A. Self-monitoring of oral anticoagulation: systematic review and meta-analysis of individual patient data. *Lancet* 2012;**379**(9813):322-34.

138. Joosten LPT, van Doorn S, van de Ven PM, Köhlen BTG, Nierman MC, Koek HL, Hemels MEW, Huisman MV, Kruip M, Faber LM, Wiersma NM, Buding WF, Fijnheer R, Adriaansen HJ, Roes KC, Hoes AW, Rutten FH, Geersing GJ. Safety of Switching From a Vitamin K Antagonist to a Non-Vitamin K Antagonist Oral

Anticoagulant in Frail Older Patients With Atrial Fibrillation: Results of the FRAIL-AF Randomized Controlled Trial. *Circulation* 2024;**149**(4):279-289.

139. Connolly SJ, Karthikeyan G, Ntsekhe M, Haileamlak A, El Sayed A, El Ghamrawy A, Damasceno A, Avezum A, Dans AML, Gitura B, Hu D, Kamanzi ER, Maklady F, Fana G, Gonzalez-Hermosillo JA, Musuku J, Kazmi K, Zühlke L, Gondwe L, Ma C, Paniagua M, Ogah OS, Molefe-Baikai OJ, Lwabi P, Chillo P, Sharma SK, Cabral TTJ, Tarhuni WM, Benz A, van Eikels M, Krol A, Pattath D, Balasubramanian K, Rangarajan S, Ramasundarahettige C, Mayosi B, Yusuf S. Rivaroxaban in Rheumatic Heart Disease-Associated Atrial Fibrillation. *N Engl J Med* 2022;**387**(11):978-988.

140. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II Study. *Lancet* 1994;**343**(8899):687-91.

141. Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomised clinical trial. *Lancet* 1996;**348**(9028):633-8.

142. Gulløv AL, Koefoed BG, Petersen P, Pedersen TS, Andersen ED, Godtfredsen J, Boysen G. Fixed minidose warfarin and aspirin alone and in combination vs adjusted-dose warfarin for stroke prevention in atrial fibrillation: Second Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation Study. *Arch Intern Med* 1998;**158**(14):1513-21.

143. Singer DE, Hughes RA, Gress DR, Sheehan MA, Oertel LB, Maraventano SW, Blewett DR, Rosner B, Kistler JP. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. *N Engl J Med* 1990;**323**(22):1505-11.

144. Macaluso GP, Pagani FD, Slaughter MS, Milano CA, Feller ED, Tatrooles AJ, Rogers JG, Wieselthaler GM. Time in Therapeutic Range Significantly Impacts Survival and Adverse Events in Destination Therapy Patients. *ASAIO J* 2022;**68**(1):14-20.

145. Alexander JH, Andersson U, Lopes RD, Hijazi Z, Hohnloser SH, Ezekowitz JA, Halvorsen S, Hanna M, Commerford P, Ruzyllo W, Huber K, Al-Khatib SM, Granger CB, Wallentin L. Apixaban 5 mg Twice Daily and Clinical Outcomes in Patients With Atrial Fibrillation and Advanced Age, Low Body Weight, or High Creatinine: A Secondary Analysis of a Randomized Clinical Trial. *JAMA Cardiol* 2016;**1**(6):673-81.

146. Wan Y, Heneghan C, Perera R, Roberts N, Hollowell J, Glasziou P, Bankhead C, Xu Y. Anticoagulation control and prediction of adverse events in patients with atrial fibrillation: a systematic review. *Circ Cardiovasc Qual Outcomes* 2008;**1**(2):84-91.

147. Vestergaard AS, Skjøth F, Larsen TB, Ehlers LH. The importance of mean time in therapeutic range for complication rates in warfarin therapy of patients with atrial fibrillation: A systematic review and meta-regression analysis. *PLoS One* 2017;**12**(11):e0188482.

148. Szummer K, Gasparini A, Eliasson S, Ärnlov J, Qureshi AR, Bárány P, Evans M, Friberg L, Carrero JJ. Time in Therapeutic Range and Outcomes After Warfarin Initiation in Newly Diagnosed Atrial Fibrillation Patients With Renal Dysfunction. *J Am Heart Assoc* 2017;**6**(3):e004925.

149. Själander S, Sjögren V, Renlund H, Norrving B, Själander A. Dabigatran, rivaroxaban and apixaban vs. high TTR warfarin in atrial fibrillation. *Thromb Res* 2018;**167**:113-118.
150. Yao X, Shah ND, Sangaralingham LR, Gersh BJ, Noseworthy PA. Non-Vitamin K Antagonist Oral Anticoagulant Dosing in Patients With Atrial Fibrillation and Renal Dysfunction. *J Am Coll Cardiol* 2017;**69**(23):2779-2790.
151. Krittayaphong R, Chantrarat T, Rojjarekumpai R, Jittham P, Sairat P, Lip GYH. Poor Time in Therapeutic Range Control is Associated with Adverse Clinical Outcomes in Patients with Non-Valvular Atrial Fibrillation: A Report from the Nationwide COOL-AF Registry. *J Clin Med* 2020;**9**(6):1698.
152. Steinberg BA, Shrader P, Thomas L, Ansell J, Fonarow GC, Gersh BJ, Kowey PR, Mahaffey KW, Naccarelli G, Reiffel J, Singer DE, Peterson ED, Piccini JP, Investigators O-A, Patients. Off-Label Dosing of Non-Vitamin K Antagonist Oral Anticoagulants and Adverse Outcomes: The ORBIT-AF II Registry. *J Am Coll Cardiol* 2016;**68**(24):2597-2604.
153. Song D, Zhou J, Fan T, Chang J, Qiu Y, Zhuang Z, Ma J, Zeng L. Decision aids for shared decision-making and appropriate anticoagulation therapy in patients with atrial fibrillation: a systematic review and meta-analysis. *Eur J Cardiovasc Nurs* 2022;**21**(2):97-106.
154. Shaikh F, Wynne R, Castelino RL, Inglis SC, Ferguson C. Effectiveness of Direct Oral Anticoagulants in Obese Adults With Atrial Fibrillation: A Systematic Review of Systematic Reviews and Meta-Analysis. *Front Cardiovasc Med* 2021;**8**:732828.
155. Grymonprez M, Simoens C, Steurbaut S, De Backer TL, Lahousse L. Worldwide trends in oral anticoagulant use in patients with atrial fibrillation from 2010 to 2018: a systematic review and meta-analysis. *Europace* 2022;**24**(6):887-898.
156. Sjalander S, Sjalander A, Svensson PJ, Friberg L. Atrial fibrillation patients do not benefit from acetylsalicylic acid. *Europace* 2014;**16**(5):631-8.
157. Vora P, Morgan Stewart H, Russell B, Asimwe A, Brobert G. Time Trends and Treatment Pathways in Prescribing Individual Oral Anticoagulants in Patients with Nonvalvular Atrial Fibrillation: An Observational Study of More than Three Million Patients from Europe and the United States. *Int J Clin Pract* 2022;**2022**:6707985.
158. Reinecke H, Engelbertz C, Bauersachs R, Breithardt G, Echterhoff HH, Gerß J, Haeusler KG, Hewing B, Hoyer J, Juergensmeyer S, Klingenberg T, Knapp G, Christian Rump L, Schmidt-Guertler H, Wanner C, Kirchhof P, Goerlich D. A Randomized Controlled Trial Comparing Apixaban With the Vitamin K Antagonist Phenprocoumon in Patients on Chronic Hemodialysis: The AXADIA-AFNET 8 Study. *Circulation* 2023;**147**(4):296-309.
159. Randhawa MS, Vishwanath R, Rai MP, Wang L, Randhawa AK, Abela G, Dhar G. Association Between Use of Warfarin for Atrial Fibrillation and Outcomes Among Patients With End-Stage Renal Disease: A Systematic Review and Meta-analysis. *JAMA Netw Open* 2020;**3**(4):e202175.
160. Rhee TM, Lee SR, Choi EK, Oh S, Lip GYH. Efficacy and Safety of Oral Anticoagulants for Atrial Fibrillation Patients With Chronic Kidney Disease: A Systematic Review and Meta-Analysis. *Front Cardiovasc Med* 2022;**9**:885548.

161. ACTIVE Investigators, Connolly SJ, Pogue J, Hart RG, Hohnloser SH, Pfeffer M, Chrolavicius S, Yusuf S. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med* 2009;**360**(20):2066-78.
162. Yasuda S, Kaikita K, Akao M, Ako J, Matoba T, Nakamura M, Miyauchi K, Hagiwara N, Kimura K, Hirayama A, Matsui K, Ogawa H, AFIRE Investigators. Antithrombotic Therapy for Atrial Fibrillation with Stable Coronary Disease. *N Engl J Med* 2019;**381**(12):1103-1113.
163. Lip GY. The role of aspirin for stroke prevention in atrial fibrillation. *Nat Rev Cardiol* 2011;**8**(10):602-6.
164. Shin DG, Kang MK, Han D, Choi S, Cho JR, Lee N. Enlarged left atrium and decreased left atrial strain are associated with atrial fibrillation in patients with hyperthyroidism irrespective of conventional risk factors. *Int J Cardiovasc Imaging* 2022;**38**(3):613-620.
165. Elvira Ruiz G, Caro Martínez C, Flores Blanco PJ, Cerezo Manchado JJ, Albendín Iglesias H, Lova Navarro A, Arregui Montoya F, García Alberola A, Pascual Figal DA, Bailén Lorenzo JL, Manzano-Fernández S. Effect of concomitant antiplatelet therapy in patients with nonvalvular atrial fibrillation initiating non-vitamin K antagonists. *Eur J Clin Invest* 2019;**49**(10):e13161.
166. Fox KAA, Velentgas P, Camm AJ, Bassand JP, Fitzmaurice DA, Gersh BJ, Goldhaber SZ, Goto S, Haas S, Misselwitz F, Pieper KS, Turpie AGG, Verheugt FWA, Dabrowski E, Luo K, Gibbs L, Kakkar AK. Outcomes Associated With Oral Anticoagulants Plus Antiplatelets in Patients With Newly Diagnosed Atrial Fibrillation. *JAMA Netw Open* 2020;**3**(2):e200107.
167. Verheugt FWA, Gao H, Al Mahmeed W, Ambrosio G, Angchaisuksiri P, Atar D, Bassand JP, Camm AJ, Cools F, Eikelboom J, Kayani G, Lim TW, Misselwitz F, Pieper KS, van Eickels M, Kakkar AK. Characteristics of patients with atrial fibrillation prescribed antiplatelet monotherapy compared with those on anticoagulants: insights from the GARFIELD-AF registry. *Eur Heart J* 2018;**39**(6):464-473.
168. Seiffge DJ, De Marchis GM, Koga M, Paciaroni M, Wilson D, Cappellari M, Macha Md K, Tsivgoulis G, Ambler G, Arihiro S, Bonati LH, Bonetti B, Kallmünzer B, Muir KW, Bovi P, Gensicke H, Inoue M, Schwab S, Yaghi S, Brown MM, Lyrer P, Takagi M, Acciarrese M, Jager HR, Polymeris AA, Toyoda K, Venti M, Traenka C, Yamagami H, Alberti A, Yoshimura S, Caso V, Engelter ST, Werring DJ. Ischemic Stroke despite Oral Anticoagulant Therapy in Patients with Atrial Fibrillation. *Ann Neurol* 2020;**87**(5):677-87.
169. Polymeris AA, Meinel TR, Oehler H, Hölscher K, Zietz A, Scheitz JF, Nolte CH, Stretz C, Yaghi S, Stoll S, Wang R, Häusler KG, Hellwig S, Klammer MG, Litmeier S, Leon Guerrero CR, Moeini-Naghani I, Michel P, Strambo D, Salerno A, Bianco G, Cereda C, Uphaus T, Gröschel K, Katan M, Wegener S, Peters N, Engelter ST, Lyrer PA, Bonati LH, Grunder L, Ringleb PA, Fischer U, Kallmünzer B, Purucker JC, Seiffge DJ. Aetiology, secondary prevention strategies and outcomes of ischaemic stroke despite oral anticoagulant therapy in patients with atrial fibrillation. *J Neurol Neurosurg Psychiatry* 2022;**93**(6):588-598.
170. Paciaroni M, Agnelli G, Caso V, Silvestrelli G, Seiffge DJ, Engelter S, De Marchis GM, Polymeris A, Zedde ML, Yaghi S, Michel P, Eskandari A, Antonenko K, Sohn SI, Cappellari M, Tassinari T, Tassi R, Masotti L, Katsanos AH, Giannopoulos

S, Acciarresi M, Alberti A, Venti M, Mosconi MG, Vedovati MC, Pierini P, Giustozzi M, Lotti EM, Ntaios G, Kargiotis O, Monaco S, Lochner P, Bandini F, Liantinioti C, Palaodimou L, Abdul-Rahim AH, Lees K, Mancuso M, Pantoni L, Rosa S, Bertora P, Galliazzo S, Ageno W, Toso E, Angelini F, Chiti A, Orlandi G, Denti L, Flomin Y, Marcheselli S, Mumoli N, Rimoldi A, Verrengia E, Schirinzi E, Del Sette M, Papamichalis P, Komnos A, Popovic N, Zarkov M, Rocco A, Diomedi M, Giorli E, Ciccone A, Mac Grory BC, Furie KL, Bonetti B, Saia V, Guideri F, Acampa M, Martini G, Grifoni E, Padroni M, Karagkiozi E, Perlepe K, Makaritsis K, Mannino M, Maccarrone M, Ulivi L, Giannini N, Ferrari E, Pezzini A, Doronin B, Volodina V, Baldi A, D'Amore C, Deleu D, Corea F, Putaala J, Santalucia P, Nardi K, Risitano A, Toni D, Tsivgoulis G. Causes and Risk Factors of Cerebral Ischemic Events in Patients With Atrial Fibrillation Treated With Non-Vitamin K Antagonist Oral Anticoagulants for Stroke Prevention. *Stroke* 2019;**50**(8):2168-2174.

171. Paciaroni M, Caso V, Agnelli G, Mosconi MG, Giustozzi M, Seiffge DJ, Engelter ST, Lyrer P, Polymeris AA, Kriemler L, Zietz A, Putaala J, Strbian D, Tomppo L, Michel P, Strambo D, Salerno A, Remillard S, Buehrer M, Bavaud O, Vanacker P, Zuurbier S, Yperzeele L, Loos CMJ, Cappellari M, Emiliani A, Zedde M, Abdul-Rahim A, Dawson J, Cronshaw R, Schirinzi E, Del Sette M, Stretz C, Kala N, Reznik M, Schomer A, Grory BM, Jayaraman M, McTaggart R, Yaghi S, Furie KL, Masotti L, Grifoni E, Toni D, Risitano A, Falcou A, Petraglia L, Lotti EM, Padroni M, Pavolucci L, Lochner P, Silvestrelli G, Ciccone A, Alberti A, Venti M, Traballi L, Urbini C, Kargiotis O, Rocco A, Diomedi M, Marcheselli S, Caliendo P, Zauli A, Reale G, Antonenko K, Rota E, Tassinari T, Saia V, Palmerini F, Aridon P, Arnao V, Monaco S, Cottone S, Baldi A, D'Amore C, Ageno W, Pegoraro S, Ntaios G, Sagris D, Giannopoulos S, Kosmidou M, Ntais E, Romoli M, Pantoni L, Rosa S, Bertora P, Chiti A, Canavero I, Saggese CE, Plocco M, Giorli E, Palaodimou L, Bakola E, Tsivgoulis G, Bandini F, Gasparro A, Terruso V, Mannino M, Pezzini A, Ornello R, Sacco S, Popovic N, Scoditti U, Genovese A, Denti L, Flomin Y, Mancuso M, Ferrari E, Caselli MC, Ulivi L, Giannini N, De Marchis GM. Recurrent Ischemic Stroke and Bleeding in Patients With Atrial Fibrillation Who Suffered an Acute Stroke While on Treatment With Nonvitamin K Antagonist Oral Anticoagulants: The RENO-EXTEND Study. *Stroke* 2022;**53**(8):2620-2627.

172. Reddy VY, Mobius-Winkler S, Miller MA, Neuzil P, Schuler G, Wiebe J, Sick P, Sievert H. Left atrial appendage closure with the Watchman device in patients with a contraindication for oral anticoagulation: the ASAP study (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology). *J Am Coll Cardiol* 2013;**61**(25):2551-6.

173. Boersma LV, Ince H, Kische S, Pokushalov E, Schmitz T, Schmidt B, Gori T, Meincke F, Protopopov AV, Betts T, Mazzone P, Foley D, Grygier M, Sievert H, De Potter T, Vireca E, Stein K, Bergmann MW, following i, institutions participated in the Es. Evaluating Real-World Clinical Outcomes in Atrial Fibrillation Patients Receiving the WATCHMAN Left Atrial Appendage Closure Technology: Final 2-Year Outcome Data of the EWOLUTION Trial Focusing on History of Stroke and Hemorrhage. *Circ Arrhythm Electrophysiol* 2019;**12**(4):e006841.

174. Tzikas A, Shakir S, Gafoor S, Omran H, Berti S, Santoro G, Kefer J, Landmesser U, Nielsen-Kudsk JE, Cruz-Gonzalez I, Sievert H, Tichelbacker T, Kanagaratnam P, Nietlispach F, Aminian A, Kasch F, Freixa X, Danna P, Rezzaghi M, Vermeersch P, Stock F, Stolcova M, Costa M, Ibrahim R, Schillinger W, Meier B, Park

JW. Left atrial appendage occlusion for stroke prevention in atrial fibrillation: multicentre experience with the AMPLATZER Cardiac Plug. *EuroIntervention* 2016;**11**(10):1170-9.

175. Boersma LV, Schmidt B, Betts TR, Sievert H, Tamburino C, Teiger E, Pokushalov E, Kische S, Schmitz T, Stein KM, Bergmann MW, investigators E. Implant success and safety of left atrial appendage closure with the WATCHMAN device: periprocedural outcomes from the EWOLUTION registry. *Eur Heart J* 2016;**37**(31):2465-74.

176. Lakkireddy D, Thaler D, Ellis CR, Swarup V, Sondergaard L, Carroll J, Gold MR, Hermiller J, Diener HC, Schmidt B, MacDonald L, Mansour M, Maini B, O'Brien L, Windecker S. Amplatzer Amulet Left Atrial Appendage Occluder Versus Watchman Device for Stroke Prophylaxis (Amulet IDE): A Randomized, Controlled Trial. *Circulation* 2021;**144**(19):1543-1552.

177. Reddy VY, Doshi SK, Sievert H, Buchbinder M, Neuzil P, Huber K, Halperin JL, Holmes D, PROTECT AF Investigators. Percutaneous left atrial appendage closure for stroke prophylaxis in patients with atrial fibrillation: 2.3-Year Follow-up of the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) Trial. *Circulation* 2013;**127**(6):720-9.

178. Osmancik P, Herman D, Neuzil P, Hala P, Taborsky M, Kala P, Poloczek M, Stasek J, Haman L, Branny M, Chovancik J, Cervinka P, Holy J, Kovarnik T, Zemanek D, Havranek S, Vancura V, Opatrny J, Peichl P, Tousek P, Lekesova V, Jarkovsky J, Novackova M, Benesova K, Widimsky P, Reddy VY, Investigators P-T. Left Atrial Appendage Closure Versus Direct Oral Anticoagulants in High-Risk Patients With Atrial Fibrillation. *J Am Coll Cardiol* 2020;**75**(25):3122-3135.

179. Holmes DR, Jr., Kar S, Price MJ, Whisenant B, Sievert H, Doshi SK, Huber K, Reddy VY. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. *J Am Coll Cardiol* 2014;**64**(1):1-12.

180. Freeman JV, Varosy P, Price MJ, Slotwiner D, Kusumoto FM, Rammohan C, Kavinsky CJ, Turi ZG, Akar J, Koutras C, Curtis JP, Masoudi FA. The NCDR Left Atrial Appendage Occlusion Registry. *J Am Coll Cardiol* 2020;**75**(13):1503-1518.

181. Kar S, Doshi SK, Sadhu A, Horton R, Osorio J, Ellis C, Stone J, Jr., Shah M, Dukkipati SR, Adler S, Nair DG, Kim J, Wazni O, Price MJ, Asch FM, Holmes DR, Jr., Shipley RD, Gordon NT, Allocco DJ, Reddy VY, Investigators PF. Primary Outcome Evaluation of a Next-Generation Left Atrial Appendage Closure Device: Results From the PINNACLE FLX Trial. *Circulation* 2021;**143**(18):1754-1762.

182. Whitlock RP, Belley-Cote EP, Paparella D, Healey JS, Brady K, Sharma M, Reents W, Budera P, Baddour AJ, Fila P, Devereaux PJ, Bogachev-Prokophiev A, Boening A, Teoh KHT, Tagarakis GI, Slaughter MS, Royse AG, McGuinness S, Alings M, Punjabi PP, Mazer CD, Folkerlinga RJ, Colli A, Avezum Á, Nakamya J, Balasubramanian K, Vincent J, Voisine P, Lamy A, Yusuf S, Connolly SJ. Left Atrial Appendage Occlusion during Cardiac Surgery to Prevent Stroke. *N Engl J Med* 2021;**384**(22):2081-2091.

183. Whitlock RP, Vincent J, Blackall MH, Hirsh J, Fremes S, Novick R, Devereaux PJ, Teoh K, Lamy A, Connolly SJ, Yusuf S, Carrier M, Healey JS. Left Atrial Appendage Occlusion Study II (LAAOS II). *Can J Cardiol* 2013;**29**(11):1443-7.

184. Park-Hansen J, Holme SJV, Irmukhamedov A, Carranza CL, Greve AM, Al-Farra G, Riis RGC, Nilsson B, Clausen JSR, Nørskov AS, Kruuse CR, Rostrup E, Dominguez H. Adding left atrial appendage closure to open heart surgery provides protection from ischemic brain injury six years after surgery independently of atrial fibrillation history: the LAACS randomized study. *J Cardiothorac Surg* 2018;**13**(1):53.
185. Caliskan E, Sahin A, Yilmaz M, Seifert B, Hinzpeter R, Alkadhi H, Cox JL, Holubec T, Reser D, Falk V, Grünenfelder J, Genoni M, Maisano F, Salzberg SP, Emmert MY. Epicardial left atrial appendage AtriClip occlusion reduces the incidence of stroke in patients with atrial fibrillation undergoing cardiac surgery. *Europace* 2018;**20**(7):e105-e114.
186. Nso N, Nassar M, Zirkiyeva M, Lakhdar S, Shaukat T, Guzman L, Alshamam M, Foster A, Bhangal R, Badejoko S, Lyonga Ngonge A, Tabot-Tabot M, Mbome Y, Rizzo V, Munira MS, Thambidorai S. Outcomes of cardiac surgery with left atrial appendage occlusion versus no Occlusion, direct oral Anticoagulants, and vitamin K Antagonists: A systematic review with Meta-analysis. *Int J Cardiol Heart Vasc* 2022;**40**:100998.
187. Ibrahim AM, Tandan N, Koester C, Al-Akchar M, Bhandari B, Botchway A, Abdelkarim J, Maini R, Labedi M. Meta-Analysis Evaluating Outcomes of Surgical Left Atrial Appendage Occlusion During Cardiac Surgery. *Am J Cardiol* 2019;**124**(8):1218-1225.
188. Soltesz EG, Dewan KC, Anderson LH, Ferguson MA, Gillinov AM. Improved outcomes in CABG patients with atrial fibrillation associated with surgical left atrial appendage exclusion. *J Card Surg* 2021;**36**(4):1201-1208.
189. Zhang S, Cui Y, Li J, Tian H, Yun Y, Zhou X, Fang H, Zhang H, Zou C, Ma X. Concomitant transcatheter occlusion versus thoracoscopic surgical clipping for left atrial appendage in patients undergoing ablation for atrial fibrillation: A meta-analysis. *Front Cardiovasc Med* 2022;**9**:970847.
190. van Laar C, Verberkmoes NJ, van Es HW, Lewalter T, Dunnington G, Stark S, Longoria J, Hofman FH, Pierce CM, Kotecha D, van Putte BP. Thoracoscopic Left Atrial Appendage Clipping: A Multicenter Cohort Analysis. *JACC Clin Electrophysiol* 2018;**4**(7):893-901.
191. Fu M, Qin Z, Zheng S, Li Y, Yang S, Zhao Y, Hu C, Zhou K, Zhou Y, Meng X. Thoracoscopic Left Atrial Appendage Occlusion for Stroke Prevention Compared with Long-Term Warfarin Therapy in Patients With Nonvalvular Atrial Fibrillation. *Am J Cardiol* 2019;**123**(1):50-56.
192. Cartledge R, Suwalski G, Witkowska A, Gottlieb G, Cioci A, Chidiac G, Ilsin B, Merrill B, Suwalski P. Standalone epicardial left atrial appendage exclusion for thromboembolism prevention in atrial fibrillation. *Interact Cardiovasc Thorac Surg* 2022;**34**(4):548-555.
193. Harskamp RE, Lucassen WAM, Lopes RD, Himmelreich JCL, Parati G, Weert H. Risk of stroke and bleeding in relation to hypertension in anticoagulated patients with atrial fibrillation: a meta-analysis of randomised controlled trials. *Acta Cardiol* 2022;**77**(3):191-195.
194. White HD, Gruber M, Feyzi J, Kaatz S, Tse HF, Husted S, Albers GW. Comparison of outcomes among patients randomized to warfarin therapy according

to anticoagulant control: results from SPORTIF III and V. *Arch Intern Med* 2007;**167**(3):239-45.

195. DiMarco JP, Flaker G, Waldo AL, Corley SD, Greene HL, Safford RE, Rosenfeld LE, Mitrani G, Nemeth M. Factors affecting bleeding risk during anticoagulant therapy in patients with atrial fibrillation: observations from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. *Am Heart J* 2005;**149**(4):650-6.

196. Gallego P, Roldán V, Torregrosa JM, Gálvez J, Valdés M, Vicente V, Marín F, Lip GY. Relation of the HAS-BLED bleeding risk score to major bleeding, cardiovascular events, and mortality in anticoagulated patients with atrial fibrillation. *Circ Arrhythm Electrophysiol* 2012;**5**(2):312-8.

197. Bouillon K, Bertrand M, Boudali L, Ducimetière P, Dray-Spira R, Zureik M. Short-Term Risk of Bleeding During Heparin Bridging at Initiation of Vitamin K Antagonist Therapy in More Than 90 000 Patients With Nonvalvular Atrial Fibrillation Managed in Outpatient Care. *J Am Heart Assoc* 2016;**5**(11):e004065.

198. Schulman S, Beyth RJ, Kearon C, Levine MN. Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008;**133**(6 Suppl):257s-298s.

199. Olesen JB, Lip GY, Lindhardsen J, Lane DA, Ahlehoff O, Hansen ML, Raunsø J, Tolstrup JS, Hansen PR, Gislason GH, Torp-Pedersen C. Risks of thromboembolism and bleeding with thromboprophylaxis in patients with atrial fibrillation: A net clinical benefit analysis using a 'real world' nationwide cohort study. *Thromb Haemost* 2011;**106**(4):739-49.

200. Kirchhof P, Haas S, Amarenco P, Hess S, Lambelet M, van Eickels M, Turpie AGG, Camm AJ. Impact of Modifiable Bleeding Risk Factors on Major Bleeding in Patients With Atrial Fibrillation Anticoagulated With Rivaroxaban. *J Am Heart Assoc* 2020;**9**(5):e009530.

201. Shireman TI, Howard PA, Kresowik TF, Ellerbeck EF. Combined anticoagulant-antiplatelet use and major bleeding events in elderly atrial fibrillation patients. *Stroke* 2004;**35**(10):2362-7.

202. Zerah L, Bonnet-Zamponi D, Ajrouche A, Collet JP, De Rycke Y, Tubach F. Inappropriate Use of Oral Antithrombotic Combinations in an Outpatient Setting and Associated Risks: A French Nationwide Cohort Study. *J Clin Med* 2021;**10**(11):2367.

203. Donze J, Clair C, Hug B, Rodondi N, Waeber G, Cornuz J, Aujesky D. Risk of falls and major bleeds in patients on oral anticoagulation therapy. *Am J Med* 2012;**125**(8):773-8.

204. Hilken NA, Algra A, Greving JP. Predicting Major Bleeding in Ischemic Stroke Patients With Atrial Fibrillation. *Stroke* 2017;**48**(11):3142-3144.

205. Gao X, Cai X, Yang Y, Zhou Y, Zhu W. Diagnostic Accuracy of the HAS-BLED Bleeding Score in VKA- or DOAC-Treated Patients With Atrial Fibrillation: A Systematic Review and Meta-Analysis. *Front Cardiovasc Med* 2021;**8**:757087.

206. Caldeira D, Costa J, Fernandes RM, Pinto FJ, Ferreira JJ. Performance of the HAS-BLED high bleeding-risk category, compared to ATRIA and HEMORR2HAGES

in patients with atrial fibrillation: a systematic review and meta-analysis. *J Interv Card Electrophysiol* 2014;**40**(3):277-84.

207. Borre ED, Goode A, Raitz G, Shah B, Lowenstern A, Chatterjee R, Sharan L, Allen LaPointe NM, Yapa R, Davis JK, Lallinger K, Schmidt R, Kosinski A, Al-Khatib SM, Sanders GD. Predicting Thromboembolic and Bleeding Event Risk in Patients with Non-Valvular Atrial Fibrillation: A Systematic Review. *Thromb Haemost* 2018;**118**(12):2171-2187.

208. Loewen P, Dahri K. Risk of bleeding with oral anticoagulants: an updated systematic review and performance analysis of clinical prediction rules. *Ann Hematol* 2011;**90**(10):1191-200.

209. Proietti M, Farcomeni A, Romiti GF, Di Rocco A, Placentino F, Diemberger I, Lip GY, Boriani G. Association between clinical risk scores and mortality in atrial fibrillation: Systematic review and network meta-regression of 669,000 patients. *Eur J Prev Cardiol* 2020;**27**(6):633-644.

210. Wang C, Yu Y, Zhu W, Yu J, Lip GYH, Hong K. Comparing the ORBIT and HAS-BLED bleeding risk scores in anticoagulated atrial fibrillation patients: a systematic review and meta-analysis. *Oncotarget* 2017;**8**(65):109703-109711.

211. Zeng J, Yu P, Cui W, Wang X, Ma J, Zeng C. Comparison of HAS-BLED with other risk models for predicting the bleeding risk in anticoagulated patients with atrial fibrillation: A PRISMA-compliant article. *Medicine (Baltimore)* 2020;**99**(25):e20782.

212. Zhu W, He W, Guo L, Wang X, Hong K. The HAS-BLED Score for Predicting Major Bleeding Risk in Anticoagulated Patients With Atrial Fibrillation: A Systematic Review and Meta-analysis. *Clin Cardiol* 2015;**38**(9):555-61.

213. Proietti M, Romiti GF, Vitolo M, Potpara TS, Boriani G, Lip GYH. Comparison of HAS-BLED and ORBIT bleeding risk scores in atrial fibrillation patients treated with non-vitamin K antagonist oral anticoagulants: a report from the ESC-EHRA EORP-AF General Long-Term Registry. *Eur Heart J Qual Care Clin Outcomes* 2022;**8**(7):778-786.

214. Fox KAA, Lucas JE, Pieper KS, Bassand JP, Camm AJ, Fitzmaurice DA, Goldhaber SZ, Goto S, Haas S, Hacke W, Kayani G, Oto A, Mantovani LG, Misselwitz F, Piccini JP, Turpie AGG, Verheugt FWA, Kakkar AK, Investigators G-A. Improved risk stratification of patients with atrial fibrillation: an integrated GARFIELD-AF tool for the prediction of mortality, stroke and bleed in patients with and without anticoagulation. *BMJ Open* 2017;**7**(12):e017157.

215. Milling TJ, Jr., Refaai MA, Sarode R, Lewis B, Mangione A, Durn BL, Harman A, Lee ML, Goldstein JN. Safety of a Four-factor Prothrombin Complex Concentrate Versus Plasma for Vitamin K Antagonist Reversal: An Integrated Analysis of Two Phase IIIb Clinical Trials. *Acad Emerg Med* 2016;**23**(4):466-75.

216. Pollack CV, Jr., Reilly PA, van Ryn J, Eikelboom JW, Glund S, Bernstein RA, Dubiel R, Huisman MV, Hylek EM, Kam CW, Kamphuisen PW, Kreuzer J, Levy JH, Royle G, Sellke FW, Stangier J, Steiner T, Verhamme P, Wang B, Young L, Weitz JI. Idarucizumab for Dabigatran Reversal - Full Cohort Analysis. *N Engl J Med* 2017;**377**(5):431-441.

217. Connolly SJ, Crowther M, Eikelboom JW, Gibson CM, Curnutte JT, Lawrence JH, Yue P, Bronson MD, Lu G, Conley PB, Verhamme P, Schmidt J, Middeldorp S,

- Cohen AT, Beyer-Westendorf J, Albaladejo P, Lopez-Sendon J, Demchuk AM, Pallin DJ, Concha M, Goodman S, Leeds J, Souza S, Siegal DM, Zotova E, Meeks B, Ahmad S, Nakamya J, Milling TJ, Jr. Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors. *N Engl J Med* 2019;**380**(14):1326-1335.
218. Fanikos J, Murwin D, Gruenenfelder F, Tartakovsky I, França LR, Reilly PA, Kermer P, Wowern FV, Lane DA, Butcher K. Global Use of Idarucizumab in Clinical Practice: Outcomes of the RE-VECTO Surveillance Program. *Thromb Haemost* 2020;**120**(1):27-35.
219. Milling TJ, Jr., Middeldorp S, Xu L, Koch B, Demchuk A, Eikelboom JW, Verhamme P, Cohen AT, Beyer-Westendorf J, Gibson CM, Lopez-Sendon J, Crowther M, Shoamanesh A, Coppens M, Schmidt J, Albaladejo P, Connolly SJ. Final Study Report of Andexanet Alfa for Major Bleeding With Factor Xa Inhibitors. *Circulation* 2023;**147**(13):1026-1038.
220. Ziff OJ, Lane DA, Samra M, Griffith M, Kirchhof P, Lip GY, Steeds RP, Townend J, Kotecha D. Safety and efficacy of digoxin: systematic review and meta-analysis of observational and controlled trial data. *BMJ* 2015;**351**:h4451.
221. Van Gelder IC, Groenveld HF, Crijns HJ, Tuininga YS, Tijssen JG, Alings AM, Hillege HL, Bergsma-Kadijk JA, Cornel JH, Kamp O, Tukkier R, Bosker HA, Van Veldhuisen DJ, Van den Berg MP, RACE II Investigators. Lenient versus strict rate control in patients with atrial fibrillation. *N Engl J Med* 2010;**362**(15):1363-73.
222. Brignole M, Pentimalli F, Palmisano P, Landolina M, Quartieri F, Occhetta E, Calò L, Mascia G, Mont L, Vernooy K, van Dijk V, Allaart C, Fauchier L, Gasparini M, Parati G, Soranna D, Rienstra M, Van Gelder IC. AV junction ablation and cardiac resynchronization for patients with permanent atrial fibrillation and narrow QRS: the APAF-CRT mortality trial. *Eur Heart J* 2021;**42**(46):4731-4739.
223. Delle Karth G, Geppert A, Neunteufl T, Priglinger U, Haumer M, Gschwandtner M, Siostrzonek P, Heinz G. Amiodarone versus diltiazem for rate control in critically ill patients with atrial tachyarrhythmias. *Crit Care Med* 2001;**29**(6):1149-53.
224. Brignole M, Pokushalov E, Pentimalli F, Palmisano P, Chieffo E, Occhetta E, Quartieri F, Calò L, Ungar A, Mont L. A randomized controlled trial of atrioventricular junction ablation and cardiac resynchronization therapy in patients with permanent atrial fibrillation and narrow QRS. *Eur Heart J* 2018;**39**(45):3999-4008.
225. Andrade JG, Roy D, Wyse DG, Tardif JC, Talajic M, Leduc H, Tourigny JC, Shohoudi A, Dubuc M, Rivard L, Guerra PG, Thibault B, Dyrda K, Macle L, Khairy P. Heart rate and adverse outcomes in patients with atrial fibrillation: A combined AFFIRM and AF-CHF substudy. *Heart Rhythm* 2016;**13**(1):54-61.
226. Olshansky B, Rosenfeld LE, Warner AL, Solomon AJ, O'Neill G, Sharma A, Platia E, Feld GK, Akiyama T, Brodsky MA, Greene HL. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study: approaches to control rate in atrial fibrillation. *J Am Coll Cardiol* 2004;**43**(7):1201-8.
227. Tisdale JE, Padhi ID, Goldberg AD, Silverman NA, Webb CR, Higgins RS, Paone G, Frank DM, Borzak S. A randomized, double-blind comparison of intravenous diltiazem and digoxin for atrial fibrillation after coronary artery bypass surgery. *Am Heart J* 1998;**135**(5 Pt 1):739-47.

228. Ulimoen SR, Enger S, Carlson J, Platonov PG, Pripp AH, Abdelnoor M, Arnesen H, Gjesdal K, Tveit A. Comparison of four single-drug regimens on ventricular rate and arrhythmia-related symptoms in patients with permanent atrial fibrillation. *Am J Cardiol* 2013;**111**(2):225-30.
229. Figulla HR, Gietzen F, Zeymer U, Raiber M, Hegselmann J, Soballa R, Hilgers R. Diltiazem improves cardiac function and exercise capacity in patients with idiopathic dilated cardiomyopathy. Results of the Diltiazem in Dilated Cardiomyopathy Trial. *Circulation* 1996;**94**(3):346-52.
230. Khand AU, Rankin AC, Martin W, Taylor J, Gemmell I, Cleland JG. Carvedilol alone or in combination with digoxin for the management of atrial fibrillation in patients with heart failure? *J Am Coll Cardiol* 2003;**42**(11):1944-51.
231. Mulder BA, Van Veldhuisen DJ, Crijns HJ, Tijssen JG, Hillege HL, Alings M, Rienstra M, Van den Berg MP, Van Gelder IC. Digoxin in patients with permanent atrial fibrillation: data from the RACE II study. *Heart Rhythm* 2014;**11**(9):1543-50.
232. Nikolaidou T, Channer KS. Chronic atrial fibrillation: a systematic review of medical heart rate control management. *Postgrad Med J* 2009;**85**(1004):303-12.
233. Scheuermeyer FX, Grafstein E, Stenstrom R, Christenson J, Heslop C, Heilbron B, McGrath L, Innes G. Safety and efficiency of calcium channel blockers versus beta-blockers for rate control in patients with atrial fibrillation and no acute underlying medical illness. *Acad Emerg Med* 2013;**20**(3):222-30.
234. Hess PL, Sheng S, Matsouaka R, DeVore AD, Heidenreich PA, Yancy CW, Bhatt DL, Allen LA, Peterson PN, Ho PM, Lewis WR, Hernandez AF, Fonarow GC, Piccini JP. Strict Versus Lenient Versus Poor Rate Control Among Patients With Atrial Fibrillation and Heart Failure (from the Get With The Guidelines - Heart Failure Program). *Am J Cardiol* 2020;**125**(6):894-900.
235. Perrett M, Gohil N, Tica O, Bunting KV, Kotecha D. Efficacy and safety of intravenous beta-blockers in acute atrial fibrillation and flutter is dependent on beta-1 selectivity: a systematic review and meta-analysis of randomised trials. *Clin Res Cardiol* 2023.
236. Segal JB, McNamara RL, Miller MR, Kim N, Goodman SN, Powe NR, Robinson K, Yu D, Bass EB. The evidence regarding the drugs used for ventricular rate control. *J Fam Pract* 2000;**49**(1):47-59.
237. Siu CW, Lau CP, Lee WL, Lam KF, Tse HF. Intravenous diltiazem is superior to intravenous amiodarone or digoxin for achieving ventricular rate control in patients with acute uncomplicated atrial fibrillation. *Crit Care Med* 2009;**37**(7):2174-9; quiz 2180.
238. Schreck DM, Rivera AR, Tricarico VJ. Emergency management of atrial fibrillation and flutter: intravenous diltiazem versus intravenous digoxin. *Ann Emerg Med* 1997;**29**(1):135-40.
239. Hou ZY, Chang MS, Chen CY, Tu MS, Lin SL, Chiang HT, Woosley RL. Acute treatment of recent-onset atrial fibrillation and flutter with a tailored dosing regimen of intravenous amiodarone. A randomized, digoxin-controlled study. *Eur Heart J* 1995;**16**(4):521-8.
240. Roth A, Harrison E, Mitani G, Cohen J, Rahimtoola SH, Elkayam U. Efficacy and safety of medium- and high-dose diltiazem alone and in combination with digoxin

for control of heart rate at rest and during exercise in patients with chronic atrial fibrillation. *Circulation* 1986;**73**(2):316-24.

241. David D, Segni ED, Klein HO, Kaplinsky E. Inefficacy of digitalis in the control of heart rate in patients with chronic atrial fibrillation: beneficial effect of an added beta adrenergic blocking agent. *Am J Cardiol* 1979;**44**(7):1378-82.

242. Hao J, Zhou J, Xu W, Chen C, Zhang J, Peng H, Liu L. Beta-Blocker Landiolol Hydrochloride in Preventing Atrial Fibrillation Following Cardiothoracic Surgery: A Systematic Review and Meta-Analysis. *Ann Thorac Cardiovasc Surg* 2022;**28**(1):18-31.

243. Gosselink AT, Crijns HJ, Van Gelder IC, Hillige H, Wiesfeld AC, Lie KI. Low-dose amiodarone for maintenance of sinus rhythm after cardioversion of atrial fibrillation or flutter. *JAMA* 1992;**267**(24):3289-93.

244. Lim KT, Davis MJ, Powell A, Arnolda L, Moulden K, Bulsara M, Weerasooriya R. Ablate and pace strategy for atrial fibrillation: long-term outcome of AIRCRAFT trial. *Europace* 2007;**9**(7):498-505.

245. Weerasooriya R, Davis M, Powell A, Szili-Torok T, Shah C, Whalley D, Kanagaratnam L, Heddle W, Leitch J, Perks A, Ferguson L, Bulsara M. The Australian Intervention Randomized Control of Rate in Atrial Fibrillation Trial (AIRCRAFT). *J Am Coll Cardiol* 2003;**41**(10):1697-702.

246. Wood MA, Brown-Mahoney C, Kay GN, Ellenbogen KA. Clinical outcomes after ablation and pacing therapy for atrial fibrillation : a meta-analysis. *Circulation* 2000;**101**(10):1138-44.

247. Huang W, Su L, Wu S, Xu L, Xiao F, Zhou X, Ellenbogen KA. Benefits of Permanent His Bundle Pacing Combined With Atrioventricular Node Ablation in Atrial Fibrillation Patients With Heart Failure With Both Preserved and Reduced Left Ventricular Ejection Fraction. *J Am Heart Assoc* 2017;**6**(4):e005309.

248. Vijayaraman P, Subzposh FA, Naperkowski A. Atrioventricular node ablation and His bundle pacing. *Europace* 2017;**19**(suppl_4):iv10-iv16.

249. Wang RX, Lee HC, Hodge DO, Cha YM, Friedman PA, Rea RF, Munger TM, Jahangir A, Srivathsan K, Shen WK. Effect of pacing method on risk of sudden death after atrioventricular node ablation and pacemaker implantation in patients with atrial fibrillation. *Heart Rhythm* 2013;**10**(5):696-701.

250. Ozcan C, Jahangir A, Friedman PA, Patel PJ, Munger TM, Rea RF, Lloyd MA, Packer DL, Hodge DO, Gersh BJ, Hammill SC, Shen WK. Long-term survival after ablation of the atrioventricular node and implantation of a permanent pacemaker in patients with atrial fibrillation. *N Engl J Med* 2001;**344**(14):1043-51.

251. Queiroga A, Marshall HJ, Clune M, Gammage MD. Ablate and pace revisited: long term survival and predictors of permanent atrial fibrillation. *Heart* 2003;**89**(9):1035-8.

252. Telles-Garcia N, Dahal K, Kocherla C, Lip GYH, Reddy P, Dominic P. Non-vitamin K antagonists oral anticoagulants are as safe and effective as warfarin for cardioversion of atrial fibrillation: A systematic review and meta-analysis. *Int J Cardiol* 2018;**268**:143-148.

253. Brunetti ND, Tarantino N, De Gennaro L, Correale M, Santoro F, Di Biase M. Direct oral anti-coagulants compared to vitamin-K antagonists in cardioversion of atrial fibrillation: an updated meta-analysis. *J Thromb Thrombolysis* 2018;**45**(4):550-556.
254. Steinberg JS, Sadaniantz A, Kron J, Krahn A, Denny DM, Daubert J, Campbell WB, Havranek E, Murray K, Olshansky B, O'Neill G, Sami M, Schmidt S, Storm R, Zabalgoitia M, Miller J, Chandler M, Nasco EM, Greene HL. Analysis of cause-specific mortality in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. *Circulation* 2004;**109**(16):1973-80.
255. Klein AL, Grimm RA, Murray RD, Apperson-Hansen C, Asinger RW, Black IW, Davidoff R, Erbel R, Halperin JL, Orsinelli DA, Porter TR, Stoddard MF, Assessment of Cardioversion Using Transesophageal Echocardiography Investigators. Use of transesophageal echocardiography to guide cardioversion in patients with atrial fibrillation. *N Engl J Med* 2001;**344**(19):1411-20.
256. Pluymaekers N, Dudink E, Luermans J, Meeder JG, Lenderink T, Widdershoven J, Bucx JJJ, Rienstra M, Kamp O, Van Opstal JM, Alings M, Oomen A, Kirchhof CJ, Van Dijk VF, Ramanna H, Liem A, Dekker LR, Essers BAB, Tijssen JGP, Van Gelder IC, Crijns H. Early or Delayed Cardioversion in Recent-Onset Atrial Fibrillation. *N Engl J Med* 2019;**380**(16):1499-1508.
257. Ezekowitz MD, Pollack CV, Jr., Halperin JL, England RD, VanPelt Nguyen S, Spahr J, Sudworth M, Cater NB, Breazna A, Oldgren J, Kirchhof P. Apixaban compared to heparin/vitamin K antagonist in patients with atrial fibrillation scheduled for cardioversion: the EMANATE trial. *Eur Heart J* 2018;**39**(32):2959-2971.
258. Cappato R, Ezekowitz MD, Klein AL, Camm AJ, Ma CS, Le Heuzey JY, Talajic M, Scanavacca M, Vardas PE, Kirchhof P, Hemmrich M, Lanius V, Meng IL, Wildgoose P, van Eickels M, Hohnloser SH. Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial fibrillation. *Eur Heart J* 2014;**35**(47):3346-55.
259. Kirchhof P, Andresen D, Bosch R, Borggrefe M, Meinertz T, Parade U, Ravens U, Samol A, Steinbeck G, Treszl A, Wegscheider K, Breithardt G. Short-term versus long-term antiarrhythmic drug treatment after cardioversion of atrial fibrillation (Flec-SL): a prospective, randomised, open-label, blinded endpoint assessment trial. *Lancet* 2012;**380**(9838):238-46.
260. Goette A, Merino JL, Ezekowitz MD, Zamoryakhin D, Melino M, Jin J, Mercuri MF, Grosso MA, Fernandez V, Al-Saady N, Pelekh N, Merkely B, Zenin S, Kushnir M, Spinar J, Batushkin V, de Groot JR, Lip GY, ENSURE-AF investigators. Edoxaban versus enoxaparin-warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): a randomised, open-label, phase 3b trial. *Lancet* 2016;**388**(10055):1995-2003.
261. Stellbrink C, Nixdorff U, Hofmann T, Lehmacher W, Daniel WG, Hanrath P, Geller C, Mugge A, Sehnert W, Schmidt-Lucke C, Schmidt-Lucke JA, Group ACES. Safety and efficacy of enoxaparin compared with unfractionated heparin and oral anticoagulants for prevention of thromboembolic complications in cardioversion of nonvalvular atrial fibrillation: the Anticoagulation in Cardioversion using Enoxaparin (ACE) trial. *Circulation* 2004;**109**(8):997-1003.
262. Zhu W, Wu Z, Dong Y, Lip GYH, Liu C. Effectiveness of early rhythm control in improving clinical outcomes in patients with atrial fibrillation: a systematic review and meta-analysis. *BMC Med* 2022;**20**(1):340.

263. Crijns HJ, Weijs B, Fairley AM, Lewalter T, Maggioni AP, Martín A, Ponikowski P, Rosenqvist M, Sanders P, Scanavacca M, Bash LD, Chazelle F, Bernhardt A, Gitt AK, Lip GY, Le Heuzey JY. Contemporary real life cardioversion of atrial fibrillation: Results from the multinational RHYTHM-AF study. *Int J Cardiol* 2014;**172**(3):588-94.
264. Lip GY, Hammerstingl C, Marin F, Cappato R, Meng IL, Kirsch B, van Eickels M, Cohen A, study XT, CLOT-AF registry investigators. Left atrial thrombus resolution in atrial fibrillation or flutter: Results of a prospective study with rivaroxaban (X-TRA) and a retrospective observational registry providing baseline data (CLOT-AF). *Am Heart J* 2016;**178**:126-34.
265. Bonfanti L, Annovi A, Sanchis-Gomar F, Saccenti C, Meschi T, Ticinesi A, Cervellin G. Effectiveness and safety of electrical cardioversion for acute-onset atrial fibrillation in the emergency department: a real-world 10-year single center experience. *Clin Exp Emerg Med* 2019;**6**(1):64-69.
266. Um KJ, McIntyre WF, Mendoza PA, Ibrahim O, Nguyen ST, Lin SH, Duceppe E, Rochwerg B, Healey JS, Koziarz A, Lengyel AP, Bhatnagar A, Amit G, Chu VA, Whitlock RP, Belley-Côté EP. Pre-treatment with antiarrhythmic drugs for elective electrical cardioversion of atrial fibrillation: a systematic review and network meta-analysis. *Europace* 2022;**24**(10):1548-1559.
267. Schmidt AS, Lauridsen KG, Møller DS, Christensen PD, Dodt KK, Rickers H, Løfgren B, Albertsen AE. Anterior-Lateral Versus Anterior-Posterior Electrode Position for Cardioverting Atrial Fibrillation. *Circulation* 2021;**144**(25):1995-2003.
268. Kirchhof P, Eckardt L, Loh P, Weber K, Fischer RJ, Seidl KH, Böcker D, Breithardt G, Haverkamp W, Borggrefe M. Anterior-posterior versus anterior-lateral electrode positions for external cardioversion of atrial fibrillation: a randomised trial. *Lancet* 2002;**360**(9342):1275-9.
269. Squara F, Elbaum C, Garret G, Liprandi L, Scarlatti D, Bun SS, Mossaz B, Rocher M, Bateau J, Moceri P, Ferrari E. Active compression versus standard anterior-posterior defibrillation for external cardioversion of atrial fibrillation: A prospective randomized study. *Heart Rhythm* 2021;**18**(3):360-365.
270. Schmidt AS, Lauridsen KG, Torp P, Bach LF, Rickers H, Løfgren B. Maximum-fixed energy shocks for cardioverting atrial fibrillation. *Eur Heart J* 2020;**41**(5):626-631.
271. Schmidt AS, Lauridsen KG, Adelborg K, Torp P, Bach LF, Jepsen SM, Hornung N, Deakin CD, Rickers H, Løfgren B. Cardioversion Efficacy Using Pulsed Biphasic or Biphasic Truncated Exponential Waveforms: A Randomized Clinical Trial. *J Am Heart Assoc* 2017;**6**(3):e004853.
272. Glover BM, Walsh SJ, McCann CJ, Moore MJ, Manoharan G, Dalzell GW, McAllister A, McClements B, McEneaney DJ, Trouton TG, Mathew TP, Adgey AA. Biphasic energy selection for transthoracic cardioversion of atrial fibrillation. The BEST AF Trial. *Heart* 2008;**94**(7):884-7.
273. Trendafilova E, Dimitrova E, Didon JP, Krasteva V. A Randomized Comparison of Delivered Energy in Cardioversion of Atrial Fibrillation: Biphasic Truncated Exponential Versus Pulsed Biphasic Waveforms. *Diagnostics (Basel)* 2021;**11**(6):1107.
274. Stiell IG, Archambault PM, Morris J, Mercier E, Eagles D, Perry JJ, Scheuermeyer F, Clark G, Gosselin S, Vadeboncoeur A, Parkash R, de Wit K, Patey

AM, Thiruganasambandamoorthy V, Taljaard M. RAFF-3 Trial: A Stepped-Wedge Cluster Randomised Trial to Improve Care of Acute Atrial Fibrillation and Flutter in the Emergency Department. *Can J Cardiol* 2021;**37**(10):1569-1577.

275. Guerra F, Pavoni I, Romandini A, Baldetti L, Matassini MV, Brambatti M, Luzi M, Pupita G, Capucci A. Feasibility of a cardiologist-only approach to sedation for electrical cardioversion of atrial fibrillation: a randomized, open-blinded, prospective study. *Int J Cardiol* 2014;**176**(3):930-5.

276. Stronati G, Capucci A, Dello Russo A, Adrario E, Carsetti A, Casella M, Donati A, Guerra F. Procedural sedation for direct current cardioversion: a feasibility study between two management strategies in the emergency department. *BMC Cardiovasc Disord* 2020;**20**(1):388.

277. Stiell IG, Eagles D, Nemnom MJ, Brown E, Taljaard M, Archambault PM, Birnie D, Borgundvaag B, Clark G, Davis P, Godin D, Hohl CM, Mathieu B, McRae AD, Mercier E, Morris J, Parkash R, Perry JJ, Rowe BH, Thiruganasambandamoorthy V, Scheuermeyer F, Sivilotti MLA, Vadeboncoeur A. Adverse Events Associated With Electrical Cardioversion in Patients With Acute Atrial Fibrillation and Atrial Flutter. *Can J Cardiol* 2021;**37**(11):1775-1782.

278. Kotecha D, Lam CS, Van Veldhuisen DJ, Van Gelder IC, Voors AA, Rienstra M. Heart Failure With Preserved Ejection Fraction and Atrial Fibrillation: Vicious Twins. *J Am Coll Cardiol* 2016;**68**(20):2217-2228.

279. Eid M, Abu Jazar D, Medhekar A, Khalife W, Javaid A, Ahsan C, Shabarek N, Saad M, Rao M, Ong K, Jneid H, Elbadawi A. Anterior-Posterior versus anterior-lateral electrodes position for electrical cardioversion of atrial fibrillation: A meta-analysis of randomized controlled trials. *Int J Cardiol Heart Vasc* 2022;**43**:101129.

280. Schmidt AS, Lauridsen KG, Adelborg K, Torp P, Bach LF, Jepsen SM, Hornung N, Deakin CD, Rickers H, Løfgren B. Cardioversion Efficacy Using Pulsed Biphasic or Biphasic Truncated Exponential Waveforms: A Randomized Clinical Trial. *J Am Heart Assoc* 2017;**6**(3).

281. Trendafilova E, Dimitrova E, Didon JP, Krasteva V. A Randomized Comparison of Delivered Energy in Cardioversion of Atrial Fibrillation: Biphasic Truncated Exponential Versus Pulsed Biphasic Waveforms. *Diagnostics (Basel)* 2021;**11**(6).

282. Singh BN, Singh SN, Reda DJ, Tang XC, Lopez B, Harris CL, Fletcher RD, Sharma SC, Atwood JE, Jacobson AK, Lewis HD, Jr., Raisch DW, Ezekowitz MD. Amiodarone versus sotalol for atrial fibrillation. *N Engl J Med* 2005;**352**(18):1861-72.

283. Markey GC, Salter N, Ryan J. Intravenous Flecainide for Emergency Department Management of Acute Atrial Fibrillation. *J Emerg Med* 2018;**54**(3):320-327.

284. Camm AJ, Capucci A, Hohnloser SH, Torp-Pedersen C, Van Gelder IC, Mangal B, Beatch G, AVRO Investigators. A randomized active-controlled study comparing the efficacy and safety of vernakalant to amiodarone in recent-onset atrial fibrillation. *J Am Coll Cardiol* 2011;**57**(3):313-21.

285. Deedwania PC, Singh BN, Ellenbogen K, Fisher S, Fletcher R, Singh SN. Spontaneous conversion and maintenance of sinus rhythm by amiodarone in patients with heart failure and atrial fibrillation: observations from the veterans affairs congestive heart failure survival trial of antiarrhythmic therapy (CHF-STAT). *The*

Department of Veterans Affairs CHF-STAT Investigators. *Circulation* 1998;**98**(23):2574-9.

286. Conde D, Costabel JP, Caro M, Ferro A, Lambardi F, Corrales Barboza A, Lavallo Cobo A, Trivi M. Flecainide versus vernakalant for conversion of recent-onset atrial fibrillation. *Int J Cardiol* 2013;**168**(3):2423-5.

287. Reisinger J, Gatterer E, Lang W, Vanicek T, Eisserer G, Bachleitner T, Niemeth C, Aicher F, Grander W, Heinze G, Kuhn P, Siostrzonek P. Flecainide versus ibutilide for immediate cardioversion of atrial fibrillation of recent onset. *Eur Heart J* 2004;**25**(15):1318-24.

288. Roy D, Pratt CM, Torp-Pedersen C, Wyse DG, Toft E, Juul-Moller S, Nielsen T, Rasmussen SL, Stiell IG, Coutu B, Ip JH, Pritchett EL, Camm AJ, Atrial Arrhythmia Conversion Trial Investigators. Vernakalant hydrochloride for rapid conversion of atrial fibrillation: a phase 3, randomized, placebo-controlled trial. *Circulation* 2008;**117**(12):1518-25.

289. Zhang N, Guo JH, Zhang H, Li XB, Zhang P, Xn Y. Comparison of intravenous ibutilide vs. propafenone for rapid termination of recent onset atrial fibrillation. *Int J Clin Pract* 2005;**59**(12):1395-400.

290. Martinez-Marcos FJ, Garcia-Garmendia JL, Ortega-Carpio A, Fernandez-Gomez JM, Santos JM, Camacho C. Comparison of intravenous flecainide, propafenone, and amiodarone for conversion of acute atrial fibrillation to sinus rhythm. *Am J Cardiol* 2000;**86**(9):950-3.

291. Khan IA. Single oral loading dose of propafenone for pharmacological cardioversion of recent-onset atrial fibrillation. *J Am Coll Cardiol* 2001;**37**(2):542-7.

292. Hofmann R, Steinwender C, Kammler J, Kypta A, Wimmer G, Leisch F. Intravenous amiodarone bolus for treatment of atrial fibrillation in patients with advanced congestive heart failure or cardiogenic shock. *Wien Klin Wochenschr* 2004;**116**(21-22):744-9.

293. Alboni P, Botto GL, Baldi N, Luzi M, Russo V, Gianfranchi L, Marchi P, Calzolari M, Solano A, Baroffio R, Gaggioli G. Outpatient treatment of recent-onset atrial fibrillation with the "pill-in-the-pocket" approach. *N Engl J Med* 2004;**351**(23):2384-91.

294. Alboni P, Botto GL, Boriani G, Russo G, Pacchioni F, Iori M, Pasanisi G, Mancini M, Mariconti B, Capucci A. Intravenous administration of flecainide or propafenone in patients with recent-onset atrial fibrillation does not predict adverse effects during 'pill-in-the-pocket' treatment. *Heart* 2010;**96**(7):546-9.

295. Valembois L, Audureau E, Takeda A, Jarzebowski W, Belmin J, Lafuente-Lafuente C. Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation. *Cochrane Database Syst Rev* 2019;**9**(9):Cd005049.

296. Kochiadakis GE, Marketou ME, Igoumenidis NE, Chrysostomakis SI, Mavrakis HE, Kaleboubas MD, Vardas PE. Amiodarone, sotalol, or propafenone in atrial fibrillation: which is preferred to maintain normal sinus rhythm? *Pacing Clin Electrophysiol* 2000;**23**(11 Pt 2):1883-7.

297. Roy D, Talajic M, Dorian P, Connolly S, Eisenberg MJ, Green M, Kus T, Lambert J, Dubuc M, Gagne P, Nattel S, Thibault B. Amiodarone to prevent recurrence of atrial fibrillation. Canadian Trial of Atrial Fibrillation Investigators. *N Engl J Med* 2000;**342**(13):913-20.

298. Stroobandt R, Stiels B, Hoebrechts R. Propafenone for conversion and prophylaxis of atrial fibrillation. Propafenone Atrial Fibrillation Trial Investigators. *Am J Cardiol* 1997;**79**(4):418-23.
299. Ehrlich JR, Look C, Kostev K, Israel CW, Goette A. Impact of dronedarone on the risk of myocardial infarction and stroke in atrial fibrillation patients followed in general practices in Germany. *Int J Cardiol* 2019;**278**:126-132.
300. Chevalier P, Durand-Dubief A, Burri H, Cucherat M, Kirkorian G, Touboul P. Amiodarone versus placebo and class Ic drugs for cardioversion of recent-onset atrial fibrillation: a meta-analysis. *J Am Coll Cardiol* 2003;**41**(2):255-62.
301. Jais P, Cauchemez B, Macle L, Daoud E, Khairy P, Subbiah R, Hocini M, Extramiana F, Sacher F, Bordachar P, Klein G, Weerasooriya R, Clementy J, Haissaguerre M. Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: the A4 study. *Circulation* 2008;**118**(24):2498-505.
302. Wilber DJ, Pappone C, Neuzil P, De Paola A, Marchlinski F, Natale A, Macle L, Daoud EG, Calkins H, Hall B, Reddy V, Augello G, Reynolds MR, Vinekar C, Liu CY, Berry SM, Berry DA, ThermoCool AF Trial Investigators. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. *JAMA* 2010;**303**(4):333-40.
303. Packer DL, Kowal RC, Wheelan KR, Irwin JM, Champagne J, Guerra PG, Dubuc M, Reddy V, Nelson L, Holcomb RG, Lehmann JW, Ruskin JN, Investigators SAC. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front (STOP AF) pivotal trial. *J Am Coll Cardiol* 2013;**61**(16):1713-23.
304. Packer DL, Mark DB, Robb RA, Monahan KH, Bahnson TD, Poole JE, Noseworthy PA, Rosenberg YD, Jeffries N, Mitchell LB, Flaker GC, Pokushalov E, Romanov A, Bunch TJ, Noelker G, Ardashev A, Revishvili A, Wilber DJ, Cappato R, Kuck KH, Hindricks G, Davies DW, Kowey PR, Naccarelli GV, Reiffel JA, Piccini JP, Silverstein AP, Al-Khalidi HR, Lee KL. Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients With Atrial Fibrillation: The CABANA Randomized Clinical Trial. *JAMA* 2019;**321**(13):1261-1274.
305. Wazni OM, Marrouche NF, Martin DO, Verma A, Bhargava M, Saliba W, Bash D, Schweikert R, Brachmann J, Gunther J, Gutleben K, Pisano E, Potenza D, Fanelli R, Raviele A, Themistoclakis S, Rossillo A, Bonso A, Natale A. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of symptomatic atrial fibrillation: a randomized trial. *JAMA* 2005;**293**(21):2634-40.
306. Cosedis Nielsen J, Johannessen A, Raatikainen P, Hindricks G, Walfridsson H, Kongstad O, Pehrson S, Englund A, Hartikainen J, Mortensen LS, Hansen PS. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. *N Engl J Med* 2012;**367**(17):1587-95.
307. Morillo CA, Verma A, Connolly SJ, Kuck KH, Nair GM, Champagne J, Sterns LD, Beresh H, Healey JS, Natale A, Investigators R-. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of paroxysmal atrial fibrillation (RAAFT-2): a randomized trial. *JAMA* 2014;**311**(7):692-700.
308. Wazni OM, Dandamudi G, Sood N, Hoyt R, Tyler J, Durrani S, Niebauer M, Makati K, Halperin B, Gauri A, Morales G, Shao M, Cerkenvenik J, Kaplon RE, Nissen

SE, Investigators SAFT. Cryoballoon Ablation as Initial Therapy for Atrial Fibrillation. *N Engl J Med* 2021;**384**(4):316-324.

309. Andrade JG, Wells GA, Deyell MW, Bennett M, Essebag V, Champagne J, Roux JF, Yung D, Skanes A, Khaykin Y, Morillo C, Jolly U, Novak P, Lockwood E, Amit G, Angaran P, Sapp J, Wardell S, Lauck S, Macle L, Verma A. Cryoablation or Drug Therapy for Initial Treatment of Atrial Fibrillation. *N Engl J Med* 2021;**384**(4):305-315.

310. Kuniss M, Pavlovic N, Velagic V, Hermida JS, Healey S, Arena G, Badenco N, Meyer C, Chen J, Iacopino S, Anselme F, Packer DL, Pitschner HF, Asmundis C, Willems S, Di Piazza F, Becker D, Chierchia GB, Cryo FI. Cryoballoon ablation vs. antiarrhythmic drugs: first-line therapy for patients with paroxysmal atrial fibrillation. *Europace* 2021;**23**(7):1033-1041.

311. Mont L, Bisbal F, Hernandez-Madrid A, Perez-Castellano N, Vinolas X, Arenal A, Arribas F, Fernandez-Lozano I, Bodegas A, Cobos A, Matia R, Perez-Villacastin J, Guerra JM, Avila P, Lopez-Gil M, Castro V, Arana JI, Brugada J, investigators S. Catheter ablation vs. antiarrhythmic drug treatment of persistent atrial fibrillation: a multicentre, randomized, controlled trial (SARA study). *Eur Heart J* 2014;**35**(8):501-7.

312. Winkle RA, Mead RH, Engel G, Patrawala RA. Long-term results of atrial fibrillation ablation: the importance of all initial ablation failures undergoing a repeat ablation. *Am Heart J* 2011;**162**(1):193-200.

313. Mohanty S, Mohanty P, L DIB, Bai R, Trivedi C, Santangeli P, Santoro F, Hongo R, Hao S, Beheiry S, Burkhardt D, Gallingshouse JG, Horton R, Sanchez JE, Bailey S, Hranitzky PM, Zagrodzky J, Natale A. Long-term outcome of catheter ablation in atrial fibrillation patients with coexistent metabolic syndrome and obstructive sleep apnea: impact of repeat procedures versus lifestyle changes. *J Cardiovasc Electrophysiol* 2014;**25**(9):930-938.

314. Bhargava M, Di Biase L, Mohanty P, Prasad S, Martin DO, Williams-Andrews M, Wazni OM, Burkhardt JD, Cummings JE, Khaykin Y, Verma A, Hao S, Beheiry S, Hongo R, Rossillo A, Raviele A, Bonso A, Themistoclakis S, Stewart K, Saliba WJ, Schweikert RA, Natale A. Impact of type of atrial fibrillation and repeat catheter ablation on long-term freedom from atrial fibrillation: results from a multicenter study. *Heart Rhythm* 2009;**6**(10):1403-12.

315. Chen S, Purerfellner H, Meyer C, Acou WJ, Schratte A, Ling Z, Liu S, Yin Y, Martinek M, Kiuchi MG, Schmidt B, Chun KRJ. Rhythm control for patients with atrial fibrillation complicated with heart failure in the contemporary era of catheter ablation: a stratified pooled analysis of randomized data. *Eur Heart J* 2020;**41**(30):2863-2873.

316. Sohns C, Fox H, Marrouche NF, Crijns H, Costard-Jaeckle A, Bergau L, Hindricks G, Dagres N, Sossalla S, Schramm R, Fink T, El Hamriti M, Moersdorf M, Sciacca V, Konietschke F, Rudolph V, Gummert J, Tijssen JGP, Sommer P. Catheter Ablation in End-Stage Heart Failure with Atrial Fibrillation. *N Engl J Med* 2023;**389**(15):1380-1389.

317. Packer DL, Piccini JP, Monahan KH, Al-Khalidi HR, Silverstein AP, Noseworthy PA, Poole JE, Bahnson TD, Lee KL, Mark DB, Investigators C. Ablation Versus Drug Therapy for Atrial Fibrillation in Heart Failure: Results From the CABANA Trial. *Circulation* 2021;**143**(14):1377-1390.

318. Hunter RJ, Berriman TJ, Diab I, Kamdar R, Richmond L, Baker V, Goromonzi F, Sawhney V, Duncan E, Page SP, Ullah W, Unsworth B, Mayet J, Dhinoja M, Earley MJ, Sporton S, Schilling RJ. A randomized controlled trial of catheter ablation versus medical treatment of atrial fibrillation in heart failure (the CAMTAF trial). *Circ Arrhythm Electrophysiol* 2014;**7**(1):31-8.
319. Di Biase L, Mohanty P, Mohanty S, Santangeli P, Trivedi C, Lakkireddy D, Reddy M, Jais P, Themistoclakis S, Dello Russo A, Casella M, Pelargonio G, Narducci ML, Schweikert R, Neuzil P, Sanchez J, Horton R, Beheiry S, Hongo R, Hao S, Rossillo A, Forleo G, Tondo C, Burkhardt JD, Haissaguerre M, Natale A. Ablation Versus Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted Device: Results From the AATAC Multicenter Randomized Trial. *Circulation* 2016;**133**(17):1637-44.
320. Prabhu S, Taylor AJ, Costello BT, Kaye DM, McLellan AJA, Voskoboinik A, Sugumar H, Lockwood SM, Stokes MB, Pathik B, Nalliah CJ, Wong GR, Azzopardi SM, Gutman SJ, Lee G, Layland J, Mariani JA, Ling LH, Kalman JM, Kistler PM. Catheter Ablation Versus Medical Rate Control in Atrial Fibrillation and Systolic Dysfunction: The CAMERA-MRI Study. *J Am Coll Cardiol* 2017;**70**(16):1949-1961.
321. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, Merkely B, Pokushalov E, Sanders P, Proff J, Schunkert H, Christ H, Vogt J, Bansch D, CASTLE-AF Investigators. Catheter Ablation for Atrial Fibrillation with Heart Failure. *N Engl J Med* 2018;**378**(5):417-427.
322. Kuck KH, Merkely B, Zahn R, Arentz T, Seidl K, Schluter M, Tilz RR, Piorkowski C, Geller L, Kleemann T, Hindricks G. Catheter Ablation Versus Best Medical Therapy in Patients With Persistent Atrial Fibrillation and Congestive Heart Failure: The Randomized AMICA Trial. *Circ Arrhythm Electrophysiol* 2019;**12**(12):e007731.
323. Andrade JG, Deyell MW, Macle L, Wells GA, Bennett M, Essebag V, Champagne J, Roux JF, Yung D, Skanes A, Khaykin Y, Morillo C, Jolly U, Novak P, Lockwood E, Amit G, Angaran P, Sapp J, Wardell S, Lauck S, Cadrin-Tourigny J, Kochhäuser S, Verma A. Progression of Atrial Fibrillation after Cryoablation or Drug Therapy. *N Engl J Med* 2023;**388**(2):105-116.
324. Parkash R, Wells GA, Rouleau J, Talajic M, Essebag V, Skanes A, Wilton SB, Verma A, Healey JS, Sterns L, Bennett M, Roux JF, Rivard L, Leong-Sit P, Jensen-Urstad M, Jolly U, Philippon F, Sapp JL, Tang ASL. Randomized Ablation-Based Rhythm-Control Versus Rate-Control Trial in Patients With Heart Failure and Atrial Fibrillation: Results from the RAFT-AF trial. *Circulation* 2022;**145**(23):1693-1704.
325. Brockmeyer M, Lin Y, Parco C, Karathanos A, Krieger T, Schulze V, Heinen Y, Bejinariu A, Müller P, Makimoto H, Kelm M, Wolff G. Uninterrupted anticoagulation during catheter ablation for atrial fibrillation: no difference in major bleeding and stroke between direct oral anticoagulants and vitamin K antagonists in an updated meta-analysis of randomised controlled trials. *Acta Cardiol* 2021;**76**(3):288-295.
326. Di Monaco A, Guida P, Vitulano N, Quadrini F, Troisi F, Langialonga T, Grimaldi M. Catheter ablation of atrial fibrillation with uninterrupted anticoagulation: a meta-analysis of six randomized controlled trials. *J Cardiovasc Med (Hagerstown)* 2020;**21**(7):483-490.
327. Noubiap JJ, Agbaedeng TA, Ndoadoumgue AL, Nyaga UF, Kengne AP. Atrial thrombus detection on transoesophageal echocardiography in patients with atrial

fibrillation undergoing cardioversion or catheter ablation: A pooled analysis of rates and predictors. *J Cardiovasc Electrophysiol* 2021;**32**(8):2179-2188.

328. Lurie A, Wang J, Hinnegan KJ, McIntyre WF, Belley-Côté EP, Amit G, Healey JS, Connolly SJ, Wong JA. Prevalence of Left Atrial Thrombus in Anticoagulated Patients With Atrial Fibrillation. *J Am Coll Cardiol* 2021;**77**(23):2875-2886.

329. Liu J, Wu Y, Li S, Song L, Hu C. The Efficacy of Non-Vitamin K Antagonist Oral Anticoagulants in the Prevention of Left Atrial Thrombus in Patients With Atrial Fibrillation Compared With Vitamin K Antagonists: A Meta-Analysis. *Heart Surg Forum* 2020;**23**(6):E733-E739.

330. Yang J, Zhang X, Wang XY, Zhang C, Chen SZ, Hu SJ. Comparison of transesophageal echocardiography findings after different anticoagulation strategies in patients with atrial fibrillation: a systematic review and meta-analysis. *BMC Cardiovasc Disord* 2019;**19**(1):261.

331. Diab M, Wazni OM, Saliba WI, Tarakji KG, Ballout JA, Hutt E, Rickard J, Baranowski B, Tchou P, Bhargava M, Chung M, Varma N, Martin DO, Dresing T, Callahan T, Cantillon D, Kanj M, Hussein AA. Ablation of Atrial Fibrillation Without Left Atrial Appendage Imaging in Patients Treated With Direct Oral Anticoagulants. *Circ Arrhythm Electrophysiol* 2020;**13**(9):e008301.

332. Patel K, Natale A, Yang R, Trivedi C, Romero J, Briceno D, Mohanty S, Alviz I, Natale V, Sanchez J, Della Rocca DG, Tarantino N, Zhang XD, Mohanty P, Horton R, Burkhardt D, Gopinathannair R, Joseph Gallinhouse G, Lakkireddy D, Di Biase L. Is transesophageal echocardiography necessary in patients undergoing ablation of atrial fibrillation on an uninterrupted direct oral anticoagulant regimen? Results from a prospective multicenter registry. *Heart Rhythm* 2020;**17**(12):2093-2099.

333. van Vugt SPG, Westra SW, Volleberg R, Hannink G, Nakamura R, de Asmundis C, Chierchia GB, Navarese EP, Brouwer MA. Meta-analysis of controlled studies on minimally interrupted vs. continuous use of non-vitamin K antagonist oral anticoagulants in catheter ablation for atrial fibrillation. *Europace* 2021;**23**(12):1961-1969.

334. Brunetti ND, Tricarico L, Tilz RR, Heeger CH, De Gennaro L, Correale M, Ieva R, Di Biase M, Rillig A, Metzner A, Santoro F. Lower Major Bleeding Rates with Direct Oral Anticoagulants in Catheter Ablation of Atrial Fibrillation: an Updated Meta-analysis of Randomized Controlled Studies. *Cardiovasc Drugs Ther* 2020;**34**(2):209-214.

335. Zhao Y, Lu Y, Qin Y. A meta-analysis of randomized controlled trials of uninterrupted periprocedural anticoagulation strategy in patients undergoing atrial fibrillation catheter ablation. *Int J Cardiol* 2018;**270**:167-171.

336. Romero J, Cerrud-Rodriguez RC, Diaz JC, Michaud GF, Taveras J, Alviz I, Gruppiso V, Cerna L, Avendano R, Kumar S, Kirchhof P, Natale A, Di Biase L. Uninterrupted direct oral anticoagulants vs. uninterrupted vitamin K antagonists during catheter ablation of non-valvular atrial fibrillation: a systematic review and meta-analysis of randomized controlled trials. *Europace* 2018;**20**(10):1612-1620.

337. Yang Q, Chen X, Zhai J, Dang Y. Comparison of major bleeding events of uninterrupted non-vitamin K antagonist oral anticoagulants versus uninterrupted vitamin K antagonist during catheter ablation of atrial fibrillation: a meta-analysis of randomised controlled trials. *Acta Cardiol* 2022;**77**(3):257-263.

338. Liu XH, Gao XF, Chen CF, Chen B, Xu YZ. Thromboembolism and bleeding risk in atrial fibrillation ablation with uninterrupted anticoagulation between new oral anticoagulants and vitamin K antagonists: insights from an updated meta-analysis. *J Thromb Thrombolysis* 2020;**50**(1):201-210.
339. Sun Y, Liu X, Xu Y. Meta-analysis of efficacy and safety of new oral anticoagulants compared with warfarin in Japanese patients undergoing catheter ablation for atrial fibrillation. *J Interv Card Electrophysiol* 2020;**58**(3):381-399.
340. Rahman H, Khan SU, DePersis M, Hammad T, Nasir F, Kaluski E. Meta-analysis of safety and efficacy of oral anticoagulants in patients requiring catheter ablation for atrial fibrillation. *Cardiovasc Revasc Med* 2019;**20**(2):147-152.
341. Asad ZUA, Akhtar KH, Jafry AH, Khan MH, Khan MS, Munir MB, Lakkireddy DR, Gopinathannair R. Uninterrupted versus interrupted direct oral anticoagulation for catheter ablation of atrial fibrillation: A systematic review and meta-analysis. *J Cardiovasc Electrophysiol* 2021;**32**(7):1995-2004.
342. Ge Z, Faggioni M, Baber U, Sartori S, Sorrentino S, Farhan S, Chandrasekhar J, Vogel B, Qadeer A, Halperin J, Reddy V, Dukkipati S, Dangas G, Mehran R. Safety and efficacy of nonvitamin K antagonist oral anticoagulants during catheter ablation of atrial fibrillation: A systematic review and meta-analysis. *Cardiovasc Ther* 2018;**36**(5):e12457.
343. Ha FJ, Barra S, Brown AJ, Begley DA, Grace AA, Agarwal S. Continuous and minimally-interrupted direct oral anticoagulant are both safe compared with vitamin K antagonist for atrial fibrillation ablation: An updated meta-analysis. *Int J Cardiol* 2018;**262**:51-56.
344. Mao YJ, Wang H, Huang PF. Meta-analysis of the safety and efficacy of using minimally interrupted novel oral anticoagulants in patients undergoing catheter ablation for atrial fibrillation. *J Interv Card Electrophysiol* 2021;**60**(3):407-417.
345. Mao YJ, Wang H, Huang PF. Peri-procedural novel oral anticoagulants dosing strategy during atrial fibrillation ablation: A meta-analysis. *Pacing Clin Electrophysiol* 2020;**43**(10):1104-1114.
346. Basu-Ray I, Khanra D, Kupó P, Bunch J, Theus SA, Mukherjee A, Shah SK, Komócsi A, Adeboye A, Jefferies J. Outcomes of uninterrupted vs interrupted Periprocedural direct oral Anticoagulants in atrial Fibrillation ablation: A meta-analysis. *J Arrhythm* 2021;**37**(2):384-393.
347. Toso E, Peyracchia M, Matta M, D'Ascenzo F, Gaita F, Kornej J, Hindricks G, Jared Bunch T, Saliba W. Incidence of thromboembolic events following atrial fibrillation catheter ablation and rate control strategies according to the kind of oral anticoagulation: A systematic review and meta-analysis. *Int J Cardiol* 2018;**270**:172-179.
348. Maduray K, Moneruzzaman M, Changwe GJ, Zhong J. Benefits and Risks Associated with Long-term Oral Anticoagulation after Successful Atrial Fibrillation Catheter Ablation: Systematic Review and Meta-analysis. *Clin Appl Thromb Hemost* 2022;**28**:10760296221118480.
349. Romero J, Cerrud-Rodriguez RC, Diaz JC, Rodriguez D, Arshad S, Alviz I, Cerna L, Rios S, Monhanty S, Natale A, Garcia MJ, Di Biase L. Oral anticoagulation after catheter ablation of atrial fibrillation and the associated risk of thromboembolic

events and intracranial hemorrhage: A systematic review and meta-analysis. *J Cardiovasc Electrophysiol* 2019;**30**(8):1250-1257.

350. Proietti R, AlTurki A, Di Biase L, China P, Forleo G, Corrado A, Marras E, Natale A, Themistoclakis S. Anticoagulation after catheter ablation of atrial fibrillation: An unnecessary evil? A systematic review and meta-analysis. *J Cardiovasc Electrophysiol* 2019;**30**(4):468-478.

351. Deng L, Xiao Y, Hong H. Withdrawal of oral anticoagulants 3 months after successful radiofrequency catheter ablation in patients with atrial fibrillation: A meta-analysis. *Pacing Clin Electrophysiol* 2018;**41**(11):1391-1400.

352. Boersma LV, Castella M, van Boven W, Berruezo A, Yilmaz A, Nadal M, Sandoval E, Calvo N, Brugada J, Kelder J, Wijffels M, Mont L. Atrial fibrillation catheter ablation versus surgical ablation treatment (FAST): a 2-center randomized clinical trial. *Circulation* 2012;**125**(1):23-30.

353. Doll N, Weimar T, Kosior DA, Bulava A, Mokracek A, Mönnig G, Sahu J, Hunter S, Wijffels M, van Putte B, Rüb N, Nemec P, Ostrizek T, Suwalski P. Efficacy and safety of hybrid epicardial and endocardial ablation versus endocardial ablation in patients with persistent and longstanding persistent atrial fibrillation: a randomised, controlled trial. *EClinicalMedicine* 2023;**61**:102052.

354. DeLurgio DB, Crossen KJ, Gill J, Blauth C, Oza SR, Magnano AR, Mostovych MA, Halkos ME, Tschopp DR, Kerendi F, Taigen TL, Shults CC, Shah MH, Rajendra AB, Osorio J, Silver JS, Hook BG, Gilligan DM, Calkins H. Hybrid Convergent Procedure for the Treatment of Persistent and Long-Standing Persistent Atrial Fibrillation: Results of CONVERGE Clinical Trial. *Circ Arrhythm Electrophysiol* 2020;**13**(12):e009288.

355. Castella M, Kotecha D, van Laar C, Wintgens L, Castillo Y, Kelder J, Aragon D, Nunez M, Sandoval E, Casellas A, Mont L, van Boven WJ, Boersma LVA, van Putte BP. Thoracoscopic vs. catheter ablation for atrial fibrillation: long-term follow-up of the FAST randomized trial. *Europace* 2019;**21**(5):746-753.

356. van der Heijden CAJ, Weberndörfer V, Vroomen M, Luermans JG, Chaldoupi SM, Bidar E, Vernooy K, Maessen JG, Pison L, van Kuijk SMJ, La Meir M, Crijns H, Maesen B. Hybrid Ablation Versus Repeated Catheter Ablation in Persistent Atrial Fibrillation: A Randomized Controlled Trial. *JACC Clin Electrophysiol* 2023;**9**(7 Pt 2):1013-1023.

357. van der Heijden CAJ, Vroomen M, Luermans JG, Vos R, Crijns H, Gelsomino S, La Meir M, Pison L, Maesen B. Hybrid versus catheter ablation in patients with persistent and longstanding persistent atrial fibrillation: a systematic review and meta-analysis. *Eur J Cardiothorac Surg* 2019;**56**(3):433-443.

358. Haldar S, Khan HR, Boyalla V, Kralj-Hans I, Jones S, Lord J, Onyimadu O, Satishkumar A, Bahrami T, De Souza A, Clague JR, Francis DP, Hussain W, Jarman JW, Jones DG, Chen Z, Mediratta N, Hyde J, Lewis M, Mohiaddin R, Salukhe TV, Murphy C, Kelly J, Khattar RS, Toff WD, Markides V, McCready J, Gupta D, Wong T. Catheter ablation vs. thoracoscopic surgical ablation in long-standing persistent atrial fibrillation: CASA-AF randomized controlled trial. *Eur Heart J* 2020;**41**(47):4471-4480.

359. Mhanna M, Beran A, Al-Abdoun A, Ayesh H, Sajdeya O, Srour O, Alsaigali M, Alhasanat OH, Burmeister C, Abumoawad AM, Chacko P. Hybrid convergent ablation

versus endocardial catheter ablation for atrial fibrillation: A systematic review and meta-analysis. *J Arrhythm* 2021;**37**(6):1459-1467.

360. Eranki A, Wilson-Smith AR, Williams ML, Flynn CD, Manganas C. Hybrid convergent ablation versus endocardial catheter ablation for atrial fibrillation: a systematic review and meta-analysis of randomised control trials and propensity matched studies. *J Cardiothorac Surg* 2022;**17**(1):181.

361. Wang JG, Xin M, Han J, Li Y, Luo TG, Wang J, Meng F, Meng X. Ablation in selective patients with long-standing persistent atrial fibrillation: medium-term results of the Dallas lesion set. *Eur J Cardiothorac Surg* 2014;**46**(2):213-20.

362. Huffman MD, Karmali KN, Berendsen MA, Andrei AC, Kruse J, McCarthy PM, Malaisrie SC. Concomitant atrial fibrillation surgery for people undergoing cardiac surgery. *Cochrane Database Syst Rev* 2016(8):CD011814.

363. Phan K, Xie A, La Meir M, Black D, Yan TD. Surgical ablation for treatment of atrial fibrillation in cardiac surgery: a cumulative meta-analysis of randomised controlled trials. *Heart* 2014;**100**(9):722-30.

364. McClure GR, Belley-Cote EP, Jaffer IH, Dvirnik N, An KR, Fortin G, Spence J, Healey J, Singal RK, Whitlock RP. Surgical ablation of atrial fibrillation: a systematic review and meta-analysis of randomized controlled trials. *Europace* 2018;**20**(9):1442-1450.

365. Pokushalov E, Romanov A, Corbucci G, Cherniavsky A, Karaskov A. Benefit of ablation of first diagnosed paroxysmal atrial fibrillation during coronary artery bypass grafting: a pilot study. *Eur J Cardiothorac Surg* 2012;**41**(3):556-60.

366. Cheng DC, Ad N, Martin J, Berglin EE, Chang BC, Doukas G, Gammie JS, Nitta T, Wolf RK, Puskas JD. Surgical ablation for atrial fibrillation in cardiac surgery: a meta-analysis and systematic review. *Innovations (Phila)* 2010;**5**(2):84-96.

367. Yoo JS, Kim JB, Ro SK, Jung Y, Jung SH, Choo SJ, Lee JW, Chung CH. Impact of concomitant surgical atrial fibrillation ablation in patients undergoing aortic valve replacement. *Circ J* 2014;**78**(6):1364-71.

368. Malaisrie SC, Lee R, Kruse J, Lapin B, Wang EC, Bonow RO, McCarthy PM. Atrial fibrillation ablation in patients undergoing aortic valve replacement. *J Heart Valve Dis* 2012;**21**(3):350-7.

369. Schill MR, Musharbash FN, Hansalia V, Greenberg JW, Melby SJ, Maniar HS, Sinn LA, Schuessler RB, Moon MR, Damiano RJ, Jr. Late results of the Cox-maze IV procedure in patients undergoing coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 2017;**153**(5):1087-1094.

370. Rankin JS, Lerner DJ, Braid-Forbes MJ, Ferguson MA, Badhwar V. One-year mortality and costs associated with surgical ablation for atrial fibrillation concomitant to coronary artery bypass grafting. *Eur J Cardiothorac Surg* 2017;**52**(3):471-477.

371. Cherniavsky A, Kareva Y, Pak I, Rakhmonov S, Pokushalov E, Romanov A, Karaskov A. Assessment of results of surgical treatment for persistent atrial fibrillation during coronary artery bypass grafting using implantable loop recorders. *Interact Cardiovasc Thorac Surg* 2014;**18**(6):727-31.

372. Maesen B, van der Heijden CAJ, Bidar E, Vos R, Athanasiou T, Maessen JG. Patient-reported quality of life after stand-alone and concomitant arrhythmia surgery:

a systematic review and meta-analysis. *Interact Cardiovasc Thorac Surg* 2022;**34**(3):339-348.

373. Musharbash FN, Schill MR, Sinn LA, Schuessler RB, Maniar HS, Moon MR, Melby SJ, Damiano RJ, Jr. Performance of the Cox-maze IV procedure is associated with improved long-term survival in patients with atrial fibrillation undergoing cardiac surgery. *J Thorac Cardiovasc Surg* 2018;**155**(1):159-170.

374. Melo J, Santiago T, Aguiar C, Berglin E, Knaut M, Alfieri O, Benussi S, Sie H, Williams M, Hornero F, Marinelli G, Ridley P, Fulquet-Carreras E, Ferreira A. Surgery for atrial fibrillation in patients with mitral valve disease: results at five years from the International Registry of Atrial Fibrillation Surgery. *J Thorac Cardiovasc Surg* 2008;**135**(4):863-9.

375. Almousa A, Mehaffey JH, Wei LM, Simsa A, Hayanga JWA, Cook C, Rankin JS, Badhwar V. Robotic-assisted cryothermic Cox maze for persistent atrial fibrillation: Longitudinal follow-up. *J Thorac Cardiovasc Surg* 2022.

376. Lauritzen DJ, Andersen FT, Modrau IS, Christensen TD, Heiberg J. Scoring systems in the prediction of atrial fibrillation recurrence after surgical ablation. *J Card Surg* 2022;**37**(10):3044-3049.

377. Kowalewski M, Pasierski M, Kolodziejczak M, Litwinowicz R, Kowalowka A, Wanha W, Los A, Stefaniak S, Wojakowski W, Jemielity M, Rogowski J, Deja M, Bartus K, Mariani S, Li T, Matteucci M, Ronco D, Massimi G, Jiritano F, Meani P, Raffa GM, Malvindi PG, Zembala M, Lorusso R, Cox JL, Suwalski P, Thoracic Research C. Atrial fibrillation ablation improves late survival after concomitant cardiac surgery. *J Thorac Cardiovasc Surg* 2022.

378. Kowalewski M, Pasierski M, Finke J, Kolodziejczak M, Staromlynski J, Litwinowicz R, Filip G, Kowalowka A, Wanha W, Blawat P, Los A, Stefaniak S, Wojakowski W, Jemielity M, Rogowski J, Deja M, Jagielak D, Bartus K, Sierakowska K, Mariani S, Li T, Ravaux JM, Matteucci M, Ronco D, Jiritano F, Fina D, Martucci G, Meani P, Raffa GM, Malvindi PG, Lorusso R, Suwalski P, Thoracic Research C. Permanent pacemaker implantation after valve and arrhythmia surgery in patients with preoperative atrial fibrillation. *Heart Rhythm* 2022;**19**(9):1442-1449.

379. Wehbe M, Albert M, Lewalter T, Ouarrak T, Senges J, Hanke T, Doll N. The German Cardiosurgery Atrial Fibrillation Registry: 1-Year Follow-up Outcomes. *Thorac Cardiovasc Surg* 2023;**71**(4):255-263.

380. Suwalski P, Kowalewski M, Jasinski M, Staromlynski J, Zembala M, Widenka K, Brykczynski M, Skiba J, Zembala MO, Bartus K, Hirnle T, Dziembowska I, Tobota Z, Maruszewski BJ, Investigators K. Survival after surgical ablation for atrial fibrillation in mitral valve surgery: Analysis from the Polish National Registry of Cardiac Surgery Procedures (KROK). *J Thorac Cardiovasc Surg* 2019;**157**(3):1007-1018 e4.

381. Suwalski P, Kowalewski M, Jasinski M, Staromlynski J, Zembala M, Widenka K, Brykczynski M, Skiba J, Zembala MO, Bartus K, Hirnle T, Dziembowska I, Deja M, Tobota Z, Maruszewski BJ. Surgical ablation for atrial fibrillation during isolated coronary artery bypass surgery. *Eur J Cardiothorac Surg* 2020;**57**(4):691-700.

382. Wehbe M, Albert M, Lewalter T, Ouarrak T, Senges J, Hanke T, Doll N. The German Cardiosurgery Atrial Fibrillation Registry: 1-Year Follow-up Outcomes. *Thorac Cardiovasc Surg* 2022.

383. Kim HJ, Kim YJ, Kim M, Yoo JS, Kim DH, Park DW, Jung SH, Choo SJ, Kim JB. Surgical ablation for atrial fibrillation during aortic and mitral valve surgery: A nationwide population-based cohort study. *J Thorac Cardiovasc Surg* 2024;**167**(3):981-993.
384. Rankin JS, Lerner DJ, Braid-Forbes MJ, McCrea MM, Badhwar V. Surgical ablation of atrial fibrillation concomitant to coronary-artery bypass grafting provides cost-effective mortality reduction. *J Thorac Cardiovasc Surg* 2020;**160**(3):675-686 e13.
385. Badhwar V, Rankin JS, Ad N, Grau-Sepulveda M, Damiano RJ, Gillinov AM, McCarthy PM, Thourani VH, Suri RM, Jacobs JP, Cox JL. Surgical Ablation of Atrial Fibrillation in the United States: Trends and Propensity Matched Outcomes. *Ann Thorac Surg* 2017;**104**(2):493-500.
386. Cannon CP, Bhatt DL, Oldgren J, Lip GYH, Ellis SG, Kimura T, Maeng M, Merkely B, Zeymer U, Gropper S, Nordaby M, Kleine E, Harper R, Manassie J, Januzzi JL, Ten Berg JM, Steg PG, Hohnloser SH, RE-DUAL PCI Steering Committee Investigators. Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation. *N Engl J Med* 2017;**377**(16):1513-1524.
387. Vranckx P, Valgimigli M, Eckardt L, Tijssen J, Lewalter T, Gargiulo G, Batushkin V, Campo G, Lysak Z, Vakaliuk I, Milewski K, Laeis P, Reimitz PE, Smolnik R, Zierhut W, Goette A. Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, phase 3b trial. *Lancet* 2019;**394**(10206):1335-1343.
388. Gibson CM, Mehran R, Bode C, Halperin J, Verheugt FW, Wildgoose P, Birmingham M, Ianus J, Burton P, van Eickels M, Korjian S, Daaboul Y, Lip GY, Cohen M, Husted S, Peterson ED, Fox KA. Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI. *N Engl J Med* 2016;**375**(25):2423-2434.
389. Dewilde WJ, Oirbans T, Verheugt FW, Kelder JC, De Smet BJ, Herrman JP, Adriaenssens T, Vrolix M, Heestermans AA, Vis MM, Tijssen JG, van 't Hof AW, ten Berg JM. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet* 2013;**381**(9872):1107-15.
390. Lopes RD, Heizer G, Aronson R, Vora AN, Massaro T, Mehran R, Goodman SG, Windecker S, Darius H, Li J, Averkov O, Bahit MC, Berwanger O, Budaj A, Hijazi Z, Parkhomenko A, Sinnaeve P, Storey RF, Thiele H, Vinereanu D, Granger CB, Alexander JH, AUGUSTUS Investigators. Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation. *N Engl J Med* 2019;**380**(16):1509-1524.
391. Fiedler KA, Maeng M, Mehilli J, Schulz-Schupke S, Byrne RA, Sibbing D, Hoppmann P, Schneider S, Fusaro M, Ott I, Kristensen SD, Ibrahim T, Massberg S, Schunkert H, Laugwitz KL, Kastrati A, Sarafoff N. Duration of Triple Therapy in Patients Requiring Oral Anticoagulation After Drug-Eluting Stent Implantation: The ISAR-TRIPLE Trial. *J Am Coll Cardiol* 2015;**65**(16):1619-1629.
392. Matsumura-Nakano Y, Shizuta S, Komasa A, Morimoto T, Masuda H, Shiomi H, Goto K, Nakai K, Ogawa H, Kobori A, Kono Y, Kaitani K, Suwa S, Aoyama T, Takahashi M, Sasaki Y, Onishi Y, Mano T, Matsuda M, Motooka M, Tomita H, Inoko

M, Wakeyama T, Hagiwara N, Tanabe K, Akao M, Miyauchi K, Yajima J, Hanaoka K, Morino Y, Ando K, Furukawa Y, Nakagawa Y, Nakao K, Kozuma K, Kadota K, Kimura K, Kawai K, Ueno T, Okumura K, Kimura T. Open-Label Randomized Trial Comparing Oral Anticoagulation With and Without Single Antiplatelet Therapy in Patients With Atrial Fibrillation and Stable Coronary Artery Disease Beyond 1 Year After Coronary Stent Implantation. *Circulation* 2019;**139**(5):604-616.

393. Alexander JH, Wojdyla D, Vora AN, Thomas L, Granger CB, Goodman SG, Aronson R, Windecker S, Mehran R, Lopes RD. Risk/Benefit Tradeoff of Antithrombotic Therapy in Patients With Atrial Fibrillation Early and Late After an Acute Coronary Syndrome or Percutaneous Coronary Intervention: Insights From AUGUSTUS. *Circulation* 2020;**141**(20):1618-1627.

394. Jensen T, Thrane PG, Olesen KKW, Würtz M, Mortensen MB, Gyldenkerne C, Thim T, Nørgaard BL, Jensen JM, Kristensen SD, Nielsen JC, Eikelboom JW, Maeng M. Antithrombotic treatment beyond 1 year after percutaneous coronary intervention in patients with atrial fibrillation. *Eur Heart J Cardiovasc Pharmacother* 2023;**9**(3):208-219.

395. Saglietto A, D'Ascenzo F, Errigo D, Leonardi S, Dewilde WJ, Conrotto F, Omedè P, Montefusco A, Angelini F, De Filippo O, Bianco M, Gallone G, Bruno F, Zaccaro L, Giannini F, Latib A, Colombo A, Costa F, De Ferrari GM. Antithrombotic strategies in patients needing oral anticoagulation undergoing percutaneous coronary intervention: A network meta-analysis. *Catheter Cardiovasc Interv* 2021;**97**(4):581-588.

396. Jeridi D, Pellat A, Ginestet C, Assaf A, Hallit R, Corre F, Coriat R. The Safety of Long-Term Proton Pump Inhibitor Use on Cardiovascular Health: A Meta-Analysis. *J Clin Med* 2022;**11**(14):4096.

397. Liao YWB, Wang TKM. Antithrombotic regimen for patients with cardiac indication for dual antiplatelet therapy and anticoagulation: a meta-analysis of randomized trials. *Coron Artery Dis* 2020;**31**(3):260-265.

398. Haller PM, Sulzgruber P, Kaufmann C, Geelhoed B, Tamargo J, Wassmann S, Schnabel RB, Westermann D, Huber K, Niessner A, Gremmel T. Bleeding and ischaemic outcomes in patients treated with dual or triple antithrombotic therapy: systematic review and meta-analysis. *Eur Heart J Cardiovasc Pharmacother* 2019;**5**(4):226-236.

399. Park DY, Wang P, An S, Grimshaw AA, Frampton J, Ohman EM, Rao SV, Nanna MG. Shortening the duration of dual antiplatelet therapy after percutaneous coronary intervention for acute coronary syndrome: A systematic review and meta-analysis. *Am Heart J* 2022;**251**:101-114.

400. Watanabe H, Morimoto T, Natsuaki M, Yamamoto K, Obayashi Y, Ogita M, Suwa S, Isawa T, Domei T, Yamaji K, Tatsushima S, Watanabe H, Ohya M, Tokuyama H, Tada T, Sakamoto H, Mori H, Suzuki H, Nishikura T, Wakabayashi K, Hibi K, Abe M, Kawai K, Nakao K, Ando K, Tanabe K, Ikari Y, Morino Y, Kadota K, Furukawa Y, Nakagawa Y, Kimura T. Comparison of Clopidogrel Monotherapy After 1 to 2 Months of Dual Antiplatelet Therapy With 12 Months of Dual Antiplatelet Therapy in Patients With Acute Coronary Syndrome: The STOPDAPT-2 ACS Randomized Clinical Trial. *JAMA Cardiol* 2022;**7**(4):407-417.

401. Bahit MC, Vora AN, Li Z, Wojdyla DM, Thomas L, Goodman SG, Aronson R, Jordan JD, Kolls BJ, Dombrowski KE, Vinereanu D, Halvorsen S, Berwanger O, Windecker S, Mehran R, Granger CB, Alexander JH, Lopes RD. Apixaban or Warfarin and Aspirin or Placebo After Acute Coronary Syndrome or Percutaneous Coronary Intervention in Patients With Atrial Fibrillation and Prior Stroke: A Post Hoc Analysis From the AUGUSTUS Trial. *JAMA Cardiol* 2022;**7**(7):682-689.
402. Bor WL, de Veer AJW, Olie RH, Rikken S, Chan Pin Yin D, Herrman JPR, Vrolix M, Meuwissen M, Vandendriessche T, van Mieghem C, Magro M, Bennaghmouch N, Hermanides R, Adriaenssens T, Dewilde WJM, Ten Berg JM. Dual versus triple antithrombotic therapy after percutaneous coronary intervention: the prospective multicentre WOEST 2 Study. *EuroIntervention* 2022;**18**(4):e303-e313.
403. Oldgren J, Åsberg S, Hijazi Z, Wester P, Bertilsson M, Norrving B. Early Versus Delayed Non-Vitamin K Antagonist Oral Anticoagulant Therapy After Acute Ischemic Stroke in Atrial Fibrillation (TIMING): A Registry-Based Randomized Controlled Noninferiority Study. *Circulation* 2022;**146**(14):1056-1066.
404. Schreuder F, van Nieuwenhuizen KM, Hofmeijer J, Vermeer SE, Kerkhoff H, Zock E, Luijckx GJ, Messchendorp GP, van Tuijl J, Bienfait HP, Booij SJ, van den Wijngaard IR, Remmers MJM, Schreuder A, Dippel DW, Staals J, Brouwers P, Wermer MJH, Coutinho JM, Kwa VIH, van Gelder IC, Schutgens REG, Zweedijk B, Algra A, van Dalen JW, Jaap Kappelle L, Rinkel GJE, van der Worp HB, Klijn CJM, Investigators A-AT. Apixaban versus no anticoagulation after anticoagulation-associated intracerebral haemorrhage in patients with atrial fibrillation in the Netherlands (APACHE-AF): a randomised, open-label, phase 2 trial. *Lancet Neurol* 2021;**20**(11):907-916.
405. SoSTART Collaboration. Effects of oral anticoagulation for atrial fibrillation after spontaneous intracranial haemorrhage in the UK: a randomised, open-label, assessor-masked, pilot-phase, non-inferiority trial. *Lancet Neurol* 2021;**20**(10):842-853.
406. Shahjouei S, Tsivgoulis G, Goyal N, Sadighi A, Mowla A, Wang M, Seiffge DJ, Zand R. Safety of Intravenous Thrombolysis Among Patients Taking Direct Oral Anticoagulants: A Systematic Review and Meta-Analysis. *Stroke* 2020;**51**(2):533-541.
407. Kermer P, Eschenfelder CC, Diener HC, Grond M, Abdalla Y, Abraham A, Althaus K, Becks G, Berrouschot J, Berthel J, Bode FJ, Burghaus L, Cangür H, Daffertshofer M, Edelbusch S, Eggers J, Gerlach R, Gröschel K, Große-Dresselhaus F, Günther A, Haase CG, Haensch CA, Harloff A, Heckmann JG, Held V, Hieber M, Kauert A, Kern R, Kerz T, Köhrmann M, Kraft P, Kühnlein P, Latta J, Leinisch E, Lenz A, Leithner C, Neumann-Haefelin T, Mäurer M, Müllges W, Nolte CH, Obermann M, Partowi S, Patzschke P, Poli S, Pulkowski U, Purrucker J, Rehfeldt T, Ringleb PA, Röther J, Rossi R, El-Sabassy H, Sauer O, Schackert G, Schäfer N, Schellinger PD, Schneider A, Schuppner R, Schwab S, Schwarte O, Seitz RJ, Senger S, Shah YP, Sindern E, Sparenberg P, Steiner T, Szabo K, Urbanek C, Sarnowski BV, Weissenborn K, Wienecke P, Witt K, Wruck R, Wunderlich S. Antagonizing dabigatran by idarucizumab in cases of ischemic stroke or intracranial hemorrhage in Germany-Updated series of 120 cases. *Int J Stroke* 2020;**15**(6):609-618.
408. Corica B, Romiti GF, Basili S, Proietti M. Prevalence of New-Onset Atrial Fibrillation and Associated Outcomes in Patients with Sepsis: A Systematic Review and Meta-Analysis. *J Pers Med* 2022;**12**(4):547.

409. McIntyre WF, Um KJ, Cheung CC, Belley-Côté EP, Dingwall O, Devereaux PJ, Wong JA, Conen D, Whitlock RP, Connolly SJ, Seifer CM, Healey JS. Atrial fibrillation detected initially during acute medical illness: A systematic review. *Eur Heart J Acute Cardiovasc Care* 2019;**8**(2):130-141.
410. Quon MJ, Behloul H, Pilote L. Anticoagulant Use and Risk of Ischemic Stroke and Bleeding in Patients With Secondary Atrial Fibrillation Associated With Acute Coronary Syndromes, Acute Pulmonary Disease, or Sepsis. *JACC Clin Electrophysiol* 2018;**4**(3):386-393.
411. Walkey AJ, Hammill BG, Curtis LH, Benjamin EJ. Long-term outcomes following development of new-onset atrial fibrillation during sepsis. *Chest* 2014;**146**(5):1187-1195.
412. Søgaaard M, Skjøth F, Nielsen PB, Smit J, Dalager-Pedersen M, Larsen TB, Lip GYH. Thromboembolic Risk in Patients With Pneumonia and New-Onset Atrial Fibrillation Not Receiving Anticoagulation Therapy. *JAMA Netw Open* 2022;**5**(5):e2213945.
413. Wang EY, Hulme OL, Khurshid S, Weng LC, Choi SH, Walkey AJ, Ashburner JM, McManus DD, Singer DE, Atlas SJ, Benjamin EJ, Ellinor PT, Trinquart L, Lubitz SA. Initial Precipitants and Recurrence of Atrial Fibrillation. *Circ Arrhythm Electrophysiol* 2020;**13**(3):e007716.
414. Gundlund A, Olesen JB, Butt JH, Christensen MA, Gislason GH, Torp-Pedersen C, Køber L, Kümler T, Fosbøl EL. One-year outcomes in atrial fibrillation presenting during infections: a nationwide registry-based study. *Eur Heart J* 2020;**41**(10):1112-1119.
415. Ziff OJ, Samra M, Howard JP, Bromage DI, Ruschitzka F, Francis DP, Kotecha D. Beta-blocker efficacy across different cardiovascular indications: an umbrella review and meta-analytic assessment. *BMC Med* 2020;**18**(1):103.
416. Abdelaziz A, Hafez AH, Elaraby A, Roshdy MR, Abdelaziz M, Eltobgy MA, Elsayed H, El-Samahy M, Elbehbeh NA, Philip KG, Abdelaty AM, Rizk MA, Al-Tawil M, AboElfah HE, Ramadan A, Ghaith HS, Wahsh EA, Abdelazeem B, Fayed B. Posterior pericardiotomy for the prevention of atrial fibrillation after cardiac surgery: a systematic review and meta-analysis of 25 randomised controlled trials. *EuroIntervention* 2023;**19**(4):e305-e317.
417. Soletti GJ, Perezgrovas-Olaria R, Harik L, Rahouma M, Dimagli A, Alzghari T, Demetres M, Bratton BA, Yaghmour M, Satija D, Lau C, Girardi LN, Salemo TA, Gaudino M. Effect of posterior pericardiotomy in cardiac surgery: A systematic review and meta-analysis of randomized controlled trials. *Front Cardiovasc Med* 2022;**9**:1090102.
418. Buckley MS, Nolan PE, Jr., Slack MK, Tisdale JE, Hilleman DE, Copeland JG. Amiodarone prophylaxis for atrial fibrillation after cardiac surgery: meta-analysis of dose response and timing of initiation. *Pharmacotherapy* 2007;**27**(3):360-8.
419. Auer J, Weber T, Berent R, Puschmann R, Hartl P, Ng CK, Schwarz C, Lehner E, Strasser U, Lassnig E, Lamm G, Eber B. Study of Prevention of Postoperative Atrial F. A comparison between oral antiarrhythmic drugs in the prevention of atrial fibrillation after cardiac surgery: the pilot study of prevention of postoperative atrial fibrillation (SPPAF), a randomized, placebo-controlled trial. *Am Heart J* 2004;**147**(4):636-43.

420. Yagdi T, Nalbantgil S, Ayik F, Apaydin A, Islamoglu F, Posacioglu H, Calkavur T, Atay Y, Buket S. Amiodarone reduces the incidence of atrial fibrillation after coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 2003;**125**(6):1420-5.
421. Group PS, Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC, Xavier D, Chrolavicius S, Greenspan L, Pogue J, Pais P, Liu L, Xu S, Malaga G, Avezum A, Chan M, Montori VM, Jacka M, Choi P. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet* 2008;**371**(9627):1839-47.
422. Daoud EG, Strickberger SA, Man KC, Goyal R, Deeb GM, Bolling SF, Pagani FD, Bitar C, Meissner MD, Morady F. Preoperative amiodarone as prophylaxis against atrial fibrillation after heart surgery. *N Engl J Med* 1997;**337**(25):1785-91.
423. Butt JH, Olesen JB, Havers-Borgersen E, Gundlund A, Andersson C, Gislason GH, Torp-Pedersen C, Køber L, Fosbøl EL. Risk of Thromboembolism Associated With Atrial Fibrillation Following Noncardiac Surgery. *J Am Coll Cardiol* 2018;**72**(17):2027-2036.
424. Gialdini G, Nearing K, Bhawe PD, Bonuccelli U, Iadecola C, Healey JS, Kamel H. Perioperative atrial fibrillation and the long-term risk of ischemic stroke. *JAMA* 2014;**312**(6):616-22.
425. Horwich P, Buth KJ, Legare JF. New onset postoperative atrial fibrillation is associated with a long-term risk for stroke and death following cardiac surgery. *J Card Surg* 2013;**28**(1):8-13.
426. Buck BH, Hill MD, Quinn FR, Butcher KS, Menon BK, Gulamhusein S, Siddiqui M, Coutts SB, Jeerakathil T, Smith EE, Khan K, Barber PA, Jickling G, Reyes L, Save S, Fairall P, Piquette L, Kamal N, Chew DS, Demchuk AM, Shuaib A, Exner DV. Effect of Implantable vs Prolonged External Electrocardiographic Monitoring on Atrial Fibrillation Detection in Patients With Ischemic Stroke: The PER DIEM Randomized Clinical Trial. *JAMA* 2021;**325**(21):2160-2168.
427. Bernstein RA, Kamel H, Granger CB, Piccini JP, Sethi PP, Katz JM, Vives CA, Ziegler PD, Franco NC, Schwamm LH. Effect of Long-term Continuous Cardiac Monitoring vs Usual Care on Detection of Atrial Fibrillation in Patients With Stroke Attributed to Large- or Small-Vessel Disease: The STROKE-AF Randomized Clinical Trial. *JAMA* 2021;**325**(21):2169-2177.
428. Wachter R, Gröschel K, Gelbrich G, Hamann GF, Kermer P, Liman J, Seegers J, Wasser K, Schulte A, Jürries F, Messerschmid A, Behnke N, Gröschel S, Uphaus T, Grings A, Ibis T, Klimpe S, Wagner-Heck M, Arnold M, Protsenko E, Heuschmann PU, Conen D, Weber-Krüger M. Holter-electrocardiogram-monitoring in patients with acute ischaemic stroke (Find-AF(RANDOMISED)): an open-label randomised controlled trial. *Lancet Neurol* 2017;**16**(4):282-290.
429. Hart RG, Sharma M, Mundl H, Kasner SE, Bangdiwala SI, Berkowitz SD, Swaminathan B, Lavados P, Wang Y, Wang Y, Davalos A, Shamalov N, Mikulik R, Cunha L, Lindgren A, Arauz A, Lang W, Czlonkowska A, Eckstein J, Gagliardi RJ, Amarenco P, Ameriso SF, Tatlisumak T, Veltkamp R, Hankey GJ, Toni D, Bereczki D, Uchiyama S, Ntaios G, Yoon BW, Brouns R, Endres M, Muir KW, Bornstein N, Ozturk S, O'Donnell MJ, De Vries Basson MM, Pare G, Pater C, Kirsch B, Sheridan P, Peters G, Weitz JI, Peacock WF, Shoamanesh A, Benavente OR, Joyner C, Themeles E,

Connolly SJ, NAVIGATE ESUS Investigators. Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source. *N Engl J Med* 2018;**378**(23):2191-2201.

430. Diener HC, Sacco RL, Easton JD, Granger CB, Bernstein RA, Uchiyama S, Kreuzer J, Cronin L, Cotton D, Grauer C, Brueckmann M, Chernyatina M, Donnan G, Ferro JM, Grond M, Kallmunzer B, Krupinski J, Lee BC, Lemmens R, Masjuan J, Odinak M, Saver JL, Schellinger PD, Toni D, Toyoda K, Committee R-SES, Investigators. Dabigatran for Prevention of Stroke after Embolic Stroke of Undetermined Source. *N Engl J Med* 2019;**380**(20):1906-1917.

431. Geisler T, Keller T, Martus P, Poli K, Serna-Higuita LM, Schreieck J, Gawaz M, Tünnerhoff J, Bombach P, Nägele T, Klose U, Aidery P, Grogga-Bada P, Kraft A, Hoffmann F, Hobohm C, Naupold K, Niehaus L, Wolf M, Bätzner H, Liman J, Wachter R, Kimmig H, Jung W, Huber R, Feurer R, Lindner A, Althaus K, Bode FJ, Petzold GC, Nguyen TN, Mac Grory B, Schrag M, Purruicker JC, Zuern CS, Ziemann U, Poli S. Apixaban versus Aspirin for Embolic Stroke of Undetermined Source. *NEJM Evid* 2024;**3**(1):EVIDoa2300235.

432. Tsivgoulis G, Katsanos AH, Köhrmann M, Caso V, Perren F, Palaiodimou L, Deftereos S, Giannopoulos S, Ellul J, Krogias C, Mavridis D, Triantafyllou S, Alexandrov AW, Schellinger PD, Alexandrov AV. Duration of Implantable Cardiac Monitoring and Detection of Atrial Fibrillation in Ischemic Stroke Patients: A Systematic Review and Meta-Analysis. *J Stroke* 2019;**21**(3):302-311.

433. Bateman BT, Heide-Jørgensen U, Einarsdóttir K, Engeland A, Furu K, Gissler M, Hernandez-Diaz S, Kieler H, Lahesmaa-Korpinen AM, Mogun H, Nørgaard M, Reutfors J, Selmer R, Huybrechts KF, Zoega H. β -Blocker Use in Pregnancy and the Risk for Congenital Malformations: An International Cohort Study. *Ann Intern Med* 2018;**169**(10):665-673.

434. European Heart Rhythm Association, European Association for Cardio-Thoracic Surgery, Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 2010;**31**(19):2369-429.

435. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, Blomstrom-Lundqvist C, Cifkova R, De Bonis M, Iung B, Johnson MR, Kintscher U, Kranke P, Lang IM, Morais J, Pieper PG, Presbitero P, Price S, Rosano GMC, Seeland U, Simoncini T, Swan L, Warnes CA, Group ESCSD. 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy. *Eur Heart J* 2018;**39**(34):3165-3241.

436. Katritsis DG, Boriani G, Cosio FG, Hindricks G, Jais P, Josephson ME, Keegan R, Kim YH, Knight BP, Kuck KH, Lane DA, Lip GYH, Malmborg H, Oral H, Pappone C, Themistoclakis S, Wood KA, Blomstrom-Lundqvist C. European Heart Rhythm Association (EHRA) consensus document on the management of supraventricular arrhythmias, endorsed by Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), and Sociedad Latinoamericana de Estimulacion Cardiaca y Electrofisiologia (SOLAECE). *Eur Heart J* 2018;**39**(16):1442-1445.

437. Moore JS, Teefey P, Rao K, Berlowitz MS, Chae SH, Yankowitz J. Maternal arrhythmia: a case report and review of the literature. *Obstet Gynecol Surv* 2012;**67**(5):298-312.
438. Georgiopoulos G, Tsiachris D, Kordalis A, Kontogiannis C, Spartalis M, Pietri P, Magkas N, Stefanadis C. Pharmacotherapeutic strategies for atrial fibrillation in pregnancy. *Expert Opin Pharmacother* 2019;**20**(13):1625-1636.
439. Wang YC, Chen CH, Su HY, Yu MH. The impact of maternal cardioversion on fetal haemodynamics. *Eur J Obstet Gynecol Reprod Biol* 2006;**126**(2):268-9.
440. Kockova R, Kocka V, Kiernan T, Fahy GJ. Ibutilide-induced cardioversion of atrial fibrillation during pregnancy. *J Cardiovasc Electrophysiol* 2007;**18**(5):545-7.
441. Jensen AS, Idorn L, Nørager B, Vejstrup N, Sondergaard L. Anticoagulation in adults with congenital heart disease: The who, the when and the how? *Heart* 2015;**101**(6):424-9.
442. Guarguagli S, Kempny A, Cazzoli I, Barracano R, Gatzoulis MA, Dimopoulos K, Ernst S. Efficacy of catheter ablation for atrial fibrillation in patients with congenital heart disease. *Europace* 2019;**21**(9):1334-1344.
443. Giamberti A, Pluchinotta FR, Chessa M, Varrica A, Vitale R, Frigiola A, Pappone C, Ranucci M. Surgery for supraventricular tachycardia and congenital heart defects: long-term efficacy of the combined approach in adult patients. *Europace* 2017;**19**(9):1542-1548.
444. Vadmann H, Nielsen PB, Hjortshøj SP, Riahi S, Rasmussen LH, Lip GY, Larsen TB. Atrial flutter and thromboembolic risk: a systematic review. *Heart* 2015;**101**(18):1446-55.
445. Rahman F, Wang N, Yin X, Ellinor PT, Lubitz SA, LeLorier PA, McManus DD, Sullivan LM, Seshadri S, Vasan RS, Benjamin EJ, Magnani JW. Atrial flutter: Clinical risk factors and adverse outcomes in the Framingham Heart Study. *Heart Rhythm* 2016;**13**(1):233-40.
446. McIntyre WF, Diederichsen SZ, Freedman B, Schnabel RB, Svennberg E, Healey JS. Screening for atrial fibrillation to prevent stroke: a meta-analysis. *Eur Heart J Open* 2022;**2**(4):oeac044.
447. Elbadawi A, Sedhom R, Gad M, Hamed M, Elwagdy A, Barakat AF, Khalid U, Mamas MA, Birnbaum Y, Elgendy IY, Jneid H. Screening for atrial fibrillation in the elderly: A network meta-analysis of randomized trials. *Eur J Intern Med* 2022;**105**:38-45.
448. Lyth J, Svennberg E, Bernfort L, Aronsson M, Frykman V, Al-Khalili F, Friberg L, Rosenqvist M, Engdahl J, Levin L. Cost-effectiveness of population screening for atrial fibrillation: the STROKESTOP study. *Eur Heart J* 2023;**44**(3):196-204.
449. Mant J, Fitzmaurice DA, Hobbs FD, Jowett S, Murray ET, Holder R, Davies M, Lip GY. Accuracy of diagnosing atrial fibrillation on electrocardiogram by primary care practitioners and interpretative diagnostic software: analysis of data from screening for atrial fibrillation in the elderly (SAFE) trial. *BMJ* 2007;**335**(7616):380.
450. Halcox JPJ, Wareham K, Cardew A, Gilmore M, Barry JP, Phillips C, Gravenor MB. Assessment of Remote Heart Rhythm Sampling Using the AliveCor Heart Monitor

to Screen for Atrial Fibrillation: The REHEARSE-AF Study. *Circulation* 2017;**136**(19):1784-1794.

451. Duarte R, Stainthorpe A, Greenhalgh J, Richardson M, Nevitt S, Mahon J, Kotas E, Boland A, Thom H, Marshall T, Hall M, Takwoingi Y. Lead-I ECG for detecting atrial fibrillation in patients with an irregular pulse using single time point testing: a systematic review and economic evaluation. *Health Technol Assess* 2020;**24**(3):1-164.

452. Svennberg E, Stridh M, Engdahl J, Al-Khalili F, Friberg L, Frykman V, Rosenqvist M. Safe automatic one-lead electrocardiogram analysis in screening for atrial fibrillation. *Europace* 2017;**19**(9):1449-1453.

453. Paul Nordin A, Carnlöf C, Insulander P, Mohammad Ali A, Jensen-Urstad M, Saluveer O, Drca N. Validation of diagnostic accuracy of a handheld, smartphone-based rhythm recording device. *Expert Rev Med Devices* 2023;**20**(1):55-61.

454. Mannhart D, Lischer M, Knecht S, du Fay de Lavallaz J, Strebel I, Serban T, Vögeli D, Schaer B, Osswald S, Mueller C, Kühne M, Sticherling C, Badertscher P. Clinical Validation of 5 Direct-to-Consumer Wearable Smart Devices to Detect Atrial Fibrillation: BASEL Wearable Study. *JACC Clin Electrophysiol* 2023;**9**(2):232-242.

455. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, Lau CP, Fain E, Yang S, Bailleul C, Morillo CA, Carlson M, Themeles E, Kaufman ES, Hohnloser SH. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med* 2012;**366**(2):120-9.

456. Morseth B, Geelhoed B, Linneberg A, Johansson L, Kuulasmaa K, Salomaa V, Iacoviello L, Costanzo S, Söderberg S, Niiranen TJ, Vishram-Nielsen JKK, Njølstad I, Wilsgaard T, Mathiesen EB, Løchen ML, Zeller T, Blankenberg S, Ojeda FM, Schnabel RB. Age-specific atrial fibrillation incidence, attributable risk factors and risk of stroke and mortality: results from the MORGAM Consortium. *Open Heart* 2021;**8**(2):e001624.

457. Magnussen C, Niiranen TJ, Ojeda FM, Gianfagna F, Blankenberg S, Njølstad I, Vartiainen E, Sans S, Pasterkamp G, Hughes M, Costanzo S, Donati MB, Jousilahti P, Linneberg A, Palosaari T, de Gaetano G, Bobak M, den Ruijter HM, Mathiesen E, Jørgensen T, Söderberg S, Kuulasmaa K, Zeller T, Iacoviello L, Salomaa V, Schnabel RB. Sex Differences and Similarities in Atrial Fibrillation Epidemiology, Risk Factors, and Mortality in Community Cohorts: Results From the BiomarCaRE Consortium (Biomarker for Cardiovascular Risk Assessment in Europe). *Circulation* 2017;**136**(17):1588-1597.

458. Staerk L, Wang B, Preis SR, Larson MG, Lubitz SA, Ellinor PT, McManus DD, Ko D, Weng LC, Lunetta KL, Frost L, Benjamin EJ, Trinquart L. Lifetime risk of atrial fibrillation according to optimal, borderline, or elevated levels of risk factors: cohort study based on longitudinal data from the Framingham Heart Study. *BMJ* 2018;**361**:k1453.

459. Schnabel RB, Yin X, Gona P, Larson MG, Beiser AS, McManus DD, Newton-Cheh C, Lubitz SA, Magnani JW, Ellinor PT, Seshadri S, Wolf PA, Vasan RS, Benjamin EJ, Levy D. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet* 2015;**386**(9989):154-62.

460. Ghelani KP, Chen LY, Norby FL, Soliman EZ, Koton S, Alonso A. Thirty-Year Trends in the Incidence of Atrial Fibrillation: The ARIC Study. *J Am Heart Assoc* 2022;**11**(8):e023583.
461. Huxley RR, Lopez FL, Folsom AR, Agarwal SK, Loefer LR, Soliman EZ, MacLehose R, Konety S, Alonso A. Absolute and attributable risks of atrial fibrillation in relation to optimal and borderline risk factors: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation* 2011;**123**(14):1501-8.
462. Rodriguez CJ, Soliman EZ, Alonso A, Swett K, Okin PM, Goff DC, Jr., Heckbert SR. Atrial fibrillation incidence and risk factors in relation to race-ethnicity and the population attributable fraction of atrial fibrillation risk factors: the Multi-Ethnic Study of Atherosclerosis. *Ann Epidemiol* 2015;**25**(2):71-6, 76.e1.
463. GBD 2019 Demographics Collaborators. Global age-sex-specific fertility, mortality, healthy life expectancy (HALE), and population estimates in 204 countries and territories, 1950-2019: a comprehensive demographic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020;**396**(10258):1160-1203.
464. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, Barengo NC, Beaton AZ, Benjamin EJ, Benziger CP, Bonny A, Brauer M, Brodmann M, Cahill TJ, Carapetis J, Catapano AL, Chugh SS, Cooper LT, Coresh J, Criqui M, DeCleene N, Eagle KA, Emmons-Bell S, Feigin VL, Fernández-Solà J, Fowkes G, Gakidou E, Grundy SM, He FJ, Howard G, Hu F, Inker L, Karthikeyan G, Kassebaum N, Koroshetz W, Lavie C, Lloyd-Jones D, Lu HS, Mirijello A, Temesgen AM, Mokdad A, Moran AE, Muntner P, Narula J, Neal B, Ntsekhe M, Moraes de Oliveira G, Otto C, Owolabi M, Pratt M, Rajagopalan S, Reitsma M, Ribeiro ALP, Rigotti N, Rodgers A, Sable C, Shakil S, Sliwa-Hahnle K, Stark B, Sundström J, Timpel P, Tleyjeh IM, Valgimigli M, Vos T, Whelton PK, Yacoub M, Zuhlke L, Murray C, Fuster V. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. *J Am Coll Cardiol* 2020;**76**(25):2982-3021.
465. Chung SC, Sofat R, Acosta-Mena D, Taylor JA, Lambiase PD, Casas JP, Providencia R. Atrial fibrillation epidemiology, disparity and healthcare contacts: a population-wide study of 5.6 million individuals. *Lancet Reg Health Eur* 2021;**7**:100157.
466. Williams BA, Chamberlain AM, Blankenship JC, Hylek EM, Voyce S. Trends in Atrial Fibrillation Incidence Rates Within an Integrated Health Care Delivery System, 2006 to 2018. *JAMA Netw Open* 2020;**3**(8):e2014874.
467. Lippi G, Sanchis-Gomar F, Cervellin G. Global epidemiology of atrial fibrillation: An increasing epidemic and public health challenge. *Int J Stroke* 2021;**16**(2):217-221.
468. Al-Khayatt BM, Saliccioli JD, Marshall DC, Krahn AD, Shalhoub J, Sikkel MB. Paradoxical impact of socioeconomic factors on outcome of atrial fibrillation in Europe: trends in incidence and mortality from atrial fibrillation. *Eur Heart J* 2021;**42**(8):847-857.
469. Alonso A, Alam AB, Kamel H, Subbian V, Qian J, Boerwinkle E, Cicek M, Clark CR, Cohn EG, Gebo KA, Loperena-Cortes R, Mayo KR, Mockrin S, Ohno-Machado L, Schully SD, Ramirez AH, Greenland P. Epidemiology of atrial fibrillation in the All of Us Research Program. *PLoS One* 2022;**17**(3):e0265498.
470. Siland JE, Geelhoed B, Roselli C, Wang B, Lin HJ, Weiss S, Trompet S, van den Berg ME, Soliman EZ, Chen LY, Ford I, Jukema JW, Macfarlane PW, Kornej J,

Lin H, Lunetta KL, Kavousi M, Kors JA, Ikram MA, Guo X, Yao J, Dörr M, Felix SB, Völker U, Sotoodehnia N, Arking DE, Stricker BH, Heckbert SR, Lubitz SA, Benjamin EJ, Alonso A, Ellinor PT, van der Harst P, Rienstra M. Resting heart rate and incident atrial fibrillation: A stratified Mendelian randomization in the AFGen consortium. *PLoS One* 2022;**17**(5):e0268768.

471. Wang N, Sun Y, Zhang H, Wang B, Chen C, Wang Y, Chen J, Tan X, Zhang J, Xia F, Qi L, Lu Y. Long-term night shift work is associated with the risk of atrial fibrillation and coronary heart disease. *Eur Heart J* 2021;**42**(40):4180-4188.

472. Lu Z, Aribas E, Geurts S, Roeters van Lennep JE, Ikram MA, Bos MM, de Groot NMS, Kavousi M. Association Between Sex-Specific Risk Factors and Risk of New-Onset Atrial Fibrillation Among Women. *JAMA Netw Open* 2022;**5**(9):e2229716.

473. Geurts S, Tilly MJ, Arshi B, Stricker BHC, Kors JA, Deckers JW, de Groot NMS, Ikram MA, Kavousi M. Heart rate variability and atrial fibrillation in the general population: a longitudinal and Mendelian randomization study. *Clin Res Cardiol* 2022.

474. Geurts S, Brunborg C, Papageorgiou G, Ikram MA, Kavousi M. Subclinical Measures of Peripheral Atherosclerosis and the Risk of New-Onset Atrial Fibrillation in the General Population: the Rotterdam Study. *J Am Heart Assoc* 2022;**11**(1):e023967.

475. Roselli C, Chaffin MD, Weng LC, Aeschbacher S, Ahlberg G, Albert CM, Almgren P, Alonso A, Anderson CD, Aragam KG, Arking DE, Barnard J, Bartz TM, Benjamin EJ, Bihlmeyer NA, Bis JC, Bloom HL, Boerwinkle E, Bottinger EB, Brody JA, Calkins H, Campbell A, Cappola TP, Carlquist J, Chasman DI, Chen LY, Chen YI, Choi EK, Choi SH, Christophersen IE, Chung MK, Cole JW, Conen D, Cook J, Crijns HJ, Cutler MJ, Damrauer SM, Daniels BR, Darbar D, Delgado G, Denny JC, Dichgans M, Dörr M, Dudink EA, Dudley SC, Esa N, Esko T, Eskola M, Fatkin D, Felix SB, Ford I, Franco OH, Geelhoed B, Grewal RP, Gudnason V, Guo X, Gupta N, Gustafsson S, Gutmann R, Hamsten A, Harris TB, Hayward C, Heckbert SR, Hernesniemi J, Hocking LJ, Hofman A, Horimoto A, Huang J, Huang PL, Huffman J, Ingelsson E, Ipek EG, Ito K, Jimenez-Conde J, Johnson R, Jukema JW, Kääb S, Kähönen M, Kamatani Y, Kane JP, Kastrati A, Kathiresan S, Katschnig-Winter P, Kavousi M, Kessler T, Kietselaer BL, Kirchhof P, Kleber ME, Knight S, Krieger JE, Kubo M, Launer LJ, Laurikka J, Lehtimäki T, Leineweber K, Lemaitre RN, Li M, Lim HE, Lin HJ, Lin H, Lind L, Lindgren CM, Lokki ML, London B, Loos RJJ, Low SK, Lu Y, Lyytikäinen LP, Macfarlane PW, Magnusson PK, Mahajan A, Malik R, Mansur AJ, Marcus GM, Margolin L, Margulies KB, März W, McManus DD, Melander O, Mohanty S, Montgomery JA, Morley MP, Morris AP, Müller-Nurasyid M, Natale A, Nazarian S, Neumann B, Newton-Cheh C, Niemeijer MN, Nikus K, Nilsson P, Noordam R, Oellers H, Olesen MS, Orho-Melander M, Padmanabhan S, Pak HN, Paré G, Pedersen NL, Pera J, Pereira A, Porteous D, Psaty BM, Pulit SL, Pullinger CR, Rader DJ, Refsgaard L, Ribasés M, Ridker PM, Rienstra M, Risch L, Roden DM, Rosand J, Rosenberg MA, Rost N, Rotter JI, Saba S, Sandhu RK, Schnabel RB, Schramm K, Schunkert H, Schurman C, Scott SA, Seppälä I, Shaffer C, Shah S, Shalaby AA, Shim J, Shoemaker MB, Siland JE, Sinisalo J, Sinner MF, Slowik A, Smith AV, Smith BH, Smith JG, Smith JD, Smith NL, Soliman EZ, Sotoodehnia N, Stricker BH, Sun A, Sun H, Svendsen JH, Tanaka T, Tanriverdi K, Taylor KD, Teder-Laving M, Teumer A, Thériault S, Trompet S, Tucker NR, Tveit A, Uitterlinden AG, Van Der Harst P, Van Gelder IC, Van Wageningen DR, Verweij N, Vlachopoulou E, Völker U, Wang B, Weeke PE, Weijs B, Weiss R, Weiss S, Wells QS, Wiggins KL, Wong JA, Woo D, Worrall BB, Yang PS, Yao J, Yoneda ZT, Zeller T,

Zeng L, Lubitz SA, Lunetta KL, Ellinor PT. Multi-ethnic genome-wide association study for atrial fibrillation. *Nat Genet* 2018;**50**(9):1225-1233.

476. Börschel CS, Ohlrogge AH, Geelhoed B, Niiranen T, Havulinna AS, Palosaari T, Jousilahti P, Rienstra M, van der Harst P, Blankenberg S, Zeller T, Salomaa V, Schnabel RB. Risk prediction of atrial fibrillation in the community combining biomarkers and genetics. *Europace* 2021;**23**(5):674-681.

477. Choi SH, Jurgens SJ, Weng LC, Pirruccello JP, Roselli C, Chaffin M, Lee CJ, Hall AW, Khera AV, Lunetta KL, Lubitz SA, Ellinor PT. Monogenic and Polygenic Contributions to Atrial Fibrillation Risk: Results From a National Biobank. *Circ Res* 2020;**126**(2):200-209.

478. Khera AV, Chaffin M, Aragam KG, Haas ME, Roselli C, Choi SH, Natarajan P, Lander ES, Lubitz SA, Ellinor PT, Kathiresan S. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. *Nat Genet* 2018;**50**(9):1219-1224.

479. Muse ED, Wineinger NE, Spencer EG, Peters M, Henderson R, Zhang Y, Barrett PM, Rivera SP, Wohlgemuth JG, Devlin JJ, Shiffman D, Topol EJ. Validation of a genetic risk score for atrial fibrillation: A prospective multicenter cohort study. *PLoS Med* 2018;**15**(3):e1002525.

480. Larstorp ACK, Stokke IM, Kjeldsen SE, Hecht Olsen M, Okin PM, Devereux RB, Wachtell K. Antihypertensive therapy prevents new-onset atrial fibrillation in patients with isolated systolic hypertension: the LIFE study. *Blood Press* 2019;**28**(5):317-326.

481. Chen LY, Bigger JT, Hickey KT, Chen H, Lopez-Jimenez C, Banerji MA, Evans G, Fleg JL, Papademetriou V, Thomas A, Woo V, Seaquist ER, Soliman EZ. Effect of Intensive Blood Pressure Lowering on Incident Atrial Fibrillation and P-Wave Indices in the ACCORD Blood Pressure Trial. *Am J Hypertens* 2016;**29**(11):1276-1282.

482. Soliman EZ, Rahman AF, Zhang ZM, Rodriguez CJ, Chang TI, Bates JT, Ghazi L, Blackshear JL, Chonchol M, Fine LJ, Ambrosius WT, Lewis CE. Effect of Intensive Blood Pressure Lowering on the Risk of Atrial Fibrillation. *Hypertension* 2020;**75**(6):1491-1496.

483. Healey JS, Baranchuk A, Crystal E, Morillo CA, Garfinkle M, Yusuf S, Connolly SJ. Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a meta-analysis. *J Am Coll Cardiol* 2005;**45**(11):1832-9.

484. Wang M, Zhang Y, Wang Z, Liu D, Mao S, Liang B. The effectiveness of SGLT2 inhibitor in the incidence of atrial fibrillation/atrial flutter in patients with type 2 diabetes mellitus/heart failure: a systematic review and meta-analysis. *J Thorac Dis* 2022;**14**(5):1620-1637.

485. Yin Z, Zheng H, Guo Z. Effect of Sodium-Glucose Co-transporter Protein 2 Inhibitors on Arrhythmia in Heart Failure Patients With or Without Type 2 Diabetes: A Meta-Analysis of Randomized Controlled Trials. *Front Cardiovasc Med* 2022;**9**:902923.

486. Li WJ, Chen XQ, Xu LL, Li YQ, Luo BH. SGLT2 inhibitors and atrial fibrillation in type 2 diabetes: a systematic review with meta-analysis of 16 randomized controlled trials. *Cardiovasc Diabetol* 2020;**19**(1):130.

487. Chang SH, Wu LS, Chiou MJ, Liu JR, Yu KH, Kuo CF, Wen MS, Chen WJ, Yeh YH, See LC. Association of metformin with lower atrial fibrillation risk among patients with type 2 diabetes mellitus: a population-based dynamic cohort and in vitro studies. *Cardiovasc Diabetol* 2014;**13**:123.
488. Tedrow UB, Conen D, Ridker PM, Cook NR, Koplan BA, Manson JE, Buring JE, Albert CM. The long- and short-term impact of elevated body mass index on the risk of new atrial fibrillation the WHS (women's health study). *J Am Coll Cardiol* 2010;**55**(21):2319-27.
489. Chokesuwattanaskul R, Thongprayoon C, Bathini T, Sharma K, Watthanasuntorn K, Lertjitbanjong P, Pachariyanon P, Prechawat S, Mao MA, Torres-Ortiz A, Cheungpasitporn W. Incident atrial fibrillation in patients undergoing bariatric surgery: a systematic review and meta-analysis. *Intern Med J* 2020;**50**(7):810-817.
490. Srivatsa UN, Malhotra P, Zhang XJ, Beri N, Xing G, Brunson A, Ali M, Fan D, Pezeshkian N, Chiamvimonvat N, White RH. Bariatric surgery to alleviate Occurrence of Atrial Fibrillation Hospitalization-BLOC-AF. *Heart Rhythm* 2020;**1**(2):96-102.
491. Lynch KT, Mehaffey JH, Hawkins RB, Hassinger TE, Hallowell PT, Kirby JL. Bariatric surgery reduces incidence of atrial fibrillation: a propensity score-matched analysis. *Surg Obes Relat Dis* 2019;**15**(2):279-285.
492. Hoskuldsdottir G, Sattar N, Miftaraj M, Naslund I, Ottosson J, Franzen S, Svensson AM, Eliasson B. Potential Effects of Bariatric Surgery on the Incidence of Heart Failure and Atrial Fibrillation in Patients With Type 2 Diabetes Mellitus and Obesity and on Mortality in Patients With Preexisting Heart Failure: A Nationwide, Matched, Observational Cohort Study. *J Am Heart Assoc* 2021;**10**(7):e019323.
493. Jamaly S, Carlsson L, Peltonen M, Jacobson P, Sjostrom L, Karason K. Bariatric Surgery and the Risk of New-Onset Atrial Fibrillation in Swedish Obese Subjects. *J Am Coll Cardiol* 2016;**68**(23):2497-2504.
494. Mishima RS, Verdicchio CV, Noubiap JJ, Ariyaratnam JP, Gallagher C, Jones D, Malik V, Agbaedeng TA, Middeldorp ME, Lau DH, Sanders P, Elliott AD. Self-reported physical activity and atrial fibrillation risk: A systematic review and meta-analysis. *Heart Rhythm* 2021;**18**(4):520-528.
495. Elliott AD, Linz D, Mishima R, Kadhim K, Gallagher C, Middeldorp ME, Verdicchio CV, Hendriks JML, Lau DH, La Gerche A, Sanders P. Association between physical activity and risk of incident arrhythmias in 402 406 individuals: evidence from the UK Biobank cohort. *Eur Heart J* 2020;**41**(15):1479-1486.
496. Jin MN, Yang PS, Song C, Yu HT, Kim TH, Uhm JS, Sung JH, Pak HN, Lee MH, Joung B. Physical Activity and Risk of Atrial Fibrillation: A Nationwide Cohort Study in General Population. *Sci Rep* 2019;**9**(1):13270.
497. Khurshid S, Weng LC, Al-Alusi MA, Halford JL, Haimovich JS, Benjamin EJ, Trinquart L, Ellinor PT, McManus DD, Lubitz SA. Accelerometer-derived physical activity and risk of atrial fibrillation. *Eur Heart J* 2021;**42**(25):2472-2483.
498. Tikkanen E, Gustafsson S, Ingelsson E. Associations of Fitness, Physical Activity, Strength, and Genetic Risk With Cardiovascular Disease: Longitudinal Analyses in the UK Biobank Study. *Circulation* 2018;**137**(24):2583-2591.

499. Morseth B, Graff-Iversen S, Jacobsen BK, Jørgensen L, Nyrnes A, Thelle DS, Vestergaard P, Løchen ML. Physical activity, resting heart rate, and atrial fibrillation: the Tromsø Study. *Eur Heart J* 2016;**37**(29):2307-13.
500. Newman W, Parry-Williams G, Wiles J, Edwards J, Hulbert S, Kipourou K, Papadakis M, Sharma R, O'Driscoll J. Risk of atrial fibrillation in athletes: a systematic review and meta-analysis. *Br J Sports Med* 2021;**55**(21):1233-1238.
501. Andersen K, Farahmand B, Ahlbom A, Held C, Ljunghall S, Michaelsson K, Sundstrom J. Risk of arrhythmias in 52 755 long-distance cross-country skiers: a cohort study. *Eur Heart J* 2013;**34**(47):3624-31.
502. Baldesberger S, Bauersfeld U, Candinas R, Seifert B, Zuber M, Ritter M, Jenni R, Oechslin E, Luthi P, Scharf C, Marti B, Attenhofer Jost CH. Sinus node disease and arrhythmias in the long-term follow-up of former professional cyclists. *Eur Heart J* 2008;**29**(1):71-8.
503. Elosua R, Arquer A, Mont L, Sambola A, Molina L, García-Morán E, Brugada J, Marrugat J. Sport practice and the risk of lone atrial fibrillation: a case-control study. *Int J Cardiol* 2006;**108**(3):332-7.
504. Molina L, Mont L, Marrugat J, Berruezo A, Brugada J, Bruguera J, Rebato C, Elosua R. Long-term endurance sport practice increases the incidence of lone atrial fibrillation in men: a follow-up study. *Europace* 2008;**10**(5):618-23.
505. Gallagher C, Hendriks JML, Elliott AD, Wong CX, Rangnekar G, Middeldorp ME, Mahajan R, Lau DH, Sanders P. Alcohol and incident atrial fibrillation - A systematic review and meta-analysis. *Int J Cardiol* 2017;**246**:46-52.
506. Csengeri D, Sprünker NA, Di Castelnuovo A, Niiranen T, Vishram-Nielsen JK, Costanzo S, Söderberg S, Jensen SM, Vartiainen E, Donati MB, Magnussen C, Camen S, Gianfagna F, Løchen ML, Kee F, Kontto J, Mathiesen EB, Koenig W, Stefan B, de Gaetano G, Jørgensen T, Kuulasmaa K, Zeller T, Salomaa V, Iacoviello L, Schnabel RB. Alcohol consumption, cardiac biomarkers, and risk of atrial fibrillation and adverse outcomes. *Eur Heart J* 2021;**42**(12):1170-1177.
507. Tu SJ, Gallagher C, Elliott AD, Linz D, Pitman BM, Hendriks JML, Lau DH, Sanders P, Wong CX. Risk Thresholds for Total and Beverage-Specific Alcohol Consumption and Incident Atrial Fibrillation. *JACC Clin Electrophysiol* 2021;**7**(12):1561-1569.
508. Lee JW, Roh SY, Yoon WS, Kim J, Jo E, Bae DH, Kim M, Lee JH, Kim SM, Choi WG, Bae JW, Hwang KK, Kim DW, Cho MC, Kim YS, Kim Y, You HS, Kang HT, Lee DI. Changes in alcohol consumption habits and risk of atrial fibrillation: a nationwide population-based study. *Eur J Prev Cardiol* 2024;**31**(1):49-58.
509. Okin PM, Hille DA, Larstorp AC, Wachtell K, Kjeldsen SE, Dahlöf B, Devereux RB. Effect of lower on-treatment systolic blood pressure on the risk of atrial fibrillation in hypertensive patients. *Hypertension* 2015;**66**(2):368-73.
510. Wachtell K, Lehto M, Gerdts E, Olsen MH, Horneftam B, Dahlöf B, Ibsen H, Julius S, Kjeldsen SE, Lindholm LH, Nieminen MS, Devereux RB. Angiotensin II receptor blockade reduces new-onset atrial fibrillation and subsequent stroke compared to atenolol: The Losartan Intervention for End point reduction in hypertension (LIFE) study. *J Am Coll Cardiol* 2005;**45**(5):712-719.

511. Schmieder RE, Kjeldsen SE, Julius S, McInnes GT, Zanchetti A, Hua TA, Group VT. Reduced incidence of new-onset atrial fibrillation with angiotensin II receptor blockade: the VALUE trial. *J Hypertens* 2008;**26**(3):403-11.
512. Dewland TA, Soliman EZ, Yamal JM, Davis BR, Alonso A, Albert CM, Simpson LM, Haywood LJ, Marcus GM. Pharmacologic Prevention of Incident Atrial Fibrillation: Long-Term Results From the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial). *Circ Arrhythm Electrophysiol* 2017;**10**(12):e005463.
513. Schaer BA, Schneider C, Jick SS, Conen D, Osswald S, Meier CR. Risk for incident atrial fibrillation in patients who receive antihypertensive drugs: a nested case-control study. *Ann Intern Med* 2010;**152**(2):78-84.
514. Liu X, Liu H, Wang L, Zhang L, Xu Q. Role of sacubitril-valsartan in the prevention of atrial fibrillation occurrence in patients with heart failure: A systematic review and meta-analysis of randomized controlled trials. *PLOS ONE* 2022;**17**(1):e0263131.
515. Butt JH, Docherty KF, Jhund PS, de Boer RA, Böhm M, Desai AS, Howlett JG, Inzucchi SE, Kosiborod MN, Martinez FA, Nicolau JC, Petrie MC, Ponikowski P, Bengtsson O, Langkilde AM, Schou M, Sjöstrand M, Solomon SD, Sabatine MS, McMurray JJV, Køber L. Dapagliflozin and atrial fibrillation in heart failure with reduced ejection fraction: insights from DAPA-HF. *Eur J Heart Fail* 2022;**24**(3):513-525.
516. Hess PL, Jackson KP, Hasselblad V, Al-Khatib SM. Is Cardiac Resynchronization Therapy an Antiarrhythmic Therapy for Atrial Fibrillation? A Systematic Review and Meta-Analysis. *Curr Cardiol Rep* 2013;**15**(2):330.
517. Zelniker TA, Bonaca MP, Furtado RHM, Mosenzon O, Kuder JF, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Budaj A, Kiss RG, Padilla F, Gause-Nilsson I, Langkilde AM, Raz I, Sabatine MS, Wiviott SD. Effect of Dapagliflozin on Atrial Fibrillation in Patients With Type 2 Diabetes Mellitus: Insights From the DECLARE-TIMI 58 Trial. *Circulation* 2020;**141**(15):1227-1234.
518. Tseng CH. Metformin Use Is Associated With a Lower Incidence of Hospitalization for Atrial Fibrillation in Patients With Type 2 Diabetes Mellitus. *Front Med (Lausanne)* 2020;**7**:592901.
519. Suzuki Y, Kaneko H, Okada A, Itoh H, Matsuoka S, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Kamiya K, Matsunaga A, Ako J, Node K, Yasunaga H, Komuro I. Comparison of cardiovascular outcomes between SGLT2 inhibitors in diabetes mellitus. *Cardiovasc Diabetol* 2022;**21**(1):67.
520. Chan YH, Chao TF, Chen SW, Lee HF, Li PR, Chen WM, Yeh YH, Kuo CT, See LC, Lip GYH. The risk of incident atrial fibrillation in patients with type 2 diabetes treated with sodium glucose cotransporter-2 inhibitors, glucagon-like peptide-1 receptor agonists, and dipeptidyl peptidase-4 inhibitors: a nationwide cohort study. *Cardiovasc Diabetol* 2022;**21**(1):118.
521. Everett BM, Conen D, Buring JE, Moorthy MV, Lee IM, Albert CM. Physical activity and the risk of incident atrial fibrillation in women. *Circ Cardiovasc Qual Outcomes* 2011;**4**(3):321-7.

522. Mozaffarian D, Furberg CD, Psaty BM, Siscovick D. Physical activity and incidence of atrial fibrillation in older adults: the cardiovascular health study. *Circulation* 2008;**118**(8):800-7.
523. Drca N, Wolk A, Jensen-Urstad M, Larsson SC. Physical activity is associated with a reduced risk of atrial fibrillation in middle-aged and elderly women. *Heart* 2015;**101**(20):1627-30.
524. Azarbal F, Stefanick ML, Salmoirago-Blotcher E, Manson JE, Albert CM, LaMonte MJ, Larson JC, Li W, Martin LW, Nassir R, Garcia L, Assimes TL, Tharp KM, Hlatky MA, Perez MV. Obesity, physical activity, and their interaction in incident atrial fibrillation in postmenopausal women. *J Am Heart Assoc* 2014;**3**(4):e001127.
525. Garnvik LE, Malmo V, Janszky I, Wisløff U, Loennechen JP, Nes BM. Physical activity modifies the risk of atrial fibrillation in obese individuals: The HUNT3 study. *Eur J Prev Cardiol* 2018;**25**(15):1646-1652.
526. Heitmann KA, Løchen ML, Styliadis M, Hopstock LA, Schirmer H, Morseth B. Associations between physical activity, left atrial size and incident atrial fibrillation: the Tromsø Study 1994-2016. *Open Heart* 2022;**9**(1):e001823.