JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION

VOL. 74, NO. 17, 2019

JACC REVIEW TOPIC OF THE WEEK

Anticoagulation in Concomitant Chronic Kidney Disease and Atrial Fibrillation

JACC Review Topic of the Week

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ABSTRACT

Atrial fibrillation (AF) and chronic kidney disease (CKD) often coexist as they share multiple risk factors, including hypertension, diabetes mellitus, and coronary artery disease. Although there is irrefutable evidence supporting anticoagulation in AF in the general population, these data may not be transferable to the setting of advanced CKD, where the decision to commence anticoagulation poses a conundrum. In this cohort, there is a progressively increased risk of both ischemic stroke and hemorrhage as renal function declines, complicating the decision to initiate anticoagulation. No definitive clinical guidelines derived from randomized controlled trials exist to aid clinical decision-making, and the findings from observational studies are conflicting. In this review, the authors outline the pathophysiological mechanisms at play and summarize the limited existing data related to anticoagulation in those with concomitant CKD and AF. Finally, the authors suggest how to approach the decision of whether and how to use oral anticoagulation in these patients.
(J Am Coll Cardiol 2019;74:2204–15) © 2019 Published by Elsevier on behalf of the American College of Cardiology Foundation.

Atrial fibrillation (AF), the most commonly occurring sustained arrhythmia worldwide, is associated with an increased risk of thromboembolic stroke and all-cause mortality. In the general population with AF at increased risk for thromboembolic complications, oral anticoagulant therapy (OAT) for stroke thromboprophylaxis is universally recommended in clinical guidelines (1–5).

Chronic kidney disease (CKD), affecting up to 15% of adults worldwide, is associated with increased cardiovascular disease (CVD) risk and age-standardized all-cause mortality, independent of other known risk factors (6,7) (**Figure 1**). It is not necessarily the case that therapeutic interventions, whose efficacy and safety profiles are well understood in the non-CKD setting, can be utilized in CKD

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Manuscript received July 10, 2019; revised manuscript received August 22, 2019, accepted August 27, 2019.

Listen to this manuscript's audio summary by Editor-in-Chief Dr. Valentin Fuster on JACC.org.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2019.08.1031

HIGHLIGHTS

- The decision to initiate OAT poses a clinical conundrum in patients with coexisting AF and advanced CKD.
- In CKD, several pathophysiological factors result in a progressively increased risk of both ischemic stroke and hemorrhage as renal function declines, irrespective of OAT.
- The limited available data suggests that DOACs should generally be favored over VKAs in view of their probable increased safety and efficacy in CKD, with a lower risk of vascular calcification and anticoagulant-associated nephropathy.
- Until dedicated RCTs are completed to define optimal management, clinical decision-making should be informed by the limited data available, which necessitates individualization and physician-patient collaboration.

patients with a similar risk-to-benefit ratio. Indeed, there are situations where it has been shown to be incorrect to extrapolate from non-CKD to CKD cohorts (e.g., statins do *not* reduce mortality in patients with stage 5 CKD) (8). To date, the few large observational studies that have specifically studied the outcomes of OAT in patients with coexisting advanced CKD and AF have yielded conflicting results, in both nondialysis (9–12) and end-stage renal disease (ESRD) cohorts (13–18). Interestingly, some series have reported a paradoxical increase in ischemic stroke in non-ESRD (12) and hemodialysis patients with AF treated with OAT (16). This highlights the compelling need for adequately powered randomized controlled trials (RCTs) to provide clarity on this issue.

It is the purpose of this review to address the evidential gap of whether, when, and how to attempt OAT in patients with concomitant AF and advanced CKD to safely reduce the risk of subsequent stroke.

ARRHYTHMIAS IN CKD

Arrhythmias including AF, atrial flutter, ventricular arrhythmias, and sudden cardiac death are frequent in patients with advanced CKD (19). They are associated with stroke, vascular dementia, myocardial infarction, heart failure, progressive CKD, and death. Population-based studies suggest that AF occurs in around 1 in 5 patients with CKD not receiving dialysis (20), and about 1 in 3 patients receiving dialysis (21,22). Although the prevalence of AF is reported to be up to 10-fold higher in patients with CKD age <55 years compared with age-matched nondialysis patients, it is in those over the age of 60 years that the prevalence of AF is the highest (21). As renal function declines, the prevalence of AF increases; among 235,818 subjects followed for 6 years, AF prevalence increased by 57% for those with an estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2 compared with 32% for those with an eGFR of 30 to 59 ml/min/1.73 m^2 (23).

A number of mechanisms have been proposed to account for why AF is more common in CKD patients. CKD is associated with a number of arrhythmogenic substrates, which can result in the development of AF (**Table 1**). Activation of the renin-angiotensin-aldosterone system, occurring in CKD and associated with progressive renal disease, increases circulating levels of angiotensin II, which contribute to atrial myocyte apoptosis and interstitial fibrosis (24). Studies in patients without CKD have found a correlation between markers of inflammation and AF burden (25), and an inverse relationship between levels of inflammation and maintenance of sinus rhythm following cardioversion (26). Similarly, inflammatory markers are elevated in CKD patients, and the prevalence of AF in patients with CKD is higher in the presence of a chronically elevated level of CRP (27). Left atrial enlargement and diastolic dysfunction are more common in patients with than without CKD, (28), and this is associated with AF (20). Myocardial fibrosis is common in CKD, and this may provide a structural substrate which enhances atrial re-entrant excitation (29).

AF in CKD is associated with stroke, heart failure, progressive CKD, and death, as well as the potential adverse consequences of stroke risk prophylaxis using OAT. In a study of over 116,000 patients with CKD (eGFR <60 ml/min/1.73 m^2), new-onset AF was associated with a higher incidence of both stroke and death (30). AF is not only an independent predictor of death, but also a marker of underlying CVD and its associated impact (19). In a study of 206,229 patients with CKD, developing AF was associated with a 67% enhanced risk of progression to end-stage renal disease (ESRD) at 5-year follow-up (31).

ABBREVIATIONS AND ACRONYMS

ACC = American College of Cardiology

AF = atrial fibrillation

AHA = American Heart Association

CKD = chronic kidney disease

DOAC = direct oral anticoagulant

EHRA = European Heart Rhythm Association

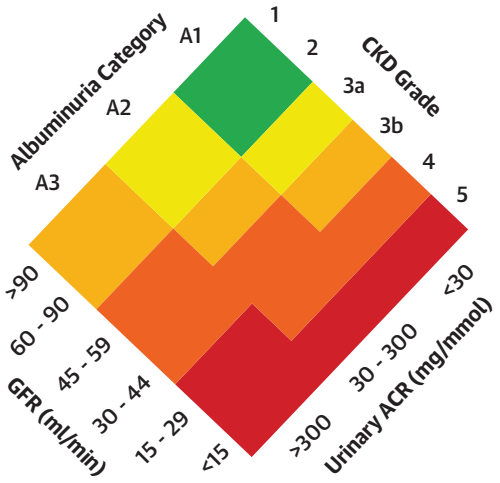
HRS = Heart Rhythm Society

KDIGO = Kidney Disease: Improving Global Outcomes

OAT = oral anticoagulant therapy

VKA = vitamin K antagonist

FIGURE 1 Stages of Chronic Kidney Disease



Colors depict risk of progression, morbidity and mortality: **green** (low risk), **yellow** (moderate risk), **light orange** (high risk), **deep orange** (very high risk), and **red** (highest risk). ACR = albumin-to-creatinine ratio; CKD = chronic kidney disease; GFR = glomerular filtration rate.

CLOTTING AND BLEEDING IN CKD

Renal dysfunction causes alterations in hemostatic systems that may result in both a prothrombotic state and a bleeding diathesis (Figures 2 and 3). Changes in coagulation are influenced by the various pathophysiological mechanisms that cause CKD and also differ in acute kidney injury (AKI) versus CKD and in patients undergoing dialysis. The pathophysiological mechanisms related to the effect of uremic toxins on various aspects of blood coagulation are poorly understood, and many of the studies that have tried to address this experimentally were performed when dialysis was in its infancy, and thus would benefit from repetition with modern dialysis patients and practices (32). The interactions among anticoagulation used for hemodialysis (typically heparin), simultaneous use of 1 or more antiplatelet agents, and OAT are poorly characterized in the dialysis population with the risk of increased bleeding (33).

TABLE 1 Why Does CKD Predispose to AF?

Factor	Mechanism
Hypertension	Left ventricular hypertrophy, frequently due to hypertension, can cause heart failure and myocardial fibrosis, each predisposing to AF.
Heart failure	This is a substrate for the development of AF through atrial dilatation, fibrosis, and electromechanical remodeling.
Vascular disease	Peripheral, cerebral, and coronary artery disease are associated with an increased risk of AF.
Diabetes mellitus	Often associated with vascular disease, and thus the risk of AF, diabetes mellitus is also associated with autonomic imbalance, and therefore AF.
Urea and electrolyte imbalance	Uremia and hyperparathyroidism are associated with myocardial fibrosis, which is arrhythmogenic. Dialysis induced ischemia and abnormal pre-dialysis potassium are associated with AF. Dysregulation of intracellular calcium flux also predisposes to AF.
Autonomic imbalance	Heightened sympathetic activity is common in CKD which, in turn, predisposes to AF.

AF = atrial fibrillation; CKD = chronic kidney disease.

AF AND STROKE IN CKD PATIENTS

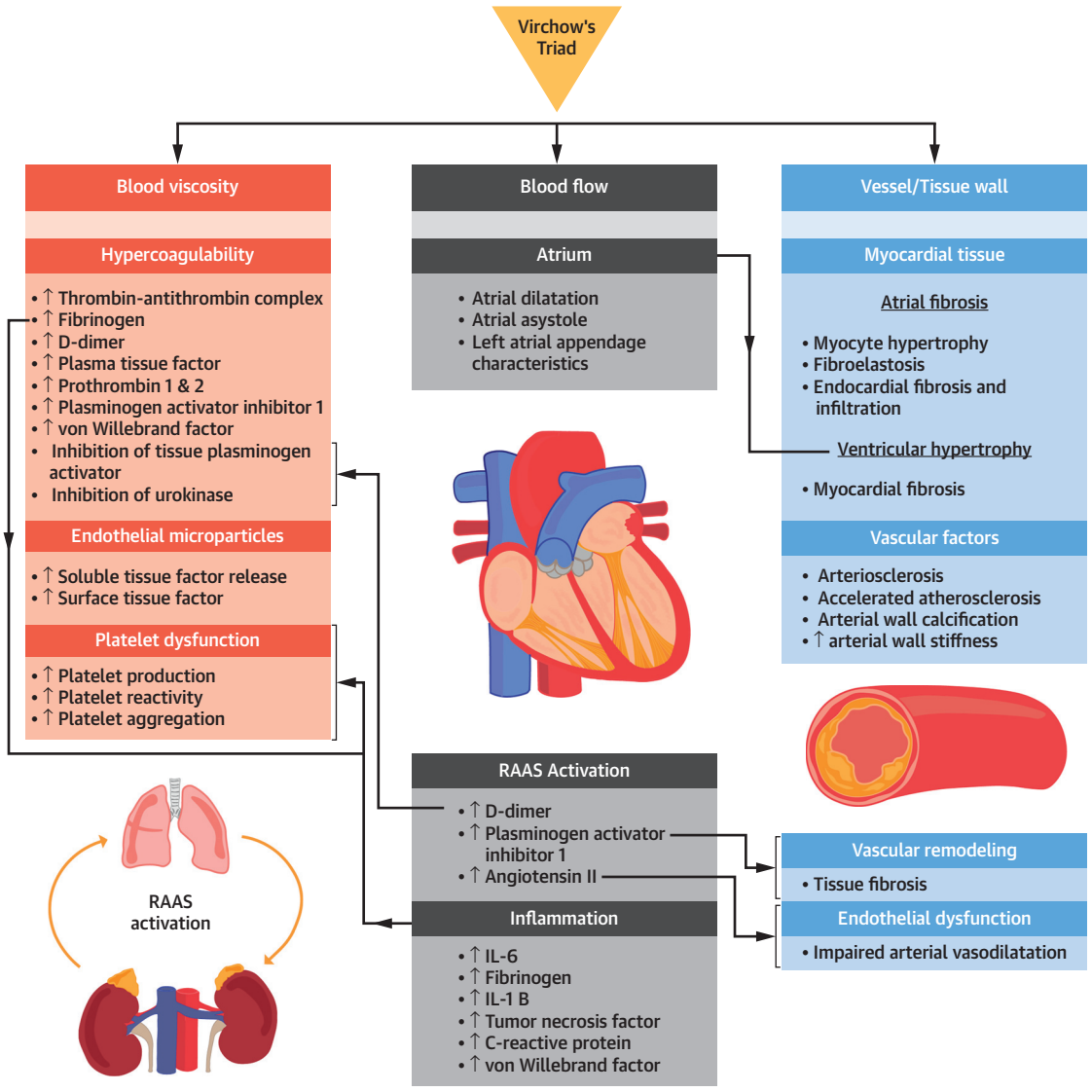
CKD is an independent risk factor for incident stroke (34). There is a linear relationship between GFR and risk of stroke increasing by 7% for every 10-ml/min/1.73 m^2 GFR decrease (35). Albuminuria is also independently associated with stroke and cognitive impairment. The presumed etiology of these pathologies in CKD is multifactorial.

Both CKD and stroke share common traditional risk factors such as diabetes mellitus, smoking, hypertension, hypercholesterolemia, and AF. Disorganized atrial contraction with a reduction in atrial blood flow, atrial fibrosis, endothelial and endocardial injury and dysfunction, augmented expression of tissue factor and von Willebrand factor, amplified platelet activation, and fibrinolysis may all predispose to thrombus formation and systemic embolization in CKD patients with AF (34).

CHALLENGES OF QUANTIFYING LOSS OF RENAL FUNCTION ON AN INDIVIDUAL PATIENT BASIS

The most commonly used renal function estimation equations based on serum creatinine concentration and demographic variables are the Cockcroft-Gault formula (CG), the Modification of Diet in Renal Disease Study (MDRD), and the most recent equation from the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (Table 2, Figure 1) (36). Although most nephrologists favor the latest CKD-EPI equation for diagnosing and classifying CKD, there is no consensus about the best formula to use for guiding drug dose choices; medical regulatory requirements still mandate the use of the dated CG formula despite it no longer being used in clinical practice. This is a concern given the potential for drug dosing errors; many commonly used medications in patients with AF or heart failure require dose adjustment according to renal function. There can be striking differences between the derived GFR values using these different equations (36).

FIGURE 2 **Pathophysiology of the Increased Thrombotic Risk in Coexistent CKD and AF**

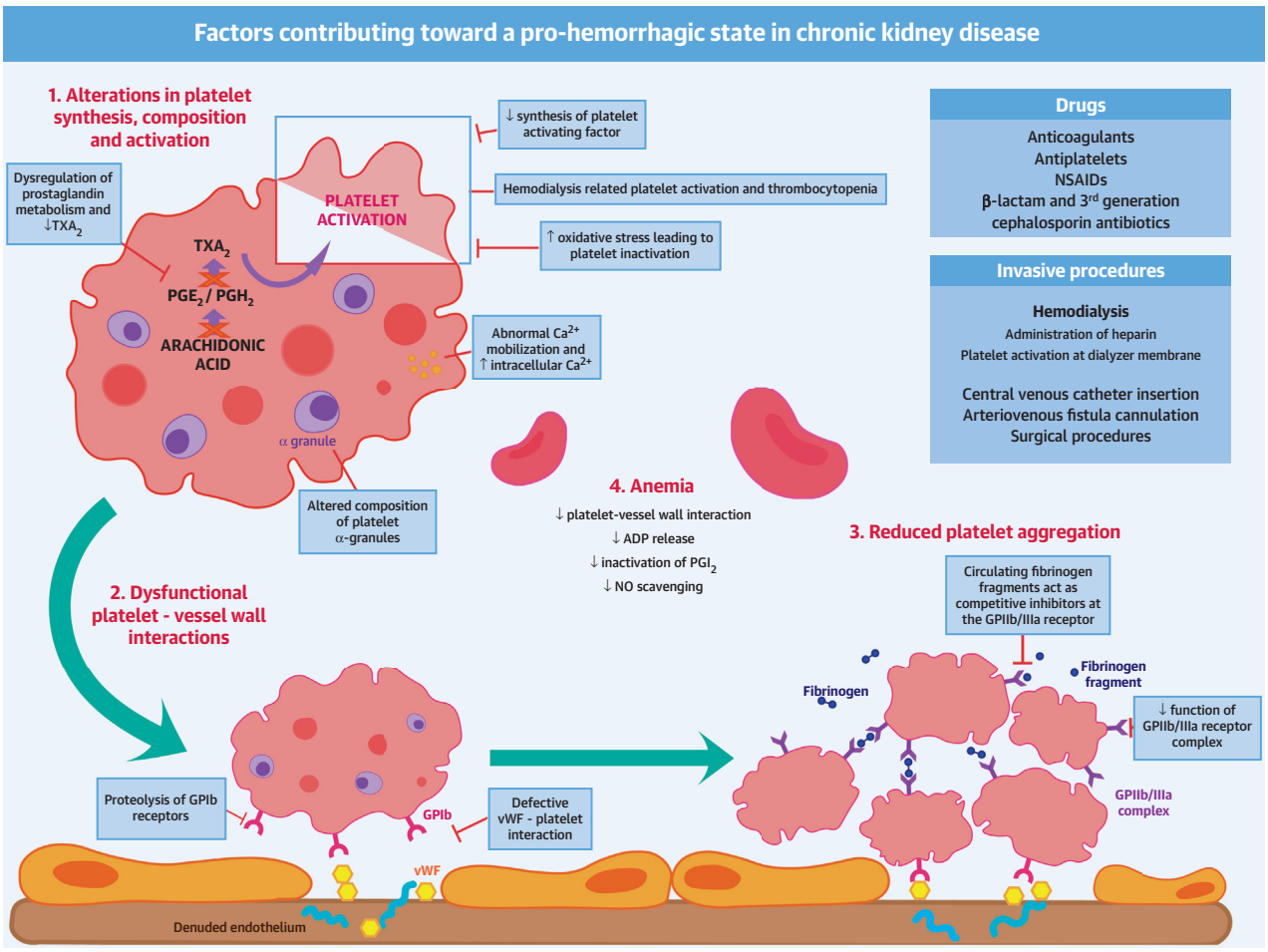


Alterations in the 3 components of Virchow's triad contribute to the increased risk of thromboembolism in coexistent CKD and AF. Altered pro-thrombotic blood constituents and increased platelet activity create a hypercoagulable state. Alterations in atrial anatomy and contractility, activation of the renin-angiotensin-aldosterone system (RAAS), and altered vessel wall contractility secondary to inflammation result in deranged hemodynamics. Injury and dysfunction of the cardiac muscle and vascular endothelium predisposes to thrombus formation. There is significant interplay between the individual effectors and the components of the triad. IL = interleukin.

THE UTILITY OF BLEEDING AND CLOTTING SCORING SCHEMES IN CKD

In the general population with AF, OAT is supported by guidelines that mandate the use of scoring systems to estimate thromboembolic and bleeding risk, most commonly through the CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke, transient ischemic attack, or thromboembolism, vascular disease, age 65-74 years, sex category [female]) and HAS-BLED (hypertension, abnormal renal or liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs or alcohol) scores, respectively (5). Other scores include $CHADS_2$ (congestive heart failure, hypertension, age, diabetes mellitus, prior stroke or transient ischemic attack), R_2CHADS_2 (renal dysfunction, congestive heart failure, hypertension, age, diabetes mellitus,

FIGURE 3 The Pathophysiology of Hemorrhage in CKD



Platelet dysfunction which is common in chronic kidney disease (CKD) can degrade hemostasis facilitating a pro-hemorrhagic state. Altered composition of α-granules, abnormal calcium mobilization, dysregulation of arachidonic acid metabolism, and increased oxidative stress all conspire to alter platelet function and activation. Proteolysis of platelet glycoprotein (GP) IIb receptors and defective interactions with von Willebrand factor (vWF) reduces adhesion to denuded endothelium. Platelet aggregation is compromised through competitive inhibition of the GPIIb/IIIa receptor complex by circulating fibrinogen fragments present in uremia and through altered receptor function. Coexistent anemia alters platelet function through a variety of indirect mechanisms. Many common medications used in the context of CKD treatment can act on the coagulation pathway; there are a number of regular dialysis and other procedures that mandate blood vessel wall breach with consequential hemorrhage. ADP = adenosine diphosphate; Ca^{2+} = calcium ion; NO = nitric oxide; NSAIDs = nonsteroidal anti-inflammatory drugs; PGE_2 = prostaglandin E_2; PGH_2 = prostaglandin H_2; PGI_2 = prostaglandin I_2; TXA_2 = thromboxane A_2.

prior stroke or transient ischemic attack), ABC (Age, Biomarkers [growth differentiation factor-15, high-sensitivity cardiac troponin T, and hemoglobin], and Clinical history [previous bleeding]), GARFIELD (Global Anticoagulant Registry in the FIELD), and ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) (to estimate stroke risk); and ABC, ATRIA, GARFIELD, ORBIT (Outcomes Registry for Better Informed Treatment), HEMORR2HAGES (hepatic or renal disease [serum creatinine >2.5 mg/dl or end-stage renal disease], alcohol abuse, malignancy, age >75 years, reduced platelet count or function, prior hemorrhage, uncontrolled hypertension, anemia, genetic factors [CYP 2C9 single nucleotide polymorphisms], excessive fall risk, and history of stroke) (to estimate hemorrhage risk) (37). Although these scoring systems have been studied in a range of populations, their transferability to the setting of CKD is largely untested.

The most commonly used score for predicting stroke risk, CHA_2DS_2-VASc, was superior to $CHADS_2$ in predicting the risk of ischemic stroke in a Taiwanese cohort of patients with ESRD requiring dialysis. However, neither of these scoring systems takes into

TABLE 2 The Most Commonly Used Equations for the Derivation of GFR From Serum Creatinine and a Number of Other Parameters

Method	Equation	Additional Variables
Cockroft and Gault	$\text{GFR (ml/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)}}{7.2 \times \text{SCr (mg/dl)}}$	× 0.085 if female
MDRD 4-Variable study equation	$\text{GFR (ml/min/1.73 m}^2\text{)} = 186 \times \text{SCr (mg/dl)}^{-1.154} \times \text{age}^{-0.203} \times 0.742 \text{ (if female)}$	× 1.21 if Black-American × 0.763 if Japanese × 1.233 if Chinese
MDRD 4-Variable study equation (IDMS traceable)	$\text{GFR (ml/min/1.73 m}^2\text{)} = 175 \times \text{SCr (mg/dl)}^{-1.154} \times \text{age}^{-0.203} \times 0.742 \text{ (if female)}$	× 1.21 if Black-American × 0.763 if Japanese × 1.233 if Chinese
CKD – EPI creatinine equation	$\text{GFR} = 141 \times \min\left(\frac{\text{SCr}}{\kappa}, 1\right)^{\alpha} \times \max\left(\frac{\text{SCr}}{\kappa}, 1\right)^{-1.209} \times 0.993^{\text{age}}$ $\alpha = -0.329$ if female, -0.411 if male $\kappa = 0.7$ if female, 0.9 if male $\min =$ the minimum of $\frac{\text{SCr}}{\kappa}$ or 1 $\max =$ the maximum of $\frac{\text{SCr}}{\kappa}$ or 1	× 1.018 if female × 1.159 if Black

A detailed discussion of this complex topic is beyond the scope of this paper, but readers are directed to Szummer et al. (36).

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; GFR = glomerular filtration rate; IDMS = isotope-dilution mass spectrometry; MDRD = Modification of Diet in Renal Disease Study; SCr = serum creatinine (mg/dl).

account of loss of renal function (38). Moreover, R_2CHADS_2, which does incorporate a measure of renal status in the form of eGFR or creatinine clearance <60 ml/min, has not yet been validated at creatinine clearances <30 ml/min. ATRIA has a single risk inflection point at an eGFR <45 ml/min/1.73 m^2 and does not further subdivide severity of renal impairment or take into consideration the different renal replacement therapy modalities that patients may be receiving.

While the commonly used scores to estimate bleeding (HAS-BLED, ATRIA, ORBIT, and HEMOR-R2HAGES) attempt to reflect kidney function, they do not utilize eGFR thresholds and they fail to differentiate between patients receiving different forms of renal replacement therapy. Current bleeding scoring systems are unreliable when applied to dialysis patients (39).

ORAL ANTICOAGULANTS IN CKD

VITAMIN K ANTAGONISTS. Vitamin K antagonists (VKAs) interfere with the synthesis of functional coagulation factors through inhibition of the vitamin K epoxide reductase. Management with VKAs is challenging due to their narrow therapeutic range, unpredictable dose-response, and interactions with drugs and food, which necessitate close monitoring of the

TABLE 3 Absorption and Metabolism of the Different DOACs

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Bioavailability	3% to 7%	50%	62%	15 mg/20 mg: 66% without food, 80% to 100% with food
Prodrug	Yes	No	No	No
Clearance nonrenal/renal of absorbed dose	20%/80%	73%/27%	50%/50%	65%/35%
Plasma protein binding	35%	87%	55%	95%
Dialyzability	50% to 60%	14% (in part dialyzable)	n.a. (in part dialyzable)	n.a. (in part dialyzable)
Liver metabolism: CYP3A4 involved	No	Yes (elimination, moderate contribution [≈25%]*)	Minimal (<4% of elimination)	Yes (hepatic elimination 18%)
Absorption with food	No effect	No effect	6% to 22% more; minimal effect on exposure	39% more (see above)
Absorption with H2B/PPI	−12% to 30% (not clinically relevant)	No effect	No effect	No effect
Asian ethnicity	+25%	No effect	No effect	No effect
Elimination half-life, h	12–17	12	10–14	5–9 (young) 11–13 (elderly)
Other	Dyspepsia (5% to 10%)			Intake of 15 mg/20 mg with food mandatory

*Hepatic metabolism in total of ≈25%, mostly via CYP3A4, with minor contributions of CYP1A2, 2J2, 2C8, 2C9, and 2C19. Adapted from Steffel et al. (3).

TABLE 4 DOAC Dosing and Oral Anticoagulation Medical Guidelines (2016 Onwards) for AF in CKD

	Guidelines (Year) (Ref. #)	Warfarin	Dabigatran	Apixaban	Rivaroxaban	Edoxaban
CrCl 30–59 ml/min	AHA/ACC/HRS (2019) (5)	Adjusted dose INR 2–3	150 mg BID	5.0 or 2.5 mg BID*	15 mg QD	30 mg QD
	CHEST guideline (2018) (4)	Adjusted dose TTR >70%	150 or 110 mg BID (non-U.S.)	5.0 or 2.5 mg BID*	15 mg QD	30 mg QD
	KDIGO (2018)† (2)	Adjusted dose INR 2–3	150 or 110 mg BID	5.0 or 2.5 mg BID*	15 mg QD	30 mg QD
	EHRA practical guide (2018) (3)	Adjusted dose INR 2–3	150 mg or 110 mg BID	5.0 or 2.5 mg BID*	20 mg (or 15 mg if CrCl <50)	30 mg QD
	ESC (2016) (1)	Adjusted dose INR 2–3	150 mg or 110 mg BID	5.0 or 2.5 mg BID*	15 mg QD	30 mg (or 15 mg if CrCl <50)
CrCl 15–29 ml/min	AHA/ACC/HRS (2019) (5)	Adjusted dose INR 2–3	75 mg BID	5.0 or 2.5 mg BID*	15 mg QD	Not recommended
	CHEST Guideline (2018) (4)	Adjusted dose TTR >70%	75 mg BID (U.S. only) Not recommended outside U.S.	2.5 mg BID	15 mg QD	30 mg QD
	KDIGO (2018)† (2)	Consider adjusted dose INR 2–3	Unknown (consider 75 mg BID)	Consider 2.5 mg BID	Consider 15 mg QD	Consider 30 mg QID
	EHRA practical guide (2018) (3)	Not discussed	Not recommended	2.5 mg BID	15 mg QD	30 mg QD
	ESC (2016) (1)	Adjusted dose INR 2–3	Not recommended	Not recommended if CrCl <25	Not recommended	Not recommended
CrCl <15 ml/min (Dialysis)	AHA/ACC/HRS (2019) (5)	Adjusted dose INR 2–3	Not recommended	5.0 or 2.5 mg BID*	Not recommended	Not recommended
	CHEST guideline (2018) (4)	Adjusted dose TTR >70%	Not recommended	5 mg BID‡	Not recommended	Not recommended
	KDIGO (2018)† (2)	Equipoise	Not recommended	Consider 2.5 mg BID	Unknown (15 mg QD mentioned)	Not recommended
	EHRA practical guide (2018) (3)	Not discussed	Not recommended	Not recommended	Not recommended	Not recommended
	ESC (2016) (1)	Not discussed	Not recommended	Not recommended	Not recommended	Not discussed

Regulatory authorities (e.g., European Medicines Agency and U.S. Food and Drug Administration) consistently use CrCl in their guidance. Many clinical authorities and clinical guideline groups use GFR. Unfortunately, these are not synonymous and very significant differences can be seen between these systems for the same patients. Also, there is not complete overlap between the clinically used eGFR classifications into CKD grades and the arbitrary subdivisions of CrCl offered in regulatory guidance. This further adds to confusion and impracticality of proffered advice. *Use apixaban 2.5 mg BID if any 2 patient characteristics are present: Cr >1.5 mg/dl (133 μmol/l), >80 years of age, body weight <60 kg. Apixaban is not recommended in patients with severe hepatic impairment. †KDIGO Controversies Conference was held in 2016 but the outcomes were published in 2018. ‡In the United States only.

AHA/ACC/HRS = American Heart Association Task Force/American College of Cardiology/Heart Rhythm Society; BID = twice daily; CrCl = creatinine clearance; EHRA = European Heart Rhythm Association; INR = International Normalized Ratio; KDIGO = Kidney Disease: Improving Global Outcomes; QD = once daily; TTR = time in the International Normalized Ratio target range.

prothrombin time (International Normalized Ratio [INR]) (40). The benefits of warfarin in AF patients with mild and moderate CKD to reduce stroke is firmly established (41). However, robust data on the benefits and risks in patients with severe CKD and ESRD are lacking.

In patients with severe CKD, the proportion of time in the INR target range is lower than in patients with milder or no CKD (42). Low time in the INR target range is associated with an increased risk for stroke, bleeding, and death (43). Even though warfarin is metabolized hepatically, patients with CKD require a lower dose of warfarin compared with patients with lesser or no renal impairment: typically 20% lower in severe CKD (42). Patients with CKD have a more labile INR and an increased risk for supratherapeutic INRs, especially during initiation.

Another important consideration of VKA in CKD is the risk of enhanced vascular calcification (44). Vascular calcification is inhibited by Matrix Gla Protein, a protein that also requires vitamin K-dependent carboxylation to interact with calcium similarly to the vitamin K-dependent coagulation factors. Uncarboxylated Matrix Gla Protein may further enhance vascular calcification, a specific concern in CKD patients who have the burden of excess calcium and phosphate body deposition (45).

CKD patients who receive OAT are susceptible to anticoagulant-related nephropathy, which manifests as AKI secondary to glomerular hemorrhage and renal tubular obstruction as a consequence of excessive anticoagulation (46). Notably, in patients treated with warfarin, biopsy-proven anticoagulant-related nephropathy occurred twice as frequently in those with CKD compared to patients without underlying renal disease (47).

DIRECT ORAL ANTICOAGULANTS. There are several direct oral anticoagulants (DOACs) currently

TABLE 5 EMA/FDA Recommendation for CKD Stages 4 and 5D Patients

		Dabigatran	Apixaban	Rivaroxaban	Edoxaban
CrCl 15-30 ml/min	FDA	75 mg BID	5 or 2.5 mg BID*	15 mg QD	30 mg QD
	EMA	Contraindicated	2.5 mg BID	Limited clinical data –15 mg QD	30 mg QD
CrCl < 15 ml/min	FDA	Not approved	5 mg BID	Limited clinical data–15 mg QD	Not approved
	EMA	Contraindicated	Contraindicated	Contraindicated	Contraindicated
Dialysis	FDA	Not approved	5 mg BID	Limited clinical data–15 mg QD	Not approved
	EMA	Contraindicated	Contraindicated	Contraindicated	Contraindicated

Regulatory authorities (e.g., EMA and FDA) consistently use CrCl in their guidance. Many clinical professional societies and guideline groups use GFR. Unfortunately, these are not synonymous, and very significant differences can be seen between these systems for the same patient. Unfortunately, there is not complete overlap between the clinically used eGFR classifications into CKD grades and the arbitrary subdivisions of CrCl offered in regulatory guidance. This further adds to confusion and impracticality of proffered advice. *Use apixaban 2.5 mg BID if any 2 patient characteristics are present: Cr >1.5 mg/dL (133 μmol/l), >80 years of age, body weight <60 kg. Apixaban is not recommended in patients with severe hepatic impairment

5D = patients receiving chronic dialysis; EMA = European Medicines Agency; FDA = U.S. Food and Drug Administration; other abbreviations as in Table 4.

approved for clinical use in AF that act as direct inhibitors of factor Xa (apixaban, edoxaban, and rivaroxaban) or of thrombin (dabigatran). RCTs have demonstrated a benefit of DOACs compared with warfarin, including in patients with mild to moderate CKD (48). A recent systematic review and meta-analysis of >78,000 patients with nondialysis CKD and AF found that DOACs had a superior safety and efficacy profile to VKA, reducing stroke consistently with fewer major bleeding events (49). Indeed, contemporary evidence-based guidelines currently recommend DOACs over VKAs if OAT is judged appropriate, including those with CKD stages 1 to 3 (1–5). However, the situation in CKD stages 4 and 5 is more nuanced, mainly because these patients have been largely excluded from all of the registration and post-registration trials.

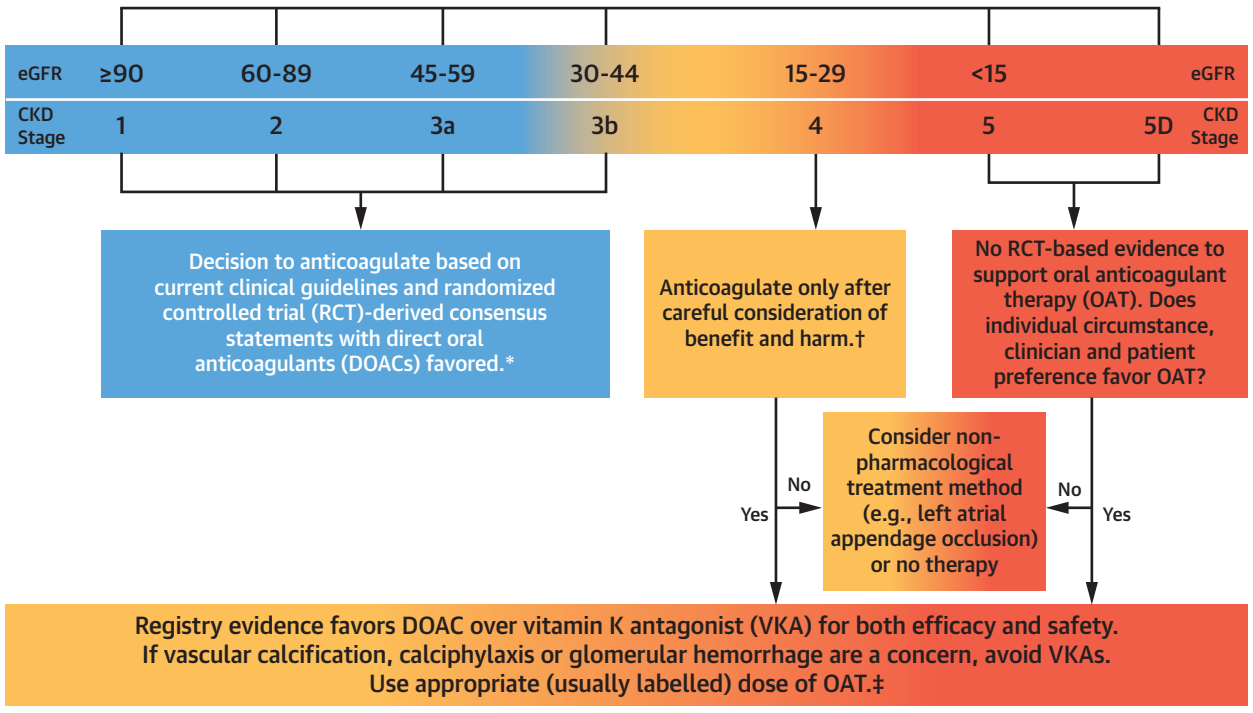
Relevant drug characteristics of DOACs are summarized in **Table 3** (3). There is concern about drug/metabolite accumulation in patients with severe CKD. Although there is a dose-response relationship for drug levels and bleeding (50,51), ideal therapeutic ranges of drug concentrations are not yet clearly established (3). Post hoc analyses of the RCTs have revealed that DOACs, particularly dabigatran and rivaroxaban, are associated with reduced loss of GFR compared to warfarin (52,53). More trials with these outcomes as their primary focus are urgently required, particularly as there are currently inconsistencies in the prescribed doses of DOACs in routine clinical practice (54).

ORAL ANTICOAGULANT THERAPY IN CKD

In patients with mild/moderate CKD (eGFR 30 to 59 ml/min or stage 3a and 3b), present evidence on OAT suggests that it can be used safely and confers benefit. In this category of patients, both VKAs and DOACs have shown similar efficacy. In the majority of studies on DOACs, their safety profile seems to be at least noninferior or even superior to VKAs (55–57). Interestingly, only when using the CKD-EPI equation was there an interaction between dabigatran and renal function in terms of risk of bleeding (58). It must be conceded, however, in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) study, the dose of dabigatran was not titrated to reflect the degree of CKD. Furthermore, in a recent systematic review and meta-analysis of 5 RCTs including 13,878 AF patients with moderate CKD, DOAC use was associated with reduced risk of stroke/systemic embolism (odds ratio [OR]: 0.79; 95% confidence interval [CI]: 0.67 to 0.94) and lower incidence of major bleeding (OR: 0.74; 95% CI: 0.65 to 0.86) (59). In this context, OAT is recommended by the European Society of Cardiology, by the European Heart Rhythm Association (EHRA), and in U.S, guidelines by the American Heart Association Task Force/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS), American College of Chest Physicians (CHEST guideline), and Kidney Disease: Improving Global Outcomes (KDIGO) conference reports (**Table 4**) (1–5).

In individuals with CKD stage 4, all guidelines allow the use of warfarin, although the net-benefit OAT itself has never been prospectively assessed in an RCT in this patient population. Additionally, AHA/ACC/HRS guidelines suggest treatment for patients with nonvalvular AF and moderate-to-severe CKD with CHA_2DS_2-VASc scores of 2 or greater, using reduced doses of dabigatran and rivaroxaban (creatinine clearance 30 to 49 ml/min), or apixaban (if creatinine clearance between 25 and 29 ml/min), Class IIb, Level of Evidence: C. Although the EHRA/KDIGO guidelines do not formally recommend the use of DOACs in this category of patients, they do suggest that they can be considered for use (**Table 4**).

CENTRAL ILLUSTRATION **Proposed Approach to Stroke Thromboprophylaxis in a Patient With Concomitant Chronic Kidney Disease and Atrial Fibrillation**



Kumar, S. et al. J Am Coll Cardiol. 2019;74(17):2204-15.

*See references 1 to 5. †Existing scoring systems are not validated in this setting. ‡Please refer to Tables 4 and 5 for current dosage recommendations. 5D = patients receiving chronic dialysis; DOAC = direct oral anticoagulant; OAT = oral anticoagulant therapy; RCT = randomized controlled trial; VKA = vitamin K antagonist.

Although there are limited efficacy and safety outcome data, both the U.S. Food and Drug Administration (FDA) and European Medicines Agency have approved reduced doses of apixaban, edoxaban, and rivaroxaban in patients with an eGFR 15 to 30 ml/min; the FDA has also approved the use of a specific low-dose dabigatran (75 mg twice daily), based solely on pharmacokinetic data, for these patients (Table 5).

In patients with CKD stage 5 and AF, there is no RCT-derived evidence that OAT has a favorable benefit-risk ratio. In this context, the EHRA did not provide specific recommendations regarding anticoagulation in HD, underlining the absence of RCTs for both VKAs and DOACs, and the contradictory results of observational studies reporting stroke prevalence. The KDIGO recommendations (2018) concluded that there is insufficient high-quality evidence to recommend VKAs for prevention of stroke in CKD stage 5 patients with AF, especially when balancing the significant risks of bleeding, accelerated vascular calcification, and calcific uremic arteriopathy associated with VKA therapy. Most recently, there was an updated 2019 AHA/ACC/HRS focused update guideline for the management of patients with AF; in this report there was a soft recommendation for using OAT with either warfarin or apixaban with the caveat "but further study is warranted" (5).

NO RCTs, BUT WHAT ABOUT REGISTRIES AND REGULATORS?

A meta-analysis of 43,850 patients from 5 observational cohort studies including CKD stage 4 to 5 or 5D found that the use of apixaban was associated with a lower risk of major bleeding compared with warfarin, and that is was relatively effective with no excess risk of thromboembolic events (60). A recent systematic review including 10 observational studies (3 with patients with eGFR <25 ml/min or on dialysis) found that in dialysis patients, there was no difference in stroke risk between apixaban, dabigatran (relative risk [RR]: 1.71; 95% CI: 0.97 to 2.99), or rivaroxaban (RR: 1.80; 95% CI: 0.89 to 3.64) versus warfarin (59). In hemodialysis patients, rivaroxaban and dabigatran were

associated with an increased major bleeding risk (RR: 1.45 to 1.76), whereas there was no major bleeding difference with apixaban compared with warfarin. A retrospective cohort study of Medicare beneficiaries included in the U.S. Renal Data System (2,351 patients on apixaban and 23,172 patients on warfarin) found that apixaban use may be associated with a lower risk of major bleeding compared with warfarin, with a standard 5-mg twice daily dose also associated with reductions in thromboembolic and mortality risk in ESRD (14). A retrospective series of AF patients with stage 4 and 5 CKD compared outcomes of 1,896 and 4,848 patients treated with rivaroxaban and warfarin, respectively, using MarketScan data. Rivaroxaban was associated with fewer major bleeding events than warfarin, although neither anticoagulant reduced stroke or systemic embolism (61).

Although the FDA does mention OAT usage, it is crucial to understand that while both VKAs and DOACs have a recommended dosing for dialysis patients with AF (**Tables 4 and 5**), the FDA itself has not endorsed this indication for use in this population. Both labels indicate, "it is not known whether these concentrations will lead to similar stroke reduction and bleed risk in patients with ESRD on dialysis as was seen in ROCKET-AF/ARISTOTLE." These decisions appear to be underpinned by very limited pharmacokinetic and pharmacodynamic studies (62–65). The European Medical Agency has not yet conformed with this approach.

NONANTICOAGULATIVE APPROACHES

Other options such as left atrial appendage occlusion (LAAO) closure or excision may be a viable alternative to OAT in patients at risk of both cardioembolic stroke related to AF and life-threatening or recurrent major bleeding. Those with advanced CKD and AF comprise the most at-risk group. One LAAO device is approved in the United States, and several are available in Europe; the technique is recommended in major guidelines (1,5) and reviewed elsewhere (66,67).

HOW TO APPROACH OAT IN PATIENTS WITH CKD AND AF

Presently, there is no RCT-based evidence regarding the benefit of OAT in patients with AF and advanced CKD (**Table 4**). A suggested approach is provided in the **Central Illustration**. A rigorous discussion of the risk and benefits of OAT, taking into account patients' characteristics and preferences is crucial to inform the decision. If it is deemed appropriate to use OAT, DOACs should generally be favored in view of the limited efficacy and safety data available, along with the increased risk of vascular calcification, calciphylaxis, and anticoagulant-associated nephropathy (glomerular hemorrhage) associated with VKAs. If OAT is not initiated, the viability of a non-pharmacological treatment such as LAAO should be considered, or whether in fact no therapy is the most prudent choice.

CONCLUSIONS

Clinical trial and real-world clinical data from the non-CKD setting cannot be reliably and safely extrapolated into clinical practice for patients with significant/dialysis-requiring CKD. Initiating OAT in CKD patients is contentious due to their increased propensity to both thrombosis and bleeding. Furthermore, conventional scoring systems for estimating bleeding and clotting risk are not validated in CKD patients and cannot be relied upon alone for clinical decision-making. Until dedicated RCTs are undertaken, the decision of whether and how to initiate OAT in patients with concomitant CKD and AF requires an individualized approach with physician-patient collaboration.

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KEY WORDS atrial fibrillation, chronic kidney disease, direct oral anticoagulant, hemorrhage, stroke, vitamin K antagonist, warfarin