REVIEW

Resistant Hypertension in Dialysis: Epidemiology, Diagnosis, and Management

Panagiotis I. Georgianos [1] *and Rajiv Agarwal* [2]

Abstract

Apparent treatment-resistant hypertension is defined as an elevated BP despite the use of ≥3 antihypertensive medications from different classes or the use of ≥4 antihypertensives regardless of BP levels. Among patients receiving maintenance hemodialysis or peritoneal dialysis, using this definition, the prevalence of apparent treatment-resistant hypertension is estimated to be between 18% and 42%. Owing to the lack of a rigorous assessment of some common causes of pseudoresistance, the burden of true resistant hypertension in the dialysis population remains unknown. What distinguishes apparent treatment-resistance from true resistance is white-coat hypertension and adherence to medications. Accordingly, the diagnostic workup of a dialysis patient with apparent treatment-resistant hypertension on dialysis includes the accurate determination of BP control status with the use of home or ambulatory BP monitoring and exclusion of nonadherence to the prescribed antihypertensive regimen. In a patient on dialysis with inadequately controlled BP, despite adherence to therapy with maximally tolerated doses of a β-blocker, a long-acting dihydropyridine calcium channel blocker, and a renin-angiotensin system inhibitor, volume-mediated hypertension is the most important treatable cause of resistance. In daily clinical practice, such patients are often managed with intensification of antihypertensive therapy. However, this therapeutic strategy is likely to fail if volume overload is not adequately recognized or treated. Instead of increasing the number of prescribed BP-lowering medications, we recommend diet and dialysate restricted in sodium to facilitate achievement of dry weight. The achievement of dry weight is facilitated by an adequate time on dialysis of at least 4 hours for delivering an adequate dialysis dose. In this article, we review the epidemiology, diagnosis, and management of resistant hypertension among patients on dialysis.

JASN 35: 505–514, 2024. doi: https://doi.org/10.1681/ASN.0000000000000315

Introduction

Among patients on hemodialysis, hypertension is common and often treated but remains poorly controlled. In one multicenter trial that included 2535 adult patients on hemodialysis, the prevalence of hypertension, defined by a 1-week average of predialysis BP, was 86%; 88% were treated, but only 30% were controlled.[1] In 369 patients on hemodialysis at a single center who underwent 44-hour ambulatory BP monitoring (ABPM) over an interdialytic interval—the gold standard for BP control—the prevalence of hypertension was 82%; 89% were treated, but only 38% were controlled.[2] In this review, we discuss the epidemiology of treatment-resistant hypertension, its diagnosis, pathophysiology, and an approach to its management.

Definition and Epidemiology of Resistant Hypertension across the Spectrum of CKD

Resistant hypertension is a phenotype that identifies a subset of high-risk hypertensive patients with inadequately controlled BP despite intensive treatment with multiple antihypertensive medications. International guidelines have specified the diagnostic criteria of this clinical entity as follows: (*1*) BP that remains above the goal in patients receiving ≥3 antihypertensives from different classes, one of which should be a diuretic, or (*2*) concurrent use of ≥4 antihypertensive medications regardless of BP levels.[3] International guidelines make a clear distinction between pseudoresistance and true resistant hypertension. Accordingly, the definition of true resistant hypertension excludes patients with the white-coat effect (*i.e.*, abnormal office BP, but normal out-of-office BP among treated patients) and patients with nonadherence to the prescribed antihypertensive regimen.[3] Thus, diagnosing true resistant hypertension requires both out-of-office BP measurements and ensuring adherence; the latter is often performed by sampling urine therapeutic drug monitoring. However, pseudoresistance is not often excluded in epidemiologic studies, and apparent treatment-resistant hypertension more appropriately describes such patients.[3] Notably, these guideline recommendations are provided for the general hypertensive population and may not be directly applicable to patients on dialysis.

Epidemiology of Resistant Hypertension in CKD

In a 2019 meta-analysis of 91 studies incorporating data from 3.2 million patients with drug-treated hypertension,[4]

[1]2nd Department of Nephrology, AHEPA Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece
[2]Division of Nephrology, Department of Medicine, Richard L. Roudebush Veterans Administration Medical Center, Indianapolis, Indiana

Correspondence: Dr. Rajiv Agarwal, email: ragarwal@iu.edu

Published Online Ahead of Print: January 16, 2024

the prevalence of true resistant hypertension was 10.3%.[4] As compared with the general population, the burden of true resistant hypertension was reported to be two-fold to three-fold higher in patients with CKD who are not yet on dialysis.[5] Furthermore, true resistant hypertension seems to be of prognostic importance. As compared with those with controlled hypertension, patients with true resistant hypertension carry the highest long-term risk of adverse cardiorenal outcomes.[6] Accordingly, in patients with CKD, classification of the severity of hypertension facilitates better stratification of cardiorenal risk.

CKD-5D

The epidemiology of resistant hypertension is less well defined in patients with kidney failure who are receiving hemodialysis or peritoneal dialysis (Table 1). The five available studies have provided prevalence rates ranging from 18.0% to 42.0%.[7–11] Several potential explanations exist. These studies used different techniques in the assessment of BP control status (*i.e.*, dialysis unit BP measurement, home BP measurement, or ABPM).[7–11] Four of five studies did not include any measure of medication nonadherence.[7,8,10,11] In line with pathophysiology and pharmacologic principles, loop diuretics were not counted as a separate antihypertensive drug category in these studies. Volume excess likely accounted for the variation; two studies that used bioimpedance spectroscopy (BIS) as a surrogate of volume excess showed that a fraction of patients with apparent treatment-resistant hypertension had subclinical hypervolemia.[8,10] Because causes of pseudoresistance were not adequately addressed in the existing literature,[7–11] the prevalence of true resistant hypertension among patients on dialysis remains unknown.

Diagnosing True Resistant Hypertension in Patients on Dialysis

Confirmation of Uncontrolled BP Outside of the Dialysis Unit

According to guidelines,[12] the first critical step in the diagnostic workup of a patient with apparent treatment-resistant hypertension is the confirmation of uncontrolled hypertension with BP measurements obtained outside of the clinic. Among patients on dialysis, interdialytic ABPM is recommended as the reference-standard technique because this method is valid and reproducible and enables the determination of BP not only under conditions of resting but also during periods of activity.[13] Furthermore, this technique enables the measurement of BP during the period of sleep, facilitating the diagnosis of an abnormal diurnal variation in BP, which is termed as "non-dipping" or "reverse dipping."[13] These BP phenotypes are commonly identified in patients on dialysis and are associated with more severe target-organ damage and increased risk of cardiovascular mortality.[14,15] For research studies, we recommend 44-hour interdialytic ABPM. Because this method is not broadly available in daily clinical practice, a more practical approach to achieve an accurate assessment of hypertension is to ask the patients to measure their BP at home over a few days with the use of a validated BP monitor.

A growing body of evidence from studies conducted specifically in the dialysis population suggests that the technique of home BP monitoring has several advantages over routine or even standardized dialysis unit BP recordings (Table 2).[13] Home BP is superior to dialysis unit BP—either routine or standardized—in diagnosing hypertension confirmed by ABPM.[16,17] Home BP is volume sensitive and can adequately detect changes in interdialytic ambulatory BP provoked by the gradual reduction in dry weight.[18] Relative to predialysis and postdialysis BP, home BP exhibits higher reproducibility and greater test–retest reliability from one week to the next.[18] As compared with dialysis unit BP, home BP is more closely associated with echocardiographically documented left ventricular hypertrophy[19] and is more informative in the prognostication of the long-term risk of adverse cardiovascular events and mortality.[14,20] Finally, a randomized trial showed that the management of hypertension in patients on dialysis with the guidance of home BP monitoring is superior to antihypertensive therapy that is guided by routine predialysis BP recordings in improving ambulatory BP control over 6 months of follow-up.[21] These data directly support the broader use of home BP monitoring in the assessment and long-term management of hypertension in patients on dialysis.

Defining the Optimal BP Target

The optimal BP threshold for the diagnosis and treatment of hypertension in the dialysis population is not yet defined. In the BP in Dialysis (BID) trial,[22] 126 patients on dialysis with hypertension were randomized to a standardized predialysis systolic BP of 110–140 mm Hg (intensive arm) versus 155–165 mm Hg (standard arm). Over a median follow-up of 365 days, there was no difference between randomized groups in change from baseline of left ventricular mass index. The BID trial reported a potential signal of safety: the risk of recurrent hospitalizations (hazard ratio [HR], 1.66; 95% confidence interval [CI], 1.18 to 2.34) and recurrent vascular access thrombotic events (HR, 2.80; 95% CI, 1.18 to 6.66) was significantly higher in the intensive arm than in the standard arm.[22]

The BID trial was a pilot study aiming to assess the feasibility and safety of intensive BP control among patients on dialysis but was limited by its design. In the BID trial, antihypertensive therapy was guided by standardized predialysis BP measurements. This was so because the investigators considered that the implementation of home BP monitoring would not be feasible.[22] However, predialysis BP, even when measured with a standardized methodology, is not an appropriate substitute for home BP monitoring.[18] Given the potential for harm when targeting predialysis BP demonstrated in the BID trial, determination of BP target for the improvement of hard or intermediate clinical outcomes is better pursued through home BP measurements. In the meantime, evidence from the Hypertension in Hemodialysis Patients treated with Atenolol and Lisinopril (HDPAL) trial suggests that lowering home systolic BP below the threshold of 140 mm Hg is a reasonable target for managing hypertension in patients on

Table 1. Cross-sectional studies investigating the prevalence of apparent treatment-resistant hypertension in patients on dialysis

First Author/Year	Population	Definition of Apparent Treatment-Resistant Hypertension	Prevalence of Apparent Treatment-Resistant Hypertension	Home or Ambulatory BP Monitoring	Assessment of Medication Nonadherence	Assessment of Volume Status	Loop Diuretics Counted as a Separate Antihypertensive Drug Category
Tanaka *et al.*/2019[7]	2999 patients with hypertension on hemodialysis	Uncontrolled BP (≥140/90 mm Hg) despite the use of ≥3 antihypertensives or use of ≥4 antihypertensives regardless of BP levels	18.0%	No	No	No	Not reported
Mallamaci *et al.*/2020[8]	506 patients on hemodialysis from ten dialysis centers in Europe	Uncontrolled interdialytic BP (≥130/80 mm Hg) despite the use of ≥3 antihypertensives or controlled hypertension by at least four drugs	24.0%	44-h interdialytic ABPM	No	BIS in an unselected subset of 104 patients	No
Li *et al.*/2022[9]	1789 patients receiving peritoneal dialysis in nine centers in Guangdong, China	Uncontrolled BP (≥130/80 mm Hg) with concurrent use of ≥3 antihypertensive drugs or controlled BP by at least four drugs	42.2%	Home BP monitoring for 3 d	Use of a questionnaire and pill count in one center	No	No
Vareta *et al.*/2022[10]	140 patients receiving peritoneal dialysis in four centers in Northern Greece	Uncontrolled BP (≥130/80 mm Hg) despite the use of ≥3 antihypertensive drugs or treatment with ≥4 drugs regardless of BP levels	30.0%	24-h ABPM	No	BIS in the overall study population	No
Symonidis *et al.*/2023[11]	5879 unselected patients receiving hemodialysis in non-tertiary centers in Poland	Uncontrolled BP (≥140/90 mm Hg) despite the use of ≥3 antihypertensives or use of ≥4 antihypertensives regardless of BP levels	40.9%	No	No	No	Not reported

ABPM, ambulatory BP monitoring; BIS, bioimpedance spectroscopy.

dialysis.[23] In this 1-year long trial, monthly monitored home systolic BP was targeted to levels <140 mm Hg with a combined therapeutic algorithm that included probing of dry weight, sodium restriction, and administration of BP-lowering medications.[23]

Assessment of Medication Nonadherence

Another important, but frequently underappreciated, cause of pseudoresistance is the suboptimal adherence to antihypertensive therapy. Medication nonadherence is associated with several factors, such as pill burden,[24] complexity of antihypertensive regimens, occurrence of drug-related side effects, and poor relationship between the patient and the clinician.[25] A 2023 meta-analysis of 42 studies involving a total of 71,353 patients with apparent treatment-resistant hypertension in the general population showed that the overall prevalence of medication nonadherence was 37% (95% CI, 27% to 47%).[26] There was a significant heterogeneity across the included studies. In part, this heterogeneity was due to the variations in the methods of documenting drug adherence. For example, when indirect measures (*i.e.*, pill counts or questionnaires) were used, the prevalence of nonadherence was 20% (95% CI, 11% to 35%).[26] By contrast, when direct measures (*i.e.*, directly observed therapy or therapeutic drug monitoring) were used, nonadherence was identified in 46% (95% CI, 40% to 52%).[26] These data indicate that direct methods are likely superior to indirect methods, and the epidemiologic methods might markedly underestimate the magnitude of drug adherence in the genesis of true resistant hypertension.

Causes of True Resistant Hypertension in Patients on Dialysis

Volume-Mediated Hypertension: The Elephant in the Room

A patient on dialysis with poorly controlled hypertension on ≥3 BP-lowering medications is volume expanded, unless

Table 2. Evidence supporting the use of home BP monitoring in patients on dialysis

1. Better diagnostic performance compared with routine or standardized dialysis unit BP recordings
2. Adequately detects response to probing dry weight
3. Good week-to-week reproducibility
4. Associated with target-organ damage (echocardiographic left ventricular hypertrophy)
5. Better associated with all-cause mortality than dialysis unit recordings
6. Compared with dialysis unit measurements, treatment guided by home BP recordings provides a better outcome

proven otherwise.[13] This notion is supported by evidence from a cross-sectional study that investigated the epidemiology of hypertension in 369 patients on dialysis using the reference-standard technique of ABPM.[2] Hypertension, defined as an average interdialytic ambulatory BP ≥135/85 mm Hg or the use of ≥1 antihypertensive medications, was prevalent in 82% of the patients. Although antihypertensive treatment was administered in 89% on hypertensives, adequate ambulatory BP control was achieved in only 38% of drug-treated patients.[2] Exploratory analyses showed that the increasing number of prescribed BP-lowering medications and subclinical volume expansion—defined as the echocardiographic diameter of the inferior vena cava at end expiration—were the two factors that were independently associated with lack of adequate ambulatory BP control.[2] In a subgroup of 114 patients, antihypertensive medications were withdrawn when BP was adequately controlled at baseline. Over a period of 3–6 weeks, 80% of these patients became hypertensive. Once again, prior use of multiple antihypertensive medications and presence of an expanded volume state were the two major determinants of developing uncontrolled hypertension.[2]

More direct evidence that hypertension in patients on dialysis is a clinical manifestation of volume excess was provided by a randomized controlled trial: the Dry-weight Reduction in Hypertensive Hemodialysis Patients (DRIP) trial.[27] In this study, 150 patients on dialysis without overt clinical signs or symptoms of hypervolemia were assigned in a 2:1 ratio in an intervention group and control group. In the intervention group, dry weight was probed through gentle and gradual intensification of ultrafiltration. In the control group, patients received only physician visits.[27] Patients enrolled in the DRIP trial had uncontrolled hypertension confirmed by ABPM, despite background treatment with an average of 2.6 BP-lowering medications daily at baseline. Thus, a substantial proportion of study participants fulfilled the diagnostic criteria of apparent treatment-resistant hypertension. At 4 weeks of follow-up, an average reduction in postdialysis weight by 0.9 kg was accompanied by a placebo-subtracted change of −7.4/−3.6 mm Hg in 44-hour ambulatory BP.[27] The proportion of patients with a ≥10 mm Hg reduction in ambulatory systolic BP was 53% (46/87 patients) in the intervention group versus 31% (14/45 patients) in the control group. The combined odds ratio for a clinically meaningful BP-lowering response to dry-weight reduction over the course of the DRIP trial was 2.24 (95% CI, 1.32 to 3.81).[27] These clinical trial data not only demonstrate the efficacy of dry-weight probing in improving BP control but also provide an estimation of the proportion of patients on dialysis with volume-responsive hypertension.

Volume assessment is especially important among patients starting on dialysis, among those returning to dialysis after a catabolic illness or prolonged hospitalization, or among those who miss or shorten dialysis treatments frequently. Thus, volume assessment is an ongoing process. For patients who are incident on dialysis, there are expressions of concern that aggressive volume management might provoke a more rapid loss of residual kidney function. In such patients, observational studies suggest that continuation of loop diuretics after dialysis initiation is possibly associated with lower interdialytic weight gain (IDWG), less intradialytic hypotensive events, and lower risk of hospitalization.[28,29] However, potential confounding from residual kidney function precludes the opportunity to deduce direct cause-and-effect relations from these observational data. By contrast, a recent interventional study showed that among patients on dialysis with substantial residual diuresis, oral furosemide administered up to a maximum dose of 320 mg/d was not effective in increasing 24-hour urine output over 18 weeks of treatment.[30] Therefore, there are limited data to support the use of loop diuretics for the improvement of volume and BP control or for the long-term preservation of residual kidney function. Irrespective of the presence or absence of residual diuresis, the achievement and maintenance of euvolemia remains the principal goal of treatment.

Interest has emerged for the clinical value of assistive technologies, such as lung ultrasound and BIS, as tools to guide management of dry weight. Observational studies showed that volume excess, as assessed with these devices, is an independent predictor of future cardiovascular morbidity and mortality.[31,32] However, in the Lung Water by Ultrasound-Guided Treatment in Hemodialysis Patients trial,[33] as compared with conventional management of dry weight, a lung ultrasound-guided strategy failed to improve the primary composite outcome of all-cause death, nonfatal myocardial infarction, or decompensated heart failure (HR, 0.88; 95% CI, 0.63 to 1.24). In a meta-analysis of ten trials involving 2111 patients on dialysis, relative to usual care, adjustment in dry weight with the guidance of assistive technologies was not associated with a benefit on survival (risk ratio [RR], 0.92; 95% CI, 0.57 to 1.51).[34] Therefore, lung ultrasound, BIS, and other tools require further validation in larger and longer-term clinical trials before being implemented in everyday clinical practice.

Sodium Gain during Dialysis

Higher dialysate sodium concentrations are commonly prescribed as a measure to maintain intradialytic hemodynamic stability.[35] However, this therapeutic approach may increase sodium balance, thirst, and IDWG, resulting in volume overload and uncontrolled interdialytic hypertension.[35] In a meta-analysis of 12 trials incorporating data from 266 patients on dialysis, relative to a neutral (138–140 mEq/L) or high (>140 mEq/L) sodium

concentration, the prescription of a lower sodium concentration in the dialysate (<138 mEq/L) was associated with less IDWG and reductions in the levels of predialysis and postdialysis BP.[36] However, these potential benefits were counteracted by a higher incidence of cramps and hypotension during dialysis.[36] Most of the included studies in this meta-analysis had small sample sizes and short duration of follow-up. With the exception of two trials, the remaining ten studies evaluated a fixed prescription of a lower versus higher sodium concentration in the dialysate.[36] Therefore, an abrupt and fixed (facility-wide) reduction in the dialysate sodium concentration probably leads to a steeply negative dialysate-to-plasma sodium gradient for a large sample of patients, magnifying the risk of dialysis-related complications. Accordingly, we believe that a positive benefit–risk ratio can be achieved if modifications in the prescribed dialysate sodium concentration are gradual and individualized, according to the predialysis levels of serum sodium and patient's response to this intervention.[13] Small interventional studies suggest that as compared with fixed prescription, an individualized prescription of the dialysate sodium concentration is effective in limiting the IDWG and in improving BP control, without excess risk of intradialytic hypotension.[37–39]

Non–Volume-Dependent Mechanisms of Hypertension in Patients on Dialysis

Arterial Stiffness

Arteriosclerosis is a long-term process of structural alterations in the wall of the aorta and large central arteries that mediates isolated systolic hypertension, left ventricular hypertrophy, subendocardial hypoperfusion, and downstream heart failure.[40] It is, therefore, not surprising that aortic pulse wave velocity (PWV), a direct marker of arterial stiffness, is an independent predictor of cardiovascular morbidity and mortality.[41,42] As compared with the typical age-related arterial stiffening in the general population, progression of the arteriosclerotic process is accelerated in patients on dialysis.[41] A cross-sectional analysis of 11,833 BP measurements from 125 patients on dialysis showed that increments in IDWG and aortic PWV substantially affected the patterns and rhythms of ambulatory BP.[43] In the trended cosinor model, each one log change in aortic PWV was associated with an increase of 18.8 in mean systolic pressure and a rise of 11.7 mm Hg in pulse pressure.[43] On the other hand, increments in IDWG predominantly influenced the rate of change in BP during the interdialytic interval. The amplitude of circadian BP variation was blunted either with increasing aortic PWV or with increments in IDWG.[43]

Because aortic PWV is associated with elevated BP and taking into consideration that arterial stiffness is difficult to modify with antihypertensive therapy, a secondary analysis of the HDPAL trial explored the hypothesis whether dialysis patients with higher aortic PWV also experience more difficult-to-control hypertension.[44] Among 179 hypertensive dialysis patients with left ventricular hypertrophy, each 1-m/s higher aortic PWV was associated with 1.34-mm Hg higher baseline ambulatory systolic BP ($\beta = 1.34 \pm 0.46$, $P = 0.004$) and 1.02-mm Hg higher baseline pulse pressure ($\beta = 1.02 \pm 0.33$, $P = 0.002$).[44] Most importantly, baseline aortic PWV did not predict the treatment-induced reduction in ambulatory systolic/diastolic BP at 3, 6, and 12 months of follow-up. In contrast to the original hypothesis, increasing aortic PWV at baseline was an independent predictor of the overall improvement in pulse pressure over the course of the HDPAL trial.[44] Taken together, although aortic PWV is a strong determinant of ambulatory BP in the dialysis population, the severity of arterial stiffness in these patients does not make hypertension more difficult to control.

Erythropoietin-Induced Hypertension

New-onset hypertension or worsening of preexisting hypertension is an important, but frequently underreported, complication of erythropoietin therapy.[45] Several clinical studies have failed to accurately detect the elevation in BP levels that is associated with the use of erythropoietin-stimulating agents either because of the lack of ABPM or because the pressor effect was blunted by the more aggressive treatment of hypertension through intensified prescription of BP-lowering medications and closer attention to dry weight.[46,47] However, in a cross-sectional study, the use of erythropoietin was an independent determinant of the prevalence of hypertension diagnosed by ABPM.[2] Other studies using ABPM showed an association of erythropoietin therapy with non-dipping ambulatory BP.[48] The exact mechanisms through which erythropoietin exerts its pressor effect are not yet fully clear, but it is unlikely that the magnitude of change in hemoglobin and increased blood viscosity are the only mediators of erythropoietin-induced hypertension.[46,49] Preclinical studies suggest that the pressor effect of erythropoietin may be also mediated through impaired regulation of nitric oxide, endothelin 1, and constrictor prostanoids[50–53] as well as through enhanced responsiveness to catecholamines and angiotensin II.[54,55] The effect of erythropoietin-stimulating agent therapy on the levels of ambulatory BP and the underlying mechanisms mediating this pressor effect are currently under investigation in an ongoing trial among anemic patients with stage 3–4 CKD (NCT03810911).

Pharmacotherapy

Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) are recommended by guidelines as first-line agents in pharmacotherapy of hypertension in the general population or in patients with earlier stages of CKD.[56,57] However, the cardioprotective benefit of ACEIs/ARBs in the dialysis population remains uncertain. Individual trials to explore the safety and efficacy of these agents have been few, have included small numbers of patients, and have provided contradictory findings.[58–62] In a 2022 meta-analysis of five trials involving a total of 1582 patients on dialysis, relative to placebo, the use of ACEIs/ARBs was not associated with a significant reduction in the risk of cardiovascular events (RR, 0.79; 95% CI, 0.57 to 1.11).[63] In addition, therapy with ACEIs/ARBs had no clear benefit on cardiovascular (RR, 0.82; 95% CI, 0.59 to 1.14) and all-cause (RR, 0.86; 95% CI, 0.64 to 1.15) mortality.[63]

β-blockers may be more effective in reducing BP in patients on hemodialysis. The HDPAL trial was an open-label, randomized controlled trial that provided a head-to-head comparison between an ACEI-based and β-blocker–based antihypertensive regimen in 200 patients on dialysis with poorly controlled hypertension and left ventricular hypertrophy.[23] Patients enrolled in the HDPAL trial were assigned in a 1:1 ratio to receive either lisinopril (10–40 mg) or atenolol (25–100 mg), each administered three times per week immediately after dialysis. In contrast to the original hypothesis that an ACEI-based regimen would be superior to atenolol in causing regression of left ventricular hypertrophy, treatment-induced improvement in left ventricular mass index did not differ between groups.[23] Furthermore, monthly monitored home BP was consistently higher in the lisinopril group than in the atenolol group, despite the need for both a greater number of BP-lowering medications and a more aggressive reduction in dry weight in lisinopril-treated patients.[23] Notably, the HDPAL trial was closed early because of cardiovascular safety reasons. The incidence rate ratio for the combined safety outcome of cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure was 2.29-fold higher in lisinopril-treated patients than in atenolol-treated patients.[23]

These clinical trial data indicate that among hypertensive dialysis patients with left ventricular hypertrophy, atenolol is possibly superior to lisinopril in improving BP control and in preventing the risk of major adverse cardiovascular events. In the absence of more conclusive evidence from larger comparative phase 3 trials, based on the results of the HDPAL trial,[23] we use the β-blocker atenolol as the first-line agent for the treatment of hypertension in patients on dialysis.

In a double-blind trial, 251 patients on dialysis with hypertension were randomized to active treatment with amlodipine or placebo over a median follow-up period of

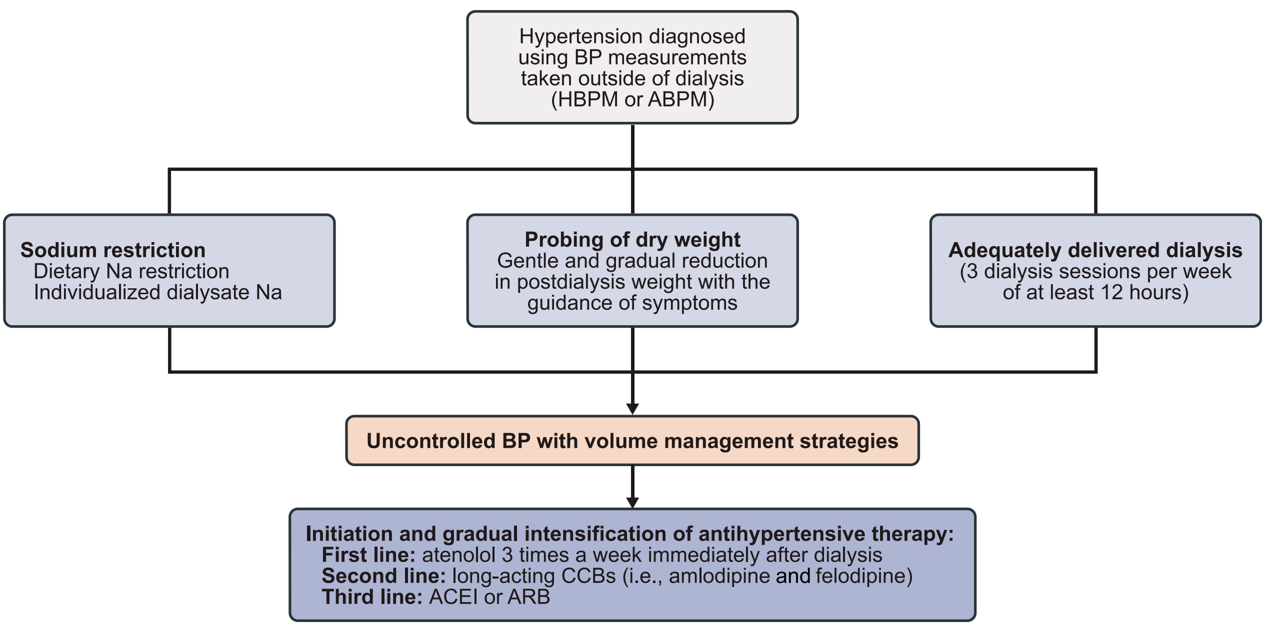

Figure 1. A step-by-step algorithm for the optimal assessment and management of hypertension among patients on dialysis. Because dialysis-unit BP recordings, even when measured with a standardized methodology, provide an imprecise estimate of interdialytic ambulatory BP, the diagnosis and overall management of hypertension should be on the basis of BP recordings obtained outside of the dialysis unit. Home BP monitoring is a feasible and reliable approach to achieve an accurate diagnosis of hypertension. Home BP monitoring is also a useful tool to guide the intensification of therapy over the long term. After an accurate diagnosis, management of hypertension relies on four pillars of therapy: (*1*) probing of dry weight with gentle and gradual reduction in postdialysis weight, as guided by the patient's symptoms; (*2*) restriction of dietary sodium intake; (*3*) individualized prescription of sodium concentration in the dialysate, according to the predialysis serum sodium levels and patient's response to this intervention; and (*4*) adequate dialysis that should be delivered three times per week with a total duration of at least 12 hours per week. When home systolic BP remains poorly controlled (*i.e.*, >140 mm Hg) despite the optimal management of volume, non–volume-dependent mechanisms are involved in the persistently uncontrolled hypertension. At this stage, antihypertensive therapy is the next step to achieve normalization in home BP levels. The selection of antihypertensive agents should be individualized and should be guided by clinical trials that explored the safety and efficacy of different BP-lowering medications, particularly in the dialysis population. We use the β-blocker atenolol, administered three times per week immediately after dialysis, as the first-line agent. If further intensification of treatment is needed, then we use long-acting dihydropiridine CCBs, such as amlodipine and felodipine, as second-line therapy. ACEIs or ARBs are our third-line agents. In patients with apparent treatment-resistant hypertension (*i.e.*, above the goal despite concurrent use of three antihypertensive agents from different classes), diagnostic workup includes confirmation of diagnosis of uncontrolled hypertension with the use of home BP monitoring, evaluation of adherence to the prescribed antihypertensive regimen, and careful assessment of dry weight. ABPM, ambulatory BP monitoring; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; aTRH, apparent treatment-resistant hypertension; CCB, calcium channel blocker; HBPM, home BP monitoring.

Table 3. Areas of uncertainty in the field of hypertension in patients on dialysis and directions for future research

Topical Area	Scientific Gaps and Existing Controversy	Research Needed
BP targets	The optimal BP targets for managing hypertension in patients on dialysis are unknown. The only study to compare a tighter versus less intensive systolic BP target was a small feasibility trial aiming to inform the design of a full-scale randomized trial	A full-scale trial comparing different goals of home systolic BP target for the improvement of cardiovascular events and all-cause mortality
Volume control	Assistive technologies, such as lung ultrasound and BIS, may be useful tools to guide management of dry weight. Currently available studies have failed to prove the superiority of these techniques over usual care	A trial comparing a volume management strategy, *i.e.*, guided by assistive technologies versus probing of dry weight with the guidance of patients' symptoms
Dialysate sodium	Small crossover studies showed that a fixed prescription of a lower versus higher dialysate sodium concentration possibly limits the IDWG and improves pre- and postdialysis BP. However, an abrupt and fixed reduction in the dialysate sodium concentration raises the risk of intradialytic cramps and hypotension	A trial comparing the safety and efficacy of a strategy using a fixed prescription of a high dialysate sodium concentration with individualized prescription of sodium concentration in the dialysate
Pharmacotherapy	On the basis of extrapolation of evidence from clinical trials conducted in the general population, ACEIs or ARBs are commonly used as first-line agents in pharmacotherapy of hypertension in patients on dialysis. However, a phase 2 trial showed that an atenolol-based regimen is possibly superior to a lisinopril-based regimen in improving BP control and in reducing the risk of major adverse cardiovascular events	A phase 3 trial comparing the safety and efficacy of a β-blocker–based regimen with a RAS blocker–based regimen in improving cardiovascular morbidity and mortality in patients on dialysis with hypertension
Pharmacotherapy	BP medications are commonly held before dialysis to prevent intradialytic hypotension. By contrast, this might provoke persistently uncontrolled hypertension	A trial to compare the safety and efficacy of taking versus holding BP-lowering medications before dialysis
Pharmacotherapy	Nocturnal hypertension is common in patients on dialysis and is associated with increased risk of adverse cardiovascular outcomes. Therefore, normalization of diurnal BP variation with bedtime dosing of antihypertensive therapy may be an effective strategy to improve cardiovascular outcomes	A trial to compare evening versus morning dosing of antihypertensive agents for the restoration of a normal diurnal BP variation and improvement of cardiovascular outcomes in patients on dialysis with nocturnal hypertension

ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BIS, bioimpedance spectroscopy; IDWG, interdialytic weight gain; RAS, renin-angiotensin system.

19 months.[64] Whereas BP remained unchanged in placebo-treated patients, a significant reduction of approximately 10 mm Hg in systolic BP was observed with amlodipine. Amlodipine did not significantly improve the primary outcome of all-cause mortality. However, relative to placebo, amlodipine lowered by 47% the occurrence of the secondary outcome, defined as the composite of nonfatal cardiovascular events or all-cause death.[64] Accordingly, we use long-acting dihydropyridine calcium channel blockers, such as amlodipine and felodipine, as second-line agents in pharmacotherapy of hypertension in patients on dialysis. ACEIs/ARBs are our third-line choice.[65]

In the general hypertensive population, the mineralocorticoid receptor antagonist (MRA) spironolactone is recommended by guidelines as the standard-of-care treatment of resistant hypertension.[56,57] However, among patients on dialysis, the benefit–risk ratio of MRA therapy remains unclear. In a 2021 Cochrane meta-analysis of 16 trials incorporating data from 1446 patients on dialysis, as compared with a control group, the use of MRAs was associated with a potential improvement in the risk of all-cause (RR, 0.45; 95% CI, 0.30 to 0.67) and cardiovascular (RR, 0.37; 95% CI, 0.22 to 0.64) mortality.[66] Regarding the safety profile, relative to control therapy, MRA use was accompanied with a 5.95-fold higher risk of gynecomastia and 1.41-fold higher incidence of hyperkalemia.[66] Notably, the potential cardioprotective effect of spironolactone and eplerenone in patients on dialysis should be interpreted with caution. Most of the trials included in this meta-analysis had an unclear or high risk of bias because of methodologic limitations, such as small sample sizes and short-term duration of follow-up.[66] Larger and longer-term phase 3 trials are ongoing with the aim to fully elucidate the safety and efficacy of MRAs. A multicenter European 644-patient trial, ALCHEMIST, compared spironolactone with placebo in patients on long-term dialysis on its potential to prevent cardiovascular outcomes. Cardiovascular outcomes were as follows: nonfatal myocardial infarction, acute coronary syndrome, hospitalization for heart failure, nonfatal stroke, or cardiovascular mortality. Rossignol revealed at the American Society of Nephrology Kidney Week meeting in November 2023 that spironolactone did not affect the primary outcome (HR, 0.996; CI, 0.729 to 1.362; $P = 0.9819$). In addition to concerns for the associated risk of hyperkalemia,[67,68] we do not routinely use spironolactone and eplerenone in our patients on dialysis.[65]

The direct vasodilators hydralazine and minoxidil are often administered in patients on dialysis with resistant hypertension as agents of last resort.[65] Hydralazine is short acting and often provokes large variations (spikes and valleys) in BP control. These pharmacokinetic properties necessitate the dosing of hydralazine 3–4 times daily, raising substantially the pill burden and making its use complex. By contrast, minoxidil has a longer duration of action that ensures BP-lowering efficacy with only once-daily dosing of this agent.[65] However, the prescription of minoxidil is often associated with hirsutism, which is a troublesome side effect for women. Another serious and not infrequent side effect of minoxidil is pericardial effusion. Centrally acting agents, such as clonidine, are also commonly prescribed to patients on dialysis with difficult-to-control BP, but dry mouth, dizziness, and episodes of orthostatic or intradialytic hypotension make once again their use problematic.[65] In our experience, patients on dialysis who are administered direct vasodilators or centrally acting antihypertensives to achieve adequate BP control require a closer examination of volume status. In such patients, nonpharmacologic interventions, such as probing of dry weight, sodium restriction, and adequate dialysis delivery, are probably much more effective in controlling hypertension.

Apart from short-acting agents, such as hydralazine, there is limited evidence to support that holding antihypertensive therapy before dialysis is effective in mitigating the risk of intradialytic hypotension. A recent cluster randomized trial failed to show that a strategy of taking BP-lowering medications was noninferior to a strategy of holding BP-lowering medications for the primary outcome of intradialytic hypotension, defined as ≥30% of dialysis sessions over a follow-up of 1 month with a nadir systolic BP <90 mm Hg.[69] However, taking was superior to holding BP-lowering medications before dialysis for the secondary outcome of uncontrolled hypertension, defined as an average predialysis systolic BP >160 mm Hg.[69] These data need to be carefully interpreted because this pilot study had a short-term duration, adherence to the assigned dosing regimens was suboptimal, and the incidence of symptomatic intradialytic hypotension was not assessed. Finally, restoration of a normal diurnal BP variation in patients on dialysis with a non-dipper or reverse-dipper BP pattern could be theoretically achieved with bedtime dosing of antihypertensive therapy.[70] However, there is currently no clinical trial evidence to demonstrate that this strategy would improve cardiovascular outcomes in this population.

Taken together, it seems that the prevalence of apparent treatment-resistant hypertension in patients on dialysis may be as high as 42%.[7–11] However, we believe that the proportion of patients on dialysis with true resistant hypertension is substantially lower if we effectively address some common causes of pseudoresistance. The diagnostic workup of a patient on dialysis with apparent treatment-resistant hypertension includes the accurate determination of BP control status with the use of home BP monitoring or ABPM and exclusion of nonadherence to the prescribed antihypertensive regimen. In a patient on dialysis with inadequately controlled BP, despite adherence to therapy with maximally tolerated doses of a β-blocker, a long-acting dihydropyridine calcium channel blocker, and an ACEI/ARB, subclinical volume expansion is typically the mediator of uncontrolled hypertension. In this rather common scenario, intensification of antihypertensive therapy is a strategy that is likely to fail if volume excess is not adequately addressed. Instead of an as-needed prescription of an additional antihypertensive agent, we recommend dietary and dialysate sodium restriction, strict management of dry weight, and adequate delivery of dialysis for the holistic care of the patient. A step-by-step algorithm for the optimal assessment and management of hypertension in patients on dialysis is shown in Figure 1. Several areas of uncertainty, such as optimal BP targets and strategies for the effective pharmacologic and nonpharmacologic treatment, need to be addressed in properly designed randomized trials in the future (Table 3).

Disclosures

R. Agarwal reports employment with VA Medical Center, Indiana University, IU Heath Physicians; consultancy for Akebia, Bayer, Boehringer Ingelheim, Chinook, Diamedica, Eli Lilly, Intercept Pharmaceuticals, Relypsa, and Vertex; honoraria from Akebia, Bayer, Boehringer Ingelheim, Chinook, Diamedica, Eli Lilly, Intercept Pharmaceuticals, Relypsa, and Vertex; royalties from UpToDate; research grants from the National Institutes of Health and the US Veterans Administration; and advisory or leadership roles for Akebia, Bayer, Boehringer Ingelheim, Chinook, Diamedica, Eli Lilly, *Hypertension*, JASH, KDIGO, *Nephrology Dialysis Transplantation*, Relypsa, *Seminars in Dialysis*, and Vertex. R. Agarwal is a member of data safety monitoring committees for Chinook and Vertex, an Associate Editor of the *American Journal of Nephrology* and *Nephrology Dialysis and Transplantation*, and has been an author for UpToDate. The remaining author has nothing to disclose.

Funding

R. Agarwal: National Heart, Lung, and Blood Institute (R01HL126903) and US Department of Veterans Affairs (5I01CX001753)

Author Contributions

Conceptualization: Rajiv Agarwal.
Investigation: Panagiotis I. Georgianos.
Supervision: Rajiv Agarwal.
Writing – original draft: Panagiotis I. Georgianos.
Writing – review & editing: Rajiv Agarwal.

References

1. Agarwal R, Nissenson AR, Batlle D, Coyne DW, Trout JR, Warnock DG. Prevalence, treatment, and control of hypertension in chronic hemodialysis patients in the United States. *Am J Med.* 2003;115(4):291–297. doi:10.1016/s0002-9343(03)00366-8
2. Agarwal R. Epidemiology of interdialytic ambulatory hypertension and the role of volume excess. *Am J Nephrol.* 2011;34(4): 381–390. doi:10.1159/000331067
3. Carey RM, Calhoun DA, Bakris GL, et al.; American Heart Association Professional/Public Education and Publications Committee of the Council on Hypertension; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Genomic and Precision Medicine; Council on Peripheral Vascular Disease; Council on Quality of Care and Outcomes Research; and Stroke Council. Resistant hypertension: detection, evaluation, and management: a scientific statement

from the American Heart Association. *Hypertension.* 2018;72(5):e53–e90. doi:10.1161/HYP.0000000000000084
4. Noubiap JJ, Nansseu JR, Nyaga UF, Sime PS, Francis I, Bigna JJ. Global prevalence of resistant hypertension: a meta-analysis of data from 3.2 million patients. *Heart.* 2019;105(2):98–105. doi:10.1136/heartjnl-2018-313599
5. Georgianos PI, Agarwal R. Resistant hypertension in chronic kidney disease (CKD): prevalence, treatment particularities, and research agenda. *Curr Hypertens Rep.* 2020;22(10):84. doi:10.1007/s11906-020-01081-x
6. De Nicola L, Gabbai FB, Agarwal R, et al. Prevalence and prognostic role of resistant hypertension in chronic kidney disease patients. *J Am Coll Cardiol.* 2013;61(24):2461–2467. doi:10.1016/j.jacc.2012.12.061
7. Tanaka S, Ninomiya T, Hiyamuta H, et al. Apparent treatment-resistant hypertension and cardiovascular risk in hemodialysis patients: ten-year outcomes of the Q-cohort study. *Sci Rep.* 2019;9(1):1043. doi:10.1038/s41598-018-37961-1
8. Mallamaci F, Torino C, Sarafidis P, et al. Treatment-resistant hypertension in the hemodialysis population: a 44-h ambulatory blood pressure monitoring-based study. *J Hypertens.* 2020;38(9):1849–1856. doi:10.1097/HJH.0000000000002448
9. Li D, Huo Z, Liu D, et al. Current apparent treatment-resistant hypertension in patients undergoing peritoneal dialysis: a multicenter cross-sectional study. *J Clin Hypertens (Greenwich).* 2022;24(4):493–501. doi:10.1111/jch.14455
10. Vareta G, Georgianos PI, Vaios V, et al. Prevalence of apparent treatment-resistant hypertension in ESKD patients receiving peritoneal dialysis. *Am J Hypertens.* 2022;35(11):918–922. doi:10.1093/ajh/hpac086
11. Symonides B, Lewandowski J, Marcinkowski W, Zawierucha J, Prystacki T, Malyszko J. Apparently resistant hypertension in polish hemodialyzed population: prevalence and risk factors. *J Clin Med.* 2023;12(16):5407. doi:10.3390/jcm12165407
12. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO 2021 clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Int.* 2021;99(3S):S1–S87. doi:10.1016/j.kint.2020.11.003
13. Georgianos PI, Agarwal R. Epidemiology, diagnosis and management of hypertension among patients on chronic dialysis. *Nat Rev Nephrol.* 2016;12(10):636–647. doi:10.1038/nrneph.2016.129
14. Agarwal R. Blood pressure and mortality among hemodialysis patients. *Hypertension.* 2010;55(3):762–768. doi:10.1161/HYPERTENSIONAHA.109.144899
15. Tripepi G, Fagugli RM, Dattolo P, et al. Prognostic value of 24-hour ambulatory blood pressure monitoring and of night/day ratio in nondiabetic, cardiovascular events-free hemodialysis patients. *Kidney Int.* 2005;68(3):1294–1302. doi:10.1111/j.1523-1755.2005.00527.x
16. Agarwal R, Andersen MJ, Bishu K, Saha C. Home blood pressure monitoring improves the diagnosis of hypertension in hemodialysis patients. *Kidney Int.* 2006;69(5):900–906. doi:10.1038/sj.ki.5000145
17. Vaios V, Georgianos PI, Vareta G, et al. Clinic and home blood pressure monitoring for the detection of ambulatory hypertension among patients on peritoneal dialysis. *Hypertension.* 2019;74(4):998–1004. doi:10.1161/HYPERTENSIONAHA.119.13443
18. Agarwal R, Satyan S, Alborzi P, et al. Home blood pressure measurements for managing hypertension in hemodialysis patients. *Am J Nephrol.* 2009;30(2):126–134. doi:10.1159/000206698
19. Agarwal R, Brim NJ, Mahenthiran J, Andersen MJ, Saha C. Out-of-hemodialysis-unit blood pressure is a superior determinant of left ventricular hypertrophy. *Hypertension.* 2006;47(1):62–68. doi:10.1161/01.HYP.0000196279.29758.f4
20. Alborzi P, Patel N, Agarwal R. Home blood pressures are of greater prognostic value than hemodialysis unit recordings. *Clin J Am Soc Nephrol.* 2007;2(6):1228–1234. doi:10.2215/CJN.02250507
21. da Silva GV, de Barros S, Abensur H, Ortega KC, Mion D Jr.; Cochrane Renal Group Prospective Trial Register: CRG060800146. Home blood pressure monitoring in blood pressure control among haemodialysis patients: an open randomized clinical trial. *Nephrol Dial Transplant.* 2009;24(12):3805–3811. doi:10.1093/ndt/gfp332
22. Miskulin DC, Gassman J, Schrader R, et al. BP in dialysis: results of a pilot study. *J Am Soc Nephrol.* 2018;29(1):307–316. doi:10.1681/ASN.2017020135
23. Agarwal R, Sinha AD, Pappas MK, Abraham TN, Tegegne GG. Hypertension in hemodialysis patients treated with atenolol or lisinopril: a randomized controlled trial. *Nephrol Dial Transplant.* 2014;29(3):672–681. doi:10.1093/ndt/gft515
24. Chiu YW, Teitelbaum I, Misra M, de Leon EM, Adzize T, Mehrotra R. Pill burden, adherence, hyperphosphatemia, and quality of life in maintenance dialysis patients. *Clin J Am Soc Nephrol.* 2009;4(6):1089–1096. doi:10.2215/CJN.00290109
25. Siddiqui M, Muntner P. The need to assess adherence in apparent treatment resistant hypertension. *Am J Hypertens.* 2023;36(7):358–359. doi:10.1093/ajh/hpad024
26. Bourque G, Ilin JV, Ruzicka M, Hundemer GL, Shorr R, Hiremath S. Nonadherence is common in patients with apparent resistant hypertension: a systematic review and meta-analysis. *Am J Hypertens.* 2023;36(7):394–403. doi:10.1093/ajh/hpad013
27. Agarwal R, Alborzi P, Satyan S, Light RP. Dry-weight reduction in hypertensive hemodialysis patients (DRIP): a randomized, controlled trial. *Hypertension.* 2009;53(3):500–507. doi:10.1161/HYPERTENSIONAHA.108.125674
28. Bragg-Gresham JL, Fissell RB, Mason NA, et al. Diuretic use, residual renal function, and mortality among hemodialysis patients in the Dialysis Outcomes and Practice Pattern Study (DOPPS). *Am J Kidney Dis.* 2007;49(3):426–431. doi:10.1053/j.ajkd.2006.12.012
29. Sibbel S, Walker AG, Colson C, Tentori F, Brunelli SM, Flythe J. Association of continuation of loop diuretics at hemodialysis initiation with clinical outcomes. *Clin J Am Soc Nephrol.* 2019;14(1):95–102. doi:10.2215/CJN.05080418
30. Flythe JE, Assimon MM, Tugman MJ, et al. Efficacy, safety, and tolerability of oral furosemide among patients receiving hemodialysis: a pilot study. *Kidney Int Rep.* 2022;7(10):2186–2195. doi:10.1016/j.ekir.2022.07.003
31. Zoccali C, Torino C, Tripepi R, et al.; Lung US in CKD Working Group. Pulmonary congestion predicts cardiac events and mortality in ESRD. *J Am Soc Nephrol.* 2013;24(4):639–646. doi:10.1681/ASN.2012100990
32. Zoccali C, Moissl U, Chazot C, et al. Chronic fluid overload and mortality in ESRD. *J Am Soc Nephrol.* 2017;28(8):2491–2497. doi:10.1681/ASN.2016121341
33. Zoccali C, Torino C, Mallamaci F, et al. A randomized multicenter trial on a lung ultrasound-guided treatment strategy in patients on chronic hemodialysis with high cardiovascular risk. *Kidney Int.* 2021;100(6):1325–1333. doi:10.1016/j.kint.2021.07.024
34. Beaubien-Souligny W, Kontar L, Blum D, Bouchard J, Denault AY, Wald R. Meta-analysis of randomized controlled trials using tool-assisted target weight adjustments in chronic dialysis patients. *Kidney Int Rep.* 2019;4(10):1426–1434. doi:10.1016/j.ekir.2019.07.003
35. Munoz Mendoza J, Sun S, Chertow GM, Moran J, Doss S, Schiller B. Dialysate sodium and sodium gradient in maintenance hemodialysis: a neglected sodium restriction approach? *Nephrol Dial Transplant.* 2011;26(4):1281–1287. doi:10.1093/ndt/gfq807
36. Dunlop JL, Vandal AC, Marshall MR. Low dialysate sodium levels for chronic haemodialysis. *Cochrane Database Syst Rev.* 2019;1:CD011204. doi:10.1002/14651858.CD011204.pub2
37. Arramreddy R, Sun SJ, Munoz Mendoza J, Chertow GM, Schiller B. Individualized reduction in dialysate sodium in conventional in-center hemodialysis. *Hemodial Int.* 2012;16(4):473–480. doi:10.1111/j.1542-4758.2012.00701.x
38. de Paula FM, Peixoto AJ, Pinto LV, Dorigo D, Patricio PJ, Santos SF. Clinical consequences of an individualized dialysate sodium prescription in hemodialysis patients. *Kidney Int.* 2004;66(3):1232–1238. doi:10.1111/j.1523-1755.2004.00876.x
39. Radhakrishnan RC, Varughese S, Chandran A, et al. Effects of individualized dialysate sodium prescription in hemodialysis -

results from a prospective interventional trial. *Indian J Nephrol.* 2020;30(1):3–7. doi:10.4103/ijn.IJN_391_18

40. Laurent S, Agabiti-Rosei C, Bruno RM, Rizzoni D. Microcirculation and macrocirculation in hypertension: a dangerous cross-link? *Hypertension.* 2022;79(3):479–490. doi:10.1161/HYPERTENSIONAHA.121.17962
41. Georgianos PI, Pikilidou MI, Liakopoulos V, Balaskas EV, Zebekakis PE. Arterial stiffness in end-stage renal disease-pathogenesis, clinical epidemiology, and therapeutic potentials. *Hypertens Res.* 2018;41(5):309–319. doi:10.1038/s41440-018-0025-5
42. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol.* 2010;55(13):1318–1327. doi:10.1016/j.jacc.2009.10.061
43. Agarwal R, Light RP. Arterial stiffness and interdialytic weight gain influence ambulatory blood pressure patterns in hemodialysis patients. *Am J Physiol Renal Physiol.* 2008;294(2):F303–F308. doi:10.1152/ajprenal.00575.2007
44. Georgianos PI, Agarwal R. Aortic stiffness, ambulatory blood pressure, and predictors of response to antihypertensive therapy in hemodialysis. *Am J Kidney Dis.* 2015;66(2):305–312. doi:10.1053/j.ajkd.2015.01.018
45. Agarwal R. Mechanisms and mediators of hypertension induced by erythropoietin and related molecules. *Nephrol Dial Transplant.* 2018;33(10):1690–1698. doi:10.1093/ndt/gfx324
46. Buckner FS, Eschbach JW, Haley NR, Davidson RC, Adamson JW. Hypertension following erythropoietin therapy in anemic hemodialysis patients. *Am J Hypertens.* 1990;3(12 Pt 1):947–955. doi:10.1093/ajh/3.12.947
47. van de Borne P, Tielemans C, Vanherweghem JL, Degaute JP. Effect of recombinant human erythropoietin therapy on ambulatory blood pressure and heart rate in chronic haemodialysis patients. *Nephrol Dial Transplant.* 1992;7(1):45–49. doi:10.1093/oxfordjournals.ndt.a091989
48. Amar J, Vernier I, Rossignol E, Lenfant V, Conte JJ, Chamontin B. Influence of nycthemeral blood pressure pattern in treated hypertensive patients on hemodialysis. *Kidney Int.* 1997;51(6):1863–1866. doi:10.1038/ki.1997.254
49. Conlon PJ, Kovalik E, Schumm D, Minda S, Schwab SJ. Normalization of hematocrit in hemodialysis patients with cardiac disease does not increase blood pressure. *Ren Fail.* 2000;22(4):435–444. doi:10.1081/jdi-100100885
50. Carlini RG, Dusso AS, Obialo CI, Alvarez UM, Rothstein M. Recombinant human erythropoietin (rHuEPO) increases endothelin-1 release by endothelial cells. *Kidney Int.* 1993;43(5):1010–1014. doi:10.1038/ki.1993.142
51. Kang DH, Yoon KI, Han DS. Acute effects of recombinant human erythropoietin on plasma levels of proendothelin-1 and endothelin-1 in haemodialysis patients. *Nephrol Dial Transplant.* 1998;13(11):2877–2883. doi:10.1093/ndt/13.11.2877
52. Roger SD, Grasty MS, Baker LR, Raine AE. Effects of oxygen breathing and erythropoietin on hypoxic vasodilation in uremic anemia. *Kidney Int.* 1992;42(4):975–980. doi:10.1038/ki.1992.376
53. Vaziri ND, Zhou XJ, Naqvi F, et al. Role of nitric oxide resistance in erythropoietin-induced hypertension in rats with chronic renal failure. *Am J Physiol.* 1996;271(1 Pt 1):E113–E122. doi:10.1152/ajpendo.1996.271.1.E113
54. Eggena P, Willsey P, Jamgotchian N, et al. Influence of recombinant human erythropoietin on blood pressure and tissue renin-angiotensin systems. *Am J Physiol.* 1991;261(5 Pt 1):E642–E646. doi:10.1152/ajpendo.1991.261.5.E642
55. Hand MF, Haynes WG, Johnstone HA, Anderton JL, Webb DJ. Erythropoietin enhances vascular responsiveness to norepinephrine in renal failure. *Kidney Int.* 1995;48(3):806–813. doi:10.1038/ki.1995.354
56. Mancia CG, Kreutz Co-Chair R, Brunstrom M, et al. 2023 ESH guidelines for the management of arterial hypertension. The task force for the management of arterial hypertension of the European Society of hypertension. Endorsed by the European Renal Association (ERA) and the International Society of Hypertension (ISH). *J Hypertens.* 2023;41(12):1874–2071. doi:10.1097/HJH.0000000000003480
57. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension.* 2018;71(6):e13–e115. doi:10.1161/HYP.0000000000000065
58. Iseki K, Arima H, Kohagura K, et al.; Olmesartan Clinical Trial in Okinawan Patients Under OKIDS OCTOPUS Group. Effects of angiotensin receptor blockade (ARB) on mortality and cardiovascular outcomes in patients with long-term haemodialysis: a randomized controlled trial. *Nephrol Dial Transplant.* 2013;28(6):1579–1589. doi:10.1093/ndt/gfs590
59. Ruggenenti P, Podesta MA, Trillini M, et al.; ARCADIA Study Organization. Ramipril and cardiovascular outcomes in patients on maintenance hemodialysis: the ARCADIA multicenter randomized controlled trial. *Clin J Am Soc Nephrol.* 2021;16(4):575–587. doi:10.2215/CJN.12940820
60. Suzuki H, Kanno Y, Sugahara S, et al. Effect of angiotensin receptor blockers on cardiovascular events in patients undergoing hemodialysis: an open-label randomized controlled trial. *Am J Kidney Dis.* 2008;52(3):501–506. doi:10.1053/j.ajkd.2008.04.031
61. Takahashi A, Takase H, Toriyama T, et al. Candesartan, an angiotensin II type-1 receptor blocker, reduces cardiovascular events in patients on chronic haemodialysis–a randomized study. *Nephrol Dial Transplant.* 2006;21(9):2507–2512. doi:10.1093/ndt/gfl293
62. Zannad F, Kessler M, Lehert P, et al. Prevention of cardiovascular events in end-stage renal disease: results of a randomized trial of fosinopril and implications for future studies. *Kidney Int.* 2006;70(7):1318–1324. doi:10.1038/sj.ki.5001657
63. Georgianos PI, Tziatzios G, Roumeliotis S, et al. Effect of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers on cardiovascular outcomes in dialysis patients: a systematic review and meta-analysis. *Nephrol Dial Transplant.* 2023;38(1):203–211. doi:10.1093/ndt/gfac253
64. Tepel M, Hopfenmueller W, Scholze A, Maier A, Zidek W. Effect of amlodipine on cardiovascular events in hypertensive haemodialysis patients. *Nephrol Dial Transplant.* 2008;23(11):3605–3612. doi:10.1093/ndt/gfn304
65. Georgianos PI, Agarwal R. Pharmacotherapy of hypertension in chronic dialysis patients. *Clin J Am Soc Nephrol.* 2016;11(11):2062–2075. doi:10.2215/CJN.00870116
66. Hasegawa T, Nishiwaki H, Ota E, Levack WM, Noma H. Aldosterone antagonists for people with chronic kidney disease requiring dialysis. *Cochrane Database Syst Rev.* 2021;2(2):CD013109. doi:10.1002/14651858.CD013109.pub2
67. Juurlink DN, Mamdani MM, Lee DS, et al. Rates of hyperkalemia after publication of the randomized aldactone evaluation study. *N Engl J Med.* 2004;351(6):543–551. doi:10.1056/NEJMoa040135
68. Walsh M, Manns B, Garg AX, et al. The safety of eplerenone in hemodialysis patients: a noninferiority randomized controlled trial. *Clin J Am Soc Nephrol.* 2015;10(9):1602–1608. doi:10.2215/CJN.12371214
69. Chang TI, Tatoian ET, Montez-Rath ME, Chertow GM. Timing of antihypertensive medications on key outcomes in hemodialysis: a cluster randomized trial. *Kidney360.* 2021;2(11):1752–1760. doi:10.34067/KID.0001922021
70. Georgianos PI, Agarwal R. Can we mend the broken clock by timing antihypertensive therapy sensibly? *Clin J Am Soc Nephrol.* 2020;15(10):1513–1515. doi:10.2215/CJN.00360120