

Uncertainties in BP management in dialysis patients

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Abstract

Hypertension in dialysis patients is extremely common. In this article, we review the current evidence for blood pressure (BP) goals in hemodialysis patients, and consider the effectiveness of interventions by which BP may be lowered, including manipulation of dietary and dialysate sodium; optimization of extracellular water; prolongation of dialysis time; and antihypertensive medication. Although two meta-analyses suggest lowering BP using antihypertensive drugs might be beneficial in reducing cardiovascular events and mortality, there are insufficient rigorously designed trials in hypertensive hemodialysis populations to determine preferred antihypertensive drug classes. We suggest aiming for predialysis systolic BP between 130 and 159 mm Hg, while at the same time acknowledge the significant limitations of the data upon which it is based. We conclude by summarizing current knowledge as regards management of hypertension in the peritoneal dialysis population and make recommendations for future research in this field.

1 | BLOOD PRESSURE TARGETS IN HEMODIALYSIS PATIENTS

Hypertension is extremely common in people receiving hemodialysis (HD) for end-stage renal disease, with prevalence estimates of between 72% and 88%.¹ Epidemiological data in the general population demonstrate a positive linear association between systolic blood pressure (SBP) and adverse outcomes including coronary artery disease, stroke, and heart failure, and randomized studies consistently demonstrate that intensively lowering BP (ie, targeting <120/80 vs 140/90 mm Hg) delivers reductions in important clinical endpoints in the majority of sub-populations.² In contrast, observational studies in HD populations show a very different relationship between BP and patient outcomes, and data from interventional trials are sparse. Several recent articles have reviewed the accumulated observational data in prevalent and incident HD patient cohorts.^{3–5} In brief, studies drawing on peri-dialytic measurements have consistently shown a “U”- or “J”-shaped relationship with mortality where lowest and,

sometimes, highest levels of BP are associated with greatest risk of death. For example, Robinson et al analyzed data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) at both facility and individual patient level and found lowest mortality in those with a pre-HD SBP of 130–159 mm Hg (facility level) and <130 mm Hg (individual patient level).⁶ Importantly, the facility-level analysis compensates for unmeasured confounding, albeit in an imperfect manner as the authors acknowledge. In a similar vein, the CRIC Investigators report a pre-HD SBP of 138–166 mm Hg to be associated with lowest risk of cardiovascular events.⁷

Various explanations have been put forward to account for the contrast between BP-mortality associations in the HD and general populations. Firstly, it should be acknowledged that routinely collected peri-dialytic BP measurements are often performed under suboptimal conditions and may, therefore, be unreliable as a means to predict risk of cardiovascular events, diagnose hypertension, and guide treatment. A recent survey conducted across 92 predominantly European HD centers supports this assertion.⁸

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Usual BP measurement practice fell significantly below recommended standards, with only 20% of HD units achieving at least 80% of standards.⁸ The reasons for sub-optimal BP measurement were not explored but, intuitively, patient-related factors are likely to exert a significant influence on measurement practice and/or BP readings themselves. For example a desire to start and finish HD without undue delay results in a reluctance to remove sufficient clothing and to “rest” adequately before BP measurements. Additionally, anticipation anxiety relating to needling, frustration related to transportation delays and other factors will inevitably augment the white-coat effect in some HD patients. Although standardized BP measurements are more reliable than routinely collected BP readings,⁹ particularly when taken postdialysis, there are practical constraints, for example patient reluctance to add further delays to the dialysis process and health professional time, that would in our opinion make implementation in routine care rather challenging.

Secondly, there is a confounding influence of comorbidities (heart failure, malnutrition) that present with or are associated with lower BP and are more directly and causally linked to mortality than BP itself.^{10,11} On the other hand, the absence of heart failure significantly modifies the “J”-shaped association between low predialysis SBP and mortality.¹² Reinforcing this latter hypothesis is the observation that dialysis vintage also modifies the BP-mortality relationship. In a study of incident HD patients those with low predialysis BP had increased mortality over the subsequent 2 years, whereas in those who survived beyond 3 years, a mortality benefit was observed with low predialysis BP.¹³ In other words, patients who were destined not to survive from preexisting comorbid conditions were more likely to have low BP at inception of dialysis, whereas those without comorbidity had better survival which was then associated with—either causally or otherwise—lower BP.

Thirdly, extracellular water (ECW) and, probably, a range of uremic toxins vary considerably over the interdialytic period with most marked changes from pre- to postdialysis, all of which will exert a considerable influence on BP.¹⁴ To an extent this and measurement-related confounders may be ameliorated by BP measurements obtained outside of dialysis facilities. Indeed, various studies in HD populations have demonstrated more consistently linear associations between Home BP monitoring (HBPM) and ambulatory blood pressure monitoring (ABPM) and both intermediate (left ventricular (LV) hypertrophy, LVH) and hard (mortality) endpoints. Forty-four-hour interdialytic ambulatory BP monitoring (ABPM) is considered the gold standard for determining BP¹⁵ and predicts LVH and mortality.^{16,17} A prospective study that enrolled 326 predominantly black American HD patients found increased risk for all-cause mortality with increasing quartiles of both ABPM and HBPM.¹⁶ More recently, Meyer & colleagues, using ABPM in 344 European HD patients found a “U”-shaped relationship. However, when separately analyzed by the presence or absence of atrial fibrillation or heart failure, which accounted for approximately one third of the population studied, a negative relationship existed between SBP and pulse pressure and all-cause and cardiovascular mortality, whereas

in those without these comorbidities the opposite relationship was found.¹⁸ However, ABPM has low patient acceptability, is expensive and complex to utilize in routine practice.^{1,19}

HBPM is similar to ABPM at predicting LVH and outcomes, with prognostic accuracy depending more on temporal relationship to the dialysis episode than the number of BP readings taken.^{7,17,20,21} A relatively small number of HBPM readings taken over a short time period, usually two to three times per day for 4 days following the mid-week HD session, has comparable accuracy to ABPM.²² HBPM is widely available, relatively inexpensive, considered user-friendly, and frequently recommended in consensus guidelines. Self-management algorithms utilizing HBPM deliver superior BP control compared to standard care, including in higher-risk populations, for example, chronic kidney disease²³ and these effects may relate to patient involvement and empowerment.²⁴ However, and while HBPM outperforms other techniques when compared to the gold standard of ABPM,⁹ we question whether this method can easily be adopted into routine practice for *all* HD patients. The recently published BP in Dialysis (BID) study showed surprisingly high attrition rates in performance of HBPM among a presumably highly motivated population who were being regularly prompted by study personnel²⁵: at 12 months follow-up, only 22% of participants achieved at least four HBPM readings per month.

A fourth explanation for the “U”- or “J”-shaped relationship worthy of consideration is that active attempts to lower BP to levels considered desirable other populations may actually be deleterious in HD patients. Intradialytic hypotension (IDH) affects up to one third of HD sessions and is independently associated with significant morbidity and mortality.^{26–30} Lowering BP by reducing ECW through “probing” for a lower target weight is effective in reducing BP³¹ but at the expense of an approximate doubling in incidence of hypotensive episodes (24.8% vs 12.7% in intervention and control arms, at 6 to 8 weeks, in the DRIP study). Burton and colleagues elegantly demonstrated how IDH and ultrafiltration (UF) volumes are independent predictors of myocardial stunning which, in turn, is predictive of LV systolic dysfunction, myocardial fibrosis, and mortality.³² In BID, a feasibility and safety study, HD patients were randomized to either a “standard” BP target range of 155–165 mm Hg or an “intensive” target range of 110–140 mm Hg.²⁵ Although not powered to deliver definitive conclusions, a number of safety signals emerged to support the hypothesis that “lower might not be better” in the HD population. Those in the intensive arm experienced a threefold higher incidence, albeit not quite reaching statistical significance, of vascular access thrombosis (incidence rate ratio [IRR] or 3.09, 95% confidence interval [CI] 0.96–8.78). Additionally, IRR for hospitalizations was 1.61 in the intensive arm (95% CI 0.87–2.97).²⁵

In an ideal world we would have at our disposal data from a well-conducted prospective randomized trial, that provides for adequate individualization of target BP depending on age, frailty, and comorbidity, and examines impacts on outcomes of importance to dialysis patients, such as vascular access patency and recovery time after dialysis³³ as well as more conventional endpoints of cardiovascular events and all-cause mortality. Until we get to this point

TABLE 1 Summary of pragmatic advice regarding BP management based on current available evidence (most relevant references provided where applicable)

Encourage adherence amongst patients and dialysis staff with recording of BP measurements on the dialysis unit according to recommendations from the AHA, ERA-EDTA/ESH, NICE, or other guideline group on BP measurement.²

Meticulous fluid volume management is of utmost importance.⁸³ Prolonged or more frequent dialysis may be required for patients with high interdialytic weight gains or frequent intradialytic hypotension.¹¹⁶ Periodic extra ultrafiltration sessions may be required to achieve and maintain euolemia in those unwilling to perform prolonged or more frequent treatments on a regular basis.

Counsel patients to take a low sodium diet of <2.5 g/d (approximates to <6 g NaCl/d).⁴⁷

Avoid dialysate Na >140 mEq/L; lowering dialysate Na can be tried in patients without intradialytic hypotension, although is of uncertain benefit, and should not be continued in a patient with intradialytic hypotension.⁶⁶

Insufficient evidence exists to make firm recommendations about choice of antihypertensive medication. Beta-blockers, angiotensin receptor blockers (or, possibly, ACE inhibitors), and dihydropyridine calcium channel blockers are all reasonable choices. For HD patients with questionable medication compliance, beta-blockers such as atenolol given three times a week following dialysis may be useful.¹²¹⁻¹²³

In the majority of patients, aim for a pre-HD BP between 130/60 and 159/99 mm Hg and post-HD BP between 120/70 and 139/99 mm Hg so long as it is tolerated.⁶ If patient experiences intradialytic hypotension, raise the goal BP.

In younger patients (eg, <30-40 y old) without significant comorbidity, consider aiming for a pre-HD SBP of <140 mm Hg, but not <125 mm Hg.³⁵

In patients who are motivated to undertake home BP measurements, or where ABPM is utilized, aim for an average home or ambulatory SBP between 120 and 130 mm Hg.¹⁶

Abbreviations: ABPM, Ambulatory Blood Pressure Monitoring; AHA, American Heart Association; BP, Blood Pressure; ERA-EDTA, European Renal Association-European Dialysis and Transplant Association; ESH, European Society of Hypertension; HD, hemodialysis; NICE, National Institute for Health and Care Excellence; SBP, Systolic Blood Pressure. It should be noted that these recommendations are based on studies with limited numbers of participants.

we recommend a pragmatic approach, the rationale for which is presented here and summarized in Table 1.

The reality is that, in the majority of HD units internationally, routinely collected BP measurements will continue to guide our interventions for the foreseeable future. It is, therefore, essential for nephrologists to ensure routinely collected HD unit BP readings are measured in accordance with recommended guidelines through healthcare professional and patient education. Although individual studies point toward slight differences in BP thresholds associated with lowest risk of all-cause or cardiovascular mortality, a range of routine pre-HD systolic BP broadly between 130-140 and 160-170 mm Hg appears to be associated with lowest mortality. Although intuitively younger, less frail patients without comorbidities, particularly diabetes, heart failure, or atherosclerotic cardiovascular

disease, and those expected to survive 3 or more years on dialysis, may benefit from lower goal BPs, there is currently a paucity of evidence to directly support this approach in the majority of HD patients. For example, in a recent Korean study of 2299 HD patients followed for 4.5 years, all-cause mortality was increased with pre-HD SBP <110 and ≥ 170 mm Hg.³⁴ When separately analyzed by age (above or below 65 years) and the presence or absence of a variety of comorbidities, the threshold at which hazard ratios significantly increased remained at 170 mm Hg. Similarly, Myers found that a "U"-shaped relationship persisted in all age groups, with the exception of those aged under 30 in whom a more conventional linear relationship between mortality risk and SBP emerged above a threshold of 140 mm Hg.³⁵ It is difficult to make firm recommendations for target BP in patients undergoing HBPM or ABPM owing to the very small numbers of patients evaluated using these methodologies, for example with 326 patients in the largest study of HBPM to date.¹⁶ In this study an average home systolic BP of 120-130 mm Hg appeared to be associated with lowest all-cause mortality.

2 | HOW TO LOWER BLOOD PRESSURE IN HEMODIALYSIS PATIENTS

2.1 | Dietary salt reduction and dialysate sodium concentration

Volume expansion by salt and water excess is a major cause of hypertension in dialysis patients^{36,37} but it is just one aspect of the complex pathophysiology that contributes to hypertension in this cohort. Higher dietary sodium intake is independently associated with greater mortality in HD patients.³⁸ Reduction in salt intake results in lower BP in the general population, in hypertensives of all ethnicities, in diabetics and non-diabetics, and in patients with chronic kidney disease (CKD).³⁹⁻⁴³

A low salt diet may be particularly beneficial in people with CKD on dialysis because they are dependent on the dialysis process to remove excess sodium and water. A number of studies in the 1990s explored dietary salt reduction together with reduction in dialysate sodium or longer HD sessions to achieve optimal dry weight and BP control.⁴⁴⁻⁴⁶ However, the relative importance of altered salt intake per se remains uncertain since the majority of studies of salt reduction in dialysis patients are heterogeneous, poorly controlled, and underpowered to show a BP difference following intervention. However, a recent meta-analysis of randomized controlled trials in 91 dialysis patients showed that a mean difference in salt intake of 5 g/day was associated with a reduction in blood pressure of 8/4 mm Hg.⁴⁷ This meta-analysis is limited by the lack of robust and adequately powered studies with the authors suggesting that dietary salt reduction may reduce BP in dialysis patients, but there is insufficient evidence to be able to inform on the effects of salt reduction on other dialysis parameters such as ultrafiltration volume, HD access survival, and mortality.

High sodium and incremental sodium dialysate prescriptions, that employ high dialysate sodium at the outset of the HD process,

were popular for many decades of dialysis delivery with a plethora of studies that appeared to show improved intradialytic hemodynamic stability in HD populations. Increased interdialytic fluid gain was the downside of these regimens, but no other major apparent adverse effects were widely reported.^{48–51} However, more recently these HD regimens, particularly sodium profiling, have been found to increase the burden of interdialytic symptoms including thirst, fatigue, and weight gain together with reports of sustained hypertension and increased mortality.^{52–54}

An acute alteration in dialysate sodium concentration leads to changes in plasma sodium concentration. A small but well-controlled intervention study found that a reduction in dialysate sodium concentration caused a fall in plasma sodium and a rapid simultaneous fall in blood pressure in HD patients, suggesting that there is a direct link between plasma sodium and BP.⁵⁵ Further observational studies have described an association between predialysis plasma sodium and predialysis SBP and diastolic blood pressure (DBP).⁵⁶ Maneuvres that alter plasma sodium are, however, contentious as lower plasma sodium has been found to be associated with increased mortality in dialysis populations^{57,58} and most likely has a “U”-shaped curve in the general population, with the lowest mortality in the range between 141 and 143 mmol/L.⁵⁹ There have now been several studies, with observational, parallel, and cross-over designs, observing the effects of lower dialysate sodium (<138 mmol/L) vs neutral (138–140 mmol/L) or high (>140 mmol/L) dialysate sodium for maintenance HD patients.^{60–62} These have been reviewed by Basile who found mixed outcomes.⁶³ A recent DOPPS analysis reported that predialysis SBP was 0.9 mm Hg higher per 2 mmol/L higher dialysate sodium.⁶⁴ Intervention studies have shown improved predialysis SBP and DBP outcomes with low sodium dialysate.^{61,62} In one study, dialysate sodium reduction from an average of 138–133 mmol/L had a beneficial effect on inter-dialytic 48-hour ABPM in chronic stable HD patients, with no reported profound hyponatremia and a fall in the measured BP outcome from 141/83 to 133/78 mm Hg ($P < .01$).⁶⁰ Another study showed improved endothelial function and a significant reduction in mean 24-hour ambulatory BP outcomes (128/78 mm Hg vs 132/81 mm Hg) with a reduction in dialysate sodium.⁶⁵ In the majority of studies there was a reduction in interdialytic weight gain with lower sodium dialysate, but even with this improved outcome there was still an increased frequency of IDH episodes.⁶³ The most informative synthesis of these data is a Cochrane review of 12 of these interventional studies randomizing 310 patients, with data available for 266 patients after dropout.⁶⁶ This review found reasonable evidence that lower dialysate sodium reduces interdialytic weight gain and probably reduces BP but at the expense of probably reducing serum sodium and increasing IDH events, both of which are associated with adverse outcomes.

2.2 | Optimization of extracellular water

Although hypertension in dialysis patients is multifactorial, volume overload plays a major role in its pathogenesis.^{67–72} Several

observational studies and an RCT have demonstrated that adequate fluid removal improves BP control in these patients.^{31,73–76} However, accurate assessment of fluid volume is challenging. Traditionally, fluid volume status is determined by clinical assessment which is a “guesstimate” based on parameters including pre- and postdialysis BP, interdialytic weight gain, the presence or absence of edema, assessment of jugular venous pressure, auscultation of lung bases, and assessment of postural BP. The reliability of these clinical signs in accurately estimating fluid volume has been questioned.^{77,78} Probing for dry weight, progressive removal of fluid by means of UF over a few HD sessions until the patient becomes symptomatic, has been demonstrated to be effective in achieving normovolemia and BP control,³¹ but is not always easy to execute and is associated with a higher risk of intradialytic hypotension, loss of residual renal function, hospitalization for cardiovascular complications, and vascular access thrombosis.^{31,79,80}

Apart from helping BP control, accurate assessment of fluid volume status is crucial in improving cardiovascular morbidities and mortality in dialysis patients. There is a good body of evidence to suggest inadequate fluid volume management is associated with adverse patient outcomes.^{54,81–86} A number of technologies are now available to aid objective assessment of fluid volume in dialysis patients but not all have been properly validated or supported by patient outcome data. These include serum Brain Natriuretic Peptide,^{87,88} continuous blood volume monitoring,^{89,90} inferior vena caval diameter measurement,⁹¹ ultrasound lung water measurement,⁹² and bio-impedance devices.⁹³

Of these technologies, bioimpedance spectroscopy (BIS) has been most widely studied.^{81,83,85,86,94–98} Whole-body (wrist-to-ankle) BIS measurements can be used to determine ECW, intracellular, and total body water volumes.⁹⁶ The addition of a three-compartment body model to distinguish excess extracellular fluid from lean and adipose tissue allows an objective assessment of excess fluid or “overhydration” (OH).⁹⁴ The BIS fluid volume model and the body model are integrated into the Body Composition Monitor (BCM, Fresenius AG, Bad Homburg), which appears to be the best-validated bio-impedance device and it provides a numerical value for fluid overload that is easy to follow.^{93,94,97,98} A recent systematic review of 46 studies suggests bio-impedance defined overhydration predicts mortality in dialysis patients independent of the influence of comorbidity.⁹⁹ An observational study from over a decade ago suggested poor correlation between predialysis SBP and BIS measured volume status.¹⁰⁰ However, more recently, two small randomized trials have demonstrated that BIS directed fluid volume management reduces blood pressure (secondary outcome) in addition to reduction in left ventricular mass, left atrial volume and arterial stiffness in hemodialysis patients,^{101,102} which has been supported by a systematic review and meta-analysis.¹⁰³ An adequately powered RCT, currently underway in the United Kingdom, will further inform the benefit of fluid volume management using BIS.¹⁰⁴ Although BIS is easy to use and takes only a few minutes to assess fluid

volume status, cost of the device (and of the electrodes in case of BCM) may hinder widespread routine use of BIS in the dialysis unit.

Lung ultrasound is a novel technique that objectively assesses fluid excess in the lung.^{105,106} It has been validated in patients undergoing hemodialysis, demonstrating that the number of US-B lines, an ultrasonographic sign of excess water in the lung, correlates with left ventricular mass and function, and is associated with cardiovascular events and mortality.^{107,108} An ongoing randomized controlled trial, Lung Water by Ultrasound Guided Treatment to Prevent Death and Cardiovascular Complications in High Risk End-Stage Renal Disease Patients with Cardiomyopathy (LUST), is investigating whether lung ultrasound-guided fluid removal is effective in lowering major cardiovascular events and death.¹⁰⁹ A recently published sub-study of LUST, involving 71 clinically euvolemic hypertensive patients, showed that lung ultrasound-guided “dry-weight probing” was effective in reducing 48-hour ambulatory BP compared with standard care with an average intergroup difference in BP of 5.9/3.3 mm Hg at 8 weeks. There was only a modest decrease in dry weight (mean $\pm$ SD of -0.71 ± 1.39 vs 0.51 ± 0.98 kg, $P < .001$) in the active group with no significant increase in hypotensive episodes or vascular access thrombosis.¹¹⁰ However, despite the putative benefit of this technology in managing fluid volume, the radiological expertise required to carry out lung ultrasound and the time required to perform the study (15 minutes in trained personnel) may preclude its routine use for the assessment of fluid volume status in dialysis patients.

Of the other currently available biomarkers and technologies, Brain Natriuretic Peptide and ultrasound measurement of inferior vena caval diameter have been found to be impractical for routine use and inaccurate in assessing fluid volume overload.⁷⁷ Relative blood volume monitoring, integrated into hemodialysis machines, is convenient and used mostly to assess fluid volume depletion during ultrafiltration.^{89,90} Although it is useful for qualitative assessment of fluid volume status, the sensitivity is low for the assessment of mild to moderate fluid overload.^{111,112} Furthermore, both observational and trial data suggest that fluid volume management guided by on-line blood volume monitoring is associated with increased risks of hospitalization and mortality.^{54,112}

Despite the compelling evidence for the importance of adequate fluid volume management in improving outcomes in hemodialysis patients, the practice is widely variable. A survey of hemodialysis centers in the United Kingdom found that only 22% of centers had a policy for fluid volume management and 56% routinely assessed patients' fluid status.¹¹³ Data from the international DOPPS study show that only 25% of the 273 centers across 12 countries had a protocol in their dialysis unit that specified how often to assess dry weight in most patients. In the others, dry weight was assessed only as clinically indicated. Interestingly, having a protocol for fluid management was associated with a 22% lower risk of all-cause mortality and 28% lower risk of cardiovascular mortality,⁸⁴ providing further evidence for the benefit of meticulous fluid volume management.

2.3 | Extended dialysis time

Increasing the duration of dialysis time, either by longer sessional hours or increased sessions, may be a consideration for individuals who fail to achieve target BP or ideal volume status during standard HD prescription hours. There is good rationale for adopting this approach, but the economic ramifications would be profound for universal provision. In 2011 the Long Dialysis Study Group found that longer HD sessions (8 hours of nocturnal HD vs conventional 4 hour HD thrice weekly) were associated with a 72% risk reduction for all-cause mortality (hazard ratio 0.28, 95% CI 0.09–0.85, $P = .02$).¹¹⁴ Subsequently, the Frequent Hemodialysis Network (FHN) Daily Trial randomized 245 patients to receive six (frequent) or three (conventional) in-center HD sessions per week for 12 months and found significantly reduced long-term mortality in the frequent HD group, with relative mortality hazard for frequent vs conventional HD of 0.54 (95% confidence interval, 0.31–0.93).¹¹⁵ The same group had previously demonstrated that 2 months of this frequent HD regimen lowered predialysis SBP by 7.7 mm Hg (95% CI -11.9 to -3.5) and DBP by 3.9 mm Hg (95% CI -6.5 to -1.3).¹¹⁶ The landmark FHN Nocturnal Trial randomized 87 patients to thrice weekly conventional HD or nocturnal HD six times per week, all with single-use high-flux dialyzers. It was underpowered for mortality outcomes but it reported a systolic BP reduction from baseline of 7.9 ± 18.4 mm Hg in the nocturnal cohort by 12 months.¹¹⁷ Another randomized controlled trial of short daily HD vs conventional HD reported similar BP levels but with significantly less antihypertensive medications in the group receiving short daily HD.¹¹⁸ In the FHN studies short daily and nocturnal schedules reduced the per-session probability of IDH by 20% and 68% respectively, compared to three sessions per week and other interventional and cross-sectional studies suggest that intensive HD regimes may also improve patient wellbeing and recovery times post-HD sessions.^{119,120} The observed reduction in adverse symptoms and mortality in the extended hours HD studies is most likely mediated through a combination of optimizing sodium and volume status together with improved BP control, but there may be other beneficial effects of enhanced solute clearance that are not immediately apparent.

2.4 | Antihypertensive medication

Use of antihypertensive medication in dialysis patients was previously the subject of two meta-analyses published in 2009.^{121,122} These meta-analyses overlapped considerably in terms of the original reports selected and there was considerable heterogeneity of inclusion criteria, with both HD and peritoneal dialysis populations included, several different antihypertensive drug classes evaluated, no requirement for a diagnosis of hypertension and three trials recruiting participants with heart failure.^{121,122} Cardiovascular events and all-cause mortality were significantly reduced by 31% and 21% respectively across five trials¹²¹ and by 29% and 20% across eight trials.¹²² Restricting the analysis to only those trials recruiting

TABLE 2 Design, intervention, participant characteristics, BP data, and key results from randomized controlled trials with cardiovascular outcomes^{123,125,127-129} assessing antihypertensive medications in hypertensive HD patients

Author and publication year	Inclusion criteria	Active treatment	Comparator treatment	Main outcomes
Takahashi (2006)	≥35 y; stable dry weight for 3 mo; post-HD cardiothoracic ratio on chest X-ray <50% (males) or <55% (females)	Candesartan 4-8 mg/d	"Nothing"	Composite of sudden death, fatal or nonfatal MI, unstable angina, HF admission or severe arrhythmia
Suzuki (2008)	30-80 y; HD for 12-60 mo; SBP >160 mm Hg or >150 mm Hg or taking antihypertensive drugs	Candesartan 12 mg/d, losartan 100 mg/d or valsartan 160 mg/d	"Other" antihypertensive not including ARB or ACEi	(i) Primary: Composite of CV mortality, nonfatal stroke or MI, revascularization and HF admission (ii) All-cause mortality
Tepel (2008)	≥18 ys; BP ≥140/90 mm Hg or taking antihypertensive drugs; on hemodialysis for ≥3 mo	Amlodipine 10 mg daily	Placebo	(i) Primary: all-cause mortality (ii) Time to composite of mortality of CV event (MI, revascularization, stroke, PVD events)
Iseki (2013)	20-79 y; average pre-HD BP 140-199/90-99 mm Hg	Olmesartan 10-40 mg/day	"Other" antihypertensive not including ACEi or ARB	(i) Primary: Composite of CV mortality, nonfatal stroke or MI, unstable angina, HF admission (ii) All-cause mortality
Agarwal (2014)	44 h ABPM average ≥135/85 mm Hg following drug washout; LVH	Atenolol 25-100 mg 3x/week post-HD	Lisinopril 10-40 mg 3x/wk post-HD	Between group difference in LVMI from baseline to 12 mo

Abbreviations: ABPM, ambulatory blood pressure monitor; ACEi, ACE inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CI, confidence interval; CV, cardiovascular; DM, diabetes mellitus; HBP, home blood pressure; HD, hemodialysis; HF, heart failure; K⁺, plasma potassium; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; PVD, peripheral vascular disease; SBP, systolic blood pressure.

*Location (clinic, dialysis unit etc) and timing of BP measurement in relation to dialysis (pre-HD or post-HD etc) is not specified in study reports.

hypertensive participants, however, appeared to increase the beneficial effect of antihypertensive medication (the angiotensin receptor blocker (ARB) candesartan in two trials and calcium channel blocker (CCB) amlodipine in one trial): for cardiovascular events RR was 0.49, 95% CI 0.35-0.69 in Agarwal & Sinha¹²¹ and RR was 0.51, 95% CI 0.43-0.74 in Heerspink et al.¹²²

Since 2009 a further four trials have been published in which dialysis patients have been randomized to receive medications that lower BP, including two trials of ARBs vs placebo, one of spironolactone vs placebo and one of atenolol vs lisinopril.¹²³⁻¹²⁶ Only two of these trials were conducted specifically in hypertensive populations.^{123,125} We have summarized in Table 2 the main findings from the five randomized trials in 1366 hypertensive HD patients published to date.^{123,125,127-129} Three trials had per protocol titration of additional antihypertensives to achieve prespecified BP targets (home BP in one study, not specified in two studies) of <140-150 mm Hg and unsurprisingly achieved BP did not differ between randomized groups in the majority studies, with the exception of Tepel et al, in which patients randomized to amlodipine vs placebo achieved 9 mm Hg lower SBP during follow-up (change in BP from baseline was -10 mm Hg ($P < .01$) in amlodipine arm vs -1 mm Hg ($P > .05$) in placebo arm).¹²⁹ Of the three trials of an ARB as the intervention, two trials ($n = 446$) showed benefit whereas one other

($n = 469$) did not. It is, therefore, difficult to conclude that there is a definite beneficial effect of prescribing an ARB in hypertensive HD patients without heart failure. For the single trial of CCBs, it is difficult to determine whether the apparent benefit of amlodipine was driven by the choice of antihypertensive or by the substantially lower BP (by design) in the intervention arm. The fifth study of 200 predominantly (86%) African-American HD patients, confirmed to be hypertensive on 44-hour intradialytic ABPM following antihypertensive medication withdrawal, randomized participants to postdialysis thrice-weekly open-label atenolol vs lisinopril with per-protocol titration of other antihypertensives to achieve home BP <140/90 mm Hg.¹²³ The authors reported a relative risk of 2.36 (95% CI 1.36-4.23) for cardiovascular events in those allocated to lisinopril compared to atenolol. BP during follow-up was numerically but non-significantly lower by 3.6/3 mm Hg in the atenolol arm. The primary endpoint in this study was reduction in LV mass index and the study was terminated early on safety grounds; it is not clear from the report whether the composite cardiovascular outcome reported was prespecified. Additionally, with this outcome analyzed as an event rate rather than by time to event, and considering the relatively small sample size, it is possible that recurrent events in a small number of higher risk participants may have biased the findings.

Participants (n)	DM (%)	Baseline BP (mm Hg)		BP during follow-up (mm Hg)		BP difference (active vs comparator, mm Hg)	Main results
		Active	Comparator	Active	Comparator		
80	33	153/82	152/85	153/83	149/80	"BP was not different between groups and no changes were noted in follow-up"	16.3% vs 45.9% experienced CV events in active vs comparator arms ($P = .0066$)
366	52	154/81	156/82	140/80	140/78	"SBP did not differ significantly"	(i) Primary composite endpoint: 49% RR reduction (95% CI 0.33-0.79, $P = .002$) (ii) All-cause mortality: 36% RR reduction (0.39-1.06, $P = .1$)
251	29	140/80	141/80	130/NA	140/NA	-9/NA ($P < .01$ for BP change from baseline in amlodine arm, $P > .05$ in placebo arm)	(i) All-cause mortality: HR 0.65 (95% CI 0.34-1.23, $P = .19$) (ii) Composite endpoint: HR 0.55 (0.31-0.93, $P = .03$)
469	32	159/80	160/81	152/78	153/78	1/0	(i) Primary composite endpoint: HR 1.00 (95% CI 0.71-1.4, $P = .99$) (ii) All-cause mortality: HR 0.97 (0.62-1.52, $P = .91$)
200	NS	152/87	"Similar to atenolol arm"	-21/-13 vs baseline	-18/-10 vs baseline	-4/-3 (difference between arms was not statistically significant)	(i) LVMI -21.5 g/m^2 in atenolol arm vs -15.1 g/m^2 in lisinopril arm (difference 6.4 g/ms , $p = \text{ns}$) (ii) Cardiovascular events: RR 2.36 (95% CI 1.36-4.23, $P = .001$) in lisinopril vs atenolol arms

Taken together, the evidence from the two previous meta-analyses^{121,122} and five trials in *hypertensive* HD populations^{123,125,127-129} suggests that use of antihypertensive medication in dialysis patients does reduce all cause and cardiovascular mortality and cardiovascular events but does not clearly support use of any particular class of antihypertensive agent.

3 | HYPERTENSION IN PERITONEAL DIALYSIS PATIENTS

Hypertension is also very common in the peritoneal dialysis (PD) population with reported prevalence of over 80% and as many as 79% of treated hypertensives having poorly controlled BP according to one report.^{130,131} A retrospective analysis elegantly outlined the natural course of hypertension in PD patients. Hypertension improved at the initiation of PD, reached a nadir between 6 and 12 months, and was followed by a steady decline in BP control over the next 5 years. Age, duration of hypertension, and loss of residual renal function were independently associated with inadequate BP control.¹³²

A "U"-shaped association between BP and mortality has also been observed in the PD population.^{133,134} An analysis of data on

2770 incident PD patients from the UK Renal Registry showed that while higher SBP, DBP, mean arterial pressure, and pulse pressure were associated with a reduced risk of all-cause mortality over the first year after starting dialysis; SBP and pulse pressure were associated with increased mortality in the later years, indicating dialysis vintage alters the association of BP with mortality.¹³⁴ As in the HD population, confounding comorbidities influence the association of lower BP and mortality. In a cohort study of 77 patients on PD, the inverse association of lower BP and mortality was mitigated following adjustment for severity of heart failure.¹³⁵ A linear relationship between higher pulse pressure, a marker of arterial stiffness, and all-cause mortality has been reported suggesting that this should perhaps be a target of antihypertensive therapy.^{134,136}

Whereas studies in the HD population have consistently found HBP measurements to have better prognostic performance than clinic based readings, evidence in PD is less clear cut. The International Society of Peritoneal Dialysis (ISPD) guidelines recommend that BP should be recorded at home at least once-weekly and at each visit to the PD unit, although this is not strongly supported by evidence.¹³⁷ Studies comparing the diagnostic accuracy of BP monitoring techniques, albeit limited by small sample size, suggest a superiority of standardized clinic BP over home BP measurements in approximating

ambulatory BP in this population.^{132,138,139} However, a recent study of 81 PD patients, has shown that home BP readings, taken as an average over 1 week may be as accurate as standardized clinic BP measurement, in diagnosing hypertension confirmed by ambulatory monitoring.¹⁴⁰ Both methods, however, overestimated systolic ambulatory BP by about 4 to 5 mm Hg. Further studies are needed to define the optimum method of BP measurement in PD patients.

The ISPD guidelines recommend a BP target of <140/90 mm Hg in the PD population.¹³⁷ However, this recommendation has been extrapolated from studies involving general and CKD populations. Until data from randomized controlled trials, evaluating hard clinical end points to define optimal BP targets in PD patients, are available, we suggest that the ISPD BP target for self-measured home BP measurements should be followed in day-to-day clinical practice.

As in the HD population, volume expansion plays an important role in the causation of hypertension in PD patients. Subclinical hypervolemia is higher in the PD population, and has been implicated in the maintenance of hypertension and cardiovascular alterations.^{141,142} Interestingly, the use of antihypertensive agents may paradoxically raise BP measurements by hindering dry weight control.⁷⁹ In the EuroBCM study, involving 639 PD patients in 28 centers across 6 countries, 60% of patients were hypervolemic and there was poor correlation between fluid volume status assessed by BIS and BP.¹⁴³ In a Chinese cohort of 307 PD patients subclinical hypervolemia was detected in 57% of participants.¹⁴⁴ Further evidence for the role of subclinical fluid volume overload comes from a small study of 17 patients demonstrating that the intensification of volume reduction in patients on PD, without clinical evidence of hypervolemia, was associated with a significant reduction in body weight, ECW, and inferior vena caval diameter; these changes were accompanied by a significant reduction in BP, decreased LV end-systolic diameter, and need for antihypertensive medication.¹⁴⁵ Taken together the evidence suggests that subclinical hypervolemia needs to be taken into account while treating hypertension in these patients.

The other factors that need to be considered are residual renal function, peritoneal membrane transporter status, and sodium excreting capacity.^{146–150} Preservation of residual renal function in maintaining sodium excreting and ultrafiltration capacity is essential for maintenance of euolemia and thereby control of hypertension. A post hoc analysis of a randomized trial of 82 patients showed greater BP control with the use of a sodium-reduced PD fluid compared to standard PD fluid in those with reduced or absent residual renal function.¹⁴⁷ Adaptation of the PD regimen to the peritoneal membrane characteristics and efforts to limit peritoneal injury are also crucial to achieving optimal volume and BP control. Observational studies have demonstrated that fast transporter membrane status is associated with a higher 24 hour BP, LV mass index, and mortality,^{146,148} possibly due to sodium and water reabsorption through the use of long dwells with glucose-containing solutions. Conversely, shorter dwells in those with slow

transporter status can limit sodium removal due to sodium sieving.¹³⁶ The use of icodextrin, a starch-derived glucose polymer, has been shown to be beneficial in BP control in small randomized trials, when used during the long overnight dwell in continuous ambulatory PD or during the long daytime dwell in automated PD as compared to glucose-containing solutions.^{142,151–154}

Renin-angiotensin-aldosterone system (RAAS) blocking agents have been shown to be beneficial in managing hypertension in PD patients. ACEi and ARB treatment was associated with a 62% reduced risk in all-cause mortality in a cohort of 306 patients on PD.¹⁵⁵ Pilot randomized controlled trials suggest a beneficial effect of RAAS blockade on short-term BP variability, LV hypertrophy, and arterial stiffness.^{156–159} A meta-analysis of six randomized trials shows that ACEi and ARB therapy is associated with a slower decline in residual renal function in patients on PD when used for longer than 12 months. No significant difference in preservation of residual renal function was demonstrated between the two classes.¹⁶⁰ More recently, in an observational cohort study of 4879 patients initiating PD, the use of ACEi or ARB was associated with a lower risk of fatal CV outcomes (HR 0.74, 95% CI 0.63–0.87).¹⁶¹ No significant differences were demonstrated in all-cause and CV death in subgroup analysis of 1892 patients when comparing ACEi and ARB therapy.^{161,162} Furthermore, pilot randomized trials have suggested that mineralocorticoid receptor antagonist add-on therapy, in patients on PD, is associated with an improvement in a number of surrogate markers such as LV mass index and ejection fraction, without a rise in the incidence of hyperkalemia.^{163–165} Therefore, limited evidence suggests that antihypertensive treatment with RAAS blocking agents may be beneficial in PD patients in terms of protecting residual renal function and improving patient outcomes. Adequately powered randomized controlled trials are needed to confirm this and to evaluate hard clinical outcomes.

4 | HOW DO WE DEAL WITH THE UNCERTAINTIES?

There are several uncertainties in the management of hypertension in dialysis patients, most applicable to both HD and PD patients. For a start, which BP measurement should be used to diagnose and guide therapy? Forty-four hour ABPM is considered gold standard, predicts outcomes, but is resource intensive, impractical and not liked by patients. Interdialytic HBPM is close to ABPM in predicting outcomes, but has high attrition rate for long-term monitoring. The use of standardized peri-dialytic BP measurements would be most pragmatic, which underscores the importance of standardized BP measurement in the dialysis unit.

What is the target BP for HD patients? Observational evidence suggests predialysis SBP between 130 and 160–170 mm Hg is associated with best outcome. An adequately powered hard endpoint RCT using ABPM and/or HBPM is required to answer the question, but this may not be practicable for complexity and cost reasons, and this view is supported by the BID trial experience (personal

communication). Should the nephrology community be looking to set up a pragmatic trial using standardized peri-dialytic BP measurements instead? Observational studies using comprehensive, large HD database and more sophisticated modeling techniques may inform design of such a trial.

What is the best approach to controlling BP? "Volume first" approach is supported by most, but clinical assessment of volume status is unreliable. Some of the currently available technologies to aid volume assessment are promising but routine use may not be feasible in all healthcare settings. Two large RCTs currently underway may inform future practice.

What antihypertensive medications should we use? Although the use of antihypertensives appears to be beneficial in dialysis patients, considerable uncertainty remains about choice of antihypertensive agents. Low-quality evidence suggests angiotensin receptor antagonists, calcium channel blockers and beta-blockers might be beneficial. Large hard outcome trials comparing different agents head-to-head are required to answer this, but we wonder whether this would be possible for the reasons already alluded to. Pragmatically, supervised administration of a thrice weekly long-acting beta-blocker such as atenolol could be a useful first-line option, especially where medication adherence is questioned.

Based on the current evidence, and taking into account the practical issues discussed above, we have come up with some suggestions that are captured in Table 1, which we hope the reader will find useful in the day-to-day management of these patients.

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