Consensus Document

Hypertension in dialysis patients: a consensus document by the European Renal and Cardiovascular Medicine (EURECA-m) working group of the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) and the Hypertension and the Kidney working group of the European Society of Hypertension (ESH)*

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In patients with end-stage renal disease treated with hemodialysis or peritoneal dialysis, hypertension is very common and often poorly controlled. Blood pressure (BP) recordings obtained before or after hemodialysis display a J-shaped or U-shaped association with cardiovascular events and survival, but this most likely reflects the low accuracy of these measurements and the peculiar hemodynamic setting related with dialysis treatment. Elevated BP by home or ambulatory BP monitoring is clearly associated with shorter survival. Sodium and volume excess is the prominent mechanism of hypertension in dialysis patients, but other pathways, such as arterial stiffness, activation of the renin–angiotensin–aldosterone and sympathetic nervous systems, endothelial dysfunction, sleep apnea and the use of erythropoietin-stimulating agents may also be involved. Nonpharmacologic interventions targeting sodium and volume excess are fundamental for hypertension control in this population. If BP remains elevated after appropriate treatment of sodium-volume excess, the use of antihypertensive agents is necessary. Drug treatment in the dialysis population should take into consideration the patient's comorbidities and specific characteristics of each agent, such as dialysability. This document is an overview of the

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diagnosis, epidemiology, pathogenesis and treatment of hypertension in patients on dialysis, aiming to offer the renal physician practical recommendations based on current knowledge and expert opinion and to highlight areas for future research.

Keywords: blood pressure, dry-weight, end-stage renal disease, hemodialysis, hypertension, peritoneal dialysis, sodium excess

Abbreviations: ABPM, ambulatory blood pressure monitoring; ACEI, angiotensin-converting enzyme inhibitor; ADMA, asymmetric dimethylarginine; AIx, augmentation index; ALCHEMIST, ALdosterone Antagonist Chronic HEModialysis Interventional Survival Trial; ARB, angiotensin-II receptor blocker; BLOCADE, beta-blocker to LOwer CArdiovascular Dialysis Events study; BP, blood pressure; CAPD, continuous ambulatory peritoneal dialysis; CCB, calcium channel blocker; CI, confidence interval; CKD, chronic kidney disease; CRIC, Chronic Renal Insufficiency Cohort study; DOHAS, Dialysis Outcomes Heart Failure Aldactone Study; DOPPS, Dialysis Outcomes and Practice Patterns Study; DRIP, Dry-Weight Reduction in Hemodialysis Patients study; eGFR, estimated glomerular filtration rate; eNOS, endothelial nitric oxide synthase; ERA-EDTA, European Renal Association – European Dialysis and Transplant Association; ESAs, erythropoietin-stimulating agents; ESH, European Society of Hypertension; ESRD, end-stage renal disease; EURECA-m, European Renal and Cardiovascular Medicine Working Group; FOSIDIAL, Fosinopril in Dialysis study; HDPAL, Hypertension in Hemodialysis Patients Treated with Atenolol or Lisinopril study; HR, hazard ratio; KEEP, Kidney Early Evaluation Program; LUST, Lung Water by Ultra-Sound Guided Treatment to Prevent Death and Cardiovascular Complications in High Risk ESRD Patients with Cardiomyopathy study; LV, left ventricular; LVH, left ventricular hypertrophy; MRA, mineralocorticoid receptor antagonist; NKF-KDOQI, National Kidney Foundation – Kidney Disease Outcomes Quality Initiative; NO, nitric oxide; OCTOPUS, Olmesartan Clinical Trial in Okinawa Patients under Dialysis study; PP, pulse pressure; PRA, plasma renin activity; PWV, pulse wave velocity; RAAS, renin–angiotensin–aldosterone system; rhuEPO, recombinant erythropoietin; RR, relative risk; TonEBP, tonicity-responsive enhancer-binding protein; VEGF, vascular endothelial growth factor

INTRODUCTION

In patients with end-stage renal disease (ESRD) receiving renal replacement therapy with hemodialysis or peritoneal dialysis, hypertension is very common and often inadequately controlled [1]. Elevated blood pressure (BP), particularly when recorded outside of the dialysis unit with home or ambulatory BP monitoring (ABPM), is directly associated with shorter survival [2–4]. Sodium and volume excess appear to be the most important causes of hypertension in dialysis patients; therefore, nonpharmacologic strategies such as dietary sodium restriction, individualized dialysate sodium prescription and gradual dry-weight reduction should be the initial therapeutic approaches to control BP [5,6], but this approach is often not adequately implemented [7,8]. In patients who remain hypertensive after management of sodium and volume excess, pharmacologic therapy is recommended to achieve BP control, taking into account the pharmacologic characteristics of each antihypertensive drug [5,6,9].

This is a document prepared by experts from the European Renal and Cardiovascular Medicine (EURECA-m) working group of the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) and the Hypertension and the Kidney working group of the European Society of Hypertension (ESH). It aims to summarize current knowledge on the diagnosis, epidemiology, pathogenesis and treatment of hypertension in ESRD patients on dialysis. As far as treatment is concerned, we discuss both nonpharmacological and pharmacological strategies to manage hypertension. This document mainly presents the evidence in patients receiving maintenance hemodialysis treatment, because most of the current knowledge derives from studies in this category of patients. Data from the fewer relevant studies in peritoneal dialysis patients are also discussed.

DIAGNOSIS OF HYPERTENSION IN DIALYSIS PATIENTS

According to the 2004 National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines [10], hypertension in hemodialysis patients is diagnosed when predialysis BP is more than 140/90 mmHg or when postdialysis BP is more than 130/80 mmHg, respectively [10]. However, the diagnosis of hypertension using conventional peridialytic BP recordings may be problematic for several reasons [11,12]. Predialysis and postdialysis BPs are recorded by dialysis unit staff often without the necessary attention to the standardization of the technique of BP measurement and the prerequisites for objective office BP recordings [13]. BP measurements pre, during and postdialysis are not made for diagnostic reasons but to exploit a major hemodynamic metric like BP in order to assess cardiovascular stability before, during and immediately after the dialysis procedure. Thus, using these readings to diagnose hypertension, assess the success of antihypertensive treatment or examine future cardiovascular risk is inherently problematic. Several factors may lead to inaccurate BP predialysis and postdialysis readings, such as the white-coat effect, limited time for relaxation – patient impatience to start dialysis and leave the unit quickly – fear or anxiety for correct arteriovenous fistula needling, previous bilateral upper limb attempts of arteriovenous fistulae and unknown validity of most oscillometric devices attached to commercially available hemodialysis machines. Furthermore, truly high BP variability (predialysis to postdialysis and day-by-day variability) in response to fluctuations in volume status and other parameters during the intradialytic and interdialytic periods is another important issue that complicates the accurate diagnosis of hypertension [14]. The typical pattern of hemodynamic response to ultrafiltration is BP decrease from predialysis to postdialysis; the magnitude of intradialytic BP reduction is for the most part related to the

magnitude and the rate of volume withdrawal during dialysis. The converse phenomenon is observed during the interdialytic interval [15], and several studies show that interdialytic weight gain is closely associated with higher predialysis BP [16]. The poor diagnostic accuracy of peridialytic BP recordings is supported by a meta-analysis showing that both predialytic and postdialytic BP readings provide imprecise estimates of the mean interdialytic BP recorded with 44-h ABPM [17]. Furthermore, in comparison with interdialytic BP recordings, peridialytic BP recordings have a weaker prognostic relationship with mortality in hemodialysis patients [2,3,11]. It must be noted that it is not known, whether peridialytic measurements following a standardized technique would exhibit stronger prognostic associations with outcome; preliminary evidence suggest that this is not very likely since even when peridialytic BP is recorded with a standardized protocol it relates poorly to 44-h ABPM values [18].

Due to the reasons described above, the rate of errors in the diagnosis of hypertension when using peridialytic BP measurements is unacceptably high [19]. The proportions of chronic kidney disease (CKD) patients with white-coat and masked hypertension are reported to be around 30 and 7%, respectively, but they are suggested to be much higher in people receiving dialysis [14,20–22]. An alternative can be the use of an average of intradialytic BP measurements, as in one study a median intradialytic cutoff BP of 140/90 mmHg during a mid-week dialysis session provided greater sensitivity and specificity in detecting interdialytic hypertension as compared with predialysis and postdialysis BP measurements [23]. Yet, BP measurements obtained outside of the dialysis unit are still needed to reliably diagnose hypertension among dialysis patients. Home BP monitoring is widely applied and strongly recommended by international guidelines for the diagnosis and management of hypertension in the general population [24]. Compared with BP recordings obtained predialysis or postdialysis, home BP exhibits stronger associations with mean 44-h ambulatory BP [18,20]. In the Dry-Weight Reduction in Hemodialysis Patients (DRIP) trial, changes in home BP after 4 and 8 weeks of dry-weight probing (i.e. supervised gradual dry-weight reduction) were closely associated with the changes in 44-h ambulatory BP; in contrast, predialysis and postdialysis BP recordings failed to detect the changes in ambulatory BP caused in response to dry-weight reduction [25]. Moreover, home BP was shown to have high short-term reproducibility from one week to the next [20] in contrast to the high variability and poor reproducibility of conventional peridialytic BP recordings [14]. Furthermore, home BP exhibits stronger associations with indices of target-organ damage [26–28] and represents a more powerful predictor of future cardiovascular events or all-cause mortality compared with the BP measurements obtained within the dialysis unit [2,3,11]. It is important to note that interdialytic BP recordings maintain their strong prognostic association with cardiovascular outcomes even when a small number (i.e. six) randomly selected measurements are used to assess the interdialytic BP burden [29]; thus, the location and time-frame covered and not the number of BP recordings is the major factor determining the strong prognostic significance of interdialytic ambulatory BP measurements, although the timing of BP recordings may be relevant for reproducibility [30]. The notion that home BP is useful to guide the management of hypertension in dialysis patients is supported by a pilot study that randomized 65 hypertensive hemodialysis patients to have their antihypertensive drug therapy adjusted either on the basis of routine predialytic BP or with home BP monitoring. Over a mean follow-up of 6 months, a significant reduction in interdialytic ambulatory BP of 9/7 mmHg was documented in the home BP-guided group, but not in the predialytic BP-guided group [31]. Similar results were registered in another small randomized trial in hemodialysis patients [32]. One important aspect, however, is for future studies to gather data to provide patients with a precise protocol on when and how often home BP measurements should be performed as it is has been done for hypertensive patients in the general population [31].

Many authors suggest that ABPM is the 'gold-standard' method for diagnosing hypertension in patients receiving dialysis [5,11,33,34]. The superiority of this approach over the conventional peridialytic BP measurements is strongly supported by comparative studies showing that mean 44-h interdialytic BP is more strongly associated with the presence of target-organ damage [such as echocardiographic left ventricular (LV) hypertrophy (LVH)] [26]. In addition, observational studies clearly suggest that ABPM predicts all-cause and cardiovascular mortality better than peridialytic BP [2,4,11]. The use of ABPM has also the advantage of recording BP during night-time, providing additional information on the circadian variation of BP; the presence of a nondipping nocturnal BP pattern is very common among dialysis patients and has been associated with LVH [35] and increased risk of all-cause and cardiovascular mortality [36]. The high prevalence of nondipping and nocturnal hypertension among dialysis patients [12] suggests that the application of ABPM for the diagnosis and the treatment of hypertension is more compelling than in the general population, where ABPM has already been strongly recommended by the an ad-hoc ESH working group [37], NICE guidelines [38] and the US preventive service [39]. The thresholds to define hypertension using home and ABPM [11] are summarized in Table 1. Of note, when neither ABPM nor home BP measurements are applicable in dialysis patients, the diagnosis and the management of hypertension can be made on the basis of office BP measurements taken during the dialysis interval, as a recent study suggested that in contrast to predialysis BP that has a U-shaped relationship with mortality, in the same patients the average of three office measurements (obtained by trained personnel from patients in the sitting position after at least 5 min of quiet rest) is almost linearly related to this risk [40]. The threshold of office BP (140/90 mmHg) recommended by current guidelines for the definition of hypertension in CKD patients [41] can be extended also to hemodialysis patients; it has to be noted, however, that the issue of the optimal BP in CKD is controversial [42] and could be reexamined in the near future in view of recent evidence [43].

Despite the above advantages, ABPM is still perceived as a technique with limited applicability in dialysis patients.

TABLE 1. Diagnosis of hypertension in dialysis patients

Hypertension in dialysis patients should be defined on the basis of home BP or ABPM measurements. Thresholds and methods proposed by the ASH/ASN [5], the EURECA-m working group of ERA-EDTA [11] and the relevant ESH Guidelines [24,41,44] can be used as follows:
Home BP in hemodialysis: An average BP $\geq$ 135/85 mmHg for measurements collected in the morning and in the evening over 6 nondialysis days (covering a period of 2 weeks). Measures should be performed in a quiet room, with the patient in seated position, back and arm supported, after 5 min of rest, and with two measurements per occasion taken 1–2 min apart
Home BP in peritoneal dialysis: an average BP $\geq$ 135/85 mmHg over 7 consecutive days with measurements collected as above
ABPM in hemodialysis: an average BP $\geq$ 130/80 mmHg over 24-h monitoring during a mid-week day free of hemodialysis. Whenever feasible ABPM should be extended to 44-h, that is covering a whole mid-week dialysis interval
ABPM in peritoneal dialysis: an average BP $\geq$ 130/80 mmHg over 24-h monitoring
For hemodialysis patients no recommendation can be made on the basis of predialysis or postdialysis BP. When neither ABPM nor home BP measurements are available in these patients, the diagnosis can be made on the basis of office BP measurements taken in a mid-week day free of hemodialysis, that is the average of three measurements with 1–2 min interval obtained in the sitting position by trained personnel after at least 5 min of quiet rest. The threshold of office BP $\geq$ 140/90 mmHg recommended by current guidelines for the definition of hypertension in CKD patients can be used for hemodialysis patients
For peritoneal dialysis patients office BP $\geq$ 140/90 mmHg obtained as described immediately above can be used for the diagnosis of hypertension

BP, blood pressure; ABPM, ambulatory blood pressure monitoring; ASH, American Society of Hypertension; ASN, American Society of Nephrology; EURECA-m, European Renal and Cardiovascular Medicine working group; ERA-EDTA, European Renal Association-European Dialysis and Transplant Association; ESH, European Society of Hypertension.

This reservation depends partly on the fact that a substantial part of studies using ABPM in dialysis patients were performed in a single American academic hemodialysis unit [2,15,26], but also on the fact that ABPM is believed to be uncomfortable and inconvenient in a group of patients with a high treatment burden, including a high proportion of sleep disturbances, especially when applied for 48 h. Furthermore, accurate ABPM readings could be challenging in patients with bilateral upper limb attempts of arteriovenous fistulae for dialysis access [11,45]. The fact that ABPM is not reimbursed in many countries is another obstacle to its wider use in hemodialysis. However, additional research is needed to define the acceptability of ABPM from the patients' side, the best BP thresholds to define hypertension, which may be different from those of the general population because of the continuous shifts of volume and other factors, the optimum frequency of its use, and the cost-effectiveness of ABPM in the dialysis population. Until ongoing studies investigating these issues will be available, home BP appears as a simpler and more efficient approach to measure BP and make therapeutic decisions in dialysis patients [19].

In contrast to the typical decline in BP during dialysis, in approximately 10–15% of dialysis patients, BP exhibits a 'paradoxical' intradialytic elevation [46,47]. Although this abnormal pattern of intradialytic hemodynamic response has been long recognized, there definition of intradialysis hypertension is still matter of debate. For example, in some studies intradialysis hypertension was defined as a rise of at least 15 mmHg in mean BP during dialysis [48] and in others as a rise of at least 10 mmHg in SBP during dialysis or immediately postdialysis in a certain number (most commonly the last three or four out of the last six) of dialysis treatments [46,47,49,50] or with the use of the regression of all intradialytic BP measurements over time with a slope greater than zero [51]. A case–control study comparing the interdialytic BP profile of 25 patients with intradialysis hypertension with that of 25 age-matched and sex-matched controls with normal intradialytic hemodynamic response [52] made the important observation that intradialysis hypertension is a phenomenon superimposed to background interdialytic hypertension, as patients with intradialysis hypertension had higher 44-h interdialytic BP than controls. Of note, patients with intradialysis hypertension had also a gradual BP decline during the first 24 h after dialysis, which contrasted with the (typical) gradual increase from postdialysis onwards in patients without intradialytic hypertension.

PREVALENCE OF HYPERTENSION IN THE HEMODIALYSIS POPULATION BY THE VARIOUS METRICS AND DEFINITIONS

The estimates of the prevalence, treatment and control of hypertension among patients on chronic dialysis are highly variable. This variability in large part arises from differences in the definitions used to diagnose hypertension and on the setting of BP measurement (i.e. routine peridialytic BP recordings or interdialytic ABPM) in the various studies [1,53–56].

Office or peridialytic blood pressure recordings

Hypertension is highly prevalent among patients with CKD who are not yet on dialysis. In a cross-sectional analysis of 10 813 CKD patients participating in the Kidney Early Evaluation Program in United States of America, hypertension (defined as BP $\geq$ 130/80 mmHg or use of antihypertensive drugs) was detected in 86.2% of the overall study cohort; prevalence of hypertension exhibited a stepwise increase with advancing stage of CKD, increasing to 95.5% (or 91% with the use of 140/90 threshold) in participants with stages 4 and 5 CKD [57]. A study of patients with predialysis CKD followed in a low-clearance clinic [mean estimated glomerular filtration rate (eGFR) 14.5 ml/min per 1.73 m^2] showed again the prevalence of hypertension to be 95% [58], indicating that almost all CKD patients just before the initiation of renal replacement therapy are hypertensive.

Initiation of dialysis may have a substantial impact on management of hypertension, as dialysis represents a potent therapeutic tool to remove sodium and fluid excess and improve BP control. Thus, hypertension prevalence in dialysis patients may appear lower than in those with predialysis CKD. However, hypertension prevalence after initiation of dialysis depends on the clinical policies adopted in each dialysis unit. In some units where long dialysis and strict control of salt intake are prescribed, hypertension has a lower prevalence than in those where such clinical policies are not applied [59]. However, increasing dialysis time to more than 4 h may be not feasible due to a number of factors including limited facility and staff resources, patient preferences and others.

TABLE 2. Prevalence, treatment and control of hypertension in hemodialysis patients

Reference	Year	*N*	Definition of hypertension	Prevalence of hypertension (%)	BP treatment among hypertensive patients (%)	BP control among hypertensive patients (%)
Salem [55]	1995	649	Prehemodialysis MAP $\geq$ 114 mmHg or use of antihypertensive agents	71.9	81.5	48.6
Rahman *et al.* [60]	1999	489	Prehemodialysis SBP $\geq$ 140 mmHg and/or DBP $\geq$ 90 mm	87.7	93.2	71.1
Agarwal *et al.* [1]	2003	2535	1-week average prehemodialysis SBP $>$ 150 mmHg and/or DBP $>$ 85 mmHg, or use of antihypertensive agents	85.8	88.4	30.3
Agarwal [56]	2011	369	44-h interdialytic ambulatory SBP $\geq$ 135 mmHg and/or DBP $\geq$ 85 mmHg or use of antihypertensive medications	82	89	38

MAP, mean arterial pressure.

In epidemiology studies in hemodialysis patients in the United States that used different ways to define hypertension, the prevalence of hypertension ranged between 72 and 88% of the total population studied (Table 2). Despite the high proportion of hypertensive patients using antihypertensive medications, the amount of those that had their BP under control was low in the majority of these studies, that is roughly between 30 and 50% [1,55,60]. Information on hypertension prevalence in dialysis patients in countries other than the United States of America is limited. In studies made within the frame of the Dialysis Outcomes and Practice Patterns Study (DOPPS), the prevalence of hypertension was very high and rising over time in all countries. In the last of these surveys (2011), hypertension prevalence ranged from 78% in Japan to 96% in Germany [61].

Interdialytic ambulatory blood pressure monitoring

When estimated by the 'gold standard' method of 44-h interdialytic ABPM and defining hypertension as average SBP at least 135 mmHg and/or DBP at least 85 mmHg or use of antihypertensive medications the prevalence of hypertension was 82% in a population of 369 predominantly African-American patients who received hemodialysis treatment in units affiliated with an American university [56]. Eighty-nine percent of hypertensive patients were treated with antihypertensive drugs, but the rate of 44-h BP control (i.e. patients with average BP below the above thresholds) was as low as 38% [56]. Poor hypertension control in this study was associated with a higher number of antihypertensive drugs and fluid overload as measured by the inferior vena cava diameter in expiration [62]. Apart from this study in African Americans, no large surveys reporting hypertension prevalence in dialysis patients based on ABPM have been performed in other ethnicities and in other countries to date.

BLOOD PRESSURE AND THE RISK FOR CARDIOVASCULAR EVENTS AND DEATH IN HEMODIALYSIS PATIENTS

The relationship of BP with all-cause and cause-specific mortality in hemodialysis patients is a controversial issue. Several studies have shown that in the BP range (e.g. SBP 110–180 mmHg) in which the event risk increases substantially with BP increase in the general population, there is either no relationship or a U-shaped association of pre or postdialysis SBP and DBP with all-cause and cardiovascular mortality [63–66] a phenomenon described as 'reverse epidemiology of hypertension' in the dialysis population. Some studies suggested that low BP in hemodialysis is associated with early mortality and deaths of primarily noncardiac origin, indicating poor physiological reserve and frailty due to comorbid conditions (i.e. terminal cancer, congestive heart failure) to be the underlying factors of mortality [67]. However, this flat or U-shaped association raised substantial concerns on whether BP-lowering as a whole is a strategy associated with benefits for these patients [68]. More recent observations support that this phenomenon is rather due to the inadequacy of peridialytic BP recordings *per se* to describe the true BP load, than to a true flat or U-shaped relationship of BP with cardiovascular morbidity and mortality. Of note, a study of more than 44 000 hemodialysis patients in the United States suggested postdialysis pulse pressure (PP) to be associated with higher risk of mortality (12% higher risk for every 10 mmHg increase in PP), whereas postdialysis SBP displayed an inverse relationships with risk [69]. In another cohort of 11 142 hemodialysis patients, high postdialysis SBP and low predialysis and postdialysis DBP were associated with mortality, implicating again high PP to be a causal factor [70]. Further to that, a recent analysis in 24 525 patients from the DOPPS study indicated that the U-shape between BP and mortality was mostly observed for SBP (predialysis SBP $<$ 130 mmHg or at least 160 mmHg was associated with higher mortality), but not for DBP, where a higher mortality rate was only observed in patients with predialysis DBP less than 60 mmHg, suggesting that increased PP/arterial stiffness and/or comorbid conditions may be responsible for these associations [71].

In contrast to the unclear association of peridialytic BP recordings with all-cause and cardiovascular mortality, prospective cohort studies have shown that interdialytic BP recorded either by home or ABPM associates more clearly with mortality and cardiovascular events as it is documented in the general population. In a group of 57 treated hypertensive hemodialysis patients prospectively followed for a mean period of 34.4 $\pm$ 20.4 months, Amar *et al.* [4] showed elevated 24-h ambulatory PP [relative risk (RR): 1.85 for each 10 mmHg increase in PP; 95%

confidence intervals (CIs): 1.28–2.65] as well as elevated nocturnal SBP (RR: 1.41 for each 10 mmHg increase in nocturnal SBP; 95% CIs: 1.08–1.84) to be independently associated with increased risk of cardiovascular mortality. In a larger study by Tripepi *et al.* [36], in 168 nondiabetic hemodialysis patients, nocturnal BP burden (as estimated by the night/day ratio) was a direct predictor of a surrogate endpoint such as LVH, as well as of cardiovascular events and death. A clear association between average interdialysis BP as measured by home BP or ABPM and mortality was described by Alborzi *et al.* [3] in a cohort of 150 hemodialysis patients, whereas no such relationship was evident for predialysis BP measurements (Fig. 1). In the largest study performed so far, undertaken in 326 mainly African-American patients, patients in the higher quartiles of home and 44-h ambulatory SBP exhibited an excessive risk of mortality that was independent of other risk factors over 32 months of follow-up [2].

Additional support to the notion that interdialytic BP recordings have closer association with outcomes is provided by a recent prospective analysis of patients participating in the Chronic Renal Insufficiency Cohort study [40]. The prognostic association of SBP with all-cause mortality was assessed at three different time-points in this prospective cohort: (i) when participants had stage 4 CKD (eGFR < 30 ml/min per 1.73 m^2); (ii) when participants initiated hemodialysis and dialysis-unit BP measurements were available; (iii) when incident hemodialysis patients had an out-of-dialysis BP measurement obtained during a prespecified follow-up visit at home. SBP had no association with mortality among participants not yet on dialysis. In accordance with earlier reports from other cohorts of hemodialysis patients, dialysis-unit SBP provided a U-shaped association with mortality. In contrast, a direct linear association between SBP and all-cause mortality was evident when BP measurements were obtained outside the unit [hazard ratio: 1.26 for each 10 mmHg higher SBP; 95% CI: 1.14–1.40] [40].

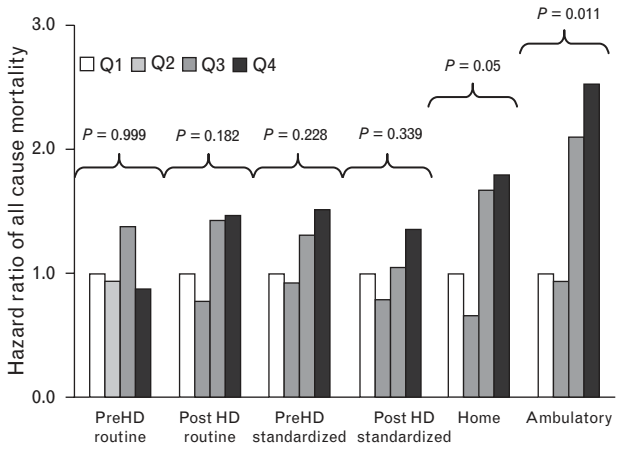

FIGURE 1 Hazard ratios for all-cause mortality for quartiles of predialysis, postdialysis, home and ambulatory SBP. Higher levels of home blood pressure and ambulatory blood pressure were significantly associated with mortality, whereas predialysis and postdialysis blood pressure was not. *P* values are those reported for linear trend. HD, hemodialysis; and Q, quartile. Reproduced with permission [3].

EPIDEMIOLOGY OF HYPERTENSION IN PATIENTS TREATED WITH PERITONEAL DIALYSIS

The prevalence of hypertension among patients on peritoneal dialysis was evaluated in a cross-sectional study conducted in 504 patients in 27 peritoneal dialysis centers of the Italian Co-operative Peritoneal Dialysis Study Group [72]. Valid ambulatory BP measurements were obtained in 414 patients (82%). Using the WHO/ISH 1999 definition of hypertension (SBP ≥ 140 or DBP ≥ 90 mmHg, or use of antihypertensive treatment), the prevalence of hypertension was 88%. When hypertension was defined using a BP load of more than 30% of values more than 140/90 at daytime or more than 120/80 at night-time during 24-h ABPM, the estimated prevalence of hypertension was lower (69%); however, the actual ability of BP load to identify a hypertension condition has been questioned [37]. The average 24-h BP in this study was $139 \pm 19/81 \pm 11$ mmHg, mmHg, suggesting again that if the currently proposed definition of average SBP ≥ 135 and/or DBP ≥ 85 mmHg in ABPM or antihypertensive treatment [5] was used instead, hypertension prevalence would also exceed 70–80% [72]. Of note, 53% of patients in this study were nondippers, and an additional 9% were reverse-dippers. Small studies comparing the ambulatory BP profile between patients treated with automated peritoneal dialysis vs continuous ambulatory peritoneal dialysis (CAPD) showed that the average 24-h BP did not differ between the treatment modalities [73,74]. Other studies have described an association between BP and peritoneal transport status; patients with high peritoneal transport (reflecting poor peritoneal ultrafiltration) have higher BP levels during both daytime and night-time periods as well as higher LV mass index compared with 'low transporters', and this difference most likely reflects volume overload triggered by high peritoneal transport and subsequent decreased ultrafiltration capacity in the first group [75]. Volume overload is frequently more marked in peritoneal dialysis than in hemodialysis patients [76], and these patients require antihypertensive drugs more frequently (65%) than hemodialysis patients (38%, $P < 0.001$). The detrimental role of volume excess in patients maintained for too long on peritoneal dialysis is well described [77]. In this regard, a strict volume control policy could reduce the need of antihypertensive medication also in peritoneal dialysis patients.

Given the more continuous nature of renal replacement therapy and the absence of cyclic variations in volume status and in several other metabolic parameters in patients receiving peritoneal dialysis, it has been hypothesized that BP control and BP diurnal variation may be substantially different between patients treated with peritoneal dialysis or hemodialysis. However, only two studies tested this so far. One [75] compared the 44-h BP profile of 22 hemodialysis patients with that of 24 patients treated with CAPD. Mean 44-h SBP and DBP was no different between the two dialytic modalities; however, in hemodialysis night-time BP recorded on the dialysis-off day was significantly higher and daytime BP recorded on the dialysis-on day was significantly lower than in CAPD patients [75]. Another

study including 33 hemodialysis and 27 peritoneal dialysis patients showed that diurnal BP pattern (i.e. dipping status) did not differ between the two modalities over an approximately 48-h BP recording, but average ambulatory SBP (142.1 ± 16.3 vs 130.4 ± 17.1 mmHg, $P < 0.01$) and SBP loads (54 ± 29 vs $30 \pm 31\%$, $P < 0.01$) were higher in those receiving hemodialysis [78]. Overall, the above studies are small and largely inconclusive however, and methodologically rigorous comparisons between hemodialysis and peritoneal dialysis are missing and seem rather unfeasible.

PATHOPHYSIOLOGY OF HYPERTENSION IN DIALYSIS PATIENTS

Increase in cardiac output (*CO*), peripheral vascular resistance or both may result in sustained BP elevation among patients on dialysis. Undoubtedly, sodium and volume overload are considered the prominent pathogenic mechanisms. A number of nonvolume mediated pathways, such as activation of the renin–angiotensin–aldosterone and sympathetic nervous systems, structural arterial wall alterations related to the long-term arteriosclerotic process, endothelial dysfunction, inflammation, sleep apnea and use of particular medications like erythropoietin-stimulating agents, are also reported to play an important role in the complex pathogenesis of hypertension in these individuals (Table 3) [79].

Volume overload

In patients with ESRD, even when residual renal function is preserved, the sodium and fluid excretory capacity is substantially impaired. Thus, sodium retention and volume overload is very common and often not easily identifiable. Moreover, ESRD patients have the highest sodium-sensitivity of BP [80,81]. It is now well documented that in addition to classical osmotic volume expansion, sodium retention may occur in the form of osmotically inactive sodium in the connective tissue and the skin where sodium accumulates linked to glycosaminoglycans [82]. Nonosmotic sodium retention triggers local macrophage recruitment; macrophages sense the hypertonic electrolyte accumulation in skin, and activate the tonicity-responsive enhancer-binding protein (TonEBP) to initiate secretion of vascular endothelial growth factor (VEGF), which enhances electrolyte clearance via cutaneous lymph vessels and increases endothelial nitric oxide (NO) synthase (eNOS) expression in blood vessels. Deletion of TonEBP in monocytes or blockade of lymph-endothelial VEGF receptor inhibit lymphogenesis, promote endothelial dysfunction and increase BP in mice in response to salt loading [83], that is promote hypertension with mechanisms different of those traditionally ascribed to iso-osmotic retention. In hemodialysis patients, sodium and water in skin and muscle are increased, and VEGF is reduced as compared with age-matched healthy individuals; these phenomena may also contribute to hypertension [84]. Due to sodium and fluid accumulation, BP steadily increases in proportion to weight gain during the interdialytic interval, a phenomenon superimposed on BP circadian variation [85]. The interdialysis increase in BP is not limited to brachial BP but extends to other critical hemodynamic parameters like aortic BP [86], and the peripheral and central BP burden is accentuated during the long dialysis interval (Fig. 2), again in proportion to fluid overload [87,88]. Until fluid and sodium overload is removed during dialysis, a rise in peripheral vascular resistance will sustain hypertension in these individuals.

TABLE 3. Main pathogenic mechanisms of hypertension in dialysis patients

Sodium and volume overload
Increased arterial stiffness
Activation of the sympathetic nervous system
Activation of the renin–angiotensin–aldosterone system
Endothelial dysfunction (i.e. imbalance between endothelium-derived vasodilators and vasoconstrictors)
High prevalence of sleep apnea
Use of recombinant erythropoietins (rhuEPOs)

Arterial stiffness increase

Patients with ESRD display premature increase in arterial stiffness, due to a combination of factors, mainly as a result of disturbed calcium–phosphate homeostasis [89]. In dialysis, arterial stiffness, assessed by aortic pulse wave velocity (PWV), determines the patterns and rhythms of BP recorded over the interdialytic period [89–91]. Agarwal *et al.* analyzed 11 833 interdialytic BP measurements from 125 hemodialysis patients and showed that log of PWV was related to BP in a linear relationship (each log increase in PWV was associated with 20.3, 7.2 and 12.8-mmHg increases in SBP, DBP and PP, respectively). Increasing PWV also blunted the circadian amplitude of SBP and PP [90]. In a post-hoc analysis of the Hypertension in Hemodialysis Patients Treated with Atenolol or Lisinopril (HDPAL) trial [91], each 1-m/s higher baseline aortic PWV was associated with 1.34 mmHg higher 44-h ambulatory SBP and 1.02 mmHg higher PP but did not predict the treatment-induced reduction in ambulatory SBP and DBP during follow-up. A study evaluating acute changes in arterial stiffness indexes during the interdialytic periods showed that augmentation index (AIx) and central PP is increased during both 3-day and 2-day interdialytic

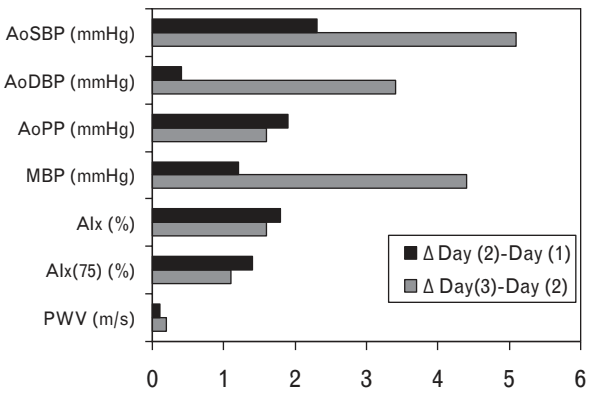

FIGURE 2 Changes in aortic blood pressures, wave reflections and arterial stiffness parameters between the first and the second interdialytic day Δ[Day(2) – Day(1)], in comparison with relevant changes between the second and the third interdialytic day Δ[Day(3) – Day(2)]. AoSBP, aortic systolic blood pressure; AoDBP, aortic diastolic blood pressure; AoPP, aortic pulse pressure; AIx, augmentation index; AIx(75), heart rate-adjusted AIx; PWV, pulse wave velocity. Reprinted with permission [87].

intervals; aortic and brachial PWV was unchanged in these short time-frames. The increase in AIx was 30% greater during the 3-day than during the 2-day interval and was associated with interdialytic weight gain [88]. Subsequent studies with ABPM recordings from the same group further confirmed the above, showing a continuous increase in wave reflection indices and central BP in both the 2-day and 3-day interdialytic intervals with minimal increase in PWV [86,87].

Sympathetic nervous system activation

Seminal microneurography studies suggested that sympathetic overactivity is an important cause of hypertension in ESRD, showing efferent sympathetic discharge rate to be doubled in hemodialysis patients with in-situ native kidneys but normal in hemodialysis patients after bilateral nephrectomy [92]. Bilateral nephrectomy of native failed kidneys produced sustained reductions in peripheral vascular resistance and dramatic BP decrease [93]. This pathogenetic role of sympathetic overactivity is also supported by recent observations where renal denervation substantially reduced BP in small series of hemodialysis patients with severe resistant hypertension [94,95]. Deficiency of renalase, an enzyme produced by the kidney that metabolizes catecholamines and catecholamine-like substances may contribute to excessive sympathetic overactivity in CKD [96,97]. Infusion of recombinant renalase in rats produced a significant reduction in BP, predominantly mediated through reduced peripheral vascular tone and *CO* [97]. The plasma concentration of renalase is markedly decreased in hemodialysis patients as compared with age-matched and sex-matched controls with normal renal function [98].

Renin–angiotensin–aldosterone system activation

It is well known that activation of the renin–angiotensin–aldosterone-system occurs even in ESRD patients on renal replacement therapy [99,100]. Plasma renin activity (PRA) is maintained within the normal range in the majority of patients but may be inappropriately elevated in relation to the total exchangeable sodium and may contribute to BP elevation [101]. This is supported by clinical studies showing a significant increase in PRA and plasma aldosterone from predialysis to postdialysis, suggesting that residual functioning nephrons in dialysis patients retain their ability to sense acute changes in sodium intravascular volume status in response to ultrafiltration [99,101]. Earlier studies showed the angiotensin II antagonist saralasin to lower BP in dialysis [102]; the angiotensin-converting enzyme inhibitor (ACEI) lisinopril was recently shown to reduce 44-h ambulatory BP [103]. The relationship between PRA, aldosterone and major clinical outcomes in dialysis patients is complex and much influenced by malnutrition and inflammation. Independently of predialysis BP, aldosterone is an inverse predictor of cardiovascular events and mortality in this population, and this seemingly paradoxical relationship is abolished by adjustment for inflammation, protein energy malnutrition and volume expansion biomarkers indicating that it is merely the expression of the confounding effect of these factors [104,105].

Endothelial dysfunction

An imbalance between endothelium-derived vasodilators and vasoconstrictors may also be involved in hypertension among dialysis patients. Endothelial dysfunction results from several mechanisms. Animal studies document a down-regulation of the endothelial and inducible NO synthase activity in rats with 5/6 nephrectomy, an alteration that resulted in sustained BP elevation [106]. Patients with CKD also show markedly reduced NO availability, measured as NO-dependent vasodilation [107]. This could be due to reduced production of NO [108], although others describe enhanced NO production in these patients [109]. Increased generation of reactive oxygen species in CKD may cause enhanced breakdown of [110]. Alterations in pteridine metabolism have also been described in chronic renal failure, which may lead to reduced BH4 availability and eNOS uncoupling [111]. High circulating levels of asymmetric dimethylarginine (ADMA) [112,113], an endogenous NO synthase inhibitor, accumulates in CKD and results in reduced generation of NO [114]. The higher levels of ADMA in ESRD result from both a diminished intracellular degradation by desamino-D-argininehydrolase and diminished renal clearance of ADMA [114]. Among ESRD patients, ADMA is associated with increased LV relative wall thickness and reduced ejection fraction. Importantly, prospective cohort studies have associated increased ADMA levels with excessive risk of cardiovascular morbidity and mortality in hemodialysis patients [112,114].

Sleep apnea

Sleep apnea is highly prevalent among dialysis patients, and volume overload may be a major player in this alteration [115]. In the recumbent position, volume overload may promote sleep-disordered breathing and nocturnal hypoxemia through an overnight fluid shift from the legs to the neck soft tissues that increases peripharyngeal and upper airway resistance [116]. Nocturnal hypoxemia in sleep apnea has been associated with a reversed circadian BP pattern, triggering in this way nocturnal hypertension. This notion is supported by a study of 32 hemodialysis patients showing that those patients experiencing sleep apnea had higher nocturnal SBP and higher LV relative wall thickness than those without sleep apnea; an inverse relationship was documented between the average nocturnal arterial oxygen saturation and LV relative wall thickness [35]. In another study, Abdel-Kader *et al.* [117] showed that ESRD patients with sleep apnea had 7.1 times higher risk of developing resistant hypertension (defined as office BP > 140/90 mmHg despite the use of >three different antihypertensive agents); in contrast, no such association between sleep apnea and resistant hypertension was noted among nondialysis-requiring CKD patients [117]. Finally, a recent study in hemodialysis patients with obstructive sleep apnea showed that after hemodialysis the obstructive apnea–hypopnea index was significantly improved only in the group of patients with a concomitant reduction of fluid overload [116]. It remains to be demonstrated whether strict management of volume status restores the blunted nocturnal BP fall in dialysis patients.

Erythropoietin-stimulating agents

Hypertension is a common but frequently overlooked complication of erythropoietin therapy [118]. Hypertension induced by recombinant erythropoietin treatment may depend on increased circulating endothelin-1 or enhanced vasoconstrictive response to endothelin-1 [119,120], increased sensitivity to the pressor effect of angiotensin II [121], increased blood viscosity and increased vascular sensitivity to noradrenergic stimuli [122]. Higher erythropoietin doses [123], higher target hemoglobin (Hb) levels [124], route of administration (intravenous vs subcutaneous) [125] and dialysis modality (hemodialysis vs peritoneal dialysis) [126,127] have all been associated with a higher BP response [128].

Secondary causes of hypertension in dialysis patients

Apart from ESRD and the inability to maintain normal sodium and water homeostasis, practicing nephrologists should not forget that a few patients with hypertension who remain resistant to treatment may have other secondary causes of hypertension that should be adequately sought for and treated [129,130]. The prevalence and incidence of these disorders can resemble that of the general population, with some exceptions. For example, renovascular disease is rather unlikely to cause hypertension in anuric patients with long dialysis vintage, but it should be looked for in patients with heavy atherosclerotic burden, recent dialysis start and residual diuresis. Similarly, primary aldosteronism is unlikely to cause severe hypertension in anuric patients, as the renal action of aldosterone in maintaining sodium would be absent, but it should be kept in mind for patients with abrupt hypertension and hypokalemia immediately after kidney transplantation [131]. Obstructive sleep apnea is particularly common in ESRD patients and is discussed in detail above. Less frequent secondary causes like pheocromocytoma, thyroid diseases, renin-secreting tumors and others should be carefully sought for in selected patients with relevant signs and symptoms and treated appropriately.

HYPERTENSION TREATMENT IN DIALYSIS PATIENTS

Nonpharmacological measures

Management of hypertension in dialysis patients should focus at correction of the primary pathogenetic mechanism, that is sodium and volume excess, by carefully implementing a series of nonpharmacological measures to achieve the dry-weight for each individual patient and to avoid intradialytic sodium loading (Table 4). Particular care needs to be given to the fact that when renal replacement therapy is initiated, 95% of patients are already hypertensive, and the vast majority are receiving antihypertensive agents [73]. This and the fact that common antihypertensive agents may be prescribed for other indications (i.e. β-blockers for angina symptoms, heart failure or rate control, renin–angiotensin system (RAS) blockers for heart failure etc.) need to be taken into account and guide careful handling of antihypertensive drugs when dry-weight is pursued. However, outside the situation of a hypertensive urgency or emergency [7], administration of antihypertensive drug therapy in dialysis patients considered to be volume overloaded should follow the attainment of dry-weight.

TABLE 4. Main nonpharmacological measures to reduce sodium and volume overload in hemodialysis patients

Achievement of individual patient's dry weight
Minimization of inter and intradialytic sodium gain
Restriction of sodium intake to less than 65 mmol (1.5 g of sodium or 4 g of sodium chloride) per day
Decreasing dialysate sodium toward predialysis sodium in selected individuals
Avoidance of sodium-containing or sodium-exchanging drugs
Avoidance of short (i.e. <4 h) dialysis duration

Achievement of patient's dry-weight

Achievement of dry-weight in dialysis patients remains a complex issue of clinical judgment [132]. Absence of a widely accepted definition of dry-weight and reliance of definitions on subjective patient symptoms rather than objective estimations are problems known to practicing nephrologists. Sinha and Agarwal [133] defined dry-weight as the lowest tolerated postdialysis weight achieved through gentle and gradual reduction in postdialysis weight at which patients experience minimal signs or symptoms of either hypovolemia or hypervolemia [133]. Typically, there are no reliable clinical signs indicating whether a patient has reached the 'ideal' dry-weight. The degree of pedal edema which is frequently used as a reference in dialysis patients was not found to be associated with more objective indices reflecting intravascular volume, such as inferior vena cava diameter, blood volume monitoring or plasma volume biomarkers [134]. In a recent subproject of the ongoing Lung Water by Ultra-Sound Guided Treatment to Prevent Death and Cardiovascular Complications in High Risk ESRD Patients with Cardiomyopathy (LUST) trial, both pedal edema and crackles in lung auscultation of hemodialysis patients reflected very poorly the degree of pulmonary congestion objectively assessed by lung ultrasound [135]. Bioimpedance methods and relative blood volume monitoring are increasingly used to assess whole body fluid status in dialysis patients [136]; a combination of these methods with lung ultrasound may provide a more precise estimate of fluid accumulation in critical organs and, thus, help towards objective definition of dry-weight [137].

Previous uncontrolled observations in small series of patients [138–140] suggested that supervised gradual reduction (probing) of dry-weight can effectively reduce BP. The DRIP was the first randomized trial to test this hypothesis by assigning 150 hemodialysis patients with hypertension in a 2 : 1 ratio to an intensive ultrafiltration group, in which the dry-weight was probed without increasing the frequency or duration of dialysis and to a control group, without modification of volume status [141]. In the ultrafiltration group, an initial additional weight loss of 0.1/10-kg body weight was prescribed. If ultrafiltration was not tolerated on the basis of symptoms and signs, such as muscle cramps, need for excessive saline, or symptomatic hypotension, the additional prescribed weight loss was reduced by 50% until 0.2-kg incremental weight loss per dialysis was not tolerated. The primary trial endpoint was the difference between the ultrafiltration and control

groups in the change of 44-h interdialytic ambulatory BP, which was performed at baseline, 4 and 8 weeks. Postdialysis weight was reduced by 0.9 kg at 4 weeks and resulted in an average difference of 7.4/3.6 mmHg in 44-h interdialytic ambulatory BP between the two groups. The overall dry-weight reduction achieved at study completion was 1 kg and associated with a difference of 7.1/3.8 mmHg [141]. This benefit was seen without any deterioration in parameters of health-related quality of life [141] and with a parallel reduction in LV chamber volume [142]. Of importance, in DRIP background antihypertensive treatment of study participants remained unchanged throughout the trial (with an average of 2.7 drugs), indicating that dry-weight reduction can be beneficial even in treated patients. The ongoing LUST trial is a multicenter randomized study within the frame of ERA-EDTA comparing the effect of dry-weight probing guided by lung ultrasound scheme vs standard clinical practice on cardiovascular events in hemodialysis patients [143]; a LUST substudy on ambulatory BP is awaited to shed further light in the field.

In accordance with hemodialysis, achieving better volume control in patients on peritoneal dialysis may help toward BP normalization. A small, open-label randomized study lasting 12 months showed that compared with standard glucose peritoneal dialysis solutions, the use of icodextrin solution as an osmotic agent is associated with greater reduction in systolic 24-h ambulatory BP in diabetic patients with high-average and high peritoneal transport type [111]. However, in a larger randomized trial comparing a glucose-sparing regimen that included icodextrin with standard glucose peritoneal dialysis solutions in diabetic patients, despite significant improvement in glycated Hb and lipid parameters, deaths and serious adverse events, including those related to volume expansion, increased in the glucose-sparing group [144]. Thus, the optimal way to achieve dry-weight in peritoneal dialysis patients remains to be defined.

Benefits on BP control by intensification of ultrafiltration in the absence of prolonging dialysis time may be counterbalanced by higher risk of intradialytic hypotension, loss of residual renal function, hospitalizations for cardiovascular complications and arteriovenous fistula clotting [5,145]. High ultrafiltration rates increase the risk of dialysis hypotension, and in one observational study, ultrafiltration rates greater than 12.4 ml/kg per h were associated with increased mortality [146]. Other uncomfortable symptoms apart from hypotension, such as cramps, nausea and vomiting, may also affect patients quality of life and interfere with the process of reaching dry-weight. Physicians often respond inappropriately to these symptoms with therapeutic interventions, which may have the exact opposite results to what is intended, such as cessation of ultrafiltration, hypertonic sodium infusions, increasing the dialysate sodium concentration, premature termination of dialysis or finally raising the dry-weight and subsequently increasing the number of prescribed antihypertensive medications (Table 5) [5,147,148]. Overall, dry-weight may be more easily and safely achieved in multiple sessions or by prolonging the dialysis time to achieve a slower ultrafiltration rate, as discussed below.

TABLE 5. Barriers towards achievement of dry weight in hemodialysis patients with hypertension

Difficulty to objectively assess dry weight
Fear of patient symptoms (intradialytic hypotension, muscle cramps, nausea and vomiting)
Risk of complications (cardiovascular events, arteriovenous access loss)
Physician and nurse inertia/ease of prescribing a new drug vs the complex procedure of dry weight probing
Absence of patient education on dietary sodium restriction/misguided emphasis in fluid restriction
Low patient compliance with sodium restriction/high interdialytic weight gain
Use of sodium containing medications
Inappropriate dialysate sodium
Use of high ultrafiltration rates
Short dialysis sessions
Concomitant diseases (heart failure, autonomic dysfunction)
Use of high number of antihypertensive agents
Use of 'fast and easy' solutions to treat intradialytic hypotension (i.e. cessation of ultrafiltration, hypertonic sodium infusions, increasing dialysate sodium concentration, premature termination of dialysis)

Minimization of interdialytic and intradialytic sodium gain

As discussed above, in ESRD patients the sodium and fluid excretory capacity is either absent or substantially impaired and BP is typically salt-sensitive. Thus, reducing the amount of sodium gained from diet or dialysate fluid is critical to achieve BP control. In a cohort study of 1770 hemodialysis patients, high reported dietary sodium (expressed as raw intake, in proportion to caloric intake, or in proportion to potassium intake) was associated with greater mortality; of note, in adjusted analysis reported sodium intake displayed a linear association with mortality, starting from the lowest examined levels of 0.5 g/day [149]. Dietary sodium restriction appears to be an effective approach to limit the sense of thirst, reduce interdialytic weight gain and facilitate the achievement of dry-weight and BP control [150]. Observational data suggest that dietary sodium restriction and achievement of dry-weight are associated with improvement of BP, LVH and less episodes of intradialytic hypotension compared with antihypertensive treatment [139,151]. It has to be noted that in Western countries with frequent consumption of ready meals and processed foods, reducing the amount of sodium intake may be a complex challenge requiring important lifestyle changes. Instead of dietary sodium restriction, patients on dialysis are often instructed to avoid excess fluid intake during the interdialytic interval; fluid restriction without concomitant sodium restriction is not supported by evidence and is frequently not feasible due to increased thirst [152]. Hypertension guidelines suggest that dietary sodium in any hypertensive patient should be reduced to less than 100 mmol (2.4 g of sodium or 6 g of sodium chloride) per day [41,153]. The effect of salt restriction on BP is typically more pronounced in salt-sensitive individuals, like those with CKD; thus in dialysis patients, dietary sodium intake should not exceed 65 mmol (1.5 g of sodium or 4 g of sodium chloride). In addition, a subset of patients may gain sodium due to use of particular medications, such as potassium-binders exchanging sodium, sodium bicarbonate to increase predialysis bicarbonate levels or drug formulations containing sodium (i.e. effervescent tablets); whenever possible avoidance of such agents is also useful.

In parallel to dietary sodium restriction, avoidance of inappropriate sodium gain during dialysis is also crucial towards effective BP control. Prescription of a high dialysate sodium concentration was common in the early days of dialysis, to ensure hemodynamic stability and minimize other intradialytic symptoms (i.e. disequilibrium symptoms, nausea, vomiting, muscle cramps etc.). This was supported by older studies showing that high dialysate sodium may minimize the incidence of intradialytic hypotensive episodes without worsening interdialytic hypertension [154,155]. However, more recent works challenged these conclusions and emphasized that a high-dialysate sodium concentration may increase thirst and interdialytic weight gain [147,156]. In a study in 1084 hemodialysis patients, Munoz Mendoza *et al*. [157] found that dialysate sodium prescriptions ranged from 136 to 149 (median, 140) mEq/l and that most patients were dialysed against a positive sodium gradient resulting in over 90% of patients having a rise in serum sodium across dialysis and, consequently higher postdialysis thirst and interdialysis weight gain. This increase in interdialytic weight gain leads to a need for greater ultrafiltration during the next dialysis session, which may act as a triggering factor for more frequent episodes of intradialytic hypotension and prescription of even higher dialysate sodium concentration, precipitating in this way a vicious cycle [104,105]. A consensus document by the Chief Medical Officers of US Dialysis Providers warns against the use of dialysate with a sodium concentration exceeding predialysis serum sodium [147,156].

A single-blind, randomized, crossover study comparing the effect of nine sessions of a standard dialysate sodium concentration (138 mEq/l) to nine sessions of individualized prescription of the dialysate sodium concentration (the dialysate sodium set to match patient's average predialysis sodium multiplied by 0.95 to allow for the Gibbs–Donnan effect) in nondiabetic, non-hypotension-prone dialysis patients documented a benefit of individualized sodium prescription on intradialytic weight gain, thirst and episodes of intradialytic BP fall. Among patients with uncontrolled BP at baseline, predialysis BP was by 16 mmHg lower during the individualized sodium dialysate period [158]. In a subsequent single-blind, crossover study receiving thrice-weekly in-center, nocturnal dialysis, lowering the dialysate sodium concentration from 140 to 136 or 134 mEq/l for a 12-week treatment period decreased interdialytic weight gain by 0.6 ± 0.6 kg and predialysis SBP by 8.3 ± 14.9 mmHg without increasing intradialytic hypotensive episodes [159]. In a 3-week randomized, crossover trial in 16 patients with intradialytic hypertension, Inrig *et al*. [50] compared the effect of a high (5 mEq/l above serum sodium) vs low (5 mEq/l below serum sodium) dialysate sodium concentration on intradialytic BP and endothelial-derived vasoregulators. The weekly averaged predialysis SBP was lower during the period of low dialysate sodium concentration (−9.9 mmHg; 95% CI: −13.3 to −6.4 mmHg; $P < 0.001$), as was the weekly average intradialytic SBP (−6.1 mmHg; 95% CI, −9.0 to −3.2 mmHg; $P < 0.001$) (Fig. 3) [50]. Overall these studies suggest that a single dialysate sodium prescription may not fit all patients. Small decreases in dialysate sodium towards predialysis levels in hypertensive patients can limit thirst, reduce intradialytic weight gain and improve BP control without aggravating the risk of intradialytic hemodynamic instability. Larger randomized trials are needed to evaluate the safety and efficacy of this approach.

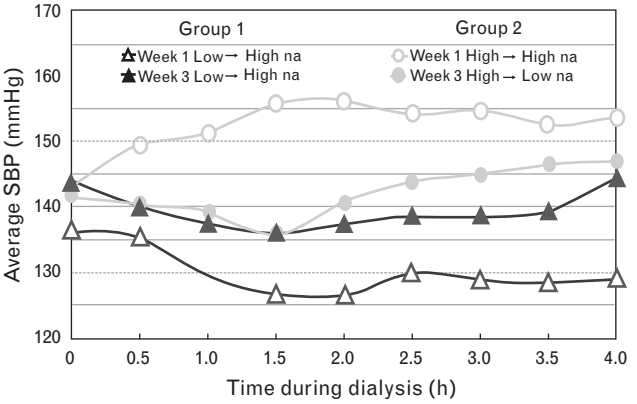

FIGURE 3 Weekly average intradialytic SBP during hemodialysis with low and high dialysate sodium by randomization sequence (Group 1: low-then-high dialysate Na) and (Group 2: high-then-low dialysate Na); $P < 0.001$ by adjusted mixed linear regression. Reprinted with permission [50].

In peritoneal dialysis patients, increasing the diffusive component of sodium removal with the use of low-sodium peritoneal dialysis fluids is suggested to be an effective intervention to improve BP control. In a nonrandomized interventional study comparing a standard vs a low-sodium peritoneal dialysis solution substituting one 3–5-h exchange per day over a mean follow-up period of 2 months, the use of low-sodium dialysate resulted in a significant increase of 30–50 mmol/dwell diffusive peritoneal sodium removal that was accompanied by reduced thirst, lower total body water and an 8-mmHg fall of in night-time SBP [160]. Overall, patients on peritoneal dialysis should also follow the above recommendations for restriction of sodium intake; modifications on peritoneal dialysis regimen with low-sodium or icodextrin solutions may facilitate sodium and volume control.

Avoiding short dialysis

Among several other potential hazards, short delivered dialysis can be an important barrier to the achievement of adequate BP control. The European Best Practice guidelines recommend that the length of the dialysis session must not be decided only on the grounds of optimal Kt/V and that hemodialysis patients should receive at least three dialysis sessions of 4 h each, per week [161], a recommendation aiming mainly to ensure optimal volume status. Exception to this could be incident dialysis patients with substantial residual renal function or patients who started dialysis early during the evolution of their CKD; these specific subgroups of dialysis patients may be able to maintain the homeostasis of volume and metabolic parameters over a longer dialysis-free interval [161–164]. However, real world data deriving from registries throughout the globe suggest that the reality is different and although the mean dialysis session length may be around 210–235 min, some patients may receive dialysis for shorter times; this is particularly relevant for United States of

America, where as much as 25% of patients may dialyse for less than 3 h and 15 min per session [165–167].

Increasing the duration of dialysis may represent an additional approach to control BP among dialysis patients who remain hypertensive despite the intensification of volume withdrawal or experience frequent episodes of intradialytic hemodynamic instability during this intensification process within their usual dialysis regimen [168]. A previous crossover study of 38 dialysis patients comparing the frequency of intradialytic symptoms during 5 vs 4-h dialysis sessions showed that the incidence of intradialytic hypotension and postdialysis orthostatic hypotension was shown to be less common during the period of extended-time dialysis [169]. This notion is supported by a post-hoc analysis of the DRIP trial [126], in which median intradialytic SBP at baseline and its change over time were modeled against the duration of delivered dialysis. At baseline, median intradialytic SBP was higher with fewer hours of delivered dialysis. Among patients in whom dry-weight was not reduced (control group), median intradialytic SBP followed an increasing trend over the course of the trial. In the ultrafiltration group, dry-weight reduction induced a significant drop in median intradialytic SBP regardless of the duration of delivered dialysis. However, patients with longer delivered dialysis required fewer dialysis sessions to gain the BP-lowering benefit of dry-weight reduction. A similar beneficial relationship was evident between the duration of delivered dialysis and the magnitude of change in 44-h interdialytic ambulatory SBP over time [126].

The fact that avoiding short dialysis may facilitate BP control is also supported by several other randomized and nonrandomized studies showing that patients assigned to longer (i.e. up to 8-h thrice weekly) or more frequent (i.e. up to six times per week) dialysis regimens achieve better BP control with reduced requirements for antihypertensive medications. This benefit is possibly mediated through better correction of sodium and volume excess [168,170–172].

Of note, a recent long-term, observational posttrial analysis of patients who took part into the Daily in-center Trial of the Frequent Hemodialysis Network [173] showed a lower risk of death in patients originally randomized to frequent hemodialysis of six times a week and 1.5–2.75 h/session (16%) as compared with those randomized to conventional hemodialysis treatment (28%). This benefit, however, was not evident in the long-term analysis of the twin Nocturnal Trial of the same network, in which mortality was largely increased in the frequent hemodialysis group (6 times a week >6 h/session) [174]; of note, the most prominent difference between groups in the main Nocturnal Trial seemed to be the faster loss of residual diuresis in the frequent dialysis arm [175]. Although a careful interpretation is necessary, current evidence rather suggests that longer or frequent hemodialysis schemes may be beneficial, but the combination of both longer and frequent treatment is not.

Pharmacological treatment

The effects of β-blockers, ACEIs, angiotensin-II receptor blockers (ARBs), calcium channel blockers (CCBs) and mineralocorticoid receptor antagonists (MRAs) on hard outcomes in hemodialysis patients have been examined in clinical trials (Table 6). Two previous meta-analyses of randomized trials clearly suggest that BP-lowering with the use of such antihypertensive drugs is associated with reduced cardiovascular morbidity and mortality in dialysis patients [176,177]. The first meta-analysis included eight trials incorporating data from 1697 dialysis patients and 495 cardiovascular events [177]. The weighted mean difference in the change of BP between the active-treatment and control groups was −4.5 mmHg for SBP and −2.3 mmHg for DBP. This BP-lowering effect of antihypertensive drug treatment was associated with 29% reduction in the risk of all-cause mortality (pooled RR: 0.71; 95% CIs: 0.55–0.92) and 29% reduction in the risk of cardiovascular mortality (pooled RR: 0.71; 95% CIs: 0.50–0.99) [177]. The second meta-analysis [176] included five randomized trials with 1202 study participants. Compared with placebo or control therapy, the overall cardiovascular benefit of BP-lowering with antihypertensive therapy was a 31% reduction in the risk of future cardiovascular events (pooled hazard ratio: 0.69; 95% CIs: 0.56–0.84) [176]. In a subanalysis according to the hypertension status of patients participating in the individual studies, it was shown that cardiovascular protection provided by BP-lowering was less pronounced when normotensive patients were included in the analysis (pooled hazard ratio: 0.86; 95% CIs: 0.67–1.12) [176]. These meta-analyses indicate that the use of antihypertensive drugs in dialysis patients may afford cardiovascular protection both in hypertensive patients and in normotensive patients with LV systolic dysfunction [176].

The major antihypertensive drug classes are useful for pharmacological treatment of hypertension in dialysis, taking into account the specific pharmacologic properties of each drug [5,9,178,179]. Exception may be diuretics, which are ineffective for BP control in patients with ESRD [5,178,179]. Echocardiographic studies conducted in anuric hemodialysis patients showed that intravenous

TABLE 6. Antihypertensive drugs in outcome clinical trials in hemodialysis patients

β-Blockers
Carvedilol reduced mortality compared to placebo in HD patients with dilated cardiomyopathy [187]
Thrice-weekly atenolol reduced cardiovascular events compared to thrice-weekly lisinopril in HD patients with hypertension and LVH in the HDPAL trial [188]
ACE-inhibitors
Fosinopril did not reduce cardiovascular events and mortality compared to placebo in HD patients with LVH in the FOSIDIAL trial [192]
ARBs
Losartan/valsartan/candesartan reduced cardiovascular events and mortality compared to treatment not including ACEIs/ARBs in HD patients [193,194]
Olmesartan did not reduce cardiovascular events or mortality compared to treatment not including ACEIs/ARBs in HD patients with hypertension in the OCTOPUS trial [195]
Calcium channel blockers
Amlodipine reduced cardiovascular events compared to placebo in HD patients with hypertension [198]
MRAs
Spironolactone may reduce cardiovascular events and mortality compared to no additional treatment or placebo in HD and PD patients [201,202]

HDPAL, Hypertension in Hemodialysis Patients Treated with Atenolol or Lisinopril trial; FOSIDIAL, Fosinopril in Dialysis trial; OCTOPUS, Olmesartan Clinical Trial in Okinawa Patients under Dialysis Study; MRA, mineralocorticoid receptor antagonist.

administration of loop diuretics, even at high doses, exerts only minimal alterations in central hemodynamic indices [180]. Given the high risk of ototoxicity, the use of loop diuretics in anuric dialysis patients should be avoided. Several small studies suggest that these compounds may help patients with preserved residual diuresis on hemodialysis or peritoneal dialysis to enhance urine output and limit fluid overload [181–184], however the effect of loop diuretics on urine output and BP control has not been properly examined in large studies.

β-Blockers

Sympathetic overactivity as measured by plasma norepinephrine is a powerful predictor of death and cardiovascular events in dialysis patients [185]. The susceptibility of dialysis patients to serious arrhythmias and sudden death along with the excessive activation of the sympathetic nervous system make β-blockers an attractive therapeutic option toward cardiovascular protection in this population [178]. Interestingly, in an analysis of the DOPPS study, use of β-blockers was associated with a lower risk of sudden death, after adjustment for comorbidities (hazard ratio, 0.88; 95% CI, 0.78–0.99; $P = 0.03$) [186]. In 114 hemodialysis patients with dilated cardiomyopathy randomized to carvedilol (up to 25 mg twice daily) or placebo for 2 years, carvedilol improved LV systolic function and significantly reduced the risk of all-cause hospitalization (hazard ratio: 0.44; 95% CI: 0.25–0.77) and all-cause mortality (hazard ratio: 0.51; 95% CI: 0.32–0.82) [187]. More recently, the HDPAL trial [188] performed a head-to-head comparison between the β-blocker atenolol and the ACEI lisinopril (both administered in a thrice-weekly regimen immediately postdialysis) in 200 hypertensive hemodialysis patients with echocardiographically documented LV hypertrophy. The trial showed that the LV mass index over the 12-month follow-up (the primary outcome) improved to a similar extent in the atenolol and lisinopril groups [188]. However, atenolol was shown to be superior to lisinopril in terms of its BP-lowering efficacy; in particular, no significant differences in BP were noted between the two groups, but lisinopril-treated patients had always numerically higher BP levels (Fig. 4) and required more aggressive volume management during dialysis and administration of higher number of antihypertensive drugs as add-on therapy to achieve the prespecified home BP target of 140/90 mmHg. Most importantly, the HDPAL trial was terminated early due to superiority of atenolol over lisinopril for the prevention of serious cardiovascular events, as the rate of the combined outcome of myocardial infarction, stroke, hospitalized heart failure and cardiovascular death was 2.29 times higher in lisinopril-treated than in atenolol-treated patients (incidence rate ratio: 2.29; 95% CI: 1.07–5.21) [188].

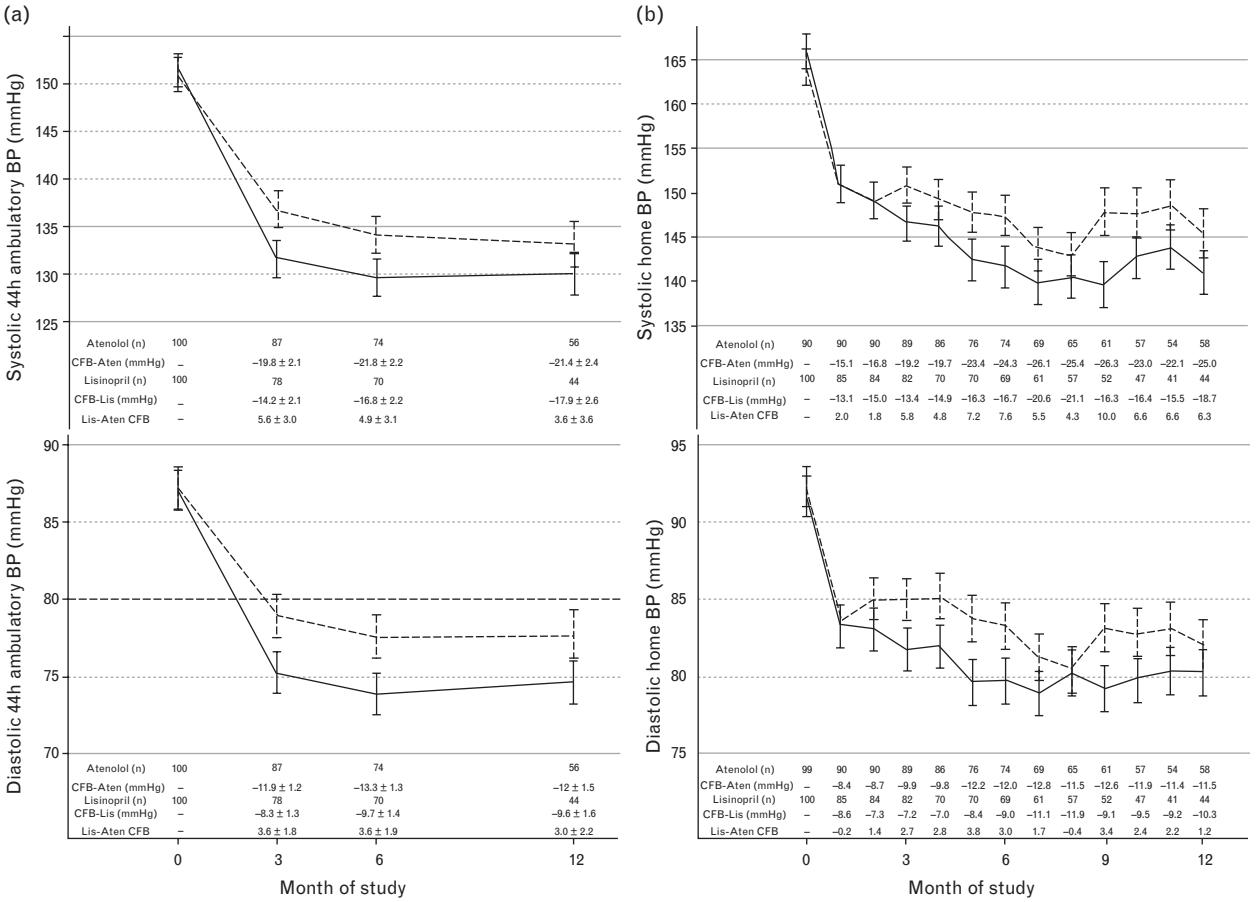

FIGURE 4 Blood pressure measured by 44-h ambulatory blood pressure monitoring over the interdialytic period (a) and self-measured by the patients at home (b) in the Hypertension in Hemodialysis Patients Treated with Atenolol or Lisinopril trial. Dotted lines: lisinopril group, solid lines: atenolol group. Reprinted with permission [188].

The beta-blocker to LOwer CArdiovascular Dialysis Events trial originally planned to study the cardioprotective role of β-blockade in hemodialysis patients. In the feasibility study, aiming to enroll 150 patients, among 1443 patients screened (including 176 who were already on treatment with beta-blockers), only 354 were eligible, 91 consented and 72 entered the 6-week active-treatment run-in period. Of these, only 49 participants (68%, 95% CI: 57–79%) tolerated carvedilol therapy (6.25 mg twice daily) during the run-in and progressed to randomization [189]. The challenging recruitment in this study emphasizes the difficulties of performing clinical studies in dialysis patients.

Pilot data by Inrig *et al.* [190] suggest that carvedilol may be useful in patients with intradialytic hypertension; these authors showed that carvedilol treatment in these patients was associated with an improvement in endothelium-dependent flow-mediated vasodilatation; this effect was accompanied by reduced occurrence of intradialytic hypertensive episodes during follow-up and with a significant drop of 7 mmHg in 44-h interdialytic ambulatory SBP. Of importance, when prescribing a β-blocker in a hemodialysis patient, one needs to take into account that there are major differences in renal clearance and dialysability between different agents of this class, as discussed in detail elsewhere [6]. Use of nondialysable β-blockers is advisable, as a recent retrospective cohort study suggest that a survival advantage may not be offered by highly dialysable β-blockers, possibly due to lack of intradialytic protection against arrhythmias due to rapid removal with dialysis [191].

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

Blockers of the RAS are among the most widely used antihypertensive agents worldwide. Of note, ACEIs and ARBs are not interchangeable for dialysis patients, as there are important differences between in their renal clearance and removal during dialysis [6,9]; most ARBs are not dialysed during conventional dialysis and may be preferred in these patients for sustained BP reduction. Through extrapolation of the cardiovascular benefits of RAS-blockers in the general population, inhibition of the RAS was often recommended as first-line BP-lowering therapy for dialysis patients [41]. However, randomized trials in hypertensive dialysis patients do not support that RAS-blockade offers the same benefits as in hypertensive patients in the general population.

In the Fosinopril in Dialysis trial [192], 397 hemodialysis patients were randomized to receive the ACEI fosinopril (titrated up to 20 mg/day) or placebo for a mean follow-up period of 48 months. Participating patients had per protocol LV hypertrophy but were not necessarily hypertensive. Although therapy with fosinopril resulted in a significant reduction of predialysis BP vs placebo in the subgroup of hypertensive participants, occurrence of fatal and nonfatal cardiovascular events during the follow-up period did not significantly differ between the active-treatment and placebo arms (RR: 0.93; 95% CIs: 0.68–1.26) [192].

Three trials [193–195], all performed in Japan, compared ARBs to either placebo or active therapy. In two of these trials (including 80 and 360 hemodialysis patients, respectively), the risk of cardiovascular events was remarkably lower in patients treated with ARBs. In the third study, which was also the largest to date, the Olmesartan Clinical Trial in Okinawa Patients under Dialysis Study [195], 469 hypertensive hemodialysis patients were randomized to the ARB olmesartan (10–40 mg/day) or control therapy not including ACEIs or ARBs. Over a mean follow-up of 3.5 years, and for similar BP control, incidence of all-cause death, nonfatal stroke, MI and coronary revascularization was similar in the olmesartan and control groups (hazard ratio: 1.00; 95% CI: 0.71–1.40) [195], suggesting that antihypertensive treatment *per se* and not the use of a RAS-blocker is rather the factor reducing cardiovascular risk. A meta-analytical estimate of the risk reduction by ARBs in these trials (which included around 900 patients and 175 deaths) showed a nonsignificant ($P = 0.10$) 42% risk reduction [196]. Overall, to date a superiority of ACEIs and ARBs over other antihypertensive drugs has not been demonstrated in dialysis patients and antihypertensive treatment *per se* rather than the use of a RAS-blocker seems the factor reducing cardiovascular risk.

Calcium-channel blockers

Dihydropyridine CCBs are potent antihypertensive agents that can effectively lower BP, even in the volume-expanded state [197], and are often used for management of hypertension in dialysis patients. In the only relevant study examining hard outcomes, Tepel *et al.* [198] randomized 251 hypertensive hemodialysis patients to receive amlodipine (5–10 mg/day) or placebo for 30 months. Amlodipine insignificantly improved survival as compared with placebo and reduced by 47% the composite secondary endpoint of all-cause death, nonfatal stroke, MI, coronary revascularization and angioplasty for peripheral vascular disease (hazard ratio: 0.53; 95% CI: 0.31–0.93) [198]. Small previous studies suggested that dihydropyridine CCBs are equally effective with ACEIs or ARBs in reducing LV hypertrophy and carotid intima–media thickness [199]. Data on non-dihydropyridine CCB use in hemodialysis patients are scarce; using these agents should at least follow the recommendations for the general population. It must be noted that all CCBs are practically not removed during standard hemodialysis, and their pharmacokinetics are unchanged in ESRD; thus, they can be dosed once-daily in these patients [6,9].

Mineralocorticoid-receptor antagonists

A cardioprotective action of MRAs in dialysis patients has solid biological underpinnings [200], and two recent trials (Table 7) [201,202] apparently support the contention that these drugs may provide substantial benefits in dialysis patients. In the Dialysis Outcomes Heart Failure Aldactone Study, 309 oligoanuric hemodialysis patients were randomized to spironolactone (25 mg/day) or no add-on therapy for 3 years. Spironolactone reduced the risk of cardiovascular mortality or cardiovascular-related hospitalization (hazard ratio: 0.38; 95% CI: 0.17–0.83), with the incidence of drug discontinuation due to serious hyperkalemia being 1.9% and due to adverse effects overall being 14.6% [201]. In another study, 253 hemodialysis or peritoneal dialysis

TABLE 7. Recent randomized studies trials on the effect of mineralocorticoid receptor antagonism on cardiovascular outcomes in hemodialysis patients

Reference	Patient characteristics	*N*	Design	Follow-up	BP medication	BP assessment	Baseline BP (mmHg)	Final BP (mmHg)	Main finding
Matsumoto *et al.* [201]	Oligoanuric HD patients	157 vs 152	Open-label RCT	36 months	Spironolactone vs Nothing	Predialysis BP	152.8/77.8 vs 148.8/76.2	152.7/77.9 vs n/a	Spironolactone reduced the risk of death or hospitalization for CV event (HR: 0.38; 95% CI: 0.17–0.83)
Lin *et al.* [202]	HD or PD patients without CHF	125 vs 128	Open-label RCT	24 months	Spironolactone vs Placebo	Predialysis BP	144.7/76.9 vs 141.9/77.4	n/a n/a	Spironolactone reduced the risk of CV death, sudden death or aborted cardiac arrest (HR: 0.42; 95% CI: 0.26–0.78)

BP, blood pressure; CHF, congestive heart failure; CI, confidence intervals; CV, cardiovascular; HD, hemodialysis; HR, hazard ratio; LVH, left-ventricular hypertrophy; n/a, not applicable; PD, peritoneal dialysis; RCT, randomized clinical trial.

patients without heart failure were randomized to 2-year-long add-on therapy with spironolactone (25 mg/day) or placebo. Add-on MRA therapy again reduced the occurrence of the composite primary endpoint of cardio-cerebrovascular mortality and mitigated the risk for cardiac arrest and sudden death (hazard ratio: 0.42; 95% CI: 0.26–0.78) [202]. The reduction in the risk of adverse clinical outcomes in these trials exceeded 50%, that is it was apparently superior to the effect of frequent in center hemodialysis on the combined end-point of death and LVH progression [170]; this was largely unexpected in a population like the ESRD population that is notoriously less sensitive to interventions aimed at reducing death and cardiovascular events than other patients populations [203]. It has to be noted, however, that these results should be further confirmed, as both the above studies were open-label. The safety profile of MRAs in the dialysis population was investigated in a recent study, in which 146 hemodialysis patients were randomly assigned to eplerenone (25–50 mg daily) or matching placebo for 13 weeks [204]. Eplerenone treatment significantly increased the incidence of hyperkalemia (defined as predialysis serum potassium >6.5 mmol/l) as compared with placebo (RR: 4.50; 95% CI: 1.0–20.2) [204], but permanent drug discontinuation due to hyperkalemia or hypotension, which was the primary study endpoint, was no different between eplerenone and placebo groups [204]. Adequately powered, properly designed studies, like the ongoing ALCHEMIST [205] (ALdosterone Antagonist Chronic HEModialysis Interventional Survival Trial; NCT01848639), are needed to assess the effectiveness and safety of mineralocorticoid receptor blockade in ESRD, before recommending the wider use of MRAs in this population.

TABLE 8. Areas in the field of hypertension in dialysis patients where future research efforts are needed

Epidemiology
Validation studies of devices used for BP recording during dialysis
Studies testing the applicability and tolerance of ambulatory BP monitoring and the availability of patients for repeated measurements over time
Studies using home or ambulatory BP monitoring to define the true burden of hypertension in HD and PD patients
Comparative studies using office, home and ambulatory BP monitoring to further delineate their predictive power for cardiovascular events and death
Randomized clinical trials with different BP targets to objectively identify targets for treatment
Pathophysiology
Human studies to delineate the interplay between established mechanisms (e.g. between variations on volume and sodium load and changes in other mechanisms) and to uncover novel pathogenic pathways
Studies to define novel, objective tools to measure volume overload
Treatment
Further clinical trials on the effect of nonpharmacologic interventions (i.e. dry weight reduction based on objective tools – e.g. the LUST study [143] – restriction of dietary sodium based on objective dietary instruments, increased duration of dialysis, etc.) on home or ambulatory BP control and hard outcomes
Further clinical trials on the effect of pharmacologic interventions (i.e. a head-to-head comparison of everyday use of β-blocker vs ACEI/ARB or CCB, a proper placebo-controlled trial with an MRA, etc.) on home or ambulatory BP control and hard outcomes

LUST, Lung Water by Ultra-Sound Guided Treatment to Prevent Death and Cardiovascular Complications in High Risk ESRD Patients with Cardiomyopathy study.

CONCLUSION

Hypertension in dialysis patients poses almost unique diagnostic, prognostic and therapeutic challenges. Evolution of studies using home or ABPM are currently needed to better define the true burden of hypertension in hemodialysis and peritoneal dialysis patients, to provide solid data on hypertension prevalence and prognostic associations and to identify objective thresholds for diagnosis and targets for treatment. Nonpharmacologic interventions targeting sodium and volume excess are fundamental towards BP reduction in this population and should be carefully implemented before pharmacological interventions. Among dialysis patients, BP-lowering with the use of antihypertensive agents is associated with improvement in cardiovascular outcomes; the use of β-blockers followed by dihydropyridine CCBs should be considered. The first-line use of ACEIs and ARBs in this population is not supported by randomized trials. Further, properly designed epidemiology studies and clinical trials to define BP targets for treatment and examine the efficacy of nonpharmacologic measures to reduce BP and antihypertensive drugs in the prevention of major cardiovascular outcomes in the ESRD population remain a public health priority (Table 8).

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Conflicts of interest

R.A. has consulted for Abbvie, Amgen, Astra Zeneca, Bayer, Boehringer Ingelheim, Celgene, Daiichi Sankyo Inc, Eli Lilly, Gilead, GlaxoSmithkline, Johnson & Johnson, Merck, Novartis, Sandoz, Relypsa and ZS Pharma. The remaining authors report no conflict of interest relevant to this work.

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