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Full Review

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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ABSTRACT

In patients with end-stage renal disease (ESRD) treated with haemodialysis or peritoneal dialysis, hypertension is common and often poorly controlled. Blood pressure (BP) recordings obtained before or after haemodialysis display a J- or U-shaped association with cardiovascular events and survival, but this most likely reflects the low accuracy of these measurements and the peculiar haemodynamic setting related to dialysis treatment. Elevated BP detected 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 apnoea and the use of erythropoietin-stimulating agents may also be involved. Non-pharmacologic interventions targeting sodium and volume excess are fundamental for hypertension control in this population. If BP remains elevated after appropriate treatment of sodium and 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 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, end-stage renal disease, haemodialysis, hypertension, peritoneal dialysis

INTRODUCTION

In patients with end-stage renal disease (ESRD) receiving renal replacement therapy with haemodialysis 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, 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, non-pharmacologic 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, pharmacological 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 in 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 non-pharmacological and pharmacological strategies to manage hypertension. This document mainly presents evidence from patients receiving maintenance haemodialysis treatment, because most of the current knowledge is derived from studies of this category of patients. Data from the few relevant studies concerning 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 haemodialysis patients is diagnosed when pre-dialysis BP is >140/90 mmHg or when post-dialysis BP is >130/80 mmHg [10]. However, the diagnosis of hypertension using conventional peridialytic BP recordings may be problematic for several reasons [11, 12]. Pre- and post-dialysis 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 post-dialysis are not made for diagnostic reasons but to exploit a major haemodynamic 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 pre- and post-dialysis 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 the unknown validity of most oscillometric devices attached to commercially available haemodialysis machines. Furthermore, truly high BP variability (pre- to post-dialysis and day by day variability) in response to fluctuations in volume status and other parameters during the

intra- and interdialytic periods is another important issue that complicates the accurate diagnosis of hypertension [14]. The typical pattern of haemodynamic response to ultrafiltration is BP decrease from pre- to post-dialysis; the magnitude of intradialytic BP reduction is, for the most part, related to the magnitude and 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 pre-dialysis BP [16]. The poor diagnostic accuracy of peridialytic BP recordings is supported by a meta-analysis showing that both pre- and post-dialytic BP readings provide imprecise estimates of the mean interdialytic BP recorded with 44-h ambulatory BP monitoring (ABPM) [17]. Furthermore, in comparison with interdialytic BP recordings, peridialytic BP recordings have a weaker prognostic relationship with mortality in haemodialysis 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 suggests 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 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; in one study, a median intradialytic cut-off BP of 140/90 mmHg during a mid-week dialysis session provided greater sensitivity and specificity in detecting interdialytic hypertension compared with pre- and post-dialysis BP measurements [23]. Yet, BP measurements obtained outside of dialysis units are still needed to reliably diagnose hypertension among dialysis patients. Home BP monitoring is widely applied and is strongly recommended by international guidelines for the diagnosis and management of hypertension in the general population [24]. Compared with BP recordings obtained pre- or post-dialysis, home BP exhibits stronger associations with mean 44-h ambulatory BP [18, 20]. In the Dry-Weight Reduction in Haemodialysis 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 changes in 44-h ambulatory BP; in contrast, pre- and post-dialysis 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 dialysis units [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 haemodialysis patients to have their antihypertensive drug therapy adjusted either on the basis of routine pre-dialytic 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 pre-dialytic BP-guided group [31]. Similar results were registered in another small randomized trial in haemodialysis patients [32]. However, one important aspect is for future studies to gather data in order to provide patients with a precise protocol on when and how often home BP measurements should be performed, as 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 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 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 also has the advantage of recording BP during the night, providing additional information on the circadian variation of BP; the presence of a non-dipping 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 non-dipping and nocturnal hypertension among dialysis patients [12] suggests that the application of ABPM for the diagnosis and treatment of hypertension is more compelling than in the general population, where ABPM has already been strongly recommended by an *ad hoc* ESH working group [37], NICE guidelines [38] and the US preventive service [39]. The thresholds to define hypertension using home and ambulatory BP monitoring [11] are summarized in Box 1. Of note, when neither ABPM nor home BP measurements are applicable in dialysis patients, the diagnosis and management of hypertension can be made on the basis of office BP measurements taken during the interdialytic interval, as a recent study suggested that, in contrast to pre-dialysis BP, which 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 [42]. The threshold of office BP (140/90 mmHg) recommended by current guidelines for the definition of hypertension in CKD patients [43] can also be extended to haemodialysis patients; however, it has to be noted that the issue of the optimal BP in CKD is controversial [43] and could be re-examined in the near future in view of recent evidence [44].

Box 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, 40, 41] can be used as follows:

- **Home BP in haemodialysis: an average BP ≥135/85 mmHg for measurements collected in the morning and in the evening over 6 non-dialysis 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 ≥135/85 mmHg over 7 consecutive days with measurements collected as above.**
- **ABPM in haemodialysis: an average BP ≥130/80 mmHg over 24-h monitoring during a mid-week day free of haemodialysis. 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 ≥130/80 mmHg over 24-h monitoring.**
- **For haemodialysis patients, no recommendation can be made on the basis of pre- or post-dialysis 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 haemodialysis, that is, the average of three measurements with 1–2 min intervals obtained in the sitting position by trained personnel after at least 5 min of quiet rest. The threshold of office BP ≥140/90 mmHg recommended by current guidelines for the definition of hypertension in CKD patients can be used for haemodialysis patients.**
- **For peritoneal dialysis patients, office BP ≥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.

Despite the above advantages, ABPM is still perceived as a technique with limited applicability in dialysis patients. This reservation is partly due to the fact that a substantial number of the studies using ABPM in dialysis patients conducted to date were performed in a single American academic haemodialysis unit [2, 15, 26], but also to 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 haemodialysis. However, additional research is needed to define the acceptability of ABPM from the patients', 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 become available, home BP monitoring appears to be 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 ~10–15% of dialysis patients, BP exhibits a 'paradoxical' intradialytic elevation [46, 47]. Although this abnormal pattern of intradialytic haemodynamic response has been long recognized, the exact definition of intradialysis hypertension is still a matter of debate. For example, in some studies, intradialysis hypertension is defined as a rise of at least 15 mmHg in mean BP during dialysis [48], while others define it as a rise of at least 10 mmHg in systolic BP (SBP) during dialysis or immediately post-dialysis 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 that compared the interdialytic BP profile of 25 patients with intradialysis hypertension with that of 25 age- and sex-matched controls with normal intradialytic haemodynamic response [52] made the important observation that intradialysis hypertension is a phenomenon superimposed upon background interdialytic hypertension, as patients with intradialysis hypertension had higher 44-h interdialytic BP than controls. Of note, patients with intradialysis hypertension also had a gradual BP decline during the first 24 h after dialysis, which contrasted with the (typical) gradual increase from post-dialysis onwards in patients without intradialytic hypertension.

FULL REVIEW

PREVALENCE OF HYPERTENSION IN THE HAEMODIALYSIS 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 arises, in large part, from differences in the definitions used to diagnose hypertension and in the setting of BP measurement (i.e. routine peridialytic BP recordings or interdialytic ABPM) in various studies [1, 53–56].

Office or peridialytic BP 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 Programme in the USA, hypertension (defined as BP ≥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 a 140/90 threshold) in participants with stage 4 and 5 CKD [57]. A study of patients with pre-dialysis CKD that were followed in a low-clearance clinic [mean estimated glomerular filtration rate (eGFR) 14.5 mL/min/1.73 m^2] similarly showed the prevalence of hypertension to be 95% [58], indicating that almost all CKD patients are hypertensive just before the initiation of renal replacement therapy.

Initiation of dialysis may have a substantial impact on the management of hypertension, as dialysis represents a potent

Table 1. Prevalence, treatment and control of hypertension in haemodialysis patients

Author	Year	*N*	Definition of hypertension	Prevalence of hypertension (%)	BP treatment among hypertensives (%)	BP control among hypertensives (%)
Salem [55]	1995	649	Pre-haemodialysis MAP ≥114 mmHg or use of antihypertensive agents	71.9	81.5	48.6
Rahman *et al.* [60]	1999	489	Pre-haemodialysis SBP ≥140 mmHg and/or DBP ≥90 mm	87.7	93.2	71.1
Agarwal *et al.* [1]	2003	2535	1-week average pre-haemodialysis 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 ≥135 mmHg and/or DBP ≥85 mmHg or use of antihypertensive medications	82	89	38

BP, MAP, blood pressure; MAP, mean arterial pressure; SBP, diastolic blood pressure; DBP, systolic blood pressure.

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 pre-dialysis 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 >4 h may be not feasible due to a number of factors, including limited facility and staff resources, patient preferences and others.

In epidemiology studies in haemodialysis patients in the USA that used different ways to define hypertension, the prevalence of hypertension ranged between 72 and 88% of the total population studied (Table 1). 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 USA is limited. In studies made within the framework of the Dialysis Outcomes and Practice Patterns Study (DOPPS), the prevalence of hypertension was very high and rose 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 BP monitoring

When estimated by the 'gold standard' method of 44-h interdialytic ABPM, with hypertension defined as average SBP ≥135 mmHg and/or diastolic BP (DBP) ≥85 mmHg or the use of antihypertensive medications, the prevalence of hypertension was 82% in a population of 369 predominantly African American patients who received haemodialysis treatment in units affiliated with an American university [56]. Eighty-nine percent of hypertensives 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 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 countries to date.

BP AND THE RISK FOR CARDIOVASCULAR EVENTS AND DEATH IN HAEMODIALYSIS PATIENTS

The relationship of BP with all-cause and cause-specific mortality in haemodialysis patients is a controversial issue. Several studies have shown that in the BP range (i.e. 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 post-dialysis 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 haemodialysis is associated with early mortality and deaths of primarily non-cardiac origin, indicating poor physiological reserve and frailty due to comorbid conditions (e.g. terminal cancer or congestive heart failure) to be the underlying factors of mortality [67]. However, this flat or U-shaped association raised substantial concerns about whether BP-lowering, as a whole, is a strategy associated with benefits for these patients [68]. More recent observations support that this phenomenon is due to the inadequacy of peridialytic BP recordings *per se* to describe the true BP load, rather than a true flat or U-shaped relationship of BP with cardiovascular morbidity and mortality. Of note, a study of more than 44 000 haemodialysis patients in the USA suggested post-dialysis pulse pressure (PP) to be associated with higher risk of mortality (12% higher risk for every 10 mmHg increase in PP), whereas post-dialysis SBP displayed an inverse relationship with risk [69]. In another cohort of 11 142 haemodialysis patients, high post-dialysis SBP and low pre- and post-dialysis DBP were associated with mortality, again implicating high PP as a causal factor [70]. Further to that, a recent analysis of 24 525 patients from the DOPPS study indicated that the U-shape between BP and mortality was

mostly observed for SBP (pre-dialysis SBP <130 mmHg or ≥160 mmHg was associated with higher mortality), but not for DBP, where a higher mortality rate was only observed in patients with pre-dialysis DBP <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 at home or by ABPM associates more clearly with mortality and cardiovascular events, as it is also documented for the general population. In a group of 57 treated hypertensive haemodialysis patients prospectively followed for a mean period of 34.4 ± 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 interval (95% CI): 1.28–2.65], as well as elevated nocturnal SBP (RR: 1.41 for each 10 mmHg increase in nocturnal SBP; 95% CI: 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 non-diabetic haemodialysis patients, nocturnal BP burden (as estimated by the night/day ratio) was a direct predictor of a surrogate end point 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.* in a cohort of 150 haemodialysis patients, while no such relationship was evident for pre-dialysis BP measurements (Figure 1) [3]. 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, which was independent of other risk factors over 32 months of follow-up [2].

Additional support for 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 [42]. 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/1.73 m^2); (ii) when participants-initiated haemodialysis and dialysis-unit BP measurements were available; and (iii) when incident haemodialysis patients had an out-of-dialysis BP measurement obtained during a pre-specified 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 haemodialysis 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 (HR): 1.26 for each 10 mmHg higher SBP; 95% CI: 1.14–1.40] [42].

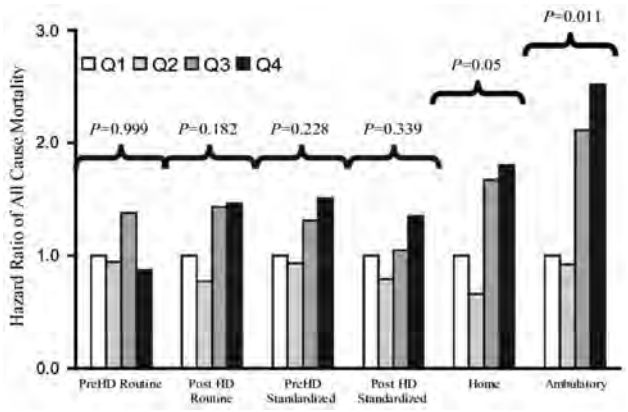

FIGURE 1: Hazard ratios for all-cause mortality for quartiles of pre-dialysis, post-dialysis, home and ambulatory systolic blood pressure (BP). Higher levels of home BP and ambulatory BP were significantly associated with mortality, whereas pre- and post-dialysis BP was not. P-values are those reported for linear trend. HD, haemodialysis; Q, quartile. Reproduced with permission from Alborzi *et al.* [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 on 504 patients in 27 peritoneal dialysis centres of the Italian Cooperative 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 >30% of values >140/90 at day-time or >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 hypertensive condition has been questioned [37]. The average 24-h BP in this study was 139 ± 19/81 ± 11 mmHg, again suggesting 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 non-dippers and an additional 9% were reverse-dippers. Small studies comparing the ambulatory BP profile between patients treated with automated peritoneal dialysis versus continuous ambulatory peritoneal dialysis 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 day-time and night-time periods, as well as higher left ventricular (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 haemodialysis patients [76] and these patients require antihypertensive drugs more frequently (65%) than haemodialysis 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 for antihypertensive medication in peritoneal dialysis patients.

Given the more continuous nature of renal replacement therapy and the absence of cyclic variations in volume status and several other metabolic parameters in patients receiving peritoneal dialysis, it has been hypothesized that BP control and BP diurnal variation may differ substantially between patients treated with peritoneal dialysis or haemodialysis. However, only two studies have tested this to date. One [75] compared the 44-h BP profile of 22 haemodialysis patients with that of 24 patients treated with continuous ambulatory peritoneal dialysis. Mean 44-h SBP and DBP was no different between the two dialytic modalities; however, in haemodialysis patients, night-time BP recorded on the dialysis-off day was significantly higher and day-time BP recorded on the dialysis-on day was significantly lower than in continuous ambulatory peritoneal dialysis patients [75]. Another study, including 33 haemodialysis and 27 peritoneal dialysis patients, showed that diurnal BP pattern (i.e. dipping status) did not differ between the two modalities over a ~48-h BP recording period, but that average ambulatory SBP (142.1 ± 16.3 versus 130.4 ± 17.1 mmHg; $P < 0.01$) and SBP loads ($54 \pm 29\%$ versus $30 \pm 31\%$; $P < 0.01$) were higher in those receiving haemodialysis [78]. Overall, the above studies are small and largely inconclusive; methodologically rigorous comparisons between haemodialysis and peritoneal dialysis patients are missing and seem rather unfeasible.

FULL REVIEW

PATHOPHYSIOLOGY OF HYPERTENSION IN DIALYSIS PATIENTS

Increase in cardiac output, 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 non-volume 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 apnoea 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 (Box 2) [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 skin, where sodium accumulates linked to glycosaminoglycans [82]. Non-osmotic sodium retention triggers local macrophage recruitment; macrophages sense the hypertonic electrolyte accumulation in the skin and activate the tonicity-responsive enhancer-binding protein to initiate the secretion of vascular endothelial growth factor (VEGF), which enhances electrolyte clearance via cutaneous lymph vessels and increases endothelial nitric oxide (NO) synthase expression in blood vessels. Deletion of tonicity-responsive enhancer-binding protein in monocytes or blockade of lymph–endothelial VEGF receptor inhibits lymphogenesis, promotes endothelial dysfunction and increases BP in mice in response to salt loading [83]; that is, hypertension is promoted by mechanisms different to those traditionally ascribed to iso-osmotic retention. In haemodialysis patients, sodium and water in skin and muscle are increased and VEGF is reduced when 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 haemodynamic parameters like aortic BP [86], and the peripheral and central BP burden is accentuated during the long dialysis interval (Figure 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 such individuals.

Arterial stiffness increase

Patients with ESRD display a premature increase in arterial stiffness due to a combination of factors, mainly as a result of

Box 2: 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 apnoea.
- Use of recombinant erythropoietins.

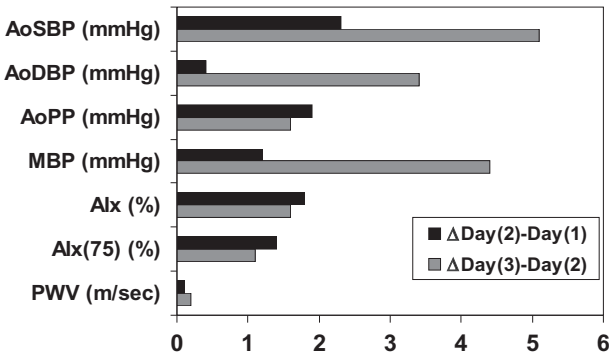

FIGURE 2: Changes in aortic blood pressures, wave reflections and arterial stiffness parameters between the first and the second interdialytic day, Δ [day (2) − day (1)], in comparison with relevant changes between the second and the third interdialytic day, Δ [day (3) − day (2)]. Reprinted with permission from Koutroumbas *et al.* [87]. AoSBP, aortic systolic blood pressure; AoDBP, aortic diastolic blood pressure; AoPP, aortic pulse pressure; MBP, mean blood pressure; AIx, augmentation index; PWV, pulse wave velocity.

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 and Light [90] analysed 11 833 interdialytic BP measurements from 125 haemodialysis 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. In a *post hoc* analysis of the Hypertension in Haemodialysis 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 indices during the interdialytic periods showed that augmentation index and central PP increased during both 3- and 2-day interdialytic intervals; aortic and brachial PWV was unchanged in these short time-frames. The increase in augmentation index 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- 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 the efferent sympathetic discharge rate to be doubled in haemodialysis patients with *in situ* native kidneys but normal in haemodialysis 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 in which renal denervation substantially reduced BP in small series of haemodialysis 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 cardiac output [97]. The plasma concentration of renalase is markedly decreased in haemodialysis patients when compared with age- 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 pre- to post-dialysis, 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 pre-dialysis 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 downregulation of 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 endothelial NO synthase 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 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 haemodialysis patients [112, 114].

Sleep apnoea

Sleep apnoea 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 apnoea has been associated with a reversed circadian BP pattern, in this way triggering nocturnal hypertension. This notion is supported by a study of 32 haemodialysis patients that showed that those patients experiencing sleep apnoea had higher nocturnal SBP and higher LV relative wall thickness than those without sleep apnoea; 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 apnoea had a 7.1 times higher risk of developing resistant hypertension (defined as office BP >140/90 mmHg despite the use of more than three different antihypertensive agents); in contrast, no such association between sleep apnoea and resistant hypertension was noted among non-dialysis-requiring CKD patients [117]. Finally, a recent study in haemodialysis patients with obstructive sleep apnoea showed that, after haemodialysis, the obstructive apnoea–hypopnoea 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 haemoglobin levels [124], route of administration (intravenous versus subcutaneous) [125] and dialysis modality (haemodialysis versus 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 that remain resistant to treatment may have other secondary causes of hypertension, which should be adequately sought 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 should 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 subjects, 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 hypokalaemia immediately after kidney transplantation [131]. Obstructive sleep apnoea is particularly common in ESRD patients and is discussed in detail above. Less frequent secondary causes, like pheocromocytoma, thyroid diseases, renin-secreting tumours and others should be carefully sought in selected patients with relevant signs and symptoms, and treated appropriately.

HYPERTENSION TREATMENT IN DIALYSIS PATIENTS

Non-pharmacological measures

Management of hypertension in dialysis patients should focus on correction of the primary pathogenetic mechanism, that is, sodium and volume excess, by carefully implementing a series of non-pharmacological measures to achieve the dry-weight for each individual patient and to avoid intradialytic sodium loading (Box 3). Particular consideration 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.], needs to be taken into account and guide the careful handling of antihypertensive drugs when dry-weight is pursued. However, outside situations of hypertensive urgency or emergency [7], the administration of antihypertensive drug therapy in dialysis patients considered to be volume overloaded should follow the attainment of dry-weight.

Achievement of patients' dry-weight. Achievement of dry-weight in dialysis patients remains a complex issue of clinical judgement [132]. The absence of a widely accepted definition of dry-weight and the 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 post-dialysis weight, achieved through a gentle and gradual reduction in post-dialysis weight, at which patients experience minimal signs or symptoms of either hypovolaemia or hypervolaemia [133]. Typically, there are no reliable clinical signs to indicate whether a patient has reached the 'ideal' dry-weight. The degree of pedal oedema, 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 oedema and crackles in lung auscultation of haemodialysis patients reflected the degree of pulmonary congestion objectively assessed by lung ultrasound very poorly [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

Box 3: Main non-pharmacological measures to reduce sodium and volume overload in haemodialysis patients

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

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 study was the first randomized trial to test this hypothesis, by assigning 150 haemodialysis 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 kg/10 kg body weight was prescribed. If ultrafiltration was not tolerated based on symptoms and signs, such as muscle cramps, a 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 end point 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. Post-dialysis 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 was associated with a difference of 7.1/3.8 mmHg [142]. 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 the DRIP trial, 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 multicentre randomized study within the framework of ERA-EDTA, comparing the effect of dry-weight probing guided by a lung ultrasound scheme versus standard clinical practice on cardiovascular events in haemodialysis patients [143]; a LUST substudy on ambulatory BP is awaited to shed further light on the field.

In accordance with haemodialysis, achievement of better volume control in patients on peritoneal dialysis may help towards 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 haemoglobin 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 to BP control by an intensification of ultrafiltration in the absence of prolonged dialysis time may be counterbalanced by higher risk of intradialytic hypotension, loss of residual renal function, hospitalization 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 >12.4 mL/kg/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 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 (Box 4) [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.

Minimization of inter- 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 haemodialysis 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, adjusted analysis reported that 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

Box 4: Barriers towards achievement of dry-weight in haemodialysis patients with hypertension

- Difficulty in objectively assessing 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 versus 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).

BP and LVH, and fewer episodes of intradialytic hypotension compared with antihypertensive treatment [139, 151]. It should 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 that requires important lifestyle changes. Instead of dietary sodium restriction, patients on dialysis are often instructed to avoid excessive 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 <100 mmol (2.4 g of sodium or 6 g of sodium chloride) per day [40, 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 via the use of particular medications, such as potassium-binders exchanging sodium, sodium bicarbonate to increase pre-dialysis bicarbonate levels or drug formulations containing sodium (i.e. effervescent tablets); whenever possible, the avoidance of such agents is also useful.

In parallel to dietary sodium restriction, the avoidance of inappropriate sodium gain during dialysis is crucial for effective BP control. Prescription of a high dialysate sodium concentration was common in the early days of dialysis, to ensure haemodynamic 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 have challenged these conclusions and emphasized that a high dialysate sodium concentration may increase thirst and interdialytic weight gain [147, 156]. In a study of 1084 haemodialysis 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 post-dialysis thirst and interdialysis weight gain. Such an 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 necessitate the prescription of even higher dialysate sodium concentration, precipitating 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 pre-dialysis serum sodium [147, 156].

A single-blind, randomized, cross-over 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 a patient's average pre-dialysis sodium multiplied by 0.95 to allow for the Gibbs–Donnan effect) in non-diabetic, 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, pre-dialysis BP was 16 mmHg lower during the individualized sodium dialysate period [158]. In a subsequent single-blind, cross-over study receiving thrice-weekly, in-centre 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 pre-dialysis SBP by 8.3 ± 14.9 mmHg, without increasing intradialytic hypotensive episodes [159]. In a 3-week randomized, cross-over trial in 16 patients with intradialytic hypertension, Inrig *et al.* [50] compared the effect of a high (5 mEq/L above serum sodium) versus low (5 mEq/L below serum sodium) dialysate sodium concentration on intradialytic BP and endothelial-derived vasoregulators. The weekly averaged pre-dialysis 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 mm Hg; $P < 0.001$) (Figure 3) [50]. Overall, these studies suggest that a single dialysate sodium prescription may not fit all patients. Small decreases in dialysate sodium towards pre-dialysis levels in hypertensive patients can limit thirst, reduce intradialytic weight gain and improve BP control without aggravating the risk of intradialytic haemodynamic instability. Larger randomized trials are needed to evaluate the safety and efficacy of this approach.

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 non-randomized interventional study comparing a standard versus a low-sodium peritoneal dialysis solution substituting one 3- to 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, which was accompanied by reduced thirst, lower total body water and an 8 mmHg fall of night-time SBP [160]. Overall, patients on peritoneal dialysis should also follow the above recommendations for restriction of sodium intake; modification of peritoneal dialysis regimens with low-sodium or icodextrin solutions may facilitate sodium and volume control.

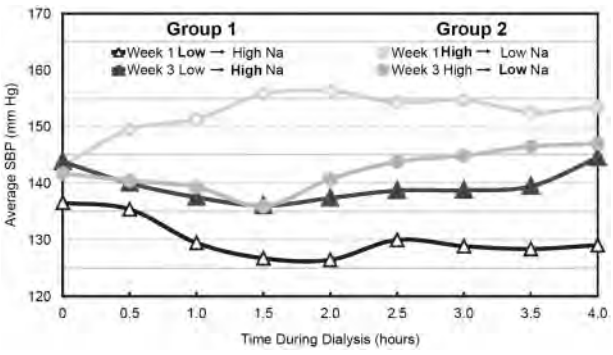

FIGURE 3: Weekly average intradialytic systolic blood pressure (SBP) during haemodialysis with low and high dialysate sodium (Na) by randomization sequence (group 1: low-then-high dialysate Na) and (group 2: high-then-low dialysate Na); $P < 0.001$ by adjusted mixed linear regression. Reprinted with permission from Inrig *et al.* [50].

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 haemodialysis patients should receive at least three dialysis sessions of 4 h each per week [161], a recommendation aimed mainly at ensuring optimal volume status. Exceptions to this could be incident dialysis patients with substantial residual renal function or patients who start 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 that, 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 registries in the USA, where as many as 25% of patients may dialyse for <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 who experience frequent episodes of intradialytic haemodynamic instability during this intensification process within their usual dialysis regimen [168]. A previous cross-over study of 38 dialysis patients comparing the frequency of intradialytic symptoms during 5-h versus 4-h dialysis sessions showed that the incidence of intradialytic hypotension and postdialysis orthostatic hypotension was 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 modelled 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 in order 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 non-randomized studies, showing that patients assigned to longer (i.e. up to 8-h thrice weekly) or more frequent (i.e. up to six times/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 post-trial analysis of patients who took part into the Daily in-centre Trial of the Frequent Haemodialysis Network [173] showed a lower risk of death in patients originally randomized to frequent haemodialysis (six times a week) and 1.5–2.75 h/session (16%), as compared with those randomized to conventional haemodialysis treatment (28%). However, this benefit was not evident in the long-term analysis of the twin Nocturnal Trial of the same network, where mortality was largely increased in the frequent haemodialysis group (six times a week >6 h/session) [174]. Of note, the most prominent difference between groups in the main Nocturnal Trial seemed to be a faster loss of residual diuresis in the frequent dialysis arm [175]. Although careful interpretation is necessary, current evidence suggests that longer or frequent haemodialysis schemes may be beneficial, but that 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 haemodialysis patients have been examined in clinical trials (Box 5). Two previous meta-analyses of randomized trials clearly suggest that BP-lowering with the use of such

Box 5: Antihypertensive drugs in outcome clinical trials in haemodialysis patients

β-blockers

- Carvedilol reduced mortality compared with placebo in haemodialysis patients with dilated cardiomyopathy [176].
- Thrice-weekly atenolol reduced cardiovascular events compared with thrice-weekly lisinopril in HD patients with hypertension and LVH in the HDPAL trial [177].

ACEIs

- Fosinopril did not reduce cardiovascular events and mortality compared with placebo in HD patients with LVH in the FOSIDIAL trial [178].

ARBs

- Losartan/valsartan/candesartan reduced cardiovascular events and mortality compared with treatment not including ACEIs/ARBs in HD patients [179, 180].
- Olmesartan did not reduce cardiovascular events or mortality compared with treatment not including ACEIs/ARBs in HD patients with hypertension in the OCTOPUS trial [181].

CCBs

- Amlodipine reduced cardiovascular events compared with placebo in HD patients with hypertension [182].

MRAs

- Spironolactone may reduce cardiovascular events and mortality compared with no additional treatment or placebo in HD and peritoneal patients [183, 184].

HD, haemodialysis; LVH, left ventricular hypertrophy; HDPAL, Hypertension in Haemodialysis Patients Treated with Atenolol or Lisinopril trial; ACEIs, angiotensin-converting enzyme inhibitors; FOSIDIAL, Fosinopril in Dialysis trial; ARBs, angiotensin-II receptor blockers; OCTOPUS, Olmesartan Clinical Trial in Okinawa Patients under Dialysis Study; CCBs, calcium channel blockers; MRAs, mineralocorticoid receptor antagonists.

antihypertensive drugs is associated with reduced cardiovascular morbidity and mortality in dialysis patients [185, 186]. The first meta-analysis included eight trials incorporating data from 1697 dialysis patients and 495 cardiovascular events [186]. 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 a 29% reduction in the risk of all-cause mortality (pooled RR: 0.71; 95% CIs: 0.55–0.92) and a 29% reduction in the risk of cardiovascular mortality (pooled RR: 0.71; 95% CIs: 0.50–0.99) [186]. The second meta-analysis [185] 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 HR: 0.69; 95% CIs: 0.56–0.84) [185]. 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 HR: 0.86; 95% CIs: 0.67–1.12) [185]. 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 [185].

The major antihypertensive drug classes are useful for the pharmacological treatment of hypertension in dialysis, taking into account the specific pharmacological properties of each drug [5, 9, 187, 188]. An exception may be diuretics, which are ineffective for BP control in patients with ESRD [5, 187, 188]. Echocardiographic studies conducted in anuric haemodialysis patients showed that intravenous administration of loop diuretics, even at high doses, exerts only minimal alterations in central haemodynamic indices [189]. 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 haemodialysis or peritoneal dialysis to enhance urine output and limit fluid overload [190–193]; 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 [194]. 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 for cardiovascular protection in this population [187]. 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 (HR: 0.88; 95% CI: 0.78–0.99; P = 0.03) [195]. In 114 haemodialysis 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 (HR: 0.44; 95% CI: 0.25–0.77) and all-cause mortality (HR: 0.51; 95% CI: 0.32–0.82) [176]. More recently, the HDPAL trial [177] performed a head-to-head comparison between the β-blocker atenolol and the ACEI lisinopril (both administered in a thrice-weekly regimen immediately post-dialysis) in 200 hypertensive haemodialysis patients with echocardiographically documented LVH. 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 [177]. 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 (Figure 4), required more aggressive volume management during dialysis and the administration of a higher number of antihypertensive drugs as add-on therapy to achieve the pre-specified home BP target of 140/90 mmHg. Most importantly, the HDPAL trial was terminated early due to the superiority of atenolol over lisinopril for the prevention of serious cardiovascular events, as the rate of the combined outcome of myocardial infarction (MI), stroke, hospitalized heart failure and cardiovascular death was 2.29 times higher in lisinopril-treated than atenolol-treated patients (incidence rate ratio: 2.29; 95% CI: 1.07–5.21) [177].

The Beta-blocker to LOwer CArdiovascular Dialysis Events trial originally planned to study the cardioprotective role of β-blockade in haemodialysis patients. In the feasibility study, which aimed to enrol 150 patients, among the 1443 patients screened (including 176 who were already on treatment with β-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 period and progressed to randomization [196]. The challenging recruitment for this study emphasize the difficulties in performing clinical studies in dialysis patients.

Pilot data by Inrig *et al.* [197] suggest that carvedilol may be useful in patients with intradialytic hypertension; the 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 a significant drop of 7 mmHg in 44-h interdialytic ambulatory SBP. Of importance, when prescribing a β-blocker to a haemodialysis 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 non-dialysable β-blockers is advisable, since a recent retrospective cohort study suggested that a survival advantage may not be offered by highly dialysable β-blockers, possibly due to a lack of intradialytic protection against arrhythmias as a consequence of rapid removal with dialysis [198].

Angiotensin-converting enzyme inhibitor 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

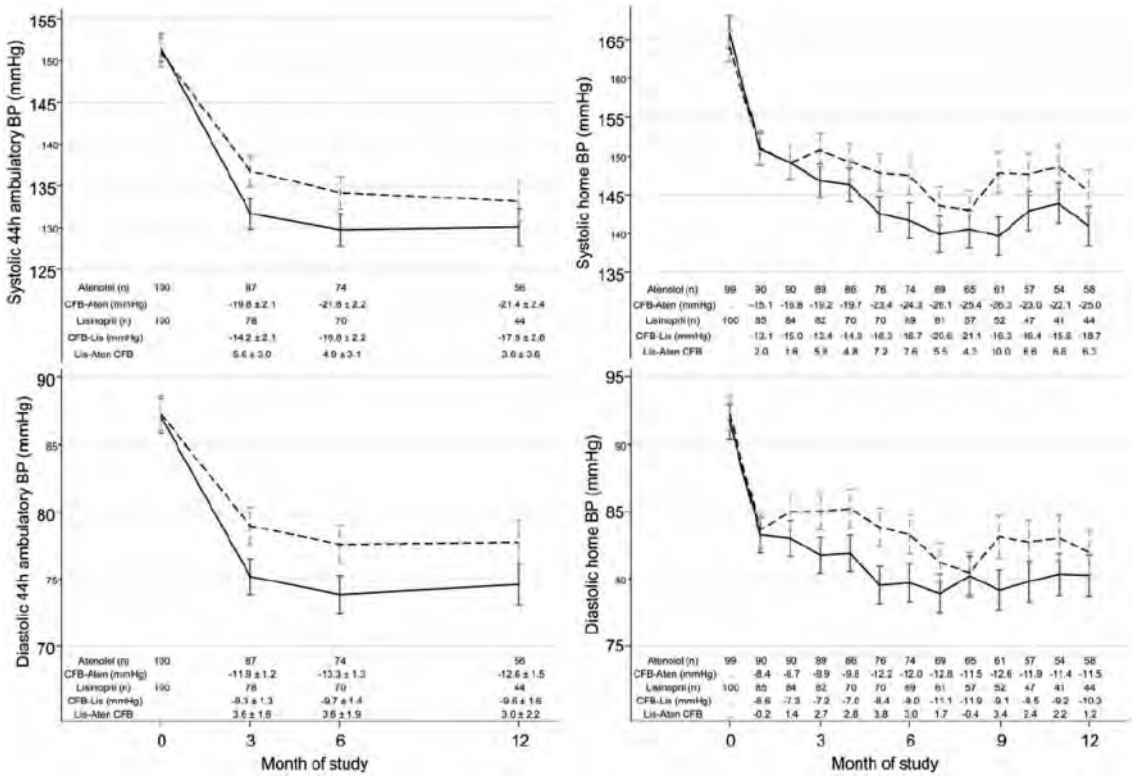

FIGURE 4: Blood pressure measured by 44-h ABPM over the interdialytic period (left panel) and self-measured by the patients at home (right panel) in the Hypertension in Hemodialysis Patients Treated with Atenolol or Lisinopril (HDPAL) trial. Dotted lines: lisinopril group; solid lines: atenolol group. Reprinted with permission from Agarwal *et al.* [177]. Solid line shows the atenolol group and the dotted line the lisinopril group; vertical bars represent standard error of mean. The table at thebottom of each graph shows the number of patients in each drug [atenolol (n), lisinopril (n)]; the change from baseline (CFB) and between group comparisons of the changes (lisinopril–atenolol CFB).

for sustained BP reduction. Through extrapolation of the cardiovascular benefits of RAS blockers in the general population, inhibition of the RAS has often been recommended as the first-line BP-lowering therapy for dialysis patients [40]. However, randomized trials in hypertensive dialysis patients do not support the notion that RAS blockade offers the same benefits as in hypertensive patients in the general population.

In the Fosinopril in Dialysis trial [178], 397 haemodialysis 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 LVH, but were not necessarily hypertensive. Although therapy with fosinopril resulted in a significant reduction of pre-dialysis BP versus placebo in the subgroup of hypertensive participants, the occurrence of fatal and non-fatal cardiovascular events during the follow-up period did not differ significantly between the active treatment and placebo arms (RR: 0.93; 95% CI: 0.68–1.26) [178].

Three trials [179–181], all performed in Japan, compared ARBs to either placebo or active therapy. In two of these trials (including 80 and 360 haemodialysis patients, respectively) the risk of cardiovascular events was remarkably lower in patients treated with ARBs. In the third study, the Olmesartan Clinical Trial in Okinawa Patients under Dialysis Study [181], which was also the largest to date, 469 hypertensive haemodialysis 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, non-fatal stroke, MI and coronary revascularization was similar in the olmesartan and control groups (HR: 1.00; 95% CI: 0.71–1.40) [181], suggesting that antihypertensive treatment *per se*, and not the use of an RAS blocker, is the factor responsible for 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 non-significant ($P = 0.10$) 42% risk reduction [199]. Overall, to date, 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 an RAS blocker seems to be 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 [200], and are often used for the management of hypertension in dialysis patients. In the only relevant study examining hard outcomes, Tepel *et al.* [182] randomized 251 hypertensive haemodialysis patients to receive amlodipine (5–10 mg/day) or placebo for 30 months. Amlodipine improved survival compared with placebo, although this was not significant, and reduced by 47% the composite secondary end point of all-cause death, non-fatal stroke, MI, coronary revascularization and angioplasty for peripheral

vascular disease (HR: 0.53; 95% CI: 0.31–0.93) [182]. Small previous studies have suggested that dihydropyridine CCBs are equally effective as ACEIs or ARBs in reducing LVH and carotid intima-media thickness [201]. Data on non-dihydropyridine CCB use in haemodialysis patients are scarce; using these agents should at least follow the recommendations for the general population. It must be noted that all CCBs are not removed during standard haemodialysis 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 [202], and two recent trials (Table 2) [183, 184] apparently support the contention that these drugs may provide substantial benefits in dialysis patients. In the Dialysis Outcomes Heart Failure Aldactone Study, 309 oligoanuric haemodialysis 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 (HR: 0.38; 95% CI: 0.17–0.83), with the incidence of drug discontinuation due to serious hyperkalaemia being 1.9% and due to adverse effects overall being 14.6% [183]. In another study, 253 haemodialysis or peritoneal dialysis 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 end point of cardio-cerebrovascular mortality, and mitigated the risk for cardiac arrest and sudden death (HR: 0.42; 95% CI: 0.26–0.78) [184]. 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-centre haemodialysis on the combined end point of death and LVH progression [170]; this was largely unexpected in a population like the ESRD population, which is notoriously less sensitive to interventions aimed at reducing death and cardiovascular events than other patient populations [203]. However, it has to be noted that these results should be further confirmed, as both of the above studies were open-label. The safety profile of MRAs in the dialysis population was investigated in a recent study, in which 146 haemodialysis patients were randomly assigned to eplerenone (25–50 mg daily) or matching placebo for 13 weeks [204]. Eplerenone treatment significantly increased the incidence of hyperkalaemia (defined as pre-dialysis 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 hyperkalaemia or hypotension, which was the primary study end point, was no different between eplerenone and placebo groups [204]. Adequately powered, properly designed studies, like the ongoing [205] ALdosterone Antagonist Chronic HEModialysis Interventional Survival Trial (NCT01848639) are needed to assess the effectiveness and safety of mineralocorticoid receptor blockade in ESRD, prior to the recommendation of wider use of MRAs in this population.

Table 2. Recent randomized trials on the effect of MRAs on cardiovascular outcomes in haemodialysis patients

Author	Patient characteristics	*N*	Design	Follow-up	BP medication	BP assessment	Baseline BP (mmHg)	Final BP (mmHg)	Main finding
Matsumoto *et al.* [183]	Oligoanuric HD patients	157 versus 152	Open-label RCT	36 months	Spironolactone versus nothing	Pre-dialysis BP	152.8/77.8 versus 148.8/76.2	152.7/77.9 versus 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.* [184]	HD or PD patients without CHF	125 versus 128	Open-label RCT	24 months	Spironolactone versus placebo	Pre-dialysis BP	144.7/76.9 versus 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)

MRAs, mineralocorticoid receptor antagonists; BP, blood pressure; CV, cardiovascular; CHF, congestive heart failure; CI, confidence intervals; HD, haemodialysis; HR, hazard ratio; LVH, left ventricular hypertrophy; PD, peritoneal dialysis; RCT, randomized clinical trial; N/A, not applicable.

CONCLUSION

Hypertension in dialysis patients poses almost unique diagnostic, prognostic and therapeutic challenges. The evolution of studies using home or ambulatory BP monitoring is currently needed in order to better define the true burden of hypertension in haemodialysis 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. Non-pharmacological interventions targeting sodium and volume excess are fundamental for 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. Furthermore, properly designed epidemiology studies and clinical trials to define BP targets for treatment and examine the efficacy of non-pharmacologic measures in reducing BP and antihypertensive drugs in the prevention of major cardiovascular outcomes in the ESRD population remain a public health priority (Box 6).

Box 6: 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 non-pharmacologic 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-blockers versus ACEI/ARBs or CCBs, a proper placebo-controlled trial with an MRA, etc.) on home or ambulatory BP control and hard outcomes.**

BP, blood pressure; HD, haemodialysis; PD, peritoneal dialysis; LUST, Lung Water by Ultra-Sound Guided Treatment to Prevent Death and Cardiovascular Complications in High Risk ESRD Patients with Cardiomyopathy study; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin-II receptor blockers; CCBs, calcium channel blockers; MRA, mineralocorticoid receptor antagonist.

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CONFLICT OF INTEREST STATEMENT

R.A. has consulted for Abbvie, Amgen, AstraZeneca, 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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