Blood pressure in chronic kidney disease stage 5D—report from a Kidney Disease: Improving Global Outcomes controversies conference

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Management of blood pressure (BP) in patients with chronic kidney disease receiving dialysis (stage 5D) provides a significant challenge for healthcare professionals. The association between BP and cardiovascular disease risk has been well studied in the general population; however, in dialysis patients, physiological and dialysis-related mechanisms influencing BP are complex, and the associated risk is poorly understood. In stage 5D, BP is determined by the complex interplay of fluid volume and prescription of post-dialysis target weight, sodium load, the renin–angiotensin and sympathetic nervous systems, and diverse exogenous factors, such as administration of erythropoiesis-stimulating agents, the type and timing of administration of antihypertensive drugs, and dialysate composition. Management of BP in this population requires both generally applicable plans and individualization in order to determine the BP target and the treatment regimen. This report summarizes the deliberations and recommendations of a conference sponsored by the Kidney Disease: Improving Global Outcomes (KDIGO) to address the following questions: (1) what is the optimal BP treatment target in relation to end-organ damage and outcomes in dialysis patients; (2) how should antihypertensive drugs be used in dialysis patients; and (3) what nonpharmacological therapies can be considered in achieving BP targets? The conference report will augment the KDIGO clinical practice guideline on blood pressure in chronic kidney disease stages 1–5, which is currently under development.

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In March 2009, Kidney Disease: Improving Global Outcomes (KDIGO) convened a Controversies Conference on Blood Pressure in chronic kidney disease (CKD) stage 5D. The conference, attended by 50 international experts, was designed to review the most current information available on the pathophysiology, epidemiology, and management of blood pressure (BP), particularly in this population. The plenary session presentations were followed by discussion in small breakout groups that were asked to address three specific issues, which the planning committee of the conference considered to be of central importance: (1) optimal BP in relation to end-organ damage in dialysis patients; (2) pharmacological therapy for cardioprotection and to achieve BP targets; and (3) nonpharmacological therapy to achieve BP targets—focus on volume and salt control. The breakout group deliberations were reported to the entire group and a consensus building process led to recommendations from the conference attendees. The following is a report on these deliberations and recommendations. The conference agenda, selected presentations, and abstracts of the meeting are posted on the KDIGO website: http://www.kdigo.org/meetings_events/BP_Controversies_Conference.php

KDIGO is an independently incorporated non-profit organization governed by an international Board of Directors with the stated mission to 'improve the care and outcomes of kidney disease patients worldwide through promoting coordination, collaboration and integration of initiatives to develop and implement clinical practice guidelines.' One of the initiatives determined by the Board of Directors of KDIGO is a series of international conferences to examine what is known, what can be done with what is known and what needs to be known on controversial topics of clinical relevance in nephrology.[1]

Epidemiological studies in the general population have shown a close relationship between BP and the incidence of

cardiovascular disease (CVD). In the past, the severity of hypertension (HTN) was classified principally on the basis of increased diastolic BP (DBP), which was considered to be the best predictor of CVD risk, with increased pulse pressure as an independent CVD risk factor in addition to DBP. DBP generally increases from birth to the fifth decade, followed by a decline starting at 50–60 years. The pulse pressure increases markedly in later life, and isolated systolic HTN becomes the predominant form of HTN after 60 years of age in the general population. In dialysis patients, increased systolic BP (SBP) and decreased DBP are both associated with CVD events. Presumably, this is related to increased arterial stiffness. In addition, decreased SBP following previous HTN is associated with adverse outcomes.[2]

Although BP is measured frequently in the dialysis treatment environment, the technical aspects are often unsatisfactory, with the use of poorly calibrated machines and poor BP cuff placement on the upper arm. Recently, quite different levels of BP in the same patients measured in the dialysis clinic before dialysis and at home using ambulatory BP measurements (ABPM) were shown, with ABPM being substantially lower than dialysis clinic measurements.[3] A U-shaped curve relating BP to outcomes was apparent in both sets of BP measurements, but home BP measurements were significantly lower and more closely associated with CVD.[3]

The pathophysiology of these BP patterns is complex, implicating three principal factors: cardiac function (cardiac output), arterial stiffness (large arteries), and intensity of wave reflections (principally vasomotor tone of resistance arterioles). The complex pathogenesis of HTN explains the difficulty of its treatment. In addition, the effect of ultrafiltration (UF) and variable plasma volume refilling rates may frequently result in hypotensive episodes during dialysis. The relationship of low systolic pressure with CVD events is complex, as low SBP in some patients may represent ideal control, but in others, it may be associated with increased mortality.[2] A practical quandary arises in the care of an individual patient when the BP measurements are in an apparently acceptable range, as this BP may be gradually falling over time because of associated cardiomyopathy. Clearly, management and outcomes are different in these instances. Cardiac studies, and especially echocardiography, are necessary to clarify the significance of apparently normal BP levels. Sound BP treatment requires information on cardiac structure and function.[4,5] In addition to consideration of the effect of changes in extracellular fluid volume, the time of administration of antihypertensive drugs is also relevant, given drug clearance during dialysis and myocardial dysfunction.

Studies of antihypertensive medication use in dialysis patients have been limited. In the randomized trials included in two recent meta-analyses, the study drugs were given for CVD management, rather than for HTN.[6,7] The relative merits of calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and β-adrenergic blockers alone and in combination with centrally acting sympatholytic agents are not satisfactorily established. A recent review points out the powerful relationship between aldosterone activation of aldosterone/mineralocorticoid receptors and inflammation, resulting in vessel wall fibrosis.[8] Blockade of these receptors may be useful, although hyperkalemia may limit their use. More needs to be learnt about the use of drugs in conjunction with salt restriction, volume control, and in the presence of specific cardiovascular (CV) comorbidities, especially those resulting in cardiac arrhythmias and sudden death. Quality-of-life considerations with regard to side effects are particularly relevant in dialysis patients.

In patients with low BP associated with fluid overload and, by necessity, low UF rates, longer dialysis treatment times or more frequent dialysis could achieve normal hydration, but this is impractical in most instances. The patients at greatest risk are those who have low predialysis BP, as a result of severe cardiac dysfunction.[2] The prognosis of these patients is poor, in part, because fluid can be removed only very slowly. To further aggravate this situation, diastolic dysfunction is often present. Even a small decrease in filling pressure after UF may result in decreased cardiac output and hypotension. As a result, fluid accumulates inexorably. In addition, autonomic neuropathy complicating uremia and diabetes, with inadequate peripheral arteriolar tone, further increases the risk of hypotension, with the patient remaining fluid overloaded.

The recent finding that excess sodium is stored without osmotic activity at concentrations of 180–190 mEq/l in the skin, bound to glucosaminoglycans, could revolutionize current views of sodium balance.[9] According to this work, the skin sodium system acts as a buffer to exogenous sodium loading, and this sodium store can be released into the circulation resulting in hypervolemia and oxidative stress. This problem may be accentuated by reduction in connective tissue mass during aging and catabolic processes, thus decreasing the capacity of the skin to serve as a sodium reservoir.

Although it has been established that interdialytic salt restriction or intradialytic removal of salt and fluid volume is effective in reducing BP, absolute success over time has been very rare, with only the Tassin and Izmir groups consistently being able to virtually discard antihypertensive drugs.[10] In the current three times per week dialysis regimen, each for 3–4 h, volume overload is common. Little consistent effort has been exerted in the United States to reduce exposure to excess sodium. Because the sodium concentration of dialysate is usually higher than that of the patient's serum, sodium concentration rises during hemodialysis (HD), with the consequence of increased thirst, extracellular volume (ECV) expansion, and interdialytic weight gain. In addition, salt balance is positive with habitual high dietary sodium intake and use of saline for 'sodium profiling' or to maintain plasma volume during UF.

A further consequence of long-term hypervolemia and an activated renin–angiotensin system is hyperactivity of the sympathetic nervous system. Factors such as renal ischemia, chronic inflammation, oxidative stress, obesity, nocturnal hypoxia, and elevated plasma levels of asymmetric di-methyl-arginine may contribute to increased sympathetic activity. The sequelae are elevated arterial pressure, cardiac arrhythmias, increased myocardial oxygen demand, and, in concert with arterial HTN, reduced compliance of large arteries. In addition to its volume effects, sodium exerts direct pro-inflammatory, pro-fibrotic effects, with the potential for aggravating kidney disease and CVD. Salt directly increases oxidative stress and is associated with the secretion of endogenous ouabain-like substances, such as marinobufagenin and endogenous ouabain. These compounds inhibit Na/K ATPase, and may induce myocardial cell hypertrophy *in vitro*. The concentration of endogenous ouabain correlates with left ventricular mass in HD patients independent of arterial pressure.[11]

The attainment of normal body hydration ('dry weight (DW)'), expressed in practice by recognition and attainment of an appropriate post-dialysis weight, is difficult without adequate means of measurement; this is a subject of much current research.[12–14] In the absence of an absolute post-dialysis weight goal, salt restriction of all kinds is usually half-hearted. A confounding factor is a lag between achieving a normal extracellular fluid volume and reduction in BP. Current public policy and societal interest in reduction of salt intake combined with intradialytic technical solutions to prevent accumulation of sodium during dialysis may reduce the frequency of sodium-related HTN. Future effectiveness studies should determine whether this will occur. Other nonpharmacological methods to decrease BP include nephrectomy.

Overall, the relative severity of CVD, fluctuations in BP with every dialysis treatment, association with inflammation, stimulation of vasoactive substances, activation of mineralocorticoid receptors, increased levels of sympathetic nervous activity, exposure to sodium loading combined with inadequate volume control, and other factors make management of HTN in the dialysis patient a difficult but fascinating problem.

Guidelines on the complex problems of HTN in CKD are being written currently. Whether the special problems of a hypertensive dialysis patient can be addressed in clinical practice guidelines is a relevant question, but evidence is sparse and more clinical trials are needed.

DISCUSSION

Optimal BP target in relation to end-organ damage in dialysis patients

How and when should BP be measured? Several options exist, such as pre- or post-dialysis BP, ABPM, and interdialytic home BP. Interdialytic ABPM is considered the standard to define a patient's BP. In the general population, ABPM provided a more accurate prediction of CV outcomes than office BP.[15–17] In a single-center cross-sectional study, 1-week-averaged home SBP was similar to interdialytic ABPM and superior to pre- and post-HD BP in predicting left ventricular hypertrophy (LVH); DBP was not associated with LVH.[18] In an earlier study, ABPM added minimal information to the prediction of LVH, compared with the average of 12 routine pre-HD BP measurements.[19]

Hemodialysis BP and ABPM correlation is poor. A recent meta-analysis showed that pre- and post-HD BP are imprecise estimates of interdialytic ambulatory BP.[20] In this meta-analysis, median pre-HD SBP and DBP were 8.6 and 2.6 mm Hg higher than ABPM, respectively. A single-center cross-sectional study showed that home BP measured by the patients was better than pre-HD in predicting LVH. ABPM added only weak predictive information.[18] Although a worthy goal, neither measurement of APBM nor self-measured home BP may be feasible for most patients throughout the world, leaving pre-HD and post-HD BP measurements to be used, but with caution and with the knowledge that these are inferior.

Which components of BP should be measured? Systolic BP and DBP are associated with end-organ damage, including vascular stiffness. Both high and low levels of either SBP or DBP are associated with poor outcomes in dialysis patients. A high prevalence of isolated systolic HTN exists in the stage 5D CKD population. Clinical decisions in managing interdialytic BP should be based on SBP and DBP, but not on mean arterial BP.

What BP level defines HTN in chronic HD patients? As referred to above, BP levels defining the presence or absence of HTN differ with the use of pre-HD, post-HD, self-measured home BP, and ABPM. The recent National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines suggest that pre-HD and post-HD BP should be $<140/90$ and $<130/80$ mm Hg, respectively.[4] These targets were largely based on the expert judgment of the workgroup, applying weak evidence. Whether the definition of HTN on the basis of home BP should be the same as that for the general population, as outlined in the Seventh Report of the Joint National Committee (JNC 7),[21] with SBP >139 mm Hg or DBP >89 mm Hg, can only be decided by future research.

What are treatment goals for BP in chronic HD patients? Current data suggest that there is a 'U-shaped' association between pre-HD BP and mortality. An analysis based on the CREED study cohort adjusted for Framingham risk factors, background CV complication, and left ventricular mass and ejection fraction shows that the risk of death is lowest in dialysis patients with a pre-dialysis SBP between 100 and 125 mm Hg,[22] whereas SBP >150 mm Hg was associated with increased mortality.[23] Severe cardiomyopathy modifies the relationship between BP and mortality, and survival is very low in ESRD patients with SBP <115 mm Hg.[2,24] On the other hand, both post-dialysis SBP $\geqslant 180$ mm Hg and DBP $\geqslant 90$ mm Hg were associated with a substantial increase in CV mortality.[22] This should be interpreted in the light of a report of increased mortality with

Table 1 | Research recommendations: optimal BP target in relation to end-organ damage in dialysis patients

- Establish the relationship between self-measured home BP, ABPM, and pre-HD BP and outcomes in diverse populations of CKD Stage 5D patients.
- Determine the optimal frequency, timing, physical location, and posture, including self-measured home BP measurement, and the validation of measurement technology used.
- The mechanisms responsible for increased PP in different HD populations should be studied, as high systolic and low diastolic pressures frequently occur together.
- Evaluate the relationship between outcomes (morbidity and mortality) and self-measured home BP in diverse populations of HD patients.
- Validation of self-measured home BP followed by an RCT comparing different home BP targets in relationship to outcomes (morbidity and mortality).
- Assessment of the feasibility and cost-effectiveness of home BP monitoring in the broad dialysis population would serve at least two purposes: (1) to monitor the effect of drugs on BP during the interdialytic interval; (2) to validate or refute the superiority of home BP values as a predictor of hard clinical outcome.

Abbreviations: ABPM, ambulatory blood pressure measurement; BP, blood pressure; CKD, chronic kidney disease; HD, hemodialysis; PP, pulse pressure; RCT, randomized controlled trial.

declining SBP.[2] The difference in outcomes in patients with very low and very high BP may lie in the presence of severe cardiomyopathy in the former. In an observational study in incident HD patients pre-HD SBP $\geqslant$ 200 mm Hg was associated with increased mortality or CV events.[2] Therefore, pre-HD SBP above this level should be treated aggressively. The BP ranges associated with the minimal risk related to the use of self-measured home BP monitoring are currently not known in CKD stage 5D patients. In the only study published so far, the best outcome was observed with a self-measured home SBP range between 120 and 145 mm Hg.[3] Research recommendations are listed in Table 1.

Pharmacological therapy for cardioprotection and to achieve BP targets

Special considerations for antihypertensive agents in dialysis patients. End-stage kidney disease is associated with a 10- to 20-fold increased risk of CV mortality, compared with age- and sex-matched controls without CKD,[25] and sudden death accounts for the majority of deaths. LVH in dialysis patients has been convincingly attributed to fluid overload, HTN, neuron–humoral activation, and severe anemia.[26] CV risk factors are accentuations of the risk factors observed in stage 4 and 5 CKD patients (for example, vascular medial calcification). In addition, dialysis patients have additional unique risk factors (for example, acute fluid and electrolyte shifts during HD).[27]

Pharmacokinetics of antihypertensive and putative cardioprotective drugs are altered by both impaired kidney excretion of the drugs and by their dialyzability. The multitude of drugs that these patients usually take reduces compliance, because of tolerability, interactions with other drugs, side effects, and financial costs.[28] Pharmacotherapy to lower BP may cause additional problems that are unique to dialysis patients, such as intradialytic hypotension and vascular access thrombosis.[29]

These patients may be more prone to side effects of certain drugs than patients with earlier stages of CKD. The presence of and propensity to these side effects may be easily overlooked. For example, minoxidil may potentiate or be confused with uremic pericardial effusion.

The evidence to guide practitioners in BP management, CV risk factors, and CV end-organ diseases is poor. Uncertainties in therapeutic indices of treatment strategies that have been proven in the nondialysis population, such as angiotensin-converting enzyme inhibitors, generate much controversy among nephrologists caring for the dialysis population. β-Blockers have been suggested to be cardioprotective in HD in a small randomized controlled trial.[30] Many practice guidelines are largely based on low-quality evidence and opinions.

Should vasoactive agents be used for their antihypertensive effects or independent cardioprotective effects? Cardiac deaths account for the majority of CV deaths in dialysis patients. The exact etiologies of these cardiac deaths are often unknown and likely include primary and secondary arrhythmias, cardiomyopathy, and coronary artery disease, and involve complex pathogeneses. Although fluid overload, increased afterload from HTN and vascular calcification, calcified valvular disease, and ischemia are probably important contributory factors, uremia *per se* seems to be an additional factor. To what extent hyperkalemia and hypokalemia, frequently present in these patients, contribute to the high incidence of sudden death in dialysis patients is not certain, but recent papers suggested the greater danger of hypokalemia.[31,32] In addition to their antihypertensive effects, some drugs are variably cardioprotective, which may be independent of their BP-lowering effects. Notable examples in this category are inhibitors of the renin–angiotensin–aldosterone system (RAAS), β-adrenergic blockers, CCBs, and aldosterone inhibitors (not in HD),[33] although the real impact beyond the BP-lowering effect of some of these agents is a matter of controversy and has been scrutinized in a number of meta-analyses.[7,34–36]

Angiotensin II has been implicated in endothelial dysfunction, smooth muscle proliferation, atherosclerotic plaque rupture, inhibition of fibrinolysis, and ventricular hypertrophy. Importantly, myocardial hypertrophy occurs when angiotensin II is increased, even when BP is controlled. Clinical studies in non-ESRD populations show that RAAS inhibition decreases CV events in patients with left ventricular dysfunction and in other high-risk individuals. Further, RAAS inhibitors in high-risk population without overt clinical heart failure and with stable coronary artery disease are associated with significantly reduced risk of sudden and arrhythmia-related deaths.[37] Similarly, substantial clinical evidence in the non-ESRD patient has shown the beneficial effects of β-adrenergic blockers in patients with heart failure, arrhythmia, and acute myocardial infarction.[38] Moreover,

CCB decrease intracellular calcium levels, including those produced by secondary hyperparathyroidism in CKD stage 5, and alter lipid profile that may, hence, reduce CV risks.[39,40]

The use of RAAS inhibitors, β-adrenergic blockers, and CCBs should be strongly considered in HD patients, as overactivity of RAAS (increased plasma renin activity), increased levels of sympathetic activity (elevated plasma levels of norepinephrine and neuropeptide Y, and reduced heart rate variability), and intracellular calcium overload are common in dialysis patients. In particular, sympathetic overactivity is associated with increased CV mortality in the HD population.[41–43] However, randomized trials of these agents with hard outcomes in dialysis patients are scant. Two recently published meta-analyses on antihypertensive medications in dialysis patients confirmed that the use of antihypertensive medications was associated with decreases in CV events. The analysis performed by Heerspink *et al.*[7] included eight randomized trials (one published only in abstract form), five of which examined RAAS blockade, two examined β-blockers and one examined a CCB. The analysis performed by Agarwal *et al.*[6] included five randomized trials, which were a subset of the eight studies examined by Heerspink *et al.* In the analysis of Agarwal *et al.*, treatment with antihypertensive medications was associated with decreases in CV events. However, when normotensive subjects were included in the meta-analysis, the beneficial effects of antihypertensive medications were markedly diminished and became statistically non-significant, raising the possibility that the beneficial impact of these agents is at least partly related to their BP-lowering effect.

These meta-analyses seem to suggest a beneficial effect of lowering BP in dialysis patients. However, there are several caveats in this interpretation. (1) The total number of subjects included in all eight trials examined by Heerspink *et al.*[7] was only 1679, with markedly heterogeneous inclusion/exclusion criteria among the trials. For example, the trial conducted by Cice *et al.*[30] on β-blockers mandated a left ventricular ejection fraction of lower than 35% in the inclusion criteria (the actual mean left ventricular ejection fraction of the cohort at baseline was 26%), whereas other trials specified certain BP values for inclusion. (2) As pointed out by Agarwal *et al.*,[6] there seemed to be publication bias of results in their meta-analysis, based on the Egger's publication bias plot and the funnel plot. (3) Most importantly, none of the trials included in either meta-analysis specifically targeted BP levels. They were designed to examine the effects of specific antihypertensive medications with independent cardioprotective properties. Therefore, causality cannot be inferred from the association between the decrease in BP and beneficial clinical effects. A example was the trial performed by Cice *et al.*, which was designed to examine the effects of carvedilol in dialysis patients with dilated cardiomyopathy and markedly diminished ejection fractions. In this trial, the mean BP was lower in the carvedilol group during follow-up. Further experience using β-blockers on the incidence of sudden death should resolve the clinical question as to the relative importance of BP lowering in relation to cardioprotective effects. In contrast, there was no difference in the BP between the group randomized to candesartan and the control group in the trial conducted by Takahashi *et al.*,[44] although there was a marked decrease in the rates of CV events and mortality in the candesartan group. Thus, the positive effects of these drugs combine both their direct cardioprotective and the BP-lowering effects. Nonetheless, the beneficial clinical effects of these agents need to be confirmed by adequately powered randomized trials with identical BP targets in both groups. Identification of the optimal BP target for dialysis patients would require separate randomized trials, with different BP targets and preferably similar agents in the randomized groups. Until such results become available, the use of RAAS inhibitors, β-blockers, and CCBs in dialysis patients for the purpose of decreasing clinical hard end points can only be recommended on the basis of studies in the general population. However, the use of these agents in dialysis patients for compelling indications in the general population (for example, β-blockers for heart failure or immediately after myocardial infarction) should be strongly considered, as it is unlikely that future large randomized trials would include these subgroups that have mortality risks even higher than the general dialysis population. It should be noted that, so far none of these putative cardioprotective agents has been shown or suggested to increase, rather than decrease, CV risks in dialysis patients.

Which antihypertensive drugs are recommended? Recommendations on antihypertensive drugs are usually based on their efficacy in BP reduction, interdialytic and intradialytic pharmacokinetics, side-effect profile, independent cardioprotective effects (see above) and non-CV effects of the specific class, as well as on the comorbidities of the patient. β-Blockers are usually more effective in patients with high normal heart rate or tachycardia than those with normal heart rate or bradycardia. They are also indicated for patients with angina or recent acute myocardial infarction. α-Adrenergic blockers alleviate symptoms of prostatic hypertrophy for those with significant residual urinary output. Clonidine would not be the agent of choice for patients with drowsiness. For dialysis patients with conditions in which a certain drug class is considered to be absolutely indicated in the nondialysis population (for example, β-blockers for post-myocardial infarction), these recommendations should still apply. Nonetheless, side effects in a particular patient and future evidence, especially that obtained specifically in the dialysis population, should obviously be taken into account. Occasionally, side effects related to the individual or HD procedure could limit the use of specific drugs, for example, the use of α-1 blocking agents in patients prone to intradialytic hypotension.

Aliskiren, the first in a new class of orally effective direct renin inhibitors, was recently approved for the treatment of HTN.[45] Experience of this class of drugs in CKD stage 5 is awaited. Consistent with its known mechanism of action, the administration of direct renin inhibitors results in a

reduction in both plasma renin activity and angiotensin II concentrations. The drug is not metabolized by cytochrome P450 enzymes, and is excreted by more than 90% unchanged through the fecal route. No adjustments are necessary for alterations in kidney function, age, ethnicity, or the concomitant administration of other drugs. It is not clear whether the suppression of plasma renin activity results in benefits beyond the BP-lowering effect. An argument may be made to prescribe drugs found to be successful in patients in the general population with CKD to the HD patients, given the balance of risk/benefits in the former.

Beyond preferences based on the literature, guidelines in the nondialysis population, and the use of common wisdom, there is no compelling evidence to recommend one class of antihypertensive agents over another. It should be noted that, although the randomized trials included in the meta-analyses described above examined specific drug classes, most of them did not target specific end-organ conditions in their cohorts. Of these, only one small trial ($n = 114$) showed a beneficial effect of a specific β-blocker, carvedilol, on hard CV end points. Thus, even the recommendations of specific drug classes for CVD should be taken with caution in dialysis patients.[46–48]

Considerations regarding pharmacokinetics and timing of drug administration. Drug dialyzability has implications beyond BP control. The removal of an antihypertensive drug that also possesses antiarrhythmic effects (for example, β-blocker) during HD may predispose to intradialytic arrhythmia, especially in the presence of dialysis-induced fluctuation in serum concentrations of electrolytes, such as potassium and calcium.

As CCBs are not removed from the plasma during HD, post-dialysis supplementation of these drugs is not necessary. In contrast, the intradialytic kinetics of various angiotensin-converting enzyme inhibitors differ significantly from each other (Table 2). For example, although ~50% of plasma lisinopril is removed during an average HD session, fosinopril is practically nondialyzable. Similarly, the intradialytic kinetics of various β-blockers also differ from one another. Approximately 75% of atenolol is removed by HD, but carvedilol is practically nondialyzable.

During HD, BP decreases in ~50% of the patients, whereas an increase in BP occurs in ~15% of the patients.[49] BP often gradually increases during the interdialytic interval, when the fluid gradually accumulates. The physiological nocturnal fall in BP (nocturnal dip) is often absent in dialysis patients. The timing, duration, severity, and etiology of intradialytic BP changes, and if available, the behavior of BP levels during the interdialytic period, should be considered in the prescription of antihypertensive agents. For example, patients with sustained HTN during the interdialytic and intradialytic periods should take long-acting drugs. Patients without the nocturnal dip may benefit from extra drugs before bedtime. Some drugs should be withheld in patients with intradialytic symptomatic hypotension before the dialysis session, or a dialyzable drug should be used such that its antihypertensive effect can be attenuated during dialysis. In contrast, patients with intradialytic HTN should avoid dialyzable drug, be supplemented with more drugs before the dialysis session, or use other maneuvers, such as a lower dialysate sodium concentration and higher UF rates and volume.

Two long-acting antihypertensive drugs, atenolol and lisinopril, have been tested for thrice-weekly administration immediately after HD.[50,51] Both agents administered in this manner have been shown to produce sustained antihypertensive effects over 44 h between dialysis sessions, without increasing intradialytic hypotensive episodes. This method is advantageous because the drug can be administered in the dialysis unit under supervision, thus enhancing pharmacoadherence.

What are the recommendations on quality-of-life issues related to BP treatment? It is recognized that quality of life is extremely important for dialysis patients, and that the pharmacotherapeutic strategies may have substantial impact on the quality of their lives. Unfortunately, there is inadequate information to warrant specific practice recommendations for this population (Table 3).

Nonpharmacological therapy to achieve BP targets—focus on volume and salt control

The majority of patients who progress to stage 5 CKD develop a positive sodium balance and an increase in ECV. Salt and water overload have a central role in the development of HTN in these patients,[52] and normalizing sodium and fluid balance is key to the control of BP and may reduce the risk of CV events. The post-dialysis DW of a dialysis patient may be defined as the post-dialysis body weight at which ECV is within the normal range. As ECV is not easily measurable, this parameter is of limited value in clinical practice and alternative definitions have been proposed. These include the post-dialysis body weight at which hypotension occurs[53] or at which both pre- and post-dialysis BP are reduced to target values without the need for antihypertensive medications.[54] These definitions do not apply to those patients who are hypotensive because of cardiomyopathy. According to the latter definition, HTN reflects ECV overload and BP normalization indicates extracellular euvolemia. Most nephrologists would agree that, at least in some patients, intradialytic HTN is undoubtedly a manifestation of fluid overload with BP correction achieved by fluid removal.[55,56] Attempts have been made to determine DW by bioimpedance (BIA).[13,14]

In clinical practice, the DW is usually established by a progressive decrease in the post-dialysis body weight, usually over a 4–8-week period after the initiation of maintenance HD.[57] This approach is endorsed by the Dry weight Reduction In hypertensive HD Patients (DRIP) study, in which a significant decrease of the pre-dialysis SBP was achieved after 4 weeks in a group of patients randomized to a 1.1% body weight reduction, as compared with those in whom no active intervention took place.[58] Unfortunately,

Table 2 | Antihypertensive drugs, excretion pathway, dosage, and supplement in CKD and chronic dialysis

				Removal with dialysis		
	Usual dose	Excretion	GFR < 10 ml/min	Hemodialysis	Peritoneal dialysis	Supplement for dialysis
Diuretics						
Acetazolamide	250 mg q6–8 h	K	Avoid	Unknown	Unknown	Not applicable
Amiloride	5–10 mg q.d.	K	Avoid	N/A	N/A	Not applicable
Bumentanide	0.5–2 mg q8–12 h	K	100%	None	None	None
Chlorthalidone	30–60 mg q.d.	K	Avoid	N/A	N/A	Not applicable
Ethacrynic acid	50–100 mg b.i.d.	L (K)	Avoid	None	None	Not applicable
Furosemide	40–80 mg b.i.d.	K (L)	100%	None	None	None
Hydrochlorothiazide	25–50 mg q.d.	K	Avoid	None	None	Not applicable
Indapamide	2.5 mg q.d.	K	Avoid	None	None	Not applicable
Metolazone	5–10 mg q.d.	K (L)	100%	None	None	None
Spironolactone	50–100 mg q.d./b.i.d.	K (L)	Avoid	N/A	N/A	Not applicable
Torsemide	5–10 mg b.i.d.	L (K)	100%	Avoid	Avoid	None
Trimaterene	25–50 mg b.i.d.	K	Avoid	N/A	N/A	Not applicable
β-blockers						
Acebutolol	400–600 mg q.d./b.i.d.	L (K)	30–50%	30%	None	150 mg
Atenolol	50–100 mg q.d.	K (L)	25–50%	50%	None	25–50 mg
Betaxolol	10–20 mg q.d.	L	50%	None	None	None
Bisoprolol	2.5–20 mg q.d.	L	100%	None	None	None
Carvedilol	25 mg b.i.d.	L (K)	50%	None	Unknown	None
Esmolol	50–150 μg/kg/min i.v.	L	100%	None	None	None
Labetalol	200–600 mg b.i.d.	K (L)	100%	None	None	None
Metoprolol	50–100 mg b.i.d.	K (L)	100%	None	None	50 mg
Nadolol	80–100 mg b.i.d.	K	25%	50%	None	80 mg
Pindolol	10–40 mg b.i.d.	K (L)	100%	None	None	None
Propanolol	80–160 mg b.i.d.	K	100%	None	None	None
Sotalol	160 mg q.d.	K	15–30%	50%	None	50 mg
Timolol	10–20 mg b.i.d.	L (K)	100%	None	None	None
CCB						
Amlodipine	2.5–10 mg q.d.	L	100%	None	None	None
Diltiazem CD	180–360 mg	L (K)	100%	None	None	None
Felodipine	5–10 mg q.d.	L	100%	None	None	None
Isradipine	2.5–10 mg b.i.d.	L	100%	None	None	None
Lacidipine	2–6 mg/day	L (K)	100%	None	None	None
Manidipine	10–20 mg/day	L	100%	None	None	None
Nicardipine	20–40 mg t.i.d.	L	100%	None	None	None
Nifedipine XL	30–90 mg q.d.	L	100%	None	None	None
Nimodipine	30 mg q8 h	K (L)	100%	None	None	None
Nisoldipine	10 mg b.i.d.	K (L)	100%	None	None	None
Nitrendipine	20 mg b.i.d.	L (K)	100%	None	None	None
Verapamil CD	180–360 mg q.d.	L	100%	None	None	None
ACEi						
Benazapril	5–40 mg q.d.	K (L)	50–75%	Negligible	None	5–10 mg
Captopril	12.5–50 mg t.i.d.	K	50%	50%	None	12.5–25 mg
Enalapril	2.5–10 mg q12 h	K (L)	50%	50%	None	2.5–5 mg
Fosinopril	10 mg q.d.	K (L)	75%	None	None	None
Lisinopril	2.5–10 mg q.d.	K	25–50%	50%	None	2.5–5 mg
Perindopril	2–8 mg/day	K (L)	25–50%	50%	None	2 mg
Quinapril	10–20 mg q.d.	K (L)	50%	25%	None	10 mg
Ramipril	5–10 mg q.d.	K (L)	25–50%	20%	None	2.5 mg
Trandolapril	0.5–4 mg/day	K (L)	25–50%	30%	None	0.5 mg
ARB						
Candesartan	8–35 mg/day	K (L)	100%	None	None	None
Eprosartan	600–1200 mg/day	L	100%	None	None	None
Ibersartan	75–300 mg/day	L	100%	None	None	None
Losartan	50–100 mg q.d.	K (L)	100%	None	None	None
Olmesartan	10–40 mg/day	K (L)	100%	None	None	None
Telmisartan	40–80 mg/day	L	100%	None	None	None
Valsartan	80–320 mg q.d.	L (K)	100%	None	None	None
DIR						
Aliskiren	150–300 mg q.d.	K	Unknown	Unknown	Unknown	Unknown

Table 2 | Continued

	Usual dose	Excretion	GFR < 10 ml/min	Removal with dialysis		Supplement for dialysis
				Hemodialysis	Peritoneal dialysis	
Central α-agonists						
Clonidine	0.1–0.3 mg b.i.d./t.i.d.	K (L)	100%	5%	None	None
Guanabenz	8–16 mg b.i.d.	L	100%	None	None	None
Guanethidine	10–100 mg q.d.	K (L)	50% (avoid)	None	None	None
Methyldopa	250–500 mg b.i.d./t.i.d.	K (L)	q12–24 h	60%	30–40%	250–500 mg
Reserpine	0.05–0.25 mg q.d.	L	Avoid	None	None	None
α_1-blockers						
Doxazosin	1–16 mg q.d.	L	100%	None	None	None
Prazosin	1–15 mg b.i.d.	L	100%	None	None	None
Terazosin	1–20 mg q.d.	L	100%	None	None	None
Vasodilators						
Diazoxide	150–300 mg bolus	L	100%	None	None	None
Hydralazine	25–50 mg t.i.d./q.i.d.	L	q8–16 h	25–40%	25–40%	None
Minoxidil	5–30 mg b.i.d.	L	100%	None	None	None
Nitroprusside	0.25–0.8 mg/kg/min i.v.	L (K)	100%	None	None	None

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blockers; CKD, chronic kidney disease; DIR, direct inhibitors of renin; GFR, glomerular filtration rate; i.v., intravenous; K, kidney; L, liver; N/A, not applicable.

Table 3 | Research recommendations: pharmacological therapy for cardioprotection and to achieve BP targets

- Examination of the pharmacokinetics, pharmacodynamics, and optimal frequency of administration of anti-hypertensive drugs in various dialysis populations (for example, defined by degrees of residual kidney function) and various dialytic modalities (conventional thrice-weekly HD, low-flux versus high-flux HD, short daily HD, nocturnal HD, hemofiltration, and peritoneal dialysis).
- Optimization of the choice (for example, long-acting versus short-acting, dialyzable versus non-dialyzable), dosing schedule, and intensity of anti-hypertensive drugs, with BP levels (not hard end points) as targets, recognizing that the optimal BP level needs to be defined in separate trials. Investigation of the effectiveness of these drugs in reducing BP in patients with fluid overload.
- Determination of any circumstances when drugs, instead of fluid volume contraction, should be the first-line strategy to lower BP; this would be appropriate when patients had reached their dry weight.
- Examination of the side-effects of anti-hypertensive drugs (for example, hyperkalemia with RAAS blockade, leg edema and pericardial effusion with minoxidil, cardiac and neurological effects of the combination of β-blockers and central-acting sympatholytic agents, and effects of drugs on the prolonged QT interval on electrocardiogram, which is associated with increased risks of sudden cardiac death), the prevalence of these side-effects in dialysis patients and interactions of anti-hypertensive drugs with the dialysis procedure (for example, does it counteract the arrhythmogenicity of acute changes in serum potassium and calcium concentrations).
- Large definitive randomized trial of putative cardioprotective drugs (for example, RAAS inhibitors and β-blockers) in the general dialysis population, independent of BP targets. Successful cardioprotective drugs may constitute the background treatment to which further anti-hypertensive drugs can be added to manage HTN.
- Development and validation of instruments to evaluate quality of life associated with pharmacotherapy used for BP management in the dialysis population. Validation in various countries would reveal how their respective cultures might modulate patients' quality of life related to the BP treatment and its manifestations.
- Examination of drugs (for example, RAAS blockade) on sleep apnea, which is a risk factor for both HTN and cardiovascular events.

Abbreviations: BP, blood pressure; HD, hemodialysis; HTN, hypertension; RAAS, renin–angiotensin–aldosterone system.

target weight reduction to normalize BP may increase the frequency of intradialytic hypotension,[59] which in turn may damage the heart,[60] and is associated with increased mortality.[61] That the same phenomena can occur in the severely over-hydrated patient, favors the achievement of a post-dialysis 'target weight' in some patients, which might be higher than the DW as a clinically practical alternative. The requirement for a difference between the DW and target weight illustrates the dilemma faced by the healthcare professional in avoiding intradialytic BP decreases while attempting to optimize DW in an effort to correct high BP. However, longer dialysis time periods and methods to reduce interdialytic weight gain attenuate the occurrence of hypotension. In attempting to achieve 'target weight', particularly in incident patients starting dialysis, clinicians should be mindful also of the lag in time (from several weeks to months) between correction of ECV and HTN.[62] Similar principles apply to patients receiving peritoneal dialysis, in whom salt and water removal is influenced by dialysis fluid sodium concentration and choice of dialysis technique.

How should ECV and DW be measured? The history and physical examination may be helpful in detecting more obvious ECV increases. For example, clinical assessment of internal jugular venous pressure provides information

Table 4 | Research recommendations: non-pharmacological therapy to achieve target BP focus on volume and salt control

- A descriptive longitudinal study characterizing the relationship between pre- and post-dialysis serum sodium concentration, ECV (measured using the bioimpedance techniques) and BP is required with long-term follow-up of clinical outcomes to identify high-risk patient groups and to facilitate the future design of RCTs.
- An RCT of different dietary sodium intakes and dialysate–plasma sodium gradients is required in hypertensive HD patients to study impact on BP and of both intradialytic and interdialytic weight gain.
- An RCT of antihypertensive drugs with and without sodium restriction, for example in a 2×2 factorial design.
- An RCT randomizing patient to two different ECV targets is required in HD patients with outcomes that include surrogate hemodynamic parameters and clinical outcomes.
- Longitudinal studies are required to assess the value of plasma brain natriuretic peptide level measurements during fluid removal in incident HD patients.

Abbreviations: BP, blood pressure; ECV, extracellular volume; HD, hemodialysis; RCT, randomized controlled trial.

concerning right atrial pressure and volume increase. Ankle edema is frequently associated with increased ECV, but its specificity is low.[63] In general, assessment of DW using such clinical parameters lacks sensitivity.[64] Many hypertensive dialysis patients may not show the physical signs of intravascular or interstitial fluid overload despite several liters increase in their ECV, although a progressive decrease in the target weight corrects their HTN.[55]

Subclinical ECV overload may be assessed using BIA analysis. Essig *et al.*[65] used a multifrequency BIA device in the early stages of CKD to describe an association between increased ECV and CV remodeling. In dialysis patients, intradialytic measurement of BIA may be helpful in the assessment of DW. By monitoring regional resistance and resistivity in the calf, Zhu *et al.*[14] showed that it was possible to decrease the prescribed 'target weight' with associated BP decrease over time to approach DW in prevalent HD patients. Other BIA devices that assess whole body composition[13] provide readouts of BP and ECV status that may be useful in longitudinal follow-up of fluid balance. Using a whole body approach to measure BIA, a recent study showed that dialysis patients with a 15% or greater ECV increase over normal displayed an increased risk of mortality.[66] Other methods of assessing ECV include measurement of vena cava diameter (to assess intravascular volume), which requires time for equilibration at the end of the dialysis session and is operator dependent.[67] Cardiac peptides, such as brain natriuretic peptide, are associated with mortality in dialysis patients[68,69] and high plasma levels are associated with volume overload.[70] However, their use as an ECV overload indicator is confounded by cardiac disease, the influence of intradialytic removal of the peptide, and fistula blood flow.[70] Methods of assessing intradialytic blood volume change have been useful in the context of prescription of UF rate, but are not valuable to accurately determine fluid overload.

What is the role of sodium balance? During the dialysis session, ECV overload is largely corrected by the process of convection. However, the prescribed dialysate sodium concentration may significantly influence sodium flux by diffusive transport. Increasing the dialysate sodium concentration above the individual patient's own pre-dialysis serum value may reduce intradialytic adverse effects, such as hypotension,[71] but may lead to increased weight gain (IDWG) driven by thirst.[72] Using BIA, Sarkar *et al.*[73] have shown that a high gradient can induce intracellular shrinking by as much as 2.5 l. It may therefore be best to adjust sodium dialysate concentration to match the patient's pre-dialysis plasma sodium and not use higher dialysate sodium concentrations. Such individualization of sodium dialysate concentration leads to a decreased IDWG, thirst score, intradialytic hypotension episodes, and lower BP in hypertensive patients, compared with a fixed sodium dialysate concentration (138 mmoles/l).[74] More conveniently, the sodium concentration in dialysate might be determined from plasma conductivity measured by the dialysis machine, but this approach is problematic because of the different sodium conductivity relationships pre- and post-dialysis.[72,75] The benefits of 'sodium profiling' with or without feedback control in an effort to maintain neutral sodium balance are unclear,[75–77] but certainly are another reason for sodium overload. Use of hypertonic dextrose rather than saline in the management of intradialytic hypotension and cramps also increases the potential for a neutral sodium balance.

Should dietary sodium be restricted? According to the World Health Organization, there is sufficient evidence to recommend a low salt diet (5 g/day) to the general population, because a large salt intake is associated with increased BP and CVDs. Dietary salt restriction was useful in the quest for optimization of DW to obtain BP control in the 'Tassin experience'.[78] Recently, Kayikcioglu *et al.*[79] have compared a group of 190 HD patients restricted to a 5-g salt diet with a control group in a cross-sectional study of 204 HD patients with free salt intake. The BP was similar in the two groups, but with only 7% of patients in the low salt intake group versus 42% of the free salt intake group requiring antihypertensive drugs. Furthermore, the IDWG was lower in the salt-restricted group (2.29 ± 0.83 kg versus 3.31 ± 1.12 kg) with fewer episodes of intradialytic hypotension, and reduction in left ventricular mass was greater in the salt-restricted group. Interventional studies assessing salt restriction have consistently reported a decrease in IDWG during salt restriction[80–83] with an associated decrease in BP.[80–82,84–86]

What is the role of longer or more frequent dialysis? A high UF rate enhances the risk of muscle cramps and hypotensive episodes. The treatment for such complications includes reducing the UF rate and administering intravenous saline,

which undermines the aims of the original intervention and may result in an expanded ECV at the end of treatment. Such corrective maneuvers thus prevent achievement of the prescribed target weight,[87] and create the conditions for perpetuation of HTN and the risk of LVH and cardiac failure.[88] These problems are illustrated by data from the DOPPS cohort study in which an independent increase of mortality risk was noted in patients with an UF rate over 10 ml/kg/hour.[61] In these patients, the risk of intradialytic hypotension was increased by 30%. In another prospective study with a 5-year follow-up,[89] an UF rate of over 12.7 ml/kg/hour was an independent risk factor for mortality. These high UF rates may reflect excess of salt and fluid intake.

The prescription of longer and/or more frequent dialysis sessions allows the decrease in UF rate and reduces the risk of intradialytic complications.[90–92] This has been shown by a number of studies in which alternative dialysis methods such as short daily, long daily, and long conventional HD improve LVH,[93–96] sympathetic overactivity, and/or vascular reactivity[97–100] and improve ejection fraction in patients with heart failure.[101,102] Research recommendations are shown in Table 4.

CONCLUSIONS

Hypertension is an ubiquitous finding in HD patients with major implications for survival. Accurate measure of BP is an essential precursor for management. As pre-HD BP measurement may not reflect the average BP experienced by the patient, the question of how and where the measurements should be made is of importance. At present, the evidence for the superiority of self-measured BP at home over pre-HD BP is impressive. Attainment of BP targets in keeping with experience in non-HD patients are practicable, but the modifying effect of cardiomyopathy in hypertensive patients resulting in declines of BP (to those targets) make it difficult without further cardiac investigation to distinguish patients with a satisfactory target BP from those with severe cardiac disease. Use of echocardiography is essential to understand this problem.

In general, all antihypertensive drugs can be used in the HD population with doses determined by dialyzability and hemodynamic instability. However, the concomitant cardioprotective effects of these drugs need to be considered when assessing outcomes, in light of the current scanty evidence. It could be argued that any established use of these drugs in the general population should probably be widely applied to HD patients as long as no firm evidence is available in this specific population.

The two major aspects differentiating the management of HTN in HD from the general population are the extremes of extracellular fluid volume present in the majority of HD patients who have lost their residual renal function and the nature of dialysis. Short intense removal of fluid and the impaired CV response in many patients to this result in intradialytic hypotension, much dreaded by patients.

The role of combined sodium restriction together with use of antihypertensive drugs has not been clarified. However, given that patients in HD are usually in positive sodium balance and would benefit from sodium restriction (inter- and intradialytically), a combination of the latter plus drugs may be the best practice. Randomized controlled trials on HTN are rare in HD and should be encouraged. Long or more frequent dialysis may solve the hemodynamic problems associated with salt restriction and short dialysis time.

DISCLOSURE

DCW has received honoraria from Novartis. All the other authors declared no competing interests.

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