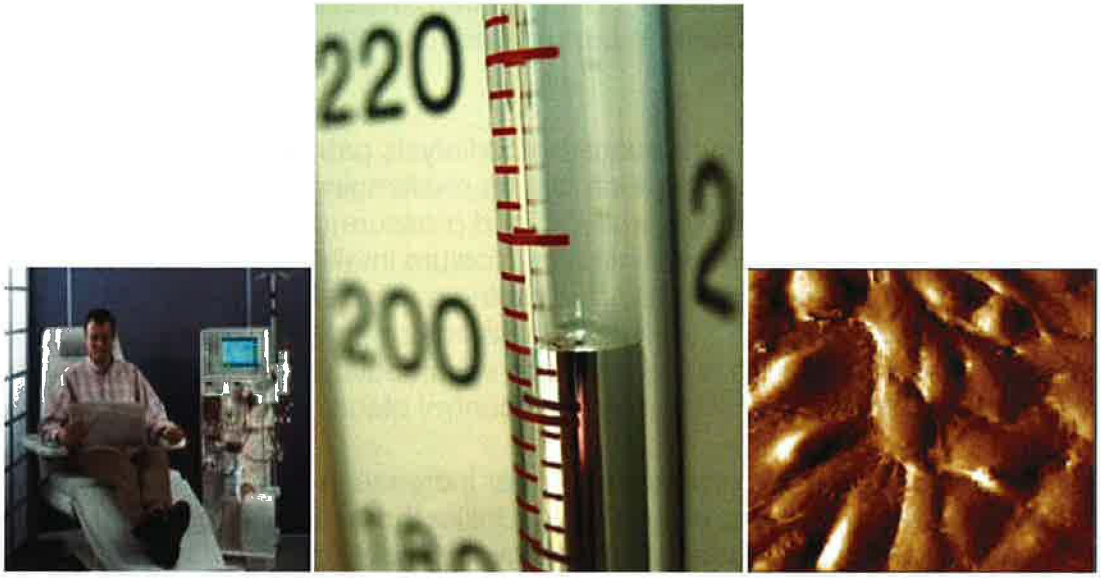
Hypertension in Dialysis: What you don't know can hurt your patients



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INTRODUCTION:

Compared to the general population, the annual mortality rates among maintenance hemodialysis patients are increased over 20 fold.(1) These high mortality rates are mostly due to cardiovascular complications. The high cardiovascular morbidity and mortality in this patient population is likely in part related to the end-organ damage caused by long-standing hypertension.

Hypertension affects up to 90% of maintenance hemodialysis patients and the management of hypertension in this population can be challenging. Extracellular fluid volume is the key contributor to poorly controlled blood pressure,(2) thus nonpharmacologic interventions such as minimizing sodium intake, limiting free water intake, ensuring adequate sodium solute removal during hemodialysis, and achievement of "dry weight" should be the initial treatment for blood pressure control.(3) Many other factors contribute to high blood pressure in hemodialysis patients and pharmacologic interventions are usually required to control blood pressure (BP).

In the general population, there is a progressive linear increase in cardiovascular complications with increasing blood pressure.(4, 5) Unlike the general population, the relationship between high blood pressure and cardiovascular outcomes in hemodialysis patients is unclear. In fact, numerous epidemiologic studies demonstrate a u-shaped relationship between blood pressure and cardiovascular outcomes in hemodialysis populations.(6-9) Furthermore, while randomized controlled trials have demonstrated blood pressure control linearly decreases cardiovascular outcomes in the general population, there are no randomized controlled trials to support aggressive blood pressure control in hemodialysis patients. However, a recent meta-analysis of small randomized controlled trials of antihypertensive therapy in hemodialysis patients, demonstrated blood pressure lowering treatment was associated with a 29% lower relative risk of cardiovascular events.(10)

The ideal blood pressure target in hemodialysis patients is unknown. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines recommend lowering predialysis BP to <140/90 mmHg and postdialysis BP to <130/80 mmHg.(11-13) However, given the paucity of evidence to support BP control in hemodialysis patients, these guidelines have been significantly criticized.(14) Ongoing research suggest non-dialysis unit BP readings (such as ambulatory BP or home BP monitoring) may improve the diagnosis of hypertension and should be utilized in patients whose dialysis unit blood pressure readings are difficult to control or who develop hypotension during hemodialysis treatments.(15, 16)

Despite dietary salt and fluid restrictions, pharmacologic therapy is usually required to control blood pressure in hemodialysis patients. Most classes of agents are appropriate for use in hemodialysis patients and a combination of agents is typically required to control blood pressure. However, further research is necessary to determine which class of antihypertensive agents to use and what BP level to target to improve outcomes in hemodialysis patients.

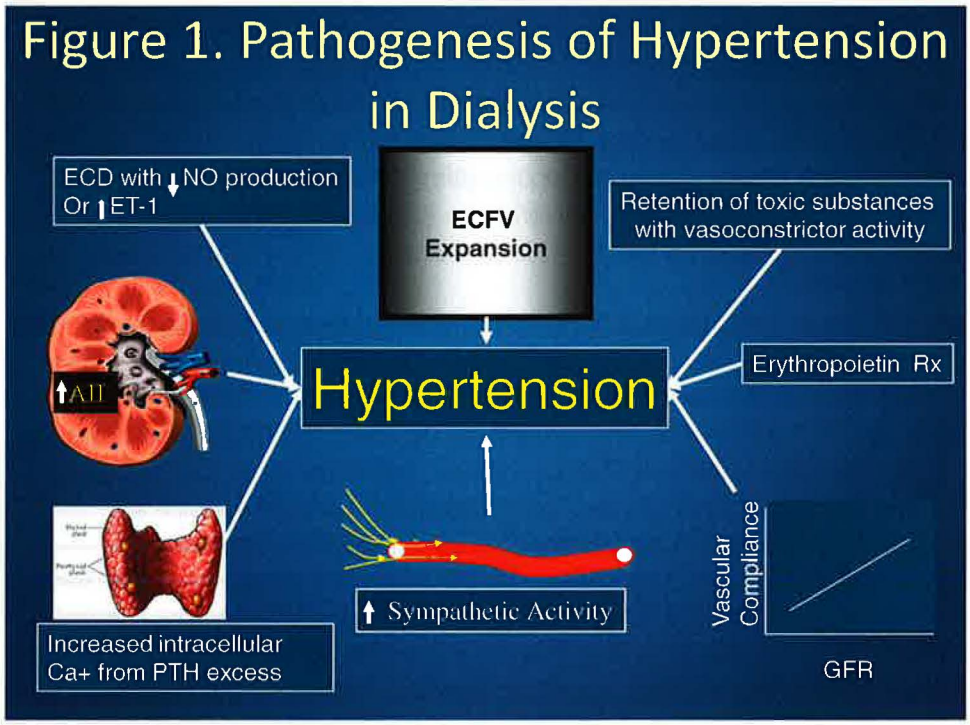
PREVALENCE AND CONTROL OF HYPERTENSION

There is a high prevalence of hypertension in dialysis patients and blood pressure control is poor

Most hemodialysis patients have high blood pressure. Among 2,535 hemodialysis patients enrolled in a randomized trial, 86% were hypertensive (defined as BP >150/85 mmHg or the use of antihypertensive medications).(17) In our analysis of baseline data from 438 patients enrolled in a randomized trial, 76% of patients were treated with antihypertensive medications and 79% were not at guideline-defined goal blood pressure targets of a predialysis BP <140/90 mmHg and postdialysis BP <130/80.(18) In an audit of 2,630 dialysis patients in the UK, only 36% achieved the predialysis BP target (<140/90) and 42% achieved the postdialysis target (<130/80).(19)

PATHOPHYSIOLOGY OF HYPERTENSION IN DIALYSIS PATIENTS

While the etiology of hypertension in dialysis patients is complex and multifactorial (**Figure 1**), the primary contributor to high blood pressure is extracellular volume expansion.



The role of extracellular volume expansion on blood pressure

Identification of a patients "true dry weight" remains a holy grail in nephrology. Currently, dry weight is identified clinically by means of physical exam findings and blood pressure during hemodialysis. A patient is deemed at their dry weight if they develop symptoms such as nauseua, vomiting, or cramping during or following dialysis

with hypotension during their treatment. Clinical trials which have attempted to augment clinical acumen in identifying dry weight (such as laboratory parameters or on-line blood volume monitoring or ultrasounds) have been disappointing. Despite this, achievement of a true dry weight is essential for adequate blood pressure control.

While inconsistent across studies, intradialytic weight gain and extracellular volume expansion influence blood pressure. In our analysis of 32,395 dialysis sessions in 443 patients over 6 months, interdialytic weight gain increased blood pressure.(20) Every 1% increase in weight gain between dialysis treatments was associated with a 1 mmHg increase in systolic BP. Thus, for an average 70 kg patient, a 5 kg weight gain results in an increase in systolic BP of 7 mmHg. The effect of interdialytic weight gain on BP was attenuated in patient with diabetes, older age and lower serum creatinine.

Supporting the effect of lowering dry weight on reducing BP, a randomized controlled trial of dry weight reduction was recently published.(3) In this trial, 150 clinically euvolemic patients were randomized 2:1 to lowering of dry weight (by 1%/session) vs usual care. Lowering of weight was stopped when the patient developed cramping, nausea, or hypotension during dialysis. Over 8 weeks, lowering the dry weight reduced ambulatory systolic BP by 7.1 mmHg beyond usual care. Therefore, in patients whose BP is difficult to control, reducing their target dry weight during dialysis is effective at lowering blood pressure.

The role of sodium on blood pressure

Extracellular fluid volume expansion is a primary contributor to high blood pressure in hemodialysis patients. Therefore, maintaining sodium balance, limiting sodium intake and minimizing interdialytic fluid intake are key to controlling blood pressure. Clinical studies have clearly demonstrated that sodium restriction lowers blood pressure and improves left ventricular hypertrophy in hemodialysis patients.

Sodium balance in hemodialysis patients is a function of salt intake and sodium removal during hemodialysis. With the onset of programmable machines, ultrafiltration volume is set into the machine which lead to a major advance in volume control. Previously, when the dialysate sodium was set to 126 meq/L and ultrafiltration was not programmable, sodium removal during dialysis was due to diffusion. Now, removal of sodium during hemodialysis is mostly due to convection (based on prescribed ultrafiltration with sodium removed from filtered plasma) and partially due to diffusion (based on the gradient between plasma and the dialysate). When larger dialyzer membranes were developed, solute clearance occurred much quicker and allowed urea removal to occur during shorter HD session. This resulted in larger osmolar shifts and resultant "dialysis dysequilibrium syndrome." Thus, dialysate sodium is now set higher to minimize dialysis dysequilibrium syndrome and the net effect is higher time averaged dialysate sodium concentrations (140-145 meq/L). Thus, many patients leave hemodialysis with relative hypernatremia and a positive sodium balance resulting in increased thirst, larger weight gains and ultimately higher blood pressure.

A small crossover study of 11 hemodialysis patients assigned to 3 different dialysate Na prescriptions (time average Na 138 meq/L, TAC 140 meq/L, TAC 147 meq/L) demonstrated a stepwise increase in thirst, interdialytic weight gain and ambulatory blood pressure with higher sodium dialysate.(21) Average ambulatory BP was 136/82 mmHg with TAC 138 meq/L vs 139/81 mmHg with TAC 140 meq/L and 147/84 mmHg with TAC 147 meq/L. Other small clinical trials have also demonstrated lowering the dialysate sodium can improve overall blood pressure control (**Table 1**).

Table 1. Published clinical studies on the effect of lowering dialysate sodium on subsequent blood pressure.

Reference	N	Dialysate Na Change	BP effect	Comments
Krautzig(22)	8	140 → 135 meq/L	Decreased	Also dietary Na restriction and fixed Na decrease
Farmer(23)	10	138-140 → 133-135 meq/L	Decreased	Fixed decrease in Na, ABP measured
Kooman(24)	6	140 → 136 meq/L	NS	Fixed decrease in Na
Ferraboli(25)	14	140→135 meq/L	Decreased	Fixed decrease in Na
De Paula(26)	27	138→135	Decreased	Tailored decrease in Na
Lambie(27)	16	136→variable	Decreased	Progressive titration in Na based on dialysate conductivity
Sayarlioglu(28)	18	Variable based on preHD Na	Decreased	Decreased IVC diameter

Sodium loading during hemodialysis clearly results in higher thirst with resultant volume expansion, increased cardiac output, and subsequent hypertension. Interestingly, recent studies suggest exposure to high sodium may result in hypertension independent of its effects on extracellular volume. In a study of young dahl-sensitive rats, increasing plasma sodium increased central sympathetic outflow.(29) Another study demonstrated increased brain sodium and osmolality increased ANGII levels and increased sympathetic outflow.(30) In vitro, high medium sodium concentrations results in hypertrophy of cardiomyocytes and vascular smooth muscle.(31) Increased sodium concentration (from 135-145) in endothelial cell culture medium produce significant endothelial cell stiffness and decreased NO in the presence of aldosterone.(32, 33) In these studies, high sodium resulted in interstitial hypertonicity (in machrophages) and decreased endothelial nitric oxide synthase expression and elevated BP. In summary, high salt diet, volume expansion, and exposure to high sodium dialysate all result in high blood pressure in hemodialysis patients.

The role of sympathetic overactivity on blood pressure

Sympathetic overactivity appears to contribute to hypertension in hemodialysis populations and it has been proposed that activation of chemoreceptors within the kidney by uremic metabolites may play an important role in hypertension. Activation of these chemoreceptors leads to a neural reflex that traverses afferent pathways to the central nervous system, resulting in increased efferent sympathetic tone. In a study by Converse et al, sympathetic nervous activity was measured in 5 hemodialysis patients

who had undergone bilateral nephrectomies and 18 hemodialysis patients without nephrectomy.(34) In comparison to 11 healthy controls, patients who had not undergone nephrectomy had significantly elevated sympathetic nervous activity on neurograms, while patients who had bilateral nephrectomy had sympathetic nervous activity similar to normal patients.

BLOOD PRESSURE AND OUTCOMES

Systolic blood pressure exhibits a U-shaped relationship with cardiovascular outcomes

The relationship between systolic BP and cardiovascular outcomes in hemodialysis is unclear. A number of epidemiologic studies have identified a reverse association between blood pressure and outcomes, suggesting higher systolic BP to be associated with improved cardiovascular outcomes.(35, 36) Other studies have identified a U-shaped relationship between systolic BP and outcomes, with low systolic BP and very high systolic BP being associated with adverse outcomes.(7) In addition, a recent study by Tentori et al, identified patients whose blood pressures were at the KDOQI guideline targets of predialysis SBP <140/90 mmHg,(37) had a nearly 2 fold higher mortality compared to patients whose BP were never <140/90.(38)

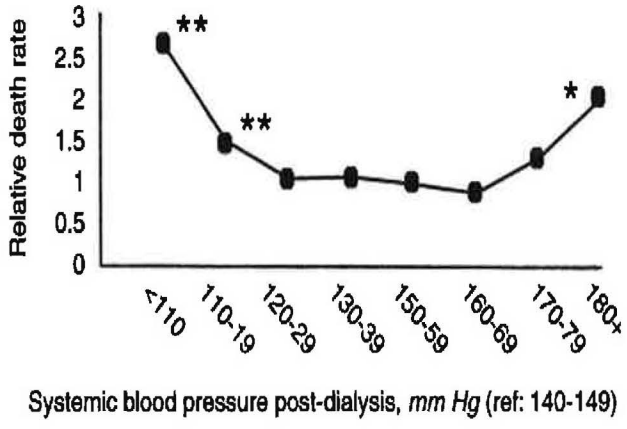


Figure 2. Relationship between postdialysis systolic BP and relative death rate among 5,422 incident hemodialysis patients followed for up to 5 years.

Higher blood pressure is associated with left ventricular hypertrophy

However, a prospective cohort with longer follow-up of 41 months, identified higher baseline mean arterial pressure to be associated with increased development of left ventricular hypertrophy, left ventricular dilation, de novo coronary artery disease and congestive heart failure.(39)

Decrease in pulse pressure during hemodialysis is associated with improved 6-month outcomes

Klassen and colleagues identified higher pulse pressure, when adjusted for systolic BP, to be associated with higher 1-year mortality among prevalent hemodialysis patients.(40) Further, lowering of pulse pressure during hemodialysis is associated with improved 6-month outcomes (**Figure 3**).(41)

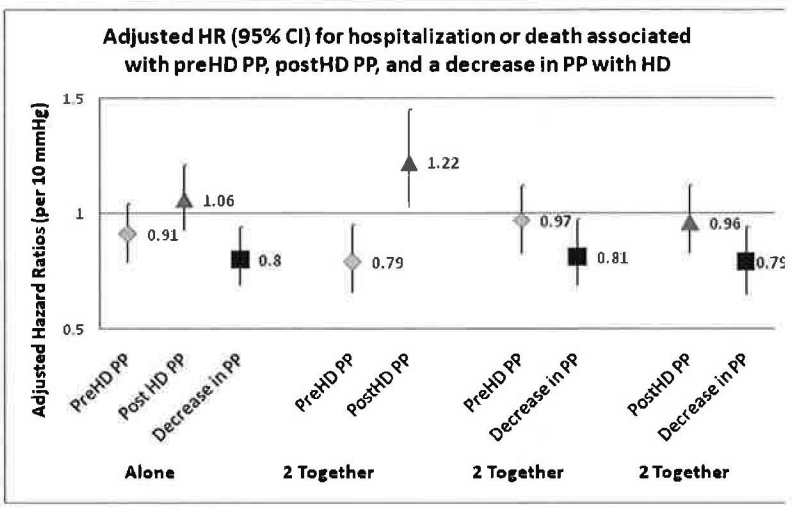


Figure 3. Relationship between predialysis pulse pressure, postdialysis pulse pressure and a decrease in pulse pressure during hemodialysis and adjusted hazard of hospitalization or death among 438 prevalent HD patients.

Interestingly, the relative change in blood pressure during hemodialysis was more predictive of clinical outcomes that either pre or postdialysis pulse pressure analyzed independently. Therefore, when determining the relationship between blood pressure and outcomes in dialysis patients, it is important to analyze pre and postdialysis blood pressure together.

INTRADIALYTIC HYPERTENSION

Intradialytic hypertension is relatively common in hemodialysis patients

While hemodialysis lowers BP in most hypertensive end-stage renal disease patients, some patients exhibit a paradoxical increase in BP during hemodialysis. This increase in BP during hemodialysis, termed intradialytic hypertension (IDH), has been recognized for many decades (42, 43); however no standard definition of IDH exists, it is often under recognized, the pathophysiology is poorly understood, and the clinical consequences have only recently been investigated.(18, 44-47)

Though no common definition of IDH exists, the occurrence of an increase in BP pre to postdialysis has been identified in up to 15% of maintenance hemodialysis patients. In our retrospective analysis of 438 prevalent hemodialysis participants enrolled in a randomized controlled trial of blood volume monitoring (CLIMB),(48) we identified 13.2% of participants exhibited an increase in SBP of more than 10 mmHg from pre to postdialysis.(18) In a separate analysis of 1,748 incident hemodialysis patients enrolled in the USRDS Dialysis Morbidity and Mortality Wave II cohort, 12% exhibited >10 mmHg increases in SBP pre to postdialysis.(45) Another author noted that 5-15% of hemodialysis patients have hypertension resistant to ultrafiltration and one survey of hemodialysis patients noted 8% of treatments over a 2-week period were associated with an increase in MAP >15 mmHg during or immediately after hemodialysis.

Intradialytic hypertension is associated with adverse outcomes

Recent investigations into the prognostic significance of intradialytic BP changes have identified intradialytic hypertension to be associated with adverse clinical outcomes. In our secondary analysis of 438 participants in CLIMB, participants whose SBP rose with hemodialysis or whose SBP failed to lower from pre to postdialysis, had a 2-fold adjusted increased odds of hospitalization or death at 6-months compared to participants whose SBP fell with hemodialysis (**Figure 4**).(18) When the cohort was restricted to participants with KDOQI defined hypertension,(49) the differences in clinical outcomes were even more striking. Hypertension affected 79% of all participants and of those with hypertension, those whose SBP increased with HD had a 2.61 fold increased odds of hospitalization or death at 6-months compared to participants whose SBP declined with HD (**Figure 4**).

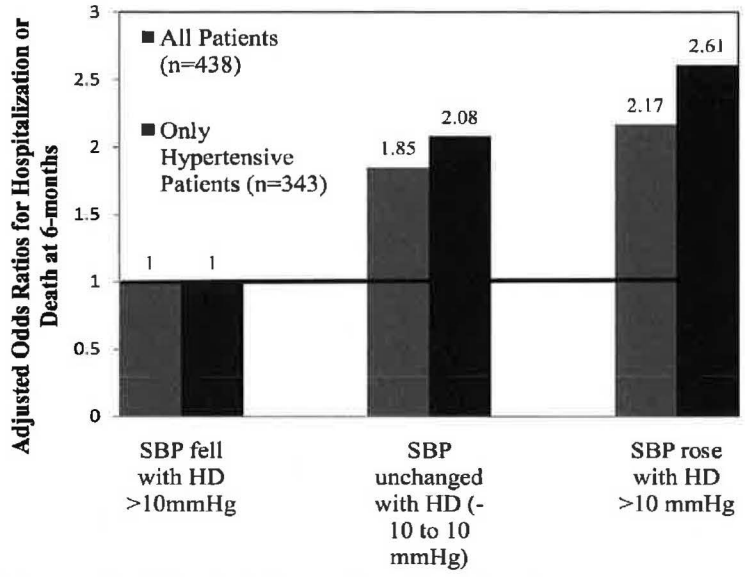


Figure 4. Adjusted 6-month odds ratio of non-access related hospitalization or death among prevalent ESRD participants categorized by systolic BP changes with HD

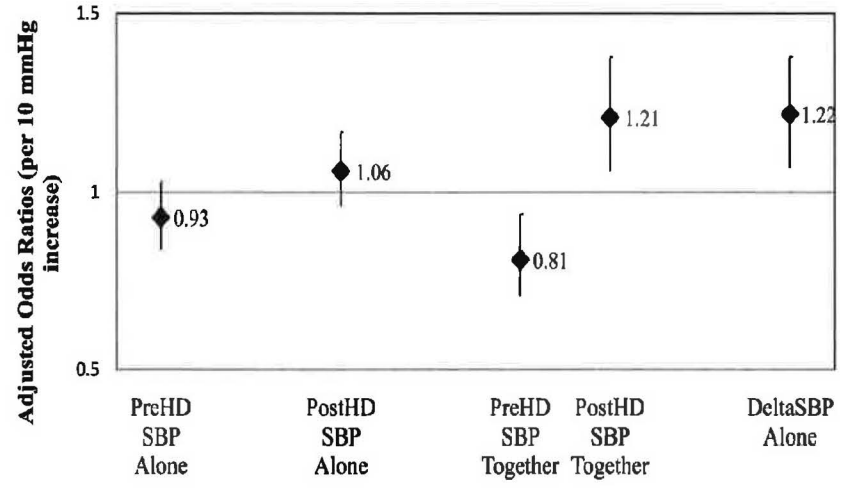


Figure 5. Adjusted 6-month odds ratio (95% confidence interval) for non-access related hospitalization or death associated with 1) predialysis SBP (per 10 mmHg increase) when tested alone, 2) postdialysis SBP (per 10 mmHg increase) when tested alone, 3) pre and postdialysis SBP when tested together (per 10 mmHg increase in each), and 4) SBP change with HD (per 10 mmHg increase)

While some studies have identified predialysis SBP to have an inverse association with mortality,(35, 36) an increased postdialysis SBP has been noted in other investigations to be associated with adverse outcomes.(7) In our analyses, neither pre nor postdialysis SBP tested alone were predictive of clinical outcomes; however, models including both pre and postdialysis

SBP together demonstrated adverse outcomes associated with a lower predialysis SBP and higher postdialysis SBP (**Figure 5**).(50) In models including change in SBP pre to postdialysis (deltaSBP), every 10 mmHg increase in SBP with HD was associated with an adjusted 22% increased odds of hospitalization or death at 6-months.(18)

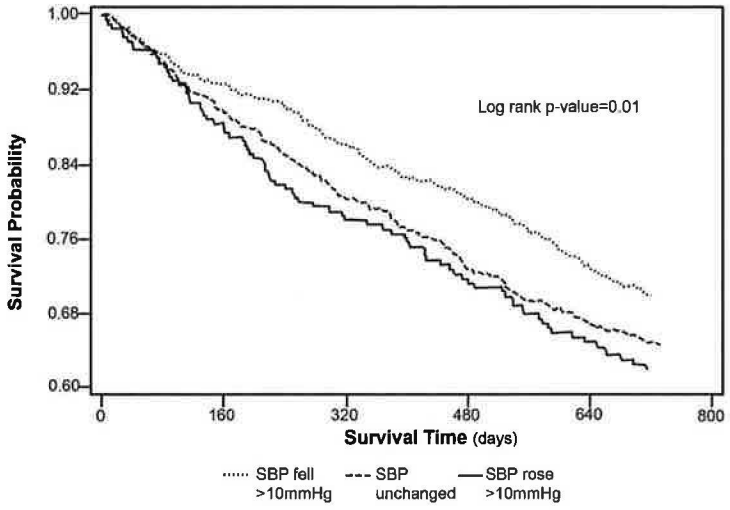


Figure 6. Among a cohort of 1,748 incident dialysis patients, patients whose systolic BP was unchanged or increased during hemodialysis exhibited higher 2-year mortality compared to patients whose systolic BP decreased during HD.

Similarly, in our analysis of 1,748 incident hemodialysis patients prospectively followed in the United States Renal Dialysis Systems Dialysis Morbidity and Mortality Wave 2 Study, intradialytic hypertension was associated with increased 2-year mortality (**Figure 6**). In this study, there was an adjusted 6% increased hazard of death at 2-years associated with every 10 mmHg increase in SBP during HD.(51)

Pathogenesis of intradialytic hypertension

While the mechanism and pathophysiology of intradialytic hypotension has been extensively investigated, the pathogenesis of intradialytic hypertension remains to be determined. Numerous factors have been suggested to contribute to intradialytic hypertension and are listed in **Box 1**.(50)

Box 1. Potential Pathophysiologic Mechanisms of Intradialytic Hypertension

- Volume overload
- Sympathetic over-activity
- Activation of the renin-angiotensin aldosterone system
- Endothelial cell dysfunction
- Dialysis-specific factors
  - net sodium gain
  - high ionized calcium
  - hypokalemia
- Medications
  - Erythropoietin stimulating agent
  - Removal of antihypertensive medications
- Vascular stiffness

Volume

Extracellular fluid overload plays a significant role in poorly controlled BP in hemodialysis patients. Prior investigations of intradialytic hypertension (IDH) have suggested volume overload may be a key contributor to its pathogenesis. Cirit and colleagues investigated 7 patients who exhibited significant cardiac dilation on echocardiography and had BP elevations with hemodialysis which were not responsive to antihypertensive medications. Following intense ultrafiltration and lowering of dry weight, the echocardiographic volume parameters improved and the BP response to hemodialysis normalized in most patients.(52) However, in another investigation of patients with IDH, volume overload measured by echocardiography was not identified in patients with IDH compared to controls.(46) Therefore, while select subsets of patients with hypervolemia may exhibit IDH, volume overload does not solely explain the pathophysiology of BP elevations with hemodialysis in all patients.

Sympathetic over-activity

IDH is caused by an increase in stroke volume and/or vasoconstriction with an inappropriate elevation in PVR during hemodialysis; therefore, it appears plausible that stimulation of the sympathetic nervous system should contribute to the development of IDH. Further, it is well recognized that hemodialysis patients have excess sympathetic nervous activity as measured by microneurography.(34, 53) However, in an investigation by Chou et al, there was neither an increase in plasma epinephrine nor plasma norepinephrine during hemodialysis to explain the increase in PVR among patients with IDH.(46) However, circulating levels of catecholamines do not always correlate with BP changes and differences in microneurography among patients with and without IDH have not been performed.

Renin-angiotensin-aldosterone system

Alternative explanations for IDH include excess stimulation of the renin-angiotensin-aldosterone system (RAAS) associated with intravascular volume reduction. However, individual responses to volume removal and activation of RAAS are not consistent. In 2 separate investigations, individual BP responses to hemodialysis and ultrafiltration (UF) were not related to blood volume (BV) changes during hemodialysis as the percent change in BV was similar between participants with and without hemodialysis-responsive BP.(54, 55) Further, in a study of 30 patients with and without IDH, there was no increase in plasma renin pre to postdialysis in patients with IDH to suggest RAAS activation contributes to IDH.(46)

Endothelin-1

More recent investigations have suggested abnormal endothelial cell responses may play a significant role in hemodynamic changes during HD.(46, 47, 56) In response to ultrafiltration, mechanical and hormonal stimuli, the endothelial cells synthesize and release humoral factors which contribute to BP homeostasis. Imbalances in endothelial-derived hormones, such as nitric oxide (a smooth muscle vasodilator) and endothelin-1 (a vasoconstrictor), can lead to hypotension or hypertension during HD. To date, 3 studies have investigated balances in endothelial-derived factors in patients with IDH. In an investigation of 27 patients (9 with IDH, 9 with intradialytic hypotension and 9 with stable intradialytic BP), the authors compared pre and postdialysis levels of fractional exhaled nitric oxide (NO), L-arginine, serum nitrite+nitrate, asymmetric dimethyl arginine (ADMA), and endothelin-1 (ET-1).(47) Predialysis fractional exhaled NO was lowest in patients whose BP did not change or rose with HD compared to those with intradialytic

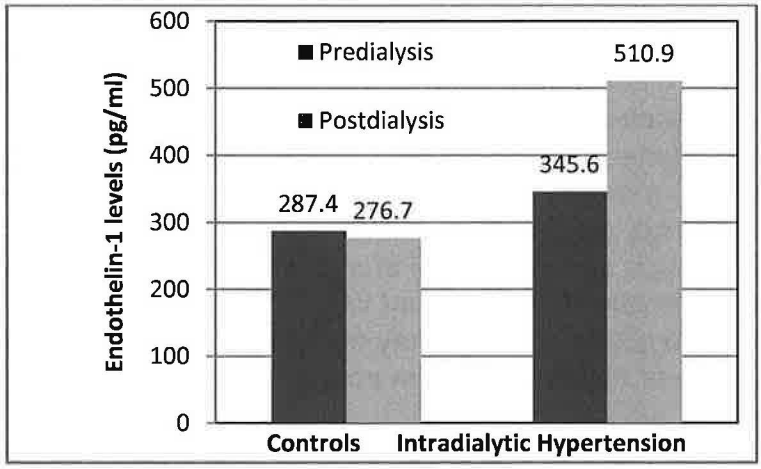


Figure 7. Comparison of pre and postdialysis endothelin-1 levels between 30 patients without intradialytic hypertension (controls) and 30 patients with intradialytic hypertension

hypotension. There was no significant difference in L-arginine, nitrite+nitrate or ADMA between groups, but ET-1 increased pre to postdialysis in the 9 patients with IDH. In a larger study of 60 patients with and without IDH, Chou et al also identified imbalances in endothelial-derived BP regulators.(46) Patients with IDH exhibited a significant increase in ET-1 pre to postdialysis compared to patients without IDH (**Figure 7**). Further the balance between NO and ET-1 (NO/ET-1 ratio), while depressed in both groups postdialysis, was significantly lower in patients with IDH. Similarly, El-Shafey and colleagues, in a study of 45 hemodialysis patients, noted pre to postdialysis ET-1 levels increased in patients with IDH, decreased in patients with intradialytic hypotension and remained unchanged in patients whose BP did not change during HD. (57) Thus, these 3 studies suggest IDH may be caused by abnormal endothelial cell response to hemodialysis resulting in inappropriately low NO and excess ET-1.

Medications

- Removal of antihypertensive medications

The dialysis procedure removes a number of antihypertensive medications and clearly removal of antihypertensive medications could precipitate IDH. Particular antihypertensive agents, such as angiotensin converting enzyme inhibitors (with the exception of fosinopril) and beta-blockers (atenolol and metoprolol) are removed by dialysis (see **Table 3**, pg 18).(37) While removal of antihypertensive agents during HD should be considered in any patient with IDH, it has not been investigated whether this plays a significant role in the pathogenesis of IDH and a prior study demonstrated IDH occurred in patients off antihypertensive agents.(46)

- Erythropoietin stimulating agents (ESA)

The use of ESA is associated with increased BP in hemodialysis patients.(58, 59) In a small investigation of the acute effects of ESA in hemodialysis patients, within 30 minutes following intravenous ESA, there was a significant increase in ET-1 and a concomitant rise in MAP which was not demonstrated in patients given subcutaneous ESA or placebo. In addition, 53% (10/19) of patients in this study given intravenous ESA had an increase in MAP >10 mmHg in the interdialytic period. Thus, if ESA is given intravenous prior to the end of hemodialysis, it is possible this may contribute to the development of intradialytic hypertension in susceptible patients.

Dialysis-specific factors

- Sodium

Hypernatric dialysate has been used to help maintain hemodynamic stability during hemodialysis, but it can result in a positive sodium balance with concomitant increased thirst, increased interdialytic weight gain, net weight gain, and interdialytic hypertension.(60) In a prospective crossover study comparing different sodium dialysate profiles in 11 patients, higher time-averaged sodium dialysate concentrations of 147 mmol/L (compared to 138 or 140 mmol/L) during hemodialysis resulted in higher 24-hour ambulatory SBP (up to 10 mmHg), diastolic BP, and BP load.(21) In addition, the use of standard sodium dialysate (such as 140 meq/L) in a patient with a predialysis sodium <140 meq/L will result in an intradialytic sodium load which could contribute to IDH. However, while inadequate sodium solute removal may contribute to poorer overall BP control, no study has tested the role of dialysate sodium concentration in the development of IDH.

- Potassium

Low serum potassium can have a direct vasoconstrictor effect but the role of dialysate potassium in intradialytic BP is uncertain. In a small investigation of 11 hemodialysis patients, Dolson et al analyzed the effects of 3 different dialysate potassium concentrations (1, 2 and 3 mmol/L) on BP predialysis, BP immediately postdialysis and BP 1 hour after hemodialysis. BP declined during hemodialysis with all dialysate potassium concentrations, however BP significantly increased 1 hour postdialysis in patients treated with 1 mmol/L and 2 mmol/L potassium dialysate.(61) While this study suggests hypokalemia induced by low potassium dialysate may cause rebound hypertension following hemodialysis, it is unlikely that low potassium dialysate plays a significant role in IDH as prior investigations identified IDH in patients regardless of the prescribed potassium baths.(46, 47)

- Calcium

It is well established that an acute increase in ionized calcium increases myocardial contractility, increases cardiac output, and can improve hemodynamic instability during hemodialysis. (62-65) In a few small studies, high calcium dialysate has been used to improve hemodynamic instability in hypotensive prone patients and/or patients with impaired cardiac function.(66-68) High calcium dialysate has also been noted to decrease arterial compliance, increase arterial stiffness and result in less of a decline in SBP during HD.(68-70) While increasing dialysate calcium can stabilize BP during hemodialysis, the role of high calcium dialysate in the pathophysiology of IDH has not been fully investigated and patients have been demonstrated to exhibit IDH on standard calcium dialysate.(46)

Treatment of intradialytic hypertension

In patients who develop intradialytic hypertension, consideration should be paid to the possible etiologies which can lead to IDH (**Box 1**). In certain instances, the etiology is clear; such as a patient who has missed a few dialysis treatments, is above their dry weight and develops intradialytic hypertension. After a few treatment sessions and a return to their normal dry weight, the intradialytic hypertension usually resolves. In other patients, the etiology and treatment may not be forthright and the following therapeutic options should be considered in hypertensive patients with intradialytic hypertension.

Volume management

Considering 2 small studies demonstrated improvement in IDH with lowering of dry weight over time in select individuals,(52, 71) an attempt to reduce dry weight should be performed in patients with IDH. Further, patients should be instructed to minimize salt and fluid intake between hemodialysis sessions. However, while lowering of dry weight may improve IDH in some patients; this is unlikely to resolve IDH in all instances.

Inhibition of the sympathetic nervous system

The role of sympathetic over-activity in IDH has not been firmly established. It is clear that patients with renal disease have evidence of sympathetic nerve activity, which normalizes after nephrectomy.(34) Whether patients who have undergone bilateral nephrectomy develop IDH is unknown but this certainly cannot be routinely advocated to control BP. Adrenergic blockers such as alpha- and beta-blockers should be considered as therapeutic options to control BP. In particular, carvedilol and labetolol with combined alpha and beta-adrenergic blockade should be considered as they are not significantly removed by hemodialysis.

Inhibition of the renin-angiotensin-aldosterone system

Activation of the renin-angiotensin-aldosterone system with ultrafiltration during HD may contribute to IDH and inhibition of RAAS can serve as a therapeutic option. In a small study of 6 patients with intradialytic hypertensive crisis, administration of captopril was beneficial in controlling BP.(72) Newer longer-acting angiotensin converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) may improve intradialytic hypertension particularly since certain RAAS inhibitors can inhibit ET-1 release,(73) however this has not been investigated to date.

Pharmacologic inhibition of endothelin-1

Three investigations have demonstrated elevated postdialysis levels of ET-1 in patients with IDH; however it is unknown whether pharmacologic inhibition of ET-1 can abolish IDH. Specific ET-1 antagonists (such as avosentan) may be effective if they can be demonstrated to be safe in hemodialysis populations. Alternatively, nonspecific ET-1 inhibitors (such as RAAS inhibition or carvedilol) could potentially improve IDH by inhibiting ET-1 release.(73-75) Our ongoing pilot study (NCT00827775) is testing the efficacy of carvedilol as treatment for intradialytic hypertension and endothelial cell dysfunction.

Antihypertensive regimen

Class of antihypertensive agents, timing and dosing should be reviewed when patients have intradialytic hypertension. As certain ACE-I and beta-blockers are removed by dialysis; these medications should be changed to non-dialyzed antihypertensives. Patients should also be instructed not to withhold BP medications prior to hemodialysis. As mentioned, administration of captopril has been shown to improve intradialytic hypertensive crisis, however considering this medication is short-acting and removed by dialysis, alternative agents may be preferred.(72)

Erythropoietin stimulating agents

As previously reviewed, intravenous administration of ESA can raise BP in certain individuals. In patients with intradialytic hypertension, discussions with the patient regarding switching from intravenous to subcutaneous ESA should occur, particularly if the patient requires large ESA doses.

Altering dialysis prescription

Inadequate sodium solute removal can result in excess fluid intake and hypertension; therefore dialysis prescriptions should be tailored to achieve a net negative sodium solute balance. Prescriptions which have a programmed variable sodium dialysate have been shown to minimize sodium solute loading during hemodialysis and can result in lower postdialysis BP, particularly in patients with serum sodium <140 mEq/L who may receive a sodium load with the use of standard sodium dialysate.(76) Second, high calcium dialysate increases cardiac contractility and cardiac output which could exacerbate hypertension during hemodialysis; therefore, high calcium dialysate should be avoided in patients with intradialytic hypertension. Other changes to the dialysis prescription which may improve intradialytic hypertension include longer duration of hemodialysis, more frequent hemodialysis, and or nocturnal hemodialysis. These alternative dialytic modalities have been demonstrated to improve BP control (77, 78) and potentially endothelial cell dysfunction(79); therefore, while they have not been specifically investigated, they should be considered in patients with refractory, difficult to treat intradialytic hypertension.

GOAL BP TARGETS IN DIALYSIS PATIENTS

The ideal blood pressure to optimize outcomes in hemodialysis patients is unknown

It remains to be determined what blood pressure should be achieved to improve outcomes in dialysis patients. It is also uncertain which blood pressure measurement to target. A number of measurements are available, including dialysis unit readings (predialysis, postdialysis, intradialytic), office visit blood pressure, home blood pressure, and ambulatory blood pressure. Recent studies have suggested home or ambulatory BP readings to be better predictors of clinical outcomes.

Based on expert opinion, KDOQI guidelines recommend targeting a predialysis BP <140/90 mmHg and a postdialysis BP <130/80 mmHg providing there is no substantial hypotension during hemodialysis.(37) The Kidney Disease Improving Global Outcomes practice guidelines recommend using predialysis BP to guide therapy and targeting a predialysis BP <140/90 but they acknowledge the optimal BP remains unknown. Considering there is little evidence to support these guidelines and epidemiologic data suggest lower predialysis BP to be associated with higher mortality, these guidelines have been extensively criticized.

Recent studies have identified dialysis unit BP readings to be poor correlates of true blood pressure as measured by ambulatory blood pressure.(80) In a meta-analysis of 18 studies including 692 hemodialysis patients, predialysis systolic BP overestimated ambulatory blood pressure by 9 mmHg and exhibited agreement limits from underestimating by 25 mmHg to overestimating ABP by as high as 45 mmHg. Postdialysis BP was also a poor estimate of BP measured by ABP and underestimated SBP on average ~2 mmHg with agreement limits from -40 mmHg to 30 mmHg.

Considering dialysis unit BP parameters are poor estimates of the hemodynamic burden a patient experiences, home blood pressure monitoring can be used to improve the diagnosis of hypertension in hemodialysis patients. In a study comparing home BP readings to ABP as the gold standard, a cutoff home SBP of >150 mmHg had a sensitivity of 80% and specificity of 84% for diagnosing hypertension by ABP (defined as ABP>135/85).(16)

Alternative options to improve the diagnosis of hypertension include using a 2-week average of dialysis unit BP or a mid-week median mid-session systolic BP.(81) In an analysis by Agarwal et al, averaging all available BP readings (predialysis, intradialytic, and postdialysis) over 2-weeks improved the diagnosis of hypertension when using a cut-off of >135/75 defining HTN. Further, if the mid-week median dialysis unit SBP was >140 mmHg, this was predictive of hypertension by ambulatory BP (defined as ABP >135/85 mmHg).

Recent investigations have identified higher blood pressure measured by either home BP readings or ambulatory BP to be important predictors of mortality.(15, 82) A recent analysis of 326 hemodialysis patients identified higher ambulatory blood pressure (>120 mmHg) to be a predictor of higher 6-year mortality.(15)

In summary, dialysis unit BP readings are poor estimates of the interdialytic hemodynamic burden and therefore have not been found to be predictors of mortality. Higher home and ambulatory BP readings are associated with higher mortality, yet the ideal BP target to improve outcomes remains to be determined.

ANTIHYPERTENSIVE AGENTS IN HEMODIALYSIS

In the US, over 80% of hemodialysis patients require antihypertensive therapy to control blood pressure. Most classes of antihypertensive agents are appropriate for use in hemodialysis patients and a combination of agents are typically required to control BP. This next section will review the choice of antihypertensive agents in hemodialysis patients, the effectiveness and safety of select antihypertensive agents, the available clinical trials investigating outcomes with antihypertensive agent class, and newer antihypertensive agents on the horizon for use in hemodialysis patients.

Renin angiotensin aldosterone system (RAAS) inhibitors

Inhibitors of the renin angiotensin aldosterone system (RAAS) should be considered as first line agents for blood pressure control in hemodialysis patients due to their documented safety, their tolerability, and their beneficial effect on left ventricular hypertrophy, arterial stiffness, endothelial cell function, and oxidative stress.(83-86) The KDOQI guidelines suggest RAAS inhibitors to be the preferred antihypertensive agents in HD patients, particularly those with diabetes mellitus or a history of heart failure.(37)

Angiotensin converting enzyme inhibitors (ACE-I)

A number of clinical trials have demonstrated ACE-I are safe and effective in hemodialysis patients. In a small study of 11 hemodialysis patients, the observed administration of lisinopril following hemodialysis thrice weekly effectively lowered ambulatory systolic blood pressure by 22 mm Hg (from 149/84 to 127/73 mmHg) and was not associated with an increase in intradialytic hypotension.(87) Other trials which measured hemodialysis unit blood pressures demonstrated a 5-12 mmHg reduction in systolic blood pressure with ACE-I.(83, 88) Clinical trials have also shown ACE-I therapy to be relatively safe in hemodialysis with no significant effect on serum potassium and <3% incidence of symptomatic hypotension.(88) ACE-I are well tolerated overall and one of the most common reason for discontinuation is cough.(89) Cough can occur in 5-20% of patients and typically resolves within 2-6 weeks of discontinuing therapy. ACE-I have also been associated with higher requirements of erythropoietin stimulating agents (ESA) and have been associated with an anaphylactoid reaction with AN69 dialyzers.(90, 91)

Retrospective analyses and small clinical trials suggest ACE-I may improve outcomes in hemodialysis patients. Efrati et al, in a retrospective analysis of 126 hemodialysis patients (60 prescribed ACE-I and 66 not prescribed ACE-I) identified the use of ACE-I to be associated with improved survival.(92) Two retrospective analyses of hemodialysis patients with acute coronary syndromes suggest the use of ACE-I following MI to be associated with lower mortality.(93, 94) Another secondary analysis suggested the use of ACE-I may be associated with improved survival following cardiac arrest.(95) Ichihara et al demonstrated in a 12-month randomized controlled trial of ACE-I vs ARB vs placebo in 64 hemodialysis patients that low dose ACE-I (and ARB) improved pulse wave velocity.(83) Another small randomized trial of daily ACE-I vs placebo in 30 hemodialysis patients demonstrated regression of left ventricular hypertrophy with ACE-I.(84)

The largest randomized controlled study testing the effect of ACE-I on cardiovascular outcomes in hemodialysis patients was the FOSIDIAL (Fosinopril in Dialysis) trial (**Table 2**). In this study, 397 patients on maintenance hemodialysis for ≥6 months and with left ventricular hypertrophy were randomized 1:1 to fosinopril 20 mg/day vs placebo and followed for 2-years. The primary outcome was a combined endpoint of cardiovascular death, nonfatal myocardial infarction, unstable angina, stroke, cardiovascular revascularization, hospitalization for heart failure, and resuscitated cardiac arrest. Of note, hypertension was not an entry criteria for the study but the administration of fosinopril in hypertensive patients lowered systolic blood pressure ~ 6 mmHg greater than placebo (with an absolute change in systolic BP of 11.7 mmHg). While there was no significant difference in the primary endpoint between fosinopril and placebo, there was a nonsignificant 10% reduction in the primary endpoint with fosinopril.(88)

Table 2. Randomized Trials of Antihypertensive Agents in Hemodialysis Patients(96)

Reference	Patients	Intervention	Follow-up (months)	Results
ACE-I Trials				

Zannad et al(88)	397 HD patients with LVH	Fosinopril vs placebo	24	No effect of fosinopril on CV event rate
Combination Trials (ACE-I and ARB and CCB)				
Ichihara et al (83)	64 HD patients	Losartan, trandolapril, or placebo	12	Reduction in PWV with losartan and trandolapril
Shibasaki et al (97)	30 HD patients with hypertension	Losartan, enalapril or amlodipine	6	Regression of LVH with losartan
London et al(98)	24 HD patients with uncontrolled hypertension	Perindopril vs nitredipine	12	Regression of LVH with perindopril
ARB Trials				
Kanno et al(99)	24 HD patients with diabetes and LVH	Losartan or placebo	12	Regression of LVH with losartan
Takahashi et al (85)	80 HD patients	Candesartan vs control	19	Reduction in CV event rate with candesartan
Suzuki et al (86)	366 HD patients with hypertension	Either losartan, candesartan or valsartan vs placebo	36	Reduction in CV events with ARB
Combined α- and β-Blocker Trials				
Cice et al (100, 101)	132 HD patients with dilated cardiomyopathy	Carvedilol vs placebo	12-24	Regression in cardiomyopathy and improved survival with carvedilol
Calcium Channel Blocker Trials				
Tepel et al(102)	251 HD patients with hypertension	Amlodipine vs placebo	30	No effect on AC mortality but lower CV events with amlodipine

While ACE-I are a good first-line antihypertensive agent, most ACE-I (with the exception of fosinpril) are removed with hemodialysis (**Table 3**). Hemodialysis removal of ACE-I is not problematic in most hypertensive patient and may help avoid intradialytic hypotension. However, in patients who experience intradialytic hypertension, dialyzable ACE-I should be changed to either an ARB or a nondialyzable ACE-I (ie, fosinopril).(18, 103) Dosing of most ACE-I should be daily, however lisinopril has a longer half life due to it primarily being renally excreted and good blood pressure control has been demonstrated with thrice weekly administration following hemodialysis.(87) For noncompliant patients, directly observed lisinopril administration immediately following hemodialysis may be a good therapeutic option.

Table 3. Pharmacokinetics of Select Antihypertensive agents in Hemodialysis(37, 96, 104, 105)

Class	$T^{1/2}$ in ESRD	Range of Dosing (initial to usual or maximum)	%Removal with HD
Angiotensin converting enzyme inhibitors			
Captopril	20-30 hrs	12.5 – 50 mg q24 hr	Yes
Benazepril	?	5 – 40 mg q24 hr	20-50%
Enalapril	Prolonged	2.5 - 10 mg q24 to 48hr	35%
Fosinopril	Prolonged	10 - 80 mg q24 hr	<10%
Lisinopril	54 hrs	2.5 - 10 mg q24-48 hrs	50%
Ramipril	prolonged	2.5 - 10 mg q24 hrs	<30%
Angiotensin receptor blockers			
Losartan	4 hrs	50 - 100 mg q24	None
Candesartan	5-9 hrs	4 - 32 mg q24	None
Eprosartan	?	400 - 600 mg q24	None
Telmisartan	24 hrs	40 - 80 mg q24	None
Valsartan	6 hrs	80 - 160 mg q24	None
Irbesartan	11-15 hrs	75 – 300 mg q24	None
Aldosterone Antagonists			
Spironolactone[a]	?	25 – 50 mg qd	None
Eplerenone[b]	?	50 – 100 mg qd	None
Renin Inhibitor			
Aliskiren	?	150 – 300 mg qd	?
β-Blockers and Combined α- and β-blockers			
Atenolol	<120 hrs	25 – 50 mg q48	75%
Metoprolol	3-8 hrs	50-200 mg bid	High
Propranolol	3-6 hrs	40 – 120 mg bid	<5%
Carvedilol	7-10 hrs	6.25 - 25 mg bid	None
Labetalol	6-8 hrs	100 – 1200 mg bid	<1%
Calcium channel blockers			
Amlodipine	?	2.5 – 10 mg qd	None
Diltiazem	Prolonged	Varies with formulation	<30%
Nifedipine	~5 hrs	30 - 180 mg qd[c]	Low
Nicardipine	Prolonged	30 – 60 mg bid[c]	?
Felodipine	11-16	2.5 – 10 mg qd[c]	No
Verapamil	Prolonged	Varies with formulation	Low
Alpha-adrenergic blockers			
doxazosin[c]	15-22 hrs	1 - 8 mg qhs	None
terazosin	9-12 hrs	1 – 20 mg qhs	None
prazosin	2-4 hrs	1 – 5 mg bid to tid	?
Other			

Clonidine	18-41 hrs	0.1 – 0.4 mg bid-tid	<5%
Hydralazine	7-16 hrs	10 – 100 mg q8hr	None
Isosorbide dinitrate	?	5 – 40 mg tid	Yes
Minoxidil	?	5 – 100 mg qd	Partially

[a]not recommended with crcl<30 ml/min and contraindicated in anuric patients
[b]contraindicated with crcl<30ml/min
[c]extended release formulations

Angiotensin receptor blockers (ARB)

Clinical trials have also demonstrated ARB to be safe and well tolerated in hemodialysis patients. In 2 small trials, the use of an ARB (vs placebo or usual care) was not associated with hyperkalemia or with higher ESA requirements.(85, 86) The effects of ARB on blood pressure seem to vary in different studies and this is likely due to differences in how blood pressure was measured (whether via dialysis unit blood pressure or the gold standard of ambulatory blood pressure). In a study by Takahashi et al, the use of candesartan (4-8 mg/day) had no effect on dialysis unit blood pressure during 3 years of follow-up (blood pressure at baseline was 153/82 and was 153/83 mmHg during follow-up), however home blood pressure recordings were not obtained.(85) In a trial by Suzuki et al, patients prescribed an ARB exhibited a ~14 mmHg decrease in blood pressure during 3 years of follow-up (from 154/81 mmHg to 140/80 mmHg) which was similar to the placebo arm.(86) In a separate small study of valsartan or candesartan in 11 hemodialysis patients, systolic blood pressure was significantly lowered ~30 mmHg with either ARB at 8 months.(106) Thus, ARB are relatively effective at lowering blood pressure and are well tolerated.

Small trials with surrogate endpoints have suggested ARB may improve cardiovascular outcomes by improving pulse wave velocity and reducing left ventricular hypertrophy (**Table 2**). Two larger studies also suggest ARB may improve hard endpoints such as cardiovascular events. In a study by Takahashi et al, 80 maintenance hemodialysis patients were randomized to candesartan 4-8 mg vs usual care and followed for 3 years for the combined primary endpoint of fatal or nonfatal myocardial infarction, unstable angina, hospitalized heart failure, ventricular tachycardia or fibrillation, or sudden death. The study was stopped early by the data safety monitoring board and the final analysis demonstrated candesartan therapy significantly reduced cardiovascular events and mortality rates in this trial.(85) In a study by Suzuki et al, 366 hypertensive hemodialysis patients were randomized in an open label fashion to either valsartan, candesartan, or losartan once daily vs placebo and followed for 36 months until the primary endpoint of fatal and nonfatal cardiovascular events (defined as the composite of cardiovascular disease (CVD) death, myocardial infarction, stroke, congestive heart failure, coronary artery bypass grafting, or percutaneous coronary intervention). In this study the use of an ARB reduced nonfatal CVD events in patients undergoing long-term hemodialysis but there was no difference in all-cause mortality.(86)

Of importance to note, none of the ARB are removed by hemodialysis (**Table 3**). Further, the simplicity of dosing of ARB (being once daily) make them an attractive option for blood pressure control when cost is not a significant consideration.

Combination therapy of ACE-I and ARB

In support of the use of more than one inhibitor of RAAS, one small study of 33 incident hemodialysis patients suggested a benefit with the combination of an ACE-I and ARB. This preliminary study randomized incident diabetic hemodialysis patients to an ACE-I vs ARB vs combination of ACE-I/ARB and achieved good blood pressure control (to <140 mmHg systolic) in all groups and regression of left ventricular mass index (LVMI) at 1-year in all arms. However, the patients treated with a combination of an ACE-I/ARB exhibited an additional 28% reduction in LVMI compared to those treated with RAAS inhibitor monotherapy.(107) While this small study suggests benefits to combination therapy, trials in non-ESRD populations at high cardiovascular risk have failed to demonstrate improved cardiovascular outcomes with a combination of RAAS inhibitors.(108) Thus, while adding an ARB to an ACE-I may improve blood pressure control and may further reduce LVH beyond monotherapy, larger studies are required to determine whether this therapeutic combination can improve CV outcomes in hemodialysis patients.

Aldosterone antagonists

While aldosterone antagonists are an attractive option for improving cardiovascular outcomes, particularly in patients with heart failure(109), the use of aldosterone antagonists in hemodialysis patients has not been fully investigated to date. Further, the clinical use of these agents may be limited due to concern about the risk of hyperkalemia. However, since most dialysis patients are anuric, hyperkalemia resulting from aldosterone blockade would have to be due to its effects on extrarenal potassium handling (such as inhibiting the intestinal elimination of potassium). In 2 small open label studies of low dose spironolactone, there was no significant increase in serum potassium in 14 patients with 6 weeks of thrice weekly spironolactone (25 mg) but 1/15 patients with daily spironolactone (25 mg) were withdrawn from the drug due to hyperkalemia (potassium of 7.6 mEq/L after 20 days of therapy).(110, 111) In one small prospective randomized double-blinded placebo-controlled crossover study of 8 hemodialysis patients, the administration of 50 mg of spironolactone twice daily in oligoanuric hemodialysis patients was effective at decreasing predialysis systolic blood pressure by 11 mm Hg and had no significant effect on pre or postdialysis plasma potassium at 2 weeks.(112) In a larger open label study of low dose spironolactone (25 mg/day) administered to 61 oligoanuric hemodialysis patients for 8 months, 11 patients discontinued use due to side effects (other than hyperkalemia) and potassium levels increased overall (4.6 mEq/L to 5.0 mEq/L) with treatment; however no patients had a potassium > 6.8 mEq/L or required ion exchange resin therapy. While these studies suggest in controlled observed settings, aldosterone antagonists maybe relatively safe, further research demonstrating their efficacy and safety are required prior to their use in hemodialysis patients.

Renin inhibitors

Aliskiren is in a new class of antihypertensive drugs and inhibits the conversion of antiotensinogen to angiotensin I (and therefore decreases the formation of angiontensin II) by directly inhibiting renin. Thus, renin inhibitors block the deleterious effects of

angiotensin II without increasing renin levels. This drug has shown promise for improving renal outcomes in patients with chronic kidney disease and diabetes.(113) The clearance of aliskiren is via hepatic metabolism with renal elimination. This drug has not been tested in hemodialysis populations and its removal with hemodialysis is unknown. Therefore, the role of this new agent in hemodialysis patients is yet to be determined as studies evaluating its efficacy and safety have not been performed to date.

β-adrenergic blockers

β-blockers continue to be important agents for blood pressure control in hemodialysis patients and should be the preferred antihypertensive agent in patients with recent acute coronary syndrome and those with heart failure.(37) In a small study of 8 hypertensive hemodialysis patients, atenolol following hemodialysis (directly observed therapy 3x/week) lowered ambulatory systolic blood pressure ~17 mmHg (from 144/80 to 127/69 mmHg) and did not significantly increase the incidence of intradialytic hypotension or hyperkalemia.(114) Notable adverse effects associated with b-blockers include bradycardia, erectile dysfunction, fatigue, and lipid and glucose abnormalities. In hemodialysis patients, nonselective β-adrenergic blockers (such as propranolol) may increase the risk of exercise-induced or fasting induced hyperkalemia, however this does not occur with selective β-adrenergic blockers (such as metoprolol).(115, 116) Overall, β-blockers are effective and fairly well tolerated in hemodialysis populations. Observational studies suggest the use of β-blockers may improve CV outcomes in hemodialysis patients. In one secondary analysis of 2,550 incident hemodialysis patients, the use of β-blockers in patients without a history of heart failure was associated with a lower risk of de novo heart failure, cardiac death and all-cause mortality. However, in this cohort only 20% of patients were administered this drug.(117) Foley et al, in a secondary analysis of 11,142 prevalent hemodialysis patient in United States Renal Database Systems Wave 3 and 4 Study identified only 8.5% of the population were prescribed β-blockers but their use was associated with a 16% lower adjusted hazard of death. Further, 2 secondary analysis suggest the use of β-blockers are associated with improved survival following cardiac arrest and acute myocardial infarction.(93, 95)

Water-soluble β-blockers such as atenolol and metoprolol are dialyzable and require supplementation to avoid exacerbation of arrhythmias following dialysis (**Table 3**). Metoprolol is mainly metabolized by the liver and therefore does not require dose adjustment while atenolol is excreted mainly by the kidneys and thus its half-life is prolonged in hemodialysis patients. However, patients who are noncompliant with medications can be given atenolol (directly observed therapy) following hemodialysis to effectively control interdialytic blood pressure.(114)

Combined α- and β-blockers

Combined α- and β-blockers are becoming increasingly popular for use in hemodialysis patients due to their effectiveness, reduced cost, and demonstrated benefit in patients with dilated cardiomyopathy. In one small trial of patients randomized to carvedilol vs placebo, carvedilol lowered systolic blood pressure ~14 mmHg (from 134/75 mmHg to

123/67 mmHg at 12 months). One caveat was that there was a fairly high rate of drop-out due to drug intolerability (20% with carvedilol vs 13% with placebo) which included hypotension, bronchospasm, and bradycardia. In this trial, 132 hemodialysis patients with New York Heart Association class II or III were randomized to carvedilol to placebo and followed for 12 months with a primary outcome of change in left ventricular (LV) volume (**Table 2**). At 12 months, carvedilol reduced LV volume and resulted in improved LV function and clinical status compared to placebo.(101) On additional follow-up of patients following completion of the study, patients assigned to carvedilol exhibited reduced all-cause mortality as well as fatal and nofatal cardiovascular events.**(100, 101)**

Combined α - and β-blockers (labetolol, carvedilol) are not significantly cleared by hemodialysis and thus provide the added benefit of not requiring additional dosing following hemodialysis. Dosing of combined α - and β-blockers are typically twice a day, however newer once a day formulations are now available (ie. Coreg CR).

Calcium channel blockers

Calcium channel blockers (CCB) can effectively lower blood pressure in hemodialysis patients and are even effective in patients with volume overload.(118) A recent randomized controlled trial found amlodipine (a dihydropyridine CCB) lowered systolic blood pressure ~10 mmHg without an increased risk of intradialytic hypotension compared to placebo (7% vs 13%, respectively).(102) Dihydropyridine CCB (examples include amlodipine, felodipine, and nicardipine) are highly selective inhibitors of vascular smooth muscle calcium channels and are thus effective at reducing systemic vascular resistance. The non-dihydropyridine CCB (diltiazem and verapamil) are more myocardial selective and their combined use with b-blockers are cautioned due to augmented suppression of cardiac contractility and increasing the risk of bradycardia and electrical conduction defects.

Two retrospective analyses suggest calcium channel blockers are associated with a lower risk of mortality in hemodialysis patients.(119, 120) However, one small clinical trial comparing a CCB (nitrendipine) to ACE-I (perindopril) failed to demonstrate a reduction in LVH with the use of a CCB despite effectively lowering blood pressure to similar levels (**Table 2**).(98) Tepel et al recently published results from a randomized controlled trial comparing amlodipine to placebo in 251 hypertensive hemodialysis patients. The primary endpoint was all-cause mortality with a secondary combined endpoint of all-cause mortality or cardiovascular events. While there was no difference in all-cause mortality at 30 months between arms, amlodipine significantly reduced the *post hoc* secondary combined endpoint of all-cause mortality and cardiovascular events.(102)

Calcium channel blockers are not removed by hemodialysis and thus do not require additional postdialysis dosing (**Table 3**). In addition, once daily dosing of most calcium channel blockers make them attractive for use in hemodialysis patients.

α-adrenergic blocking agents

α-adrenergic blocking agents, such as doxazosin, prazosin, and terazosin, are used less frequently for blood pressure control following the results of the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT).(121) In high-risk hypertensive patients randomized to doxazosin vs diuretic in ALLHAT, there was a higher rate of CV events in patients randomized to doxazosin. However, in hemodialysis patients requiring multiple antihypertensive agents to control blood pressure, these agents can be safely used and do not require additional dosing with hemodialysis. For longer acting formulations, nocturnal dosing is preferred to try to minimize the occurrence of postural hypotension.

Centrally acting sympathetic agonists

The central nervous system sympathetic agonists, such as methyldopa, guanabenz, guanfacine and clonidine, are used less frequently for blood pressure control because of their higher rates of adverse effects. These adverse effects include dry mouth, erectile dysfunction, fatigue and rebound hypertension. Clonidine is the main sympathetic agonist still in use in hemodialysis populations, particularly in those with difficult to control hypertension and those with significant hypertension during hemodialysis. Some nephrologists have found clonidine patches to be effective and well tolerated while avoiding the frequent dosing requirements of oral formulations.(122) While clonidine patches are preferred by some patients, they are not universally effective and some patients find them difficult to keep in place during strenuous activity and with showering.

Direct vasodilators

Hydralazine and isosorbide dinitrate are potent vasodilators and are effective at lowering blood pressure in patients with resistant or refractory hypertension. Hydralazine plus nitrates in addition to standard therapy (including an ACE-I and b-blocker) have been demonstrated to improve outcomes in African Americans with heart failure.(123) However, this drug combination has not been tested in hemodialysis patients. While this drug combination maybe effective, the major limitation is compliance due to thrice daily dosing and a pill burden of atleast 6 pills. Thus, in hemodialysis patients already prescribed other antihypertensive agents and phosphorus binders, this drug regimen is a less practical option. Hydralazine is not removed by hemodialysis, but isosorbide dinitrate is removed by hemodialysis and requires extra dosing around dialysis (**Table 3**). Due to reflex stimulation of the sympathetic nervous system with vasodilators, these drugs should be administered simultaneously with a β-blocker to offset tachycardia. The major side effects of hydralazine are fluid retention (managed by dialysis) and less commonly a drug-induced lupus-like syndrome including arthralgias, myalgias, joint swelling, pericarditis/pleuritis, rash, or fever.

Minoxidil appears to be a more potent vasodilator than hydralazine and can be reserved for patients who remain hypertensive despite other drug therapies. The benefit to minoxidil over hydralazine/nitrates is the ease of dosing which is once or twice a day (**Table 3**). While minoxidil is quite effective and is not extensively removed by hemodialysis, significant fluid retention including pleural and pericardial effusions can

occur during therapy and may require discontinuation if not controlled with hemodialysis.

Diuretics

Diuretics are used infrequently in hemodialysis patients. One study identified up to 32% of hemodialysis patients to be prescribed a diuretic during the first 30 days of hemodialysis initiation which declined to ~10% at 2 years.(124) In a secondary analysis of 16,420 hemodialysis patients from Dialysis Outcomes and Practice Patterns Study, diuretic use was associated with lower interdialytic weight gain and a lower relative risk of cardiac death which may have been due to confounding by indication with higher residual renal function in patients prescribed diuretics. However, this study supports the clinical experience that in select patients, such as those with residual renal function and urine output, diuretics can be helpful at controlling interdialytic weight gain and blood pressure and should not necessarily be stopped upon initiation of hemodialysis.

Endothelin-1 antagonists

Increasing evidence suggests endothelin, a potent vasoconstrictor, may play a role in the pathogenesis of hypertension.(75) Endothelin (ET) exerts its vasoconstrictor effect by binding to and activating the ETA receptor in vascular smooth muscle cells resulting in vasoconstriction.(125) This vasoconstrictor effect is counterbalanced by binding of endothelin to the ETB receptor on endothelial cells which results in nitric oxide mediated vasodilation.(126) In recent years, several antagonists to endothelin receptors have been discovered and tested in clinical trials of essential hypertension. In a trial comparing the effectiveness of bosentan, a nonselective ETA/ETB receptor antagonist, to an ACE-I and placebo in patients with essential hypertension, bosentin was as effective as an ACE-I in lowering blood pressure.(127) Selective ETA antagonist darusentan has been demonstrated to be effective at lowering blood pressure in 2 phase II clinical trials in patients with essential hypertension and resistant hypertension.(128, 129) However, the recent phase III trial failed to reach its primary endpoint of BP reduction. While ET receptor antagonists are generally well tolerated in clinical trials, the major adverse effects are peripheral edema, a mild decrease in hemoglobin (thought to be related to hemodilution secondary to increased extracellular fluid), headache, and flushing. As these drugs are primarily metabolized and eliminated by the liver, one significant adverse effect is hepatic dysfunction, which is dose-dependent and reversible upon discontinuation of the drug. The role of endothelin antagonists in controlling blood pressure in hemodialysis patients is yet to be determined as these drugs have not been tested in this patient population. One potential role for ET receptor antagonists are in ESA- induced hypertension. Selective ETA receptor antagonist darusentan (LU 135252), but not ETA/ETB receptor antagonist bosentan, prevented the aggravation of hypertension in renal failure rats treated with ESA.(130)

Dosing of antihypertensive agents

Many blood pressure agents can be dosed once daily and should preferentially be administered at night to control nocturnal blood pressure and minimize intradialytic hypotension. In patients who are noncompliant with therapy, renally eliminated agents

(such as lisinopril and atenolol) can be given thrice weekly following hemodialysis. Older antihypertensive agents which require thrice daily dosing should be avoided given the high pill burden with these regimens and the concern for noncompliance resulting in rebound hypertension.

Meta-analyses suggest antihypertensive agents are associated with improved outcomes in hemodialysis patients

Recent studies demonstrate antihypertensive therapy in hemodialysis patients contributes to regression of left ventricular hypertrophy and improved cardiovascular morbidity and mortality.(10, 131, 132) In a meta-analysis of randomized controlled trials of antihypertensive therapy in hemodialysis patients, blood pressure lowering treatment was associated with a 29% lower relative risk of cardiovascular events, a 29% lower relative risk of cardiovascular mortality and a 20% lower relative risk of all-cause mortality.(10)

SUMMARY

Hypertension is common in hemodialysis patients and can often be difficult to control. Considering the high cardiovascular burden hemodialysis patients, control of blood pressure is important to improve outcomes, yet the ideal BP target remains unknown.(10) Until further research identifies which BP to target, predialysis BP of <140/90 mmHg should be the goal if a patient does not develop intradialytic hypotension. First-line interventions for blood pressure control should focus on salt restriction, adequate sodium removal during hemodialysis, and attaining an adequate "dry weight". Despite these interventions, adequate blood pressure control with thrice weekly hemodialysis typically requires the addition of pharmacologic agents. First-line pharmacologic agents for blood pressure control in hemodialysis patients should be RAAS inhibitors (either ACE-I or ARB) due to their documented benefit on left ventricular hypertrophy, pulse wave velocity, and potentially cardiovascular events. Second line agents include the addition of beta-blockers (particularly in patients with coronary artery disease), combined α- and β-blockers in patients with heart failure, calcium channel blockers, and alternative agents such as direct vasodilators. Most hemodialysis patients require a combination of antihypertensive agents to achieve adequate blood pressure control. Considering the high pill burden and high rates of noncompliance among hemodialysis patients, once daily (or thrice weekly) formulations should be used preferentially.

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