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## Management of Hypertension in In-Center Hemodialysis Patients – An Opinion–Based Update

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### Abstract

Hypertension is highly prevalent in hemodialysis patients but its management remains a matter of debate. In this review, we discuss the observational studies on the association of blood pressure with outcomes, measurement of blood pressure in hemodialysis patients and present an opinion-based approach to treating hypertension.

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Hypertension is a leading cause of end-stage kidney disease (ESRD) and prevalence estimates of hypertension in dialysis patients range from 70% to 90% worldwide (1). Management of hypertension in dialysis patients continues to be a topic of debate in nephrology. Blood pressure (BP) is routinely measured, in a non-standardized manner before, during, and after each hemodialysis treatment. In addition, some nephrologists obtain standardized BP measurements in the dialysis unit and home and perform ambulatory blood pressure monitoring in select patients. Therefore, dialysis providers collect a plethora of BP data. Unfortunately, however, there are few data from randomized controlled trials (RCT) to guide providers on data interpretation, treatment methods and therapeutic goals. This article reviews the salient features of available observational studies and discusses strategies, based on expert opinion, for evaluating and managing hypertension in hemodialysis patients. (2)

### Clinical Context

In clinical decision making it is important to recognize the impact of the environment in which BP is measured. In the vast majority of dialysis units, BP is not measured in accordance with the American Heart Association guidelines. Pre-dialysis BP is typically measured when the patient is seated in the dialysis chair. BP is usually measured at a convenient body site with an automated device and then rechecked at approximately thirty minute intervals during dialysis and once at the end of dialysis. The reason for the frequent BP measurements is to ensure safety during the hemodialysis procedure, avoid recurrent symptomatic intradialytic hypotension and marked post-dialysis hypotension, which may pose immediate safety concerns regardless of the long-term consequences of poorly controlled hypertension (3).

### Reminder: What is Hypertension?

In 2005 the American Society of Hypertension proposed a revised definition of hypertension: “*Hypertension is a progressive cardiovascular syndrome arising from*

*complex and interrelated etiologies. Early markers of the syndrome are often present before blood pressure elevation is observed; therefore, hypertension cannot be classified solely by discrete blood pressure thresholds. Progression is strongly associated with functional and structural cardiac and vascular abnormalities that damage the heart, kidneys, brain, vasculature, and other organs and lead to premature morbidity and death.”(4) In this framework, BP is a “biomarker” for this cardiovascular syndrome and “it is helpful to consider [individual] BP patterns rather than discrete BP thresholds” (4, 5). Therefore, to adequately assess the cardiovascular syndrome in hemodialysis patients, we need to establish the validity of different BP measurements and if we are to develop protocols for optimal management of hypertension we need to understand the implications of different BP patterns.*

## **BP Measurement in Dialysis Patients**

The issues surrounding the challenges of BP measurement in dialysis patients have been recently reviewed by Roberts et al(6). The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF KDOQI) guidelines recommend standardized measurement of BP in dialysis patients by trained personnel using the auscultatory method in accordance with the AHA guidelines(7). However, the guidelines are generally not followed and the BP is routinely measured using oscillometric devices. Very few studies have validated the use of these devices in dialysis patients (5). Routine' BP measurements may differ significantly from standardized measurements made by trained personnel in accordance with AHA guidelines. Rahman et al. reported that routine BP readings were, on average, higher than standardized readings both pre- (14.3/7 mm Hg) and post-dialysis (13.6/4 mm Hg). In 55% of patients, the routine postdialysis BP readings were 10 mm Hg higher than the standardized readings.

If dialysis unit BP assessments are “safety measures” to avoid complications during dialysis then BP measurements between dialysis sessions may be more indicative of the overall impact of hypertension on an individual. The American Heart Association and the European Society of Hypertension recommend home BP monitoring for all patients with hypertension (8, 9). In dialysis patients, home BP monitoring has greater prognostic significance in detecting left ventricular hypertrophy and cardiovascular events than routine dialysis unit BP measurements (10, 11). Ambulatory BP monitoring remains the gold standard for assessing BP control (12) but is unlikely to be routinely available for use in clinical practice due to cost and logistical considerations. Dialysis patients have substantially more healthcare provider contact and opportunity for learning proper use of home BP monitors than non-dialysis patients. However, KDIGO guidelines provide conflicting comments on the use of home BP monitoring stating on one hand that “*At present, the evidence for the superiority of self-measured BP at home over pre-hemodialysis BP is impressive.*” but recommending that “*Although a worthy goal, neither measurement of APBM nor self-measured home BP may be feasible for most patients throughout the world, leaving pre-hemodialysis and post-hemodialysis BP measurements to be used, but with caution and with the knowledge that these are inferior.*” (13) Effective management of hypertension in dialysis patients may be difficult to achieve without the use of home BP monitoring (14).

## **BP in Dialysis Patients and Outcomes – Observational Studies**

Landmark observational studies were instrumental in highlighting the risk of cardiovascular disease and kidney failure with hypertension(15, 16). These studies were followed by pivotal RCTs that demonstrated the benefit of BP lowering (17-19). Together these studies form the basis for recommendations for BP targets in the general population (20-22). However, recent reviews of observational studies in hemodialysis patients have suggested

that pre-dialysis systolic BP <140 mmHg may be associated with increased mortality versus a systolic BP of 140-150 mm Hg. Even more surprising is that higher systolic BP values were not associated with increased risk and might even be associated with increased short-term survival (23, 24). These findings have been recently described in detail (25-27) and have led some to surmise that BP per se should not be the focus of treatment in dialysis patients(25, 28).

There appears to be a potential dilemma for the casual reader. If the findings of observational studies of BP and outcomes in the general population are valid then why should we question the results of similar studies in hemodialysis patients? To begin to answer this question it is important to recognize how the observational studies in the general population and hemodialysis patients differ. First, most studies in hemodialysis patients use routine BP measurements while those in the general population used BP measurements made by trained personnel using standardized protocols. Errors in the measurement of BP may lead to differential misclassification, which can bias apparent associations between BP and outcomes. (29) Second, in most well designed general population observational studies, there is careful assessment of baseline comorbidities and outcomes are adjudicated. In contrast, many hemodialysis studies using registry data rely only on claims data for comorbidities and as a result underestimate the comorbidities(30). Third, antihypertensive medication data are incomplete in the dialysis registries and most analyses do not adequately account for the potential impact of medications on outcomes. Finally, it is often inferred that the higher risk of death with lower BP in dialysis patients means that *lowering* BP in dialysis patients is harmful. However, the correct interpretation of these findings is that *people with lower BP* are at increased risk of adverse outcomes compared to people with higher BP. The effect of lowering BP on outcomes while accounting for comorbidities, volume removal on dialysis and antihypertensive medications use has not been evaluated in studies of dialysis patients. In summary, observational data on the association between BP and outcomes in dialysis patients cannot be used to infer BP goals in dialysis patients. An RCT of different blood pressure targets in hemodialysis patients is underway but results are not yet available (31).

## Goal BP in Hemodialysis Patients

Since BP is a biomarker of the “cardiovascular syndrome”, management of hypertension should address prevention and treatment of the full range of cardiovascular complications of hypertension. In the absence of data from RCT in dialysis patients, the goals have to be extrapolated from general population studies. Based on these guidelines, it is reasonable to aim for a predialysis BP 140/90 mm Hg or a home BP 135/85 mm Hg (13, 32, 33). Although the recent KDIGO BP guidelines did not recommend BP goals in dialysis patients due to lack of evidence to support any guidelines in dialysis patients, the general strategies to “*Individualize BP targets and agents according to age, co-existent cardiovascular disease and other co-morbidities ... and tolerance of treatment*” and “*Inquire about postural dizziness and check for postural hypotension*” are relevant to the management of hypertension in dialysis patients.

## BP Patterns in Hemodialysis Patients

There are a large number of potential BP patterns in hemodialysis patients. Home and pre-dialysis systolic BP can be low (<110 mm Hg), normal (110 to 140 mm Hg) or high (>140 mm Hg). During dialysis the BP may be stable, decrease or increase. Combining all these scenarios may result in 27 different patterns of systolic BP in hemodialysis patients (Figure 1). Individual patients may also move from one pattern to the other over time with treatment of hypertension. These large numbers of patterns contribute to the difficulty in managing

hypertension in hemodialysis patients. The current KDOQI recommendations are applicable to only two patterns; those with high predialysis and home BP without intradialytic hypotension. In the absence of home BP data, persistent hypertension ( $> 160$  mm Hg), before, during and at the end of hemodialysis sessions suggests the presence of sustained hypertension and warrants investigation of possible contributing factors and initiation or modification of treatment.

## **Factors Contributing to Uncontrolled Hypertension in Hemodialysis Patients**

Sodium and volume excess are perhaps the most important factors contributing to uncontrolled hypertension in dialysis patients. Sodium and volume excess may result from patient level factors such as non-adherence to dietary salt and fluid restriction, treatment level factors such as use of high dialysate sodium concentrations and sodium modeling (34) and limitations imposed by thrice weekly dialysis. In the Frequent Hemodialysis Network Trial, dialysis six versus three times per week was associated with an 18% increase in fluid removal per week and a 10 mm Hg decrease in systolic BP and lower use of antihypertensive medications (34) implying improved dry weight. In the Dry-Weight Reduction in Hypertensive Hemodialysis Patients (DRIP) trial, dry weight probing reduced postdialysis weight by 1 kg at 8 weeks and resulted in 6.6/3.3 mm Hg lower BP in the intervention arm (35).

Non adherence with prescribed medications is common and may contribute to uncontrolled hypertension. The prescribed pill burden for hemodialysis patients may exceed 25 pills per day (36). Non-adherence to beta blockers and clonidine may cause rebound hypertension. Sleep apnea is common in hemodialysis patients and may be associated with hypertension (37). Treatment of obstructive sleep apnea with continuous positive airway pressure (CPAP) therapy can reduce BP and may also have beneficial effects on left ventricular ejection fraction (38, 39). Other secondary causes of hypertension such as primary hyperaldosteronism, Cushing's syndrome and pheochromocytoma should also be considered in patients with uncontrolled BP (40, 41).

## **Special Considerations**

### **Blood Pressure Variability**

BP variability is a risk factor for adverse outcomes in patients with hypertension (42, 43). Dialysis patients are particularly prone to higher BP variability due to vascular stiffness and dialysis related volume changes. We recently reported that in a cohort of incident hemodialysis patients a one standard deviation increase in pre-dialysis systolic BP variability was associated with an 18% higher risk for all-cause and CVD mortality. Greater fluid removal during dialysis was associated with lower BP variability(44). Increased pre-dialysis systolic BP variability was also associated with increased all-cause mortality in the HEMO trial (45). In a retrospective analysis of the Fosinopril in Dialysis (FOSIDIAL) study, increased pre-dialysis BP variability was associated with a higher risk of CV events (46). Flythe et al. recently reported that greater fluid removal during dialysis was associated with higher intradialytic systolic BP variability and the higher variability was associated with an increased risk of mortality (47, 48). Therefore, in addition to absolute BP levels, we should also pay attention to pre-dialysis and intradialytic BP variability.

### **Intradialytic Hypertension**

Intradialytic hypertension can occur frequently and is often under-recognized, since unlike intradialytic hypotension it is not associated with immediate complications. However, even

over a short-term follow-up of six months, an intradialytic rise in systolic BP  $\geq 10$  mm Hg was associated with a two-fold greater risk of hospitalization or death (49). Lower ultrafiltration during dialysis leading to volume overload is a major contributing factor to intradialytic hypotension. Novel mechanisms for intradialytic hypotension include endothelial cell dysfunction and sympathetic hyperactivity during dialysis are putative mechanisms for intradialytic hypertension (50-52). In one small prospective open label study, carvedilol reduced the frequency of intradialytic hypertension episodes by approximately 50% ( $p < 0.001$ ). (53)

## Management of Hypertension

### Standardization of BP measurements

Reliable data to guide management is the first step towards management of hypertension in dialysis patients. BP measurement in the dialysis unit should be standardized. AHA guidelines for BP measurements should be used to identify the correct cuff size and position (54). Devices used to measure BP should be validated and calibrated. Site of BP measurement should be kept constant and should be clearly identified in medical records. NKF KDOQI guidelines recommend measurement of BP in thighs or legs of patients that have undergone multiple surgical vascularization procedures in both arms (55). However, the goal BP recommendations are valid only for brachial BP measurement and the reference values for lower limb BP are unknown (55).

### Home BP Monitoring

Home BP monitoring is recommended for all patients with hypertension by the AHA and the European Society of Hypertension (8, 9). In a single unit open label randomized controlled trial, decision-making based on home BP monitoring compared with predialysis BP measurements led to better BP control as assessed by ABPM (56). Importantly, symptomatic intradialytic hypotension did not increase. It is possible that home BP monitoring may increase patients' self-efficacy and involvement in care although this has not been scientifically investigated.

### Patient-Centered Management

Although dialysis patients have much greater access to trained healthcare professionals than non-dialysis patients, much of the emphasis on self-care is focused on dietary phosphate management. Compounding the problem is low health literacy, which is common in dialysis patients and is associated with higher BP (57, 58). Educating and empowering dialysis patients to take responsibility for their own care may improve self-efficacy and improve BP control and quality of life (58). In a recent study, patient education and counseling regarding BP, salt and volume intake reduced BP levels (59). Moattari et al. conducted a randomized controlled trial of six-week intervention that included a combination of individual and group empowerment counseling sessions (60). The intervention improved self-efficacy, decreased interdialytic weight gain by 0.4 kg and reduced predialysis BP by 14/5 mm Hg.

### Management of Volume Overload

Volume overload is common among dialysis patients and may precede initiation of dialysis (61). Dry weight attainment is the most important factor for BP control in dialysis patients (62). Greater fluid removal with dialysis and lowering of dry-weight is associated with BP lowering, decreased predialysis systolic BP variability, lower left ventricular mass, and less use of antihypertensive medications (34, 35, 44). In the DRIP trial, the following technique was used to probe and decrease dry-weight successfully (35): at each dialysis treatment, an additional ultrafiltration of 0.1-kg/10 kg-body weight was prescribed. If the ultrafiltration was not tolerated, the additional removal was reduced by 50% and another 50% if still not



tolerated. Dry weight was established when a 0.2-kg incremental ultrafiltration was not tolerated.

Hur et al. recently reported the results of a randomized controlled trial designed to evaluate the impact of bioimpedance-guided assessment of dry weight in dialysis patients(63). Bioimpedance spectroscopy was performed pre-dialysis at the mid-week dialysis treatment twice a month. In the intervention group, bioimpedance data was provided to the treating physician and used to adjust ultrafiltration targets. In the intervention group, volume overload gradually decreased by 0.5 L at year one and predialysis systolic BP decreased by 4.5/2.6 mm Hg, antihypertensive medication use decreased by 9% and left ventricular mass index decreased by 10.2 g/m<sup>2</sup>. The advantage of this technique over dry-weight probing as performed in the DRIP trial appears to be the reduction of fluid overload without an increase in intradialytic hypotension or vascular access complications. However, bioimpedance remains a research tool whereas dry-weight probing can be performed routinely without requiring purchase of additional equipment.

Relative plasma volume (RPV) monitoring during hemodialysis can be used to infer the presence of volume overload. During ultrafiltration, patients with volume overload continue to fill the intravascular space from interstitial space and maintain plasma volume resulting in flat RPV slopes whereas patients at dry weight start developing hemoconcentration and have steep RPV slopes as there is no refill from interstitial to intravascular space (64). However, inference of volume overload can only be made retrospectively after the treatment has been completed. Moreover, a RCT of RPV versus conventional monitoring showed increased risk of access and non-access related hospitalizations in the RPV group (65). While the results of the trial have been questioned, the role of RPV for determining volume overload in dialysis patients remains unclear.

### **Dietary and Dialysate Sodium**

The KDIGO 5D guidelines emphasize the importance of restriction of dietary salt intake for control of BP (13). In a recent secondary analysis of the HEMO trial, higher dietary salt intake was associated with higher predialysis systolic BP and a linear increase in the hazard for death (66). A positive dialysate-serum sodium gradient is another potential cause of net positive sodium balance during dialysis (67). Lowering dialysate sodium may reduce thirst, lower interdialytic weight gain; reduce BP and antihypertensive medication use (68). It may also be associated with lower carotid intimal medial thickness and flow-mediated dilatation (69). Individualized dialysate sodium prescription can also reduce interdialytic weight gain and lower BP (70). In the absence of RCTs, it is difficult to recommend whether dialysate sodium should be lowered for all dialysis patients or individualized based on serum sodium concentrations. A randomized control trial to assess the effectiveness of lower dialysate sodium concentrations is underway in Australia and New Zealand(71).

### **Antihypertensive Medications**

Many dialysis patients will require antihypertensive medications to control BP. The KDIGO 5D report stated *“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”* (13). Most patients on dialysis have a longstanding history of hypertension prior to the start of dialysis and have been receiving antihypertensive medications. Antihypertensive regimens are often modified in the pre-ESRD period due to volume overload and hyperkalemia. Most patients with ESRD take multiple antihypertensive medications, and the optimal regimen to control BP and reduce morbidity and mortality is unknown.

We recently assessed the relationships of antihypertensive medications to mortality in two retrospective cohorts of incident hemodialysis patients; a cohort of 11,291 patients treated in facilities operated by Dialysis Clinic Inc. (DCI), a not-for-profit provider and a cohort of all US incident dialysis patients with Medicare parts A, B and D eligibility (72, 73). In both cohorts, a RAS-based regimen without a  $\beta$ -blocker was associated with significant decrease in mortality risk compared to a  $\beta$ -blocker-based regimen that did not contain a RAS agent. A regimen that combined a RAS agent and a  $\beta$ -blocker was associated with a further decrease in mortality risk(73). These findings provide strong evidence of the beneficial effects of RAS agents in dialysis patients. However, a randomized controlled trial is needed to confirm the results of these observational studies.

### Renal Denervation

Sympathetic hyperactivity is common in ESRD and is contributing factor to hypertension and CVD (74-76). Bilateral nephrectomy may help control resistant hypertension in part by reducing renal sympathetic activity (77). However, there is significant morbidity associated with nephrectomy and it is not routinely performed. Renal denervation alone may also lower BP by decreasing renal sympathetic activity (78, 79). In a recent study, renal denervation was attempted in 12 hemodialysis patients with uncontrolled hypertension. Three patients could not undergo denervation due to atrophic renal arteries. In the remaining nine patients, systolic BP was reduced by 28 mm Hg at 12 months (80). These potential benefits will need to be weighed against the risk of significant complications and at present this approach should be considered experimental.

### Management of Hypertension – A Suggested Approach

Effective management of hypertension in dialysis patients will require system-level changes in addition to individual physician- and patient-level interventions. For many nephrologists, the patterns of BP change during the dialysis procedure may take precedence over hypertension control. Current clinical guidelines do not offer any recommendations on treatment based on these BP patterns. In a recent nonrandomized controlled trial, a computer-based clinical decision support reminded physicians of the pre- and postdialysis BPs and the current BP guidelines but did not improve hypertension control (81). These findings reflect the complexity of hypertension management in dialysis patients.

An opinion-based approach to management of hypertension in dialysis patients is described in Figure 2. The first step in management is to obtain standardized BP measurements in accordance with AHA guidelines. Next, patients and caregivers must be educated regarding salt restriction and use of home BP devices. The data from home devices and dialysis unit BP measurements should be presented to the nephrologist in a monthly composite report that also includes the frequency and severity of intradialytic hypotension and hypertension. RAS agents should be considered for all dialysis patients that require antihypertensive medications. Dry-weight probing protocols should be adapted for use in clinical practice in a manner similar to the use of anemia management protocols in dialysis units. Serum and dialysate sodium concentrations should be included in the BP section of the monthly physician reports and dialysate sodium should be individualized to avoid positive sodium balance. Organized delivery of dialysis care in the US offers a great opportunity to implement such a change and improve outcomes in dialysis patients.

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		Home Systolic BP								
		Low (<110 mm Hg)			Normal (110-140 mm Hg)			High (>140 mm Hg)		
Predialysis Systolic BP	Low (<110 mm Hg)	L	N	H	L	N	H	L	N	H
	Normal (110-140 mm Hg)	L	N	H	L	N	H	L	N	H
	High (>140 mm Hg)	L	N	H	L	N	H	L	N	H

Abbreviation: BP, Blood Pressure

Note: L, N and H refer to changes in BP during dialysis.

L = intradialytic hypotension

N = no change in BP during dialysis

H = intradialytic hypertension

Shaded boxes highlight scenarios in which BP lowering is appropriate

**Figure 1.**

- 1) Standardize BP measurements
- 2) Patient education and home BP monitoring
- 3) Monthly BP report
- 4) Identify goal BP for each patient
- 5) Report serum and dialysate sodium in the BP section of the report
- 6) Consider RAS agents for all patients with uncontrolled BP
- 7) Dry-weight probing protocols

**Figure 2.**