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*Semin Dial*. Author manuscript; available in PMC 2013 July 01.

Published in final edited form as:
*Semin Dial*. 2012 July ; 25(4): 370–376. doi:10.1111/j.1525-139X.2012.01092.x.

# The controversies of diagnosing and treating hypertension among hemodialysis patients

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## Abstract

This review discusses ten current controversies regarding the dialysis patient with hypertension. The clinician is faced with a dilemma at the bedside on how to evaluate blood pressure and treat this condition in a patient on long-term hemodialysis. The evidence base to give firm recommendations is thin, but the epidemiological evidence tells us to do nothing. This appears to be the incorrect strategy, at least based on what we know today. Evaluating home BP in every dialysis patient, evaluating volume status on a regular basis, and treating hypertension predominantly with non-pharmacological strategies are worthwhile.

The Merriam-Webster dictionary defines controversy as a discussion marked especially by the expression of opposing views. That hypertension, a ubiquitous and an indubitable renal and a cardiovascular risk factor in the general population, would elicit controversy in the hemodialysis (HD) population is surprising. In fact, there was even a conference organized to discuss this controversy[1]. Discussion of this controversy is the purpose of this review. Ten prominent controversies are listed in Table 1.

There is not even consensus regarding the diagnosis of hypertension among HD patients. A meeting report of the Kidney Disease Improving Global Outcomes (KDIGO) controversy conference concluded the following: “Although a worthy goal, neither measurement of ambulatory blood pressure monitoring 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”[1].

The current National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines suggest that pre-HD and post-HD BP should be <140/90 and <130/80 mm Hg, respectively[2]. These targets were based on the opinion of the workgroup. Could these definitions be erroneous? The answer appears to be “yes” based on a substantial amount of accumulated data that are discussed further.

## Variability of Pre-dialysis and post-dialysis BP recordings

Even a casual observer in the HD unit will attest to the variability of BP in the dialysis patients. BP is often extraordinarily elevated prior to HD and plummets to often hypotensive levels during dialysis. These excursions in BP within a short period of time make the application of the traditional definitions of hypertension problematic[3]. In fact, BP is so variable that the variability within patients from one visit to the next is about the same as between patients[4]. Quantitatively, the standard deviation of predialysis systolic BP between patients is 17.9 mmHg whereas visit-to-visit standard deviation within patient is 18.0

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mmHg[4]. The standard deviation for postdialysis BP between patients is 17.4 mmHg and within patient 18.4 mmHg[4].

Even when BP is recorded in the interdialytic period, the timing is critically important. There may be large differences when the BP is recorded 12 hours v 36 hrs after the end of dialysis[5;6]. Furthermore, the interdialytic weight gain affects the rate of rise in interdialytic BP. The rate of change in both the systolic and diastolic BP are steeper when more weight is gained between dialysis treatments[5;7]. Conversely, on average, the decline in BP is steeper when more ultrafiltration is performed during dialysis.

Given this variability it is not surprising that pre-dialysis and post-dialysis measurements correlate only roughly with the interdialytic ambulatory BP recording. A meta-analysis reporting on this variability noted that the individual prediction of ambulatory BP using predialysis or postdialysis BP measurement could be erroneous by 35 mmHg in either direction[8]. Thus, use of predialysis or postdialysis BP measurements to make management decisions in the interdialytic period is problematic. In fact, in a survey in the United Kingdom, centers that achieved better post-dialysis BP targets had more intradialytic hypotension[9]. Whether achieving these targets would cause clinical harm (or benefit) remains unknown.

## Evaluation of ambulatory BP monitoring as a reference standard

While ambulatory BP monitoring is the accepted gold standard for making a diagnosis of hypertension[10] among hypertension experts, there appears to be less acceptance of this tool among nephrologists[11]. Among hemodialysis patients, two lines of evidence now confirm what has been noted in the general population. First, compared to predialysis or postdialysis BP measurements, ambulatory BP better correlates with echocardiographic left ventricular hypertrophy[12]. Second, compared to predialysis or postdialysis BP measurements, ambulatory BP better correlates with all-cause mortality[13;14]. The recent guidelines from the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom for the clinical management of primary hypertension in adults (Clinical Guideline 127, August 2011) recommend that if the clinic BP is 140/90 mmHg or higher, ambulatory BP monitoring should be offered to confirm the diagnosis of hypertension. This is a rather revolutionary guideline recommendation at a national level for all patients newly diagnosed as being hypertensive. Thus, ambulatory BP monitoring will likely emerge as mainstream technology for the diagnosis of hypertension rather than remain a laboratory tool.

## Home BP monitoring for hypertension screening

Notably,, ambulatory BP monitoring is both resource intensive and cumbersome to perform. Thus, in the United States, the American Heart Association recommends the use of home BP monitoring in all patients[15]. In those patients where the results of home BP monitoring are unclear (borderline home BP 125–135/75–85 mmHg) ambulatory BP monitoring is then recommended[15].

In hemodialysis patients, this strategy can be practically implemented; emerging data suggest that home BP monitoring is a valid and useful tool to diagnose hypertension in this population[16]. For example, in a validation study that used ambulatory BP measurements as a reference standard, home BP recordings had excellent diagnostic test characteristics[17]. A seven day averaged home BP value of 150 mmHg systolic or more had a sensitivity of 80% and specificity of 84% in diagnosing hypertension. The area under the receiver operating characteristic curve was 0.89 which means that if home BP were to be used to diagnose hypertension a correct diagnosis would be made 89% of the time. Home BP can track changes in BP evoked by probing dry-weight[18].

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Home BP was as good as ambulatory BP in predicting target organ damage as assessed by echocardiographic left ventricular hypertrophy; predialysis and postdialysis measurements were less accurate predictors[12]. Moreover, the prognostic value for all-cause mortality of home BP monitoring (but not predialysis or postdialysis BP) was similar to that of ambulatory BP recordings[13;14]. Compared to a single time-point measurement in the dialysis unit, a study in Japanese hemodialysis patients also confirms the superiority of weekly averaged home BP measurements in predicting all-cause and cardiovascular mortality.[19]. Finally, a randomized trial assessed improvement in interdialytic ambulatory BP at 6 months when antihypertensive therapy was guided by home BP recordings or predialysis BP measurements[20]. Greater and clinically significant reductions in ambulatory systolic BP was seen only among patients treated according to home BP recordings.

## What if ambulatory or home BP measurements are unavailable?

Predialysis and postdialysis BP are imprecise estimates of interdialytic ambulatory BP. However, median intradialytic BP may better reflect interdialytic ambulatory BP recordings. In a validation study median intradialytic midweek BP of 140 mmHg or more, even if measured over a single dialysis, was closer to interdialytic ambulatory BP than pre or post dialysis values[21]. Furthermore, this median BP can track BP trajectories evoked by probing dry-weight[22]. This BP can be thought of as “clinic blood pressure” as might be obtained in a patient with primary hypertension without kidney disease.

Using median intradialytic midweek BP to define clinic BP, it is now possible to classify patients into 4 categories. Two categories are concordant: sustained normotension where both clinic and ambulatory BP is normal and sustained hypertension where both are high. However, the discordant categories are of greater interest. White coat hypertension where clinic BP is high but ambulatory is normal is not associated with excess mortality even among hemodialysis patients[23]. Masked hypertension where clinic BP is normal but ambulatory BP is high is associated with increased all-cause mortality[23]. These findings emphasize the importance of BP measurements beyond those measured in the clinic alone.

## Can the controversy be resolved?

According to a Kidney Disease Improving Global Outcomes controversies conference: “Although a worthy goal, neither measurement of ambulatory blood pressure monitoring 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”[24]. The NICE guidelines call for ambulatory BP monitoring in every patient diagnosed with hypertension in the clinic. But managing hypertension using repeated ambulatory BP monitoring is both difficult and impractical using the current equipment. However, home BP monitoring is feasible for most dialysis patients. Worldwide guidelines endorse the use of home BP monitoring for the diagnosis and the management of hypertension.

Since home BP is 5 mmHg lower than clinic, the goal BP generally recommended is <135/85 mmHg. Although, home BP treatment targets are not known with certainty, it seems reasonable to lower BP to those in the general population, provided hemodynamic stability and interdialytic quality of life can be maintained in these patients. Predialysis or postdialysis BP measurements should have little or no role in guiding BP pharmacological or non-pharmacological therapy of hypertension among hemodialysis patients.

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## Should hypertension be treated?

The controversy regarding treatment of hypertension among hemodialysis patients is well outlined by Lacson and Lazarus[25]. They state: “Observational studies reveal that the association between BP and death risk in ESRD patients is not the same as in the general population. The sooner we accept this reality, the faster we can move to elucidate this difference….Because of the higher mortality risk associated with low or “normal” BP, diagnostic and therapeutic options and strategies for ESRD patients whose BP falls within “goal” should be addressed in future iterations of clinical practice guidelines.” Thus, in the general population, BP of 120/80 mmHg would not be cause for concern, but this normal BP would be cause for concern in the hemodialysis population according to the controversy.

Numerous studies have pointed out the inverse risk between BP and survival among dialysis patients[25;26]. These studies were performed using BP measurements either before or after dialysis. Despite their large size, most of them have no information on the condition of the patients, important information to have because it informs the risk associated with a given BP. As an example, a BP of 120/80 mmHg in a young otherwise healthy dialysis patient without cardiac disease and on no antihypertensive agent would portend a good prognosis. However, this BP in an elderly diabetic with heart failure and osteomyelitis on antibiotics would indicate an unfavorable prognosis. These modifying influences are not captured in large administrative databases that often lack even information on antihypertensive drug use. Nephrologists take comfort in the results, given their large size, but causality is difficult to imply with these studies. Causality can be better evaluated by considering randomized trial data especially in the context of target and achieved blood pressure.

## Target versus achieved blood pressure

There are no trials among hemodialysis patients that have randomized patients to two levels of blood pressure and evaluated clinically relevant outcomes. However, there are three such studies among patients with CKD which have randomized patients to two different blood pressure goals with clinically relevant end points[27]. One of the three studies, illustrative of the power of randomized trials, is the African American Study of Kidney Disease (AASK) which randomized Black patients with hypertensive kidney disease to two levels of mean arterial pressure (MAP) (92 vs 102–107 mmHg)[28]. One primary end point was the rate of decline in measured GFR. No difference was found in the rate of decline in GFR over the course of the trial, thus the null hypothesis could not be rejected. Accordingly, compared to a higher MAP, a lower MAP was no more effective than a higher MAP in reducing the rate of decline in GFR. However, in either randomized stratum, those who achieved a lower BP experienced a slower rate of decline in GFR[29]. Thus, the results of observed BP were radically different from the results of target BP.

Observational studies do not inform clinical practice adequately; in fact they have misled us to believe that higher BP is better. Similar, paradoxes have been observed for anemia and dialysis dose. For example, targeting a higher hemoglobin is associated with harm, but achieving a higher hemoglobin is associated with benefit[30]. Note that the studies targeting a higher hemoglobin were done on relatively a small number of patients. In comparison, the observational studies were literally done on the entire population of dialysis patients[31]. Targeting a higher Kt/V is associated with no survival benefit[32], but achieving a higher Kt/V is associated with a survival benefit[33]. Again the targeting studies were done in a few hundred whereas the observational studies were done in thousands[34]. Observational data have simply not been adequate in guiding clinical decision making. Large sample size, narrow confidence intervals, and small p values does not imply causality. Simply associating

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lower systolic BP with increased mortality among dialysis patients does not imply that lowering blood pressure is the cause of mortality.

## Randomized controlled trials versus observational studies

No single randomized trial has proven the value of blood pressure lowering among hemodialysis patients. We therefore have to fall back on meta-analyzing a heterogenous group of studies, generally small and sometimes of suboptimal quality to inform care. Two different meta-analyses show that treatment with antihypertensive drugs does not increase cardiovascular events or mortality[35;36]. In fact, treatment reduces the risk of cardiovascular events. Furthermore, it appears that the cardiovascular benefit is greater among patients who are hypertensive at baseline[36]. Thus, despite the small trials, the signal for harm with antihypertensive drug therapy is absent. In fact, the signal for benefit appears quite large. For example, among 1202 patients who in 5 randomized trials, the overall benefit of antihypertensive therapy compared with the control or placebo group had a combined hazard ratio for cardiovascular events of 0.69 (95% CI: 0.56 to 0.84) using a fixed-effects model and 0.62 (95% CI: 0.45 to 0.86) using a random-effects model[36]..

## Prognostic importance of out-of-dialysis-unit BP measurements

Unlike the relationship between BP obtained in the dialysis unit and mortality, all studies to date have reported a direct relationship between BP obtained outside the dialysis unit and mortality. In the first study reporting the link between ambulatory BP and outcomes, only 10 cardiovascular deaths were seen among 57 treated hypertensive hemodialysis patients. In this small study from France, nocturnal systolic BP was an independent and significant predictor of cardiovascular mortality (RR 1.41 95% CI 1.08 to 1.84)[37]. The next study from Italy reported the association of 24-hour ambulatory BP and cardiovascular outcomes among 168 non-diabetic HD patients without pre-existing cardiovascular events[38]. The ratio of the average systolic BP during the night and day (night/day systolic ratio) was used to indicate the nocturnal fall in BP or the dipping phenomenon. This ratio (dipping) was the only BP indicator that was associated with all-cause and cardiovascular mortality on both bivariate and multivariate analyses.

The third study by Alborzi et al reported that ambulatory BP was of greater prognostic value compared to dialysis unit BP recordings[13]. Systolic hypertension (135 mmHg systolic or more) recorded by ambulatory monitoring increased the risk of all-cause mortality by 2.12 fold (95% CI 1.16–3.87) and by 1.82 fold (95% CI 1.006 – 3.29) when detected by home BP monitoring One standard deviation (SD) increase in systolic BP increased the risk of all-cause death by 1.46, (95% confidence interval [CI] 1.09 – 1.94), for ambulatory, 1.35 (95% CI 0.99 – 1.84) for home, and between 0.97 – 1.19 ($p>0.20$) for dialysis unit BP recording.

Agarwal reported the largest cohort study to date of 326 patients on long-term hemodialysis[14]. BP was self-measured at home over an interdialytic interval by ambulatory recording for one week, and before and after dialysis over two weeks. Systolic BP but not diastolic BP was found to be of prognostic importance. Increasing quartiles of ambulatory and home systolic BP were associated with all-cause mortality (adjusted hazard ratios for increasing quartiles of ambulatory: 2.51, 3.43, 2.62 and for home BP: 2.15, 1.7, 1.44). Analysis based on restricted cubic splines revealed that mortality was lowest when home systolic BP was between 120–130 mm Hg and ambulatory systolic BP was between 110–120 mmHg. BP recorded before and after dialysis were not statistically significant in predicting mortality. Out-of-dialysis unit BP measurement provided superior prognostic information compared to BP within the dialysis unit.

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Taking these four studies together, it appears that out-of-dialysis-unit BP among hemodialysis patients is prognostically more informative than that recorded just before and after dialysis.

## How should BP be best managed?

Controversy exists how BP among hemodialysis patients should be best managed. For example, some recommend, "that all HD patients, even if normotensive, should be given an ACE inhibitor (or AngII antagonist). Sodium restriction and ultrafiltration should then be used to achieve normotension in this population[39]" Practice patterns also suggest that in the United States predominantly medication-directed approaches are implemented to improve BP control.

Others recommend that cornerstone of improving BP among hypertensive hemodialysis patients is to improve volemia by probing dry-weight[40] Probing dry-weight may be defined as a gradual change in post-dialysis weight at which there are minimal signs or symptoms of either hypovolemia or hypervolemia. Probing is the current gold-standard by which dry-weight is defined. Briefly, dry-weight is defined as the lowest tolerated post dialysis weight achieved via gradual change in post-dialysis weight at which there are minimal signs or symptoms of either hypovolemia or hypervolemia. Volume excess as judged by large inferior vena cava diameter is associated with difficult to control hypertension[41]. By limiting interdialytic weight gain, dietary or dialysate sodium restriction can facilitate the achievement of dry-weight. However, simply reducing dietary or dialysate sodium without probing dry-weight is unlikely to lower BP.

## Dietary and dialysate sodium restriction and dry-weight reduction

Although there are observational studies that show a relationship between achieved post-dialysis weight and BP, there is only one randomized trial to demonstrate the benefit of probing dry weight on interdialytic ambulatory BP. The dry-weight reduction in hypertensive hemodialysis patients (DRIP) trial, randomly assigned long-term hypertensive hemodialysis patients to ultrafiltration or control groups[18]. The 100 patients assigned to the additional ultrafiltration group had the dry weight probed without increasing time or duration of dialysis, whereas the 50 patients in the control group only had physician visits. Postdialysis weight was reduced by 0.9 kg at 4 weeks and resulted in −6.9 mm Hg change in systolic BP and −3.1 mm Hg change in diastolic BP. At 8 weeks, dry weight was reduced 1 kg, and the change from baseline in systolic BP was −6.6 mm Hg, and diastolic BP −3.3 mm Hg. The odds ratio for systolic BP reduction of at least 10 mm Hg was 2.24. Hypotensive signs and symptoms occurred frequently during this study because this is the only established way to define dry-weight. Despite an increase in intradialytic signs and symptoms of hypotension, there was no deterioration seen in any domain of the kidney disease quality of life health survey.

## Are there risks to dry-weight reduction?

A KDIGO controversy conference brought forth a controversy regarding reduction in dry-weight[24]. As stated in the proceedings, "Unfortunately, target weight reduction to normalize BP may increase the frequency of intradialytic hypotension, which in turn may damage the heart, and is associated with increased mortality. That the same phenomena can occur in the severely overhydrated patient, favors the achievement of a post-dialysis `target weight' in some patients, which might be higher than the dry-weight as a clinically practical alternative. The requirement for a difference between the dry-weight and target weight illustrates the dilemma faced by the healthcare professional in avoiding intradialytic BP decreases while attempting to optimize dry-weight in an effort to correct high BP. However,

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longer dialysis time periods and methods to reduce interdialytic weight gain attenuate the occurrence of hypotension"[24].

A relationship has been described between intradialytic hypotension and cardiac stunning even among patients with normal coronary arteries[42;43]. A relationship has also been described between cardiac stunning and lowered survival[44]. However, no randomized trial will likely be performed to answer the question of whether patients with volume overload fare worse than those with intradialytic hypotension. However, little recognition has been given to the fact that patients at dry-weight (as assessed by intradialytic relative plasma volume monitoring) have a better survival than those who are volume overloaded[45]. In fact this relationship holds even after adjusting for interdialytic ambulatory BP. Hospitalizations for congestive heart failure are a major source of morbidity and mortality among dialysis patients and it appears that achieving euvolemia may be desirable. However, the risks and benefits of reducing dry-weight on clinical outcomes can only be answered by a long-term randomized clinical trial. Whereas, increasing treatment times such as by frequent dialysis reduce intradialytic hypotensive events, it also controls hypervolemia more effectively. Nonetheless, the current randomized trials were too small to detect a mortality benefit from this procedure.

Other potential risks of probing dry weight include the following: loss of residual renal function, increased risk of access clotting, and possibly increased post dialysis fatigue and post-dialysis symptoms. To best assess the risks and benefits of probing dry-weight will require clinical trials.

## The controversy of lag phenomenon

The proceedings of the KDIGO controversy conference state, "In attempting to achieve `target weight', particularly in incident patients starting dialysis, clinicians should be mindful also of the lag in time (from several weeks to months) between correction of ECV and HTN"[24].

The existence of the lag phenomenon in this population remains speculative. Observational studies have used predialysis or postdialysis BP measurements to make decisions about existence of the lag phenomenon[46]. A randomized trial found a prompt improvement in interdialytic ambulatory BP within 4 weeks without further reduction in BP at 8 weeks discounting the presence of a lag phenomenon. It is important to recognize a threshold effect of weight loss and BP reduction among hemodialysis patients. In other words, BP may not decline untill a certain state of euvolemia is achieved. Once achieved, BP decline may be rapid and precipitous. Accordingly, among incident patients where dry-weight is challenged gradually a lag phenomenon may appear to exist when in fact there may be simply a threshold effect of volume on BP.

## Can relative plasma volume monitoring predict dry-weight reduction?

The KDIGO controversy conference states: "Methods of assessing intradialytic blood volume change have been useful in the context of prescription of UF rate, but are not valuable to accurately determine fluid-overload."

Data have accumulated since the controversy conference suggest that in the context of randomized controlled trials, relative plasma volume monitoring may, in fact, be useful to judge response to dry-weight reduction. For example, probing dry-weight among hypertensive hemodialysis patients led to steeper relative plasma volume slopes[47]. Those with flatter slopes at baseline had steeper slopes when their dry-weight was probed; in contrast those who had steeper slopes simply had more symptoms. Most importantly, on

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probing dry-weight those with the flattest slopes had the greatest declines in ambulatory BP. This suggests that this technique may be clinically useful. Observations on long-term follow up of patients with volemia assessed by relative plasma volume monitoring suggest an increased mortality risk with greater volemia[45] (i.e. those with flatter slopes sustained throughout treatment). Nonetheless, prospective trials are needed to confirm the value of this technique in guiding clinical management of hypertensive hemodialysis patients.

## Is increasing the frequency or duration of dialysis the only way to improve cardiovascular risk?

The seminal finding of the Frequent Hemodialysis Network (FHN) study which compared conventional three times weekly dialysis to more frequent incenter dialysis was an improvement in systolic BP, reduction in antihypertensive drug use, and improvement in left ventricular mass and volumes[48]. One mechanism might be better achievement of dry-weight[49]. In fact, left ventricular mass index was also improved to a comparable degree in the DRIP trial participants where the duration of dialysis was not altered but the dry-weight was challenged[50]. Increasing dialysis duration may improve hemodynamic stability, making the procedure more tolerable.

## The role of antihypertensive medications and timing of administration

Although probing dry-weight appears to be effective in improving BP control among hemodialysis patients, whether medications should be primarily used to control BP is uncertain. Some physicians feel that given the benefits seen with ACE inhibitors and ARBs in the general population, all patients should be given these drugs[39]. Dry-weight should then be adjusted based on BP responses. Others feel that dry-weight should be managed first[40;51;52]. In fact, BP control is considered by some to be the reference by which the adequacy of dialysis is judged[53–55]. Similarly, it is not clear whether BP medications should be held before dialysis or not. My own view is that most antihypertensive medications are long-acting and withholding long-acting drugs prior to dialysis has little benefit.

In conclusion, the clinician is faced with a dilemma at the bedside on how to evaluate blood pressure and treat this condition. The evidence base to give firm recommendations is thin, but the epidemiological evidence would tell us to do nothing. This appears to be the incorrect strategy, at least based on what we know today. Evaluating home BP in every dialysis patient, evaluating volume status on a regular basis, and treating hypertension predominantly with nonpharmacological strategies are worthwhile.

## Acknowledgments

Supported by a research award from NIH (NIDDK 2 RO1- DK062030-08)

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## Table 1

Ten controversies in hypertension in dialysis patients

| One view | Opposing view |
|---|---|
| 1 Ambulatory or home BP monitoring is not feasible more most patients throughout the world. Predialysis and postdialysis BP measurements should remain standards by which patients are treated for hypertension. | Home BP is feasible for most patients on dialysis and should be routinely performed by most. Peridialytic BP recordings should be abandoned for making decisions regarding hypertension management in dialysis patients. |
| 2 Goal BP recommended by KDOQI work group should remain standards by which patients should be treated. | These standards are obsolete given new studies. They should be abandoned. |
| 3 Patients should be evaluated if they have normal BP, since it is they who carry excess cardiovascular risk. | Hypertension diagnoses by home BP monitoring should be treated. |
| 4 Observational studies can guide treatment decisions among dialysis patients. | These studies cannot draw a cause and effect relationship and many randomized trials in nephrology have failed to confirm observational data. |
| 5 ACE inhibitors or Ang II antagonist should be administered to all patients. Dry-weight should come next. | Volume control should be the primary method of managing these patients. |
| 6 Patients on dialysis should be fluid restricted. | There is no role for fluid restriction. Dialysate sodium and dietary salt restriction can be useful to facilitate achievement of dry-weight in these patients. |
| 7 Longer treatment times are required to improve volume state | Volume state can be improved even with standard 4-hour dialysis provided attention is paid to hemodynamic stability. |
| 8 BP drop can lag weeks or months after lowering dry weight | There is little evidence for lag phenomenon among prevalent dialysis patients. |
| 9 Intradialytic blood volume monitoring cannot detect fluid-overload. | Intradialytic blood volume monitoring is useful to judge dry weight. |
| 10 Antihypertensive medications should be held before dialysis | Antihypertensive medications are long-acting and there is little role for holding them prior to dialysis. |