

## TITLE PAGE

**Title:** Blood pressure in hemodialysis: targets?

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## **Abstract**

***Purpose of review:*** In the absence of “hard” clinical-trial evidence to define optimal blood pressure (BP) targets and validate different BP measurement techniques, management of hypertension in hemodialysis is based on expert opinions. In this review, we provide a comparative evaluation of out-of-dialysis BP monitoring versus dialysis-unit BP recordings in diagnosing hypertension, guiding its management and prognosticating mortality risk.

***Recent findings:*** Owing to their high variability and poor reproducibility, pre- and postdialysis BP recordings provide inaccurate reflection of the actual BP load outside of dialysis. Contrary to the reverse association of peridialytic BP with mortality, elevated home and ambulatory BP provides a direct mortality signal. Out-of-dialysis BP monitoring, even when done in the clinic, is a reliable approach to manage hypertension in the dialysis unit. When none of these measures are available, median intradialytic systolic BP can provide a better estimate of interdialytic BP levels compared to peridialytic BP measurements.

***Summary:*** Although out-of-dialysis BP monitoring have better diagnostic accuracy and prognostic validity, randomized trials are needed to ascertain BP targets for managing hypertension in hemodialysis patients.

***Key-words:*** blood pressure targets, hypertension, hemodialysis, mortality, treatment,

## **Introduction**

People with end-stage-renal-disease (ESRD) on hemodialysis have one of the highest rates of cardiovascular morbidity and mortality [1]. Although elevated blood pressure (BP) is a well-established cardiovascular risk factor in the general population [2,3], the contribution of hypertension to cardiovascular and all-cause mortality among patients on hemodialysis is antithetical; observational studies show an inverse relationship of pre- and postdialysis BP with mortality [4]. In sharp contrast, elevated BP recorded outside of dialysis is directly related to mortality [5-7]. Furthermore, at odds with observational studies, deliberate BP-lowering with antihypertensive medications improves clinical outcomes [8,9]. Till date, no trial has randomized patients to two different BP targets in dialysis, therefore optimal BP thresholds remain unknown [10].

More than a decade ago, the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines based the management of hypertension in hemodialysis on an arbitrarily chosen BP standard <140/90 mmHg for predialysis BP and <130/80 for postdialysis BP [11]. These recommendations were based either on weak evidence or on expert opinion. Since the publication of those guidelines, a growing body of evidence suggests that out-of-dialysis BP recordings are superior to pre- and postdialysis BP in diagnosing hypertension [12,13], detecting evidence of target-organ damage [14], prognosticating the risk for future cardiovascular events and mortality [5-7] and guiding the overall management of hypertension in hemodialysis [15,16].

In this article, we review the currently available evidence from observational and randomized studies aiming to provide a comparative evaluation of out-of-dialysis BP monitoring versus dialysis-unit BP recordings with respect to their diagnostic accuracy and prognostic validity in hemodialysis. We conclude with a call for properly-designed randomized trials comparing different home BP targets in relation to clinical outcomes and mortality in order to obtain the highest level of scientific evidence in this important area.

## **Out-of-dialysis BP versus dialysis-unit BP recordings in the management of hypertension in hemodialysis**

### ***Dialysis-unit BP recordings***

Management of hypertension among patients on hemodialysis is currently based on conventional peridialytic BP recordings [11]. Peridialytic recordings are not adequate for diagnosing, managing or assessing the prognosis of hypertension among hemodialysis patient for 3 main reasons.

#### *(i) Poor precision*

Compared with the “gold-standard” method of interdialytic ambulatory BP monitoring (ABPM) peridialytic BP recordings are imprecise [13]. The precision of peridialytic BP recordings remains poor even if BP measurements are obtained using a standardized technique [17]. The precision is likewise poor even if many readings are averaged such as over 6 consecutive dialysis sessions over 2 weeks [18]. This suggests that the poor measurement technique or the truly high variability of BP from one dialysis session to the next can only partially explain the poor agreement between peridialytic and interdialytic ambulatory BP [19].

*(ii) Peridialysis BP and intradialytic hypotension*

Surveys of peridialysis unit BP recordings indicate that associate that among patients who achieve currently recommended predialysis BP targets have a higher risk for intradialytic hypotension [20]. Intradialytic hypotension is a serious and potentially life-threatening dialysis-related complication [21,22].

*(iii) Poor relationship with target organ damage and mortality*

Another factor that raises concerns regarding the external validity of peridialytic BP recordings is their poor correlation with indices of target-organ damage [14,23,24] as well as their inverse relationship with mortality that contrasts the direct and linear prognostic association of home and ambulatory BP recordings [5-7], as discussed in detail below.

***Out-of-dialysis BP monitoring***

Home BP monitoring (HBPM) is widely applied and strongly recommended by international guidelines for the diagnosis and management of hypertension in the general population [25]. More than any other patient population, the technique of HBPM may be particularly valuable among those on hemodialysis for several reasons. Contrary to the poor agreement between peridialytic BP and interdialytic ambulatory BP, an average self-measured home systolic BP (SBP)  $\geq 150$  mmHg had both sensitivity and specificity  $>80\%$  in detecting interdialytic hypertension, using 44-hour ABPM as the reference standard [18]. Contrary to the high short-term variability of pre- and postdialysis BP recordings [19], home BP is more reproducible from one week to the next [26]. Home BP can also reliably track the changes in 44-hour ambulatory BP induced after 4 and 8 weeks of dry-weight reduction, whereas these BP responses were less reliably detected when peridialytic BP was used as indicator

[26]. Home BP is also superior to peridialytic BP in detecting the presence of target-organ damage (i.e., echocardiographic left ventricular hypertrophy) [14] and predicting the risk for future cardiovascular events and mortality [5,6].

In addition to the above, HBPM emerges as a simple and reliable approach to guide the management of hypertension in hemodialysis as shown in 4 studies. In the first study, 41 drug-treated hypertensive hemodialysis patients underwent discontinuation of their BP-lowering medications while home BP was being monitored on a weekly basis [27]. After the full withdrawal of antihypertensive medications over a 3-week wash-out period, 80% of study participants became hypertensive, but the other 20% had sustained normotension, suggesting that HBPM is a useful tool to assess the appropriateness of antihypertensive therapy [27]. A second study, a randomized trial, assigned 65 hemodialysis patients to either home BP-guided or predialysis BP-guided management of hypertension over a 6-month-long follow-up [28]. Compared with the predialysis BP-guided group, a significantly greater reduction of 9/7 mmHg in 24-hour ambulatory BP was noted among patients assigned to home BP-guided management of hypertension [28]. Between-group differences in the change of left ventricular mass index were not evident at 6 months. This is not surprising given the small size and short duration of the study. A third study, another randomized trial, assigned 34 hemodialysis patients to home BP-guided management of hypertension or to standard care. Using HBPM in decision making was associated with a significantly higher reduction in weekly averaged predialysis BP [29]. The value of home BP monitoring was evaluated in the Hypertension in Hemodialysis treated with Atenolol or Lisinopril (HDPAL) trial [30]. HDPAL participants measured their BP twice daily (on waking-up and before going to bed) at home for 4 days after the mid-week dialysis session and HBPM was repeated on a

monthly basis over the 12-month-long course of the trial [30]. HBPM was sufficient to guide the management of hypertension in the research setting. HBPM may be similarly useful to guide hypertension management in the clinical setting, if this method is widely applied in hemodialysis as a simple approach to improve decision making.

Interdialytic ABPM is considered the “gold-standard” technique of BP measurement among patients on hemodialysis [31]. Interdialytic ambulatory BP readings are valid [32], highly reproducible [33], display strong associations with electrocardiographic evidence of left ventricular hypertrophy [14] and share a direct relationship with all-cause mortality [5,6]. The strong prognostic significance of interdialytic ambulatory BP is not relied only on the higher number of measurements obtained during a 44-hour ABPM, because interdialytic BP is shown to retain its strong prognostic association with mortality, even if a small number of randomly selected measurements are analyzed [34]. The superiority of out-of-dialysis BP (both home and ambulatory) over dialysis-unit BP is more likely explained by the fact that measurements sampled over a broader spectrum of situations and activities may provide a more precise reflection of the patient’s typical BP burden over time [35,36]. In addition, whereas dialysis-unit BP is unavoidably influenced by the white-coat effect (i.e. high BP only in-dialysis and normal BP outside of dialysis), the white-coat effect is mitigated with self-measured home BP readings and eliminated with the use of interdialytic ABPM [25]. Dialysis-unit BP recordings are unable to detect masked hypertension (i.e., high BP outside of dialysis and normal BP within dialysis), while masked hypertension is easily detectable with HBPM or ABPM [25]; the latter may also explain, at least in part, their strong prognostic value, since masked hypertension is shown to affect up to 15% of hemodialysis patients and is associated with higher

mortality risk in comparison with sustained (intra- and interdialytic) normotension [37].

Although interdialytic ABPM provides intense BP sampling in the short time-frame (such as 24 or 48 hours), the feasibility to use this technique repeatedly in order to guide the management of hypertension over several weeks, months or years is low [38]. This has been for long the main reason why BP targets and the overall management of hypertension have been based on the readily available pre- and postdialysis BP recordings. Instead of basing our therapeutic decisions on this unreliable approach, we use HBPM as a simple tool to guide hypertension management in the long-term.

### ***Median intradialytic BP as a proxy of interdialytic ambulatory BP***

Agarwal et al. have shown that all the BP readings taken during the dialysis procedure including pre- and postdialysis BP measurements provides a more accurate reflection of mean interdialytic ambulatory BP [39]. Since both mean and median are measures of central tendency and because the calculation of an average is time consuming and often impractical to use at the bedside, an alternative approach to detect hypertension is the use of the median of the BP readings taken during a single dialysis session. Using 44-hour ABPM as the reference method, a mid-week median intradialytic BP  $\geq 140/90$  mmHg provides approximately 80% sensitivity and specificity in diagnosing interdialytic hypertension [39]. Moreover, median intradialytic BP is responsive to dry-weight probing and can reliably track the changes in interdialytic ambulatory BP evoked by dry-weight reduction [40]. Although the use of intradialytic BP may improve the diagnostic accuracy of dialysis-unit BP recordings, this approach can be used when neither home nor ambulatory BP is



available to diagnose or guide the management of hypertension in hemodialysis patients.

### **“Reverse” epidemiology of hypertension in hemodialysis and its association with peridialytic BP**

Unlike the direct association of BP with mortality in the general population, numerous observational studies have shown that among incident or prevalent hemodialysis patients, the relationship between pre- or postdialysis BP recordings with mortality is antithetical [4,41]. Indeed, lower predialysis BP is associated with higher mortality [42-45], whereas higher pre- and postdialysis BP is either not associated or minimally associated with excess mortality [42-45]. This U-shaped pattern has been described as “reverse epidemiology” of hypertension, raising substantial concerns and uncertainties on whether BP should be lowered in the hemodialysis population. It is increasingly recognized, however, that the prognostication of the mortality risk is substantially variant when BP is recorded outside of dialysis [4]. In sharp contrast to the U-shaped association of peridialytic BP recordings with mortality, elevated interdialytic BP is directly related to higher mortality hazard [5-7,46,47].

In the first study to support this notion, Amar et al. [7] prospective followed 57 treated hypertensive hemodialysis patients over a mean follow-up of  $34.4 \pm 20.4$  months. After adjustment for age, gender and history of pre-existing cardiovascular disease, Cox-regression hazard analysis showed that each 10 mmHg higher 24-hour pulse pressure (PP) was associated with 85% increased risk of cardiovascular mortality [Relative Risk (RR): 1.85; 95% Confidence Interval (CI): 1.28-2.65] [7]. In another cohort of 168 non-diabetic hemodialysis patients without overt cardiovascular disease, Tripepi et al. [47] reported that the elevated ratio of the average SBP during

night-time and day-time periods (an indicator of the nocturnal BP dipping) was associated with 2.52 times higher risk for all-cause mortality [Hazard Ratio (HR): 2.52; 95% CI: 1.03–6.15) and 4.33 times higher risk for cardiovascular mortality (HR: 4.33; 95% CI: 0.96–19.61) over a mean follow-up of 3.2 years [47].

The relative importance of out-of-dialysis versus dialysis-unit BP recordings as predictors of mortality was evaluated in 2 subsequent cohorts of prevalent hemodialysis patients. The first study incorporated data from 150 hemodialysis patients who had their BP assessed with the use of HBPM for 1 week, ABPM over an entire interdialytic interval as well as with routine pre- and postdialysis BP measurements over 6 consecutive dialysis treatments [6]. Over a median follow-up of 24 months, each 1-standard deviation (SD) higher home SBP increased the risk of all-cause mortality by 35% (HR: 1.35; 95% CI: 0.99-1.84) and each 1-SD higher 44-hour ambulatory SBP increased the risk of all-cause death by 46% (HR: 1.46; 95% CI: 1.09-1.94). In contrast, peridialytic BP recordings had no prognostic association with mortality [6]. In a larger cohort of 326 prevalent hemodialysis patients, Agarwal et al. [5] showed that over a mean follow-up of 32 months, increasing quartiles of self-measured home SBP and 44-hour ambulatory SBP were both associated with increased mortality (adjusted HRs for increasing quartiles of home SBP: 2.15, 1.7, 1.44; and for 44-hour ambulatory SBP: 2.51, 3.43, 2.62) [5]. Once again, no such relationship was detectable using pre- and postdialysis BP [5].

In an observational analysis of Chronic Renal Insufficiency Cohort (CRIC) participants with advanced chronic kidney disease (CKD) [46], the relationship of BP with mortality was assessed in 3 different time-periods and clinical settings: (i) when participants had an estimated-glomerular-filtration-rate (eGFR) <30 ml/min/1.73m<sup>2</sup> (n=1,708); (ii) when participants initiated hemodialysis and dialysis-unit BP was

available (n=403); (iii) when participants had an out-of-dialysis BP measurement in the office setting during a prespecified CRIC follow-up visit (n=326). No association between SBP and mortality was detectable among participants not yet on hemodialysis. A typical U-shaped association between dialysis-unit SBP and mortality was evident among incident hemodialysis patients. In contrast, out-of-dialysis SBP exhibited a direct and linear association with mortality (HR: 1.26; 95% CI: 1.14-1.40 for each 10 mmHg higher SBP) [46]. These data suggest that even if the techniques of HBPM and ABPM are not available, a few out-of-dialysis BP recordings taken in the office setting in a standardized manner retain a superior prognostic association with mortality than that of dialysis-unit BP.

Although the observational design of these studies does not provide cause-and-effect associations, hemodialysis patients with self-measured home SBP ranging from 125 to 145 mmHg or 44-hour ambulatory SBP ranging from 115 to 125 mmHg appear to carry the lowest risk for all-cause and cardiovascular mortality (**Figure 1**) [6]. Whether targeting home and ambulatory BP at these thresholds is translated into a survival benefit requires randomized controlled trials (RCTs).

### **Treating hypertension improves clinical outcomes in hemodialysis patients**

To investigate the potential hazards and benefits of deliberate BP-lowering via antihypertensive drug therapy, Heerspink et al. [9] performed a meta-analysis of 8 RCTs incorporating data from 1,697 patients and 495 cardiovascular events. The weighted mean difference in change of BP during follow-up between actively treated patients and controls was -4.5 mmHg for SBP and -2.3 mmHg for diastolic BP (DBP). This BP-lowering effect was associated with a 29% reduction in the risk of cardiovascular morbidity (RR: 0.71; 95% CI: 0.55-0.92) and 20% reduction in the risk

of all-cause mortality (RR: 0.80; 95% CI: 0.66-0.96) [9]. In a second meta-analysis of 5 RCTs that was restricted to hemodialysis patients (n= 1,202), Agarwal et al. [8] showed that compared with the control therapy or placebo, active-treatment reduced by 31% the risk of future cardiovascular events (HR: 0.69; 95% CI: 0.56-0.84). When the analysis was stratified according to the hypertension status of patients participating in individual RCTs, it was shown the cardiovascular protection offered by antihypertensive therapy was greater among hypertensives (HR: 0.49; 95% CI: 0.35-0.67) [8].

It has to be noted that these 2 meta-analyses included RCTs aiming to evaluate the effect of different antihypertensive agents on clinical outcomes and not RCTs directly comparing different BP targets [8,9]. Accordingly, the causality between BP-lowering and subsequent improvement in clinical outcomes remains unproven. The results of these 2 meta-analyses, however, add to the growing body of observational evidence supporting the notion that hypertension among hemodialysis patients is harmful and should be appropriately treated.

### **Perspectives and directions for future research**

In light of a growing body of evidence supporting the superiority of out-of-dialysis over dialysis-unit BP recordings in detecting hypertension and prognosticating the risk of mortality, a high priority goal of future research is the assessment of the feasibility and cost-effectiveness of HBPM in the hemodialysis population. Ideally, we need RCTs comparing the effect of home BP-guided versus dialysis-unit BP guided management of hypertension on interdialytic ambulatory BP, regression of target-organ damage and improvement in clinical outcomes and mortality. The absence of “hard” clinical-trial evidence to prove that BP-lowering is

directly translated into survival benefit is another critical gap in the management of hypertension in hemodialysis. The Blood Pressure in Dialysis (BID) is a proof of concept study that attempts to target BP to different targets in this population [48]. Briefly, BID is a safety and feasibility study and is planning to randomize 120 hemodialysis patients to either a predialysis SBP target of 110-140 mmHg or 155-165 mmHg. As feasibility parameters, BID will assess recruitment and withdrawal rates, adherence to the prespecified BP measurement methods as well as the adequate separation in the achieved BP levels between the 2 study arms [48]. As safety endpoints, the BID trial will evaluate the difference between the lower and the higher SBP target in the incidence of intradialytic hypotension and other serious adverse events. A number of surrogate risk markers, such as the between-group differences in change of left ventricular mass index, aortic pulse wave velocity and health-related quality of life will be assessed as secondary efficacy endpoints [48]. This trial is a first step in the long road towards an optimal management of hypertension in hemodialysis. Additional research efforts, mainly RCTs using out-of-dialysis BP monitoring and evaluating different home BP targets in relation to clinical outcomes and mortality, are needed to fully elucidate this critical issue [49,50]. In the meantime and until compelling clinical-trial evidence become available, lowering self-measured home BP <140/90 mmHg appears to be a reasonable target for management of hypertension in hemodialysis. If home BP is not available, median midweek intradialytic BP <140/90 mmHg would appear a reasonable target.

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### **KEY POINTS**

- Home and ambulatory BP recordings are superior to conventional BP readings obtained shortly before or after dialysis in diagnosing hypertension, assessing BP control, detecting evidence of target-organ damage and prognosticating the risk for future cardiovascular events and mortality among patients on hemodialysis.
- Home BP-guided management of hypertension culminates in significantly higher reduction in interdialytic ambulatory BP versus conventional management based on peridialytic BP recordings.
- The “reverse” epidemiology of hypertension in hemodialysis is debated by prospective observational studies showing that elevated home and ambulatory BP are directly and linearly associated with excess mortality risk.
- Meta-analyses of randomized controlled trials showed that deliberate BP-lowering with antihypertensive medication is associated with improvement in clinical outcomes and mortality, providing additional support to the notion that hypertension in hemodialysis is harmful and should be controlled.
- In the absence of “hard” clinical-trial evidence to define optimal BP targets, the design of properly-designed RCTs comparing different home BP thresholds in relation to clinical outcomes and mortality in a high-priority goal of future research in the field of hypertension in hemodialysis.

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### **Figure titles and legends**

**Figure 1:** Prognostic association of dialysis-unit and interdialytic BP with mortality among patients on hemodialysis.

Hazard ratios for all-cause mortality for quartiles of systolic BP. Both home BP and ambulatory BP were prognostically informative. Conversely, dialysis-unit BP recordings did not achieve statistical significance in terms of prognostic value. Home systolic BP ranging from 125 to 145 mmHg or 44-hour ambulatory systolic BP ranging from 115 to 125 mmHg appear to carry the lowest risk for all-cause mortality. (Reprinted with permission from Alborzi et al. Home blood pressures are of greater prognostic value than hemodialysis unit recordings. *Clin J Am Soc Nephrol* 2007; 2:1228–34)

