

REVIEW ARTICLE

Blood pressure target for the dialysis patient

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Abstract

The appropriate blood pressure (BP) target for dialysis patients remains controversial. Although there have been remarkable advances in this area in the general population, extrapolation of these data to dialysis patients is not possible. Observational studies in dialysis patients suggest that low BP is associated with worse outcomes. However, this is likely a result of confounding, considering that among dialysis patients with fewer cardiovascular comorbidities and longer survival, a more linear relationship exists between BP and mortality. Use of home BP measurements and ambulatory blood pressure monitoring (ABPM) measurements are more useful from a prognostic standpoint than in-center predialysis BP measurements. Large clinical trial data are, however, lacking and firm recommendations on BP targets for dialysis patients are not possible.

1 | INTRODUCTION

The management of blood pressure (BP) for patients with end-stage kidney disease (ESKD) being treated with dialysis is challenging. Up to 70%-90% of dialysis patients carry a diagnosis of hypertension, and yet there are few data regarding the appropriate management of BP in this population. Clinical practice has relied on extrapolation of BP guidelines for the general population in whom hypertension is associated with greater cardiovascular mortality and morbidity, and in whom treatment of the hypertension leads to reduction in cardiovascular mortality. However, the relationship between BP and outcomes among dialysis patients is more complex and there are few trial data on BP targets in this population.

Given that cardiovascular disease (CVD) is the leading cause of death among dialysis patients,¹ addressing BP targets is however of paramount importance. In this review, we examine the observational data evaluating the relation between BP with CVD and mortality in dialysis patients and provide some interpretation of the differences in the relationships compared to the general population. We then discuss the prognostic importance of ambulatory blood pressure monitoring (ABPM) or home BP in comparison with in-center BP measurements. We conclude with discussion of the limited clinical trials in this area.

2 | BLOOD PRESSURE TARGETS IN THE GENERAL POPULATION

There have been recent updates in the recommendations regarding the BP target for the general population after publication of Systolic Blood Pressure Intervention Trial (SPRINT). SPRINT enrolled 9361 nondiabetic patients and randomized them to a target systolic BP of <120 mm Hg vs <140 mm Hg, and found a 25% reduction in the primary composite outcome of cardiovascular mortality and cardiovascular morbidity among those randomized to the intensive BP target (HR of 0.75, 95% CI 0.64, 0.89).² In contrast to SPRINT, the Action to Control Cardiovascular Risk in Diabetes-Blood Pressure (ACCORD BP) trial found no reduction in cardiovascular mortality or nonfatal myocardial infarction and nonfatal stroke with similar BP targets among patients with type 2 diabetes mellitus (T2DM).³ The exact reasons for the differences in results are unknown but one possibility that has been hypothesized is the lower than expected event rate in ACCORD, resulting in decreased statistical power. Based on a review of the literature including systematic review of 15 trials,⁴ the American College of Cardiology/American Heart Association (ACC/AHA) guideline on high BP updated their recommendation in 2017 to a target BP of <130/80 for all individuals.⁵

Patients with CKD, defined by an estimated glomerular filtration rate (eGFR) of <60 ml/min/1.73 m², were also included in the ACC/AHA guideline with recommendations of a target BP of $<130/80$ mm Hg. In the SPRINT trial, there was no effect modification by CKD and, in a priori subgroup analysis of those with CKD (mean baseline eGFR of 47.9 ml/min/1.73 m² and median albuminuria of 12.2 mg/g), randomization to a systolic BP target of <120 mm Hg (N = 1330) compared to a target of <140 mm Hg (N = 1316) was associated with decreased mortality (HR = 0.72, 95% CI, 0.53, 0.99).⁶ With regard to the prespecified kidney outcome, a decline in eGFR of 50% or greater, there was no evidence of harm or benefit with lower BP targets, although only 31 patients reached this end-point. These data suggest that at least in early stage CKD, targeting a lower BP is associated with improved CVD outcomes.

3 | BLOOD PRESSURE AND OUTCOMES: OBSERVATIONAL DATA

3.1 | Relationship of BP with mortality

While in the general population, there is a linear relationship between systolic BP and mortality, this is not evident in the dialysis population. That is, the risk of mortality is higher among those with systolic BP <140 mm Hg,⁷⁻⁹ rather than among those with higher systolic BP, creating a J-shaped or U-shaped curve (Figure 1). Prospectively collected predialysis systolic BP among 9333 hemodialysis patients in France using BP as a time-varying covariate also found a U-shaped association between systolic BP and mortality, with a systolic BP of 165 mm Hg associated with the lowest risk.¹⁰ This seemingly paradoxical observation has been labeled “reverse epidemiology,” in that the relationship between BP and outcomes is the reverse of what has been illustrated in the general population.

3.2 | Effect of length of follow-up

Time appears to be an important factor in the relationship between BP and mortality, with the risk attributable to BP changing over the length of follow-up (Figure 2). In a study of 16 959 dialysis patients, there was a shift in the relationship between BP and mortality over time.¹¹ In the first 2 years of follow-up, low systolic BP of <120 mm Hg was associated with increased mortality. However, among those patients who survived ≥ 3 years, a systolic BP of ≥ 150 mm Hg was associated with increased mortality. These data suggest that low BP may be a proxy for the degree of illness and not necessarily a causal risk factor for adverse outcomes.

3.3 | Effect of confounding

The general consensus has been that the J- or U-shaped relationship may reflect confounding from many different factors, including illness as well as prevalent CVD. For example, in an analysis of predialysis BP among 4499 hemodialysis patients from the U.S. Renal Data System (USRDS), patients with prevalent heart failure (HF) had a 2.5-fold (RR = 2.5, $P < 0.01$) risk of death when the predialysis systolic BP was <110 mm Hg as compared to those with HF who had a systolic BP of 120-149 mm Hg.¹² In contrast, this relationship was not significant in those without HF (RR = 1.5, P -value not reported).

In another study of 446 patients from the Choices for Healthy Outcomes in Caring for ESRD (CHOICE) study, patients were stratified by the level of CVD biomarkers using troponin and N-terminal pro b-type natriuretic peptide (NT-proBNP).¹³ Those with low levels of CVD biomarkers (troponin <0.1 ng/ml or NT-proBNP <9252 pg/ml) had longer survival, and similar to a nondialysis population; a systolic BP of >140 mm Hg was associated with a 7% increased risk of all-cause mortality (HR = 1.07, 95% CI 1.01, 1.14).¹³ In contrast, among those with higher biomarkers levels, median survival was

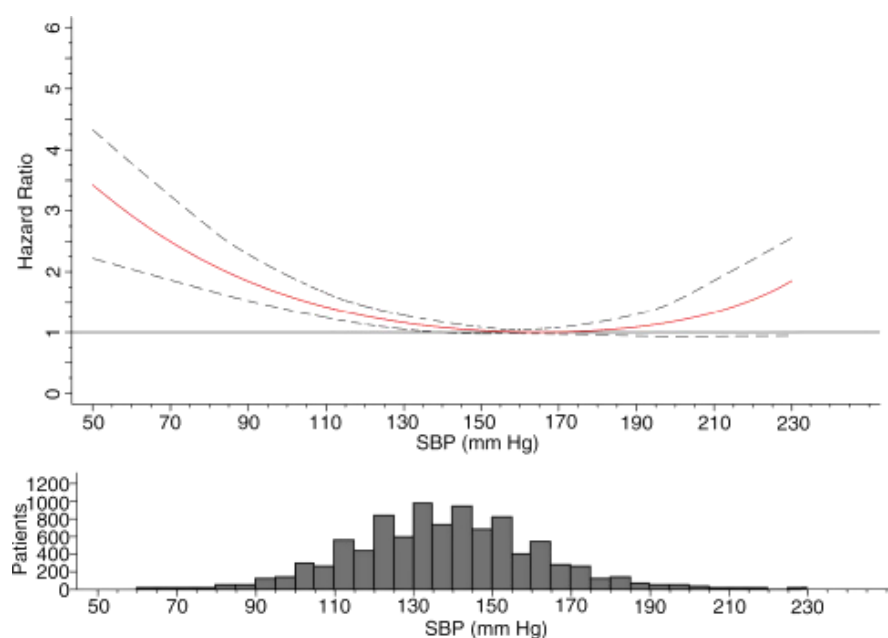


FIGURE 1 Multivariable adjusted hazard ratios for all-cause mortality associated with systolic blood pressure. Risk for mortality noted to be lowest at a predialytic systolic BP of approximately 165 mm Hg. Figure adapted from Hannedouche et al KI 2016. Used under Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International license <https://creativecommons.org/licenses/by-nc-nd/4.0/> [Color figure can be viewed at wileyonlinelibrary.com]

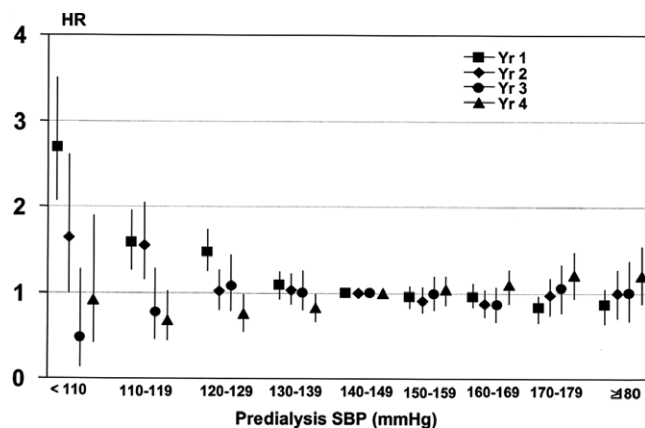


FIGURE 2 Hazard ratios for all-cause mortality by baseline predialysis systolic BP. For patients who survived for less than 1 y, low systolic BP was associated with increased mortality. In contrast, for patients who survived for >3 y, low systolic BP was associated with decreased hazard for mortality. Figure adapted from Stidley et al JASN 2006, reprinted with permission from American Society of Nephrology

1.1 years shorter and there was no association between BP and mortality (HR = 0.99, 95% CI 0.92, 1.06).

Similar results have also been found in studies using 24-hour ABPM. In a study of 344 hemodialysis patients, 105 patients had either atrial fibrillation or HF, or both. A linear relationship between SBP and mortality was only noted in those without cardiovascular comorbidities.¹⁴

All three of these analyses support the notion that dialysis patients have a high burden of CVD and high risk of mortality, and that low BP may be a proxy of poor cardiac function and overall illness. Interpreting mortality risk in relation to BP in observational studies is therefore challenging.

3.4 | Effect of method and timing of BP measurement

There is enormous variability of BP among dialysis patients particularly during the dialysis period. Blood pressure is often measured before dialysis, and predialysis BP is often what has been evaluated in observational studies. However, systolic BP drops by an average 8-10 mm Hg following dialysis, with large variability both between patients as well as within individuals.¹⁵⁻¹⁷ Given this variability, there has been debate as to which BP measurement should be used, both in studies and in clinical practice. Regarding in-center measurements, there have been three conventional methods of measuring BP, which include predialysis, intradialysis, and postdialysis.

Given the issues with BP variability, others have proposed using home measurements, especially given observations that in-center BPs have had no correlation with evidence of end-organ damage such as left ventricular hypertrophy (LVH).¹⁸ Home BPs that were taken twice daily and then averaged over the course of a week had a linear correlation with end-organ damage such as LVH as well as

with higher risk of mortality.^{18,19} In addition, there have been two prospective studies evaluating ambulatory BP monitoring (ABPM) for the 44-hour period between dialysis shifts compared to home or in-center readings. In one study of 150 dialysis patients, there was a 46% increase (HR = 1.46, 95% CI 1.09, 1.94) in risk for mortality for each standard deviation (SD) higher systolic BP obtained by ABPM.²⁰ There was a similar pattern using home BP measurements (HR = 1.35 per SD higher systolic BP, 95% CI 0.99, 1.84), but this association was not seen when using in-center predialysis measurements (HR = 0.97 per SD increase, 95% CI 0.72, 1.30) (Figure 3). Similarly, in a second study of 326 dialysis patients, the top quartile of ABPM measurements was associated with a hazard ratio of 2.51 (95% CI of 1.29, 4.29) for mortality in comparison to the lowest quartile.²¹ Predialysis BP was not, however, associated with mortality.

These data suggest that incorporation of home BP measurements or ABPM may be useful in dialysis patients, albeit may be cumbersome or difficult to obtain. Likewise, guidelines from the Kidney Disease Outcomes Quality Initiative (KDOQI) have also suggested that addition of home or ABPM BP may provide better prognostic information, but are admittedly less practical and more expensive.²²

4 | BLOOD PRESSURE AND OUTCOMES: TRIAL DATA

There have been numerous trials assessing various antihypertensive agents ("blood pressure agent" trials) in dialysis patients, which suggest that treatment of BP may be important, but they do not provide data on BP targets. Two meta-analyses have been published.^{23,24} The first meta-analysis included eight trials which randomized patients to different BP agents vs placebo, mean systolic BP was 4.5 mm Hg lower and diastolic BP was 2.3 mm Hg lower in

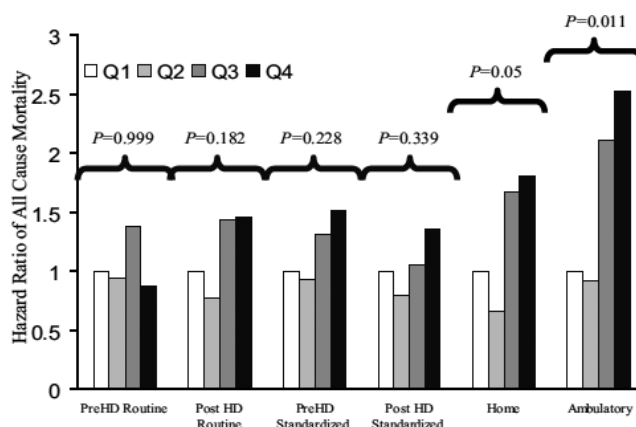


FIGURE 3 Hazard ratios for all-cause mortality for quartiles of systolic BP. The highest quartile of BP among both home and ambulatory measures was associated with increased mortality, but not for the other in-unit dialysis BP measurements. HD: hemodialysis; Q: quartile. Figure adapted from Alborzi et al 2007 CJASN, reprinted with permission from the American Society of Nephrology

the treatment groups; treatment was associated with lower risk of cardiovascular events (RR 0.71, 95% CI, 0.55, 0.92), all-cause mortality (RR 0.80, 95% CI, 0.66, 0.96), and cardiovascular mortality (RR 0.71, 95% CI, 0.50, 0.99) (Figure 4).²⁴ The mortality benefit associated with treatment was consistent across all sub-groups, including patients with HF. The second meta-analysis included five studies and reached similar conclusions (HR 0.69 for treatment vs no treatment, 95% CI, 0.56, 0.84).²³ Given that these were "agent trials" rather "target trials" it is not possible to distinguish whether the benefit was due to the agent versus the lower BP achieved.

We are only aware of one pilot trial assessing feasibility and safety of randomizing dialysis patients to different BP targets.²⁵ In the Blood Pressure in Dialysis (BID) trial, 126 patients who had been treated with dialysis for ≥ 3 months and with a 2-week average predialysis SBP of ≥ 155 mm Hg were randomized to either a predialysis SBP target of 110-140 mm Hg ($n = 62$) or 155-165 mm Hg ($n = 64$). The mean difference in systolic BP achieved between the two arms was 12.9 mm Hg. Results of the primary outcome showed no significant difference between the median change in left ventricular mass (LVM) from baseline to follow-up assessment at 12 months (median difference of -0.84 g/m² [IQR of $-17.1, 10.0$] in the intensive arm, compared to 1.4 g/m², [IQR of $-11.6, 10.4$] in the standard arm, $P = 0.43$). There was an increase in hospitalizations and vascular access thromboses in the intensive arm, but given the small size and relatively short follow-up time, these were not statistically significant.

5 | POTENTIAL HARMS OF BP REDUCTION

5.1 | Intradialytic hypotension

While the growing body of evidence suggests that treatment of hypertension in dialysis patients may have a mortality benefit over the long term, there are potential risks. Patients with ESKD tend to be older and more frail, and predisposed to complications such as syncope, presyncope, and falls that could be amplified by treatment to tight BP targets. Additionally, symptomatic intradialytic hypotension (IDH) affects an estimated 20%-30% of all dialysis sessions²⁶ and there are numerous dialysis-specific harms that can occur in association with IDH. In addition to limiting ultrafiltration and causing interruptions to dialysis treatments, IDH has been associated with tissue ischemia including cerebral, myocardial and gastrointestinal ischemia, and increased rates of venous access thrombosis and increased mortality.²⁷⁻³⁰

However, it remains to be determined whether treatment to specific targets is necessarily linked to the occurrence of IDH. Following the introduction of BP targets by the United Kingdom Renal Association standards committee in 2002 (targets of $<140/90$ mm Hg predialysis and $<130/80$ mm Hg postdialysis), an observational study was conducted in 11 hemodialysis units in the Greater London area. Over the course of 1-week, it was found that the centers which achieved the highest percentage of patients meeting these BP targets had a higher per patient antihypertensive medication use but

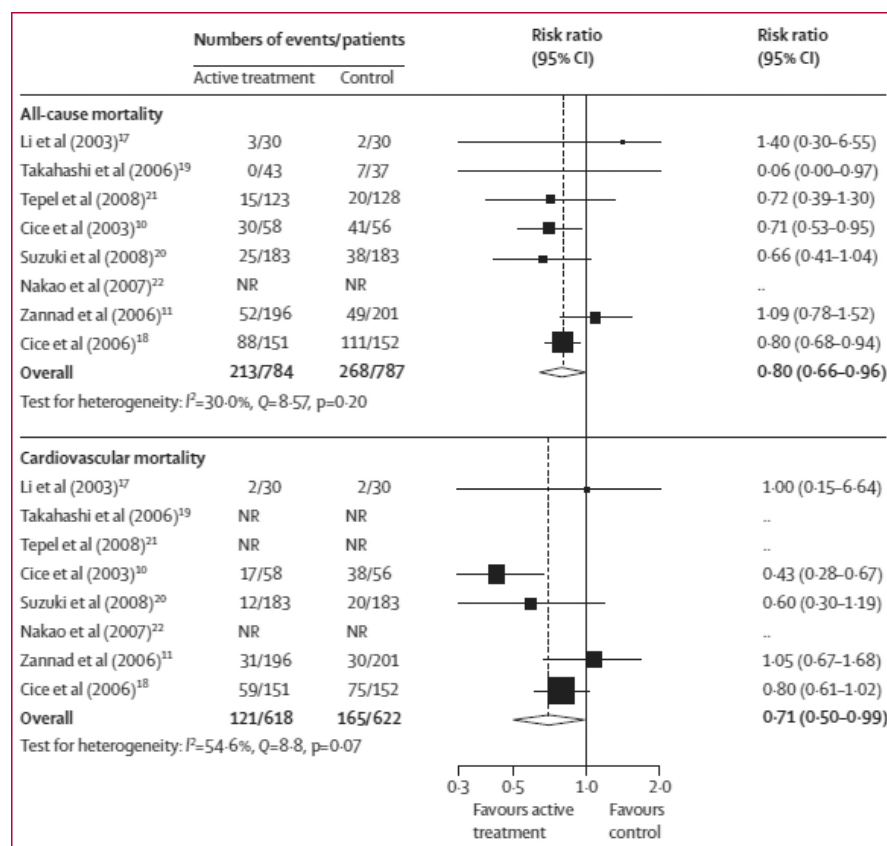


FIGURE 4 Risk of all-cause mortality and cardiovascular mortality based upon blood pressure lowering treatment or placebo control. Figure adapted from Heerspink Lancet 2009, reprinted with permission from Elsevier Science and Technology Journals [Color figure can be viewed at wileyonlinelibrary.com]

also had the highest rates of IDH.³¹ These data suggested that the cost of achieving BP targets was more frequent IDH; however, with the observational nature of the study, there was no way of determining if using medications to achieve BP targets at the level of the individual patient was linked to IDH. In the data gathered from trials of BP-lowering interventions, even though systolic BP was lower in the treatment arms, there were no differences in rates of IDH observed.^{23,24,32}

5.2 | Wide pulse pressure and low diastolic BP

Higher pulse pressure, which is thought to be a marker of vascular stiffness,^{33,34} is recognized as a risk factor for cardiovascular outcomes in the general population.^{35,36} Low diastolic BP has also been associated with adverse outcomes in the general population, with lower coronary perfusion (which primarily occurs in diastole) hypothesized as a potential explanation of this association.³⁷ However, a recent analysis from the SPRINT trial has demonstrated a benefit of intensive systolic BP control even in those within the lowest quintile of diastolic BP (mean diastolic BP of 61 ± 5 mm Hg) (HR of 0.74, 95% CI 0.61, 0.90).³⁸

Dialysis patients have a high prevalence of wide pulse pressures.^{39,40} In addition, both wide pulse pressure and low diastolic BP are associated with adverse outcomes in dialysis patients.⁴⁰ Given the limitations of observational data and the lack of trial data on BP targets in dialysis patients, it remains to be determined whether, and if so how, to incorporate either pulse pressure or diastolic BP into decision-making regarding BP targets in this population.

6 | CURRENT GUIDELINES

Drawing data from observational studies and small randomized controlled trials, there is insufficient evidence to provide strong recommendations regarding BP targets in the dialysis population. Most of the recommendations within various guidelines are therefore based on expert opinion. The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines from 2005 recommended a predialysis BP target of <140/90 mm Hg and postdialysis BP of <130/80 mm Hg (Table 1). However, without trial-level evidence, the strength of these recommendations was given a rating of "Grade C," indicating that they were either based on weak evidence or opinions of the work group. The 2015 update of these guidelines stated that there is not enough evidence to support a specific BP target.⁴¹ The European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) concur with this assessment in their guidelines.⁴²

In Canada and Japan, guidelines have recommended a predialysis BP of <140/90 mm Hg,^{43,44} but both with the caveat that there is an absence of sufficient data to define an optimal BP in the dialysis population. The UK Renal Association Standards Committee has recommended predialysis BP target of <140/90 mm Hg and postdialysis target of <130/80, but an audit of 11 hemodialysis centers in the Greater London area performed after these guidelines found that only 26% of patients (of a total N = 2630) were meeting both BP targets.³¹

TABLE 1 Blood pressure targets according to major clinical practice guidelines

Guideline	Blood pressure target
KDOQI 2005 Guidelines ²²	Predialysis BP <140/90 mm Hg Postdialysis BP <130/80 mm Hg
KDOQI 2015 Guideline Update ⁴¹	No target defined, citing paucity of clinical trial data
Canadian Society of Nephrology 2006 Guidelines ⁴³	Predialysis BP <140/90 mm Hg
European ERA-EDTA 2017 Guidelines ⁴²	No target defined, citing paucity of clinical trial data
Japanese Society for Dialysis Therapy 2012 Guidelines ⁴⁴	Predialysis BP <140/90 mm Hg

7 | CONCLUSIONS

It is important to acknowledge that the data used to generate BP target guidelines for the general population cannot be extrapolated to the dialysis population. Dialysis patients have a high burden of CVD and general illness that confounds the relationship between BP and clinical outcomes. Dialysis patients also have widely varying BPs and suffer greater short-term adverse consequences of hypotension, including end-organ damage from ischemia, vascular access thrombosis, and interruptions to dialysis leading to issues with volume management. The current observational data do not, therefore, allow for firm BP target recommendations. However, it does appear that home BP measurements are more predictive of outcomes than in-center measurements, making it reasonable to recommend the use of home BP measurements or ABPM results for clinical management decisions if possible. Large randomized controlled trials evaluating different BP targets are necessary to help in defining BP targets in this population.

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