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The lingering dilemma of arterial pressure in CKD: what do we know, where do we go?

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Despite many advances in the management of hypertensive chronic kidney disease (CKD) patients, both on and off dialysis, there exist several gaps in our knowledge. Although the modern techniques to measure blood pressure (BP) indirectly have been available for a long time, among those with CKD, how to best assess hypertension and the level to which it should be lowered are mired in controversy. Other controversial areas relate to a lack of a consensus definition of hypertension among hemodialysis patients, uncertainty in the definition and assessment of volume excess, and the lack of adequately powered randomized trials to evaluate the level to which BP can be lowered in those on dialysis. This review discusses the limitations of the available evidence base and suggests areas for future research. Suggestions include evaluation of techniques to assess volume, randomized trials to target different levels of BP among hypertensive hemodialysis patients, evaluation of ambulatory BP monitoring, and non-pharmacological means to lower BP in CKD. It is hoped that among patients with CKD these data will improve the dismal cardiovascular outcomes.

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Hypertension is both a cause and effect of chronic kidney disease (CKD). There is little doubt about this bidirectional and causal relationship, the evidence for which comes from epidemiological, clinical, and research models. Although the modern techniques to measure blood pressure (BP) were described over a 100 years ago by Riva Rocci and Nikolai Korotkoff, how to best assess hypertension and the level to which it should be lowered among those with CKD is mired in controversy. This controversy is especially vexing among patients with end-stage renal disease on chronic hemodialysis. In these patients, large volume shifts from before to after dialysis cause wide BP variations. These variations make the optimal timing and definition of hypertension problematic. The gaps in our knowledge that need to be addressed in patients with CKD and those on dialysis are discussed further.

CKD PATIENTS NOT ON DIALYSIS

Joint National Commission-6 recommended lowering BP to $<125/75$ mm Hg among those with >1 g proteinuria. However, these recommendations were removed as they were based on *post hoc* analyses. Among patients with CKD who are not on dialysis, Joint National Commission-7 guidelines recommend lowering BP to $<130/80$ mm Hg.[1] However, even these recommendations are based on largely observational data or *post hoc* analyses of randomized controlled trial data. In fact, the three randomized controlled clinical trials that targeted BP to two different levels among patients with CKD have failed to confirm the superiority of one level over

the other with respect to renal or cardiovascular outcomes.[2–4] Each of these three clinical trials targeted BP measured in the clinic. It is now becoming increasingly apparent that BP levels assessed in the clinic do not agree well with the usual level of BP; the usual level of BP is commonly assessed using 24-h ambulatory BP monitoring.[5] Using 24-h ambulatory BP monitoring as the reference standard, a recent meta-analysis revealed that ~20% of patients with CKD have white coat hypertension and about 5–10% have masked hypertension.[6] Other studies using more liberal definitions of masked hypertension have found a much higher prevalence of masked hypertension. The classification of patients into these two categories of masked hypertension and white coat hypertension is of more than statistical importance. Patients with white coat hypertension, whether assessed using ambulatory BP or home BP recordings, have a prognosis that is substantially better than those with sustained hypertension.[7] On the other hand, patients with masked hypertension have a prognosis that is substantially worse than those with persistent normotension.[8] These data suggest that the diagnosis and treatment of hypertension based on home BP recordings would be superior to those based on clinical recordings alone.[9] In fact, both European and US guidelines suggest home BP monitoring for all patients, including those with CKD.[10,11] Despite these recommendations, the precise method of how to measure home BP, how frequently to measure it, and how low to target the BP goal requires more study. Accordingly, home measurements should be systematically tested in larger populations of patients with CKD.

Although many trials have demonstrated that management of hypertension in the population without CKD with home BP monitoring leads to better BP control, only two such trials have been conducted in those with CKD.[12,13] Accordingly, there is an urgent need to conduct such trials in those with CKD to evaluate the risks and benefits of this simple and effective therapy to treat hypertension. If trials demonstrate that superior outcomes can be obtained with home BP monitoring, it could transform the management of patients with CKD.

It has long been recognized that the presence of even the slightest kidney disease causes blunting of the usual nocturnal decline in systolic BP with sleep.[14,15] This phenomenon of non-dipping among patients with CKD has been associated with poor outcomes in some but not all studies.[16–18] BP patterns, besides the usual level of BP, may or may not contain prognostic information.[19] Determination of the independent prognostic significance of BP patterns among patients with CKD needs to be further studied.[20] In particular, it is unknown whether non-dipping is a mediator or a marker of poor outcomes. This notion can only be tested in randomized trials.

CKD is a state of accelerated vascular aging. Many studies have used pulse pressure as a proxy of vascular age. These studies have shown a strong and linear relationship between pulse pressure and mortality among dialysis patients. However, pulse pressure is not the best proxy of vascular age. Vascular age is better reflected by increased arterial stiffness; this can be easily measured by carotid to femoral pulse wave velocity. There is an excellent relationship between directly measured intra-aortic pulse wave velocity and systolic interdialytic ambulatory BP.[21] There is also ample evidence to draw a direct relationship between pulse wave velocity and adverse outcomes among dialysis patients.[20] How the evaluation of arterial stiffness adds to the management of hypertension among patients with CKD now needs to be better defined. As arterial stiffness through the measurement of pulse wave velocity and central BP can be measured using the same equipment, it is possible to evaluate the role of central BP and pulse wave velocity simultaneously.

END-STAGE RENAL DISEASE PATIENTS

Among patients on chronic dialysis, the clinical guidelines for the level to which BP should be lowered are opinion based. These opinions suggest lowering predialysis BP to $<140/90$ mm Hg and postdialysis BP to $<130/80$ mm Hg.[22] However, some data suggest that achieving these targets is associated with increased episodes of intradialytic hypotension.[23] In fact, collective evidence suggests that predialysis and postdialysis BP measurements are poor estimates of interdialytic ambulatory BP measurements.[24] In contrast to peridialytic BP measurements, BP measurements outside the dialysis unit are associated with target organ damage and prognosis.[25–27] Furthermore, at least one randomized trial has suggested that when BP is targeted using home BP rather than pre- or postdialysis measurements, better ambulatory BP control is achieved at 6 months.[12] These data further support the use of home BP monitoring in the management of hypertension among hemodialysis patients.

A vexing problem especially among chronic hemodialysis patients is that of assessment of volume and its relationship with BP. The concept of dry weight has evolved over time and its definition has changed. Although there is no consensus on its definition, one such definition defines dry weight as the lowest tolerated postdialysis weight achieved by a gradual change in postdialysis weight at which there are minimal signs or symptoms of either hypovolemia or hypervolemia. Although clinical examination does not adequately detect latent increase in dry weight, several technologies such as relative plasma volume monitoring and body impedance analysis are emerging that may help in assessing dry weight in the future. There is a need to better evaluate these technologies.

Among dialysis patients, volume overload, often subclinical, is the primary cause of resistant hypertension. Sodium restriction is a modifiable risk factor that can lead to better BP control. However, dietary sodium restriction requires lifestyle modifications that are difficult to implement, and even harder to sustain over the long term. Newer options may include resins that bind dietary sodium. Restricting dialysate sodium is a simpler but underexplored strategy that can reduce thirst, limit interdialytic weight gain, and assist in the achievement of dry weight. However, larger studies with

1. What is the optimal level of target blood pressure (BP) among patients with chronic kidney disease (CKD)? Does this target depend on the severity of proteinuria? Should elderly patients with CKD have the same target levels of BP as younger patients?
2. What is the optimal level of target BP in patients with end-stage renal disease (ESRD) on dialysis? How should these targets be achieved: diet, drugs, or dry weight? What is the impact of lowering BP on residual renal function, cardiac function, and overall outcomes among hemodialysis patients?
3. What is the role of excess volume in the genesis of hypertension among patients with CKD? Does the pathophysiology vary as a function of clinical and demographic factors such as age, sex, race, and proteinuria?
4. What markers indicate excess volume among dialysis patients?
5. What is the optimal BP measurement technique and timing among those with CKD, including those on dialysis? What should be the reference standard for the diagnosis and management of these patients? Clinic or dialysis unit BP, home BP, or ambulatory BP?
6. What are the treatable causes of resistant hypertension among patients with CKD? What is the magnitude and time course of benefit that can be expected with treatment?
7. What is the role of non-volume factors in sustaining hypertension in CKD? Sympathetic activation, the renin–angiotensin system, endothelin, asymmetrical dimethylarginine (ADMA), renalase, etc.
8. What are the risks and benefits of mineralocorticoid receptor antagonists in the treatment of hypertension in patients with CKD?
9. What is the independent prognostic significance of BP patterns among patients with CKD?
10. How does the evaluation of arterial stiffness add to the management of hypertension among patients with CKD?

Figure 1 | Research questions.

firm end points are needed. Achievement of dry weight can improve interdialytic BP, reduce pulse pressure, and limit hospitalizations. Accordingly, reduction of volume overload with dietary and dialysate sodium restriction and periodic probing of dry weight is believed to be good clinical practice.[28] Avoiding medication-directed control of BP may enhance the opportunity to probe dry weight, facilitate removal of volume, and limit the risk for pressure–volume overload, which may be a significant concern leading to myocardial remodeling in the hemodialysis patient. Probing dry weight among patients with end-stage renal disease has the potential to improve dismal cardiovascular outcomes.

The use of drugs to improve BP control among chronic hemodialysis patients is even more debatable. Epidemiological studies demonstrate that a lower BP and decline in BP over months or years are associated with higher mortality in dialysis patients. In contrast, randomized, controlled trials so far available have a low power to establish the benefits of antihypertensive therapy. A meta-analysis of five studies among 1202 hemodialysis patients demonstrated the overall benefit of antihypertensive therapy compared with the control or placebo group. It found a combined hazard ratio for cardiovascular events of 0.69 (95% confidence interval: 0.56–0.84).[29] This meta-analysis suggests benefit but does not establish the value of the antihypertensive drug among hemodialysis patients. It remains unclear whether strategies to control BP with dry weight or drugs have associated risks such as increased episodes of intradialytic hypotension, subclinical myocardial ischemia, access dysfunction, and an accelerated demise of residual renal function. Thus, the risks and benefits of these techniques on cardiovascular outcomes need to be evaluated in adequately powered randomized trials.

In conclusion, despite many advances in the management of patients with CKD, both on and off dialysis, there exist several gaps in our knowledge. These relate to the definition of hypertension, assessment of volume, and evaluation of outcomes (see Figure 1).

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