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Hypertension Treatment for Patients with Advanced Chronic Kidney Disease

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Abstract

Chronic kidney disease is common and frequently complicated with hypertension. As a major modifiable risk factor for cardiovascular disease in this high risk population, treatment of hypertension in chronic kidney disease is of paramount importance. We review the epidemiology and pathogenesis of hypertension in chronic kidney disease and then update the latest study results for treatment including salt restriction, invasive endovascular procedures, and pharmacologic therapy. Recent trials draw into question the efficacy of renal artery stenting or renal denervation for hypertension in chronic kidney disease, as well as renin-angiotensin-aldosterone system blockade as first line therapy of hypertension in end stage renal disease. Positive trial results reemphasize salt restriction and challenge the prevailing prejudice against the use of thiazide-like diuretics in advanced chronic kidney disease. Lastly, clinical practice guidelines are trending away from recommending tight blood pressure control in chronic kidney disease.

Keywords

chronic kidney disease; end stage renal disease; hemodialysis; hypertension; resistant hypertension

INTRODUCTION

Chronic kidney disease (CKD) is defined as the presence of kidney damage or abnormal kidney function for at least three months duration [1]. CKD is a major public health concern on account of both its prevalence and its complications. Based on National Health and Nutrition Examination Survey (NHANES) data the prevalence of CKD has been increasing, up to more recent estimates of 13.1% of the population in the United States, a proportion similar to that of diabetes mellitus [2]. As with diabetes, CKD is increasingly being recognized as a cardiovascular risk equivalent [3]. Notably the many adverse sequelae of

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Conflict of Interest

Rajiv Agarwal and Arjun Sinha declare no conflicts of interest.

Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by the author.

CKD become more common with advancing stage, and the prevalence of at least moderate (stage 3) CKD is estimated at over 8% of the population [2].

EPIDEMIOLOGY

Hypertension is a frequent complication of CKD and when present it is often poorly controlled in the CKD population. As a recent example, a cross sectional study of CKD patients from the Chronic Renal Insufficiency Cohort (CRIC) study found a prevalence of 85.7% for hypertension defined as BP $\geq 140/90$ or use of an antihypertensive medication [4]. Hypertension control rates were higher in the CRIC study compared to previous cohorts with 67.1% and 46.1% controlled to a goal BP of $< 140/90$ or $< 130/80$ respectively. However it should be noted that within the hypertensive CRIC cohort, 58% were on treatment with 3 or more antihypertensive medications suggesting that a large proportion of the cohort had resistant hypertension.

While the exact prevalence varies depending on whether pre-dialysis BP, post-dialysis BP, or interdialytic ambulatory BP is examined, hypertension is also common in patients with end stage renal disease (ESRD) on dialysis. A recent cross sectional study of 369 HD patients illustrates this point as 82% of subjects had hypertension defined as use of antihypertensive drugs or 44 hour interdialytic ambulatory average BP $\geq 135/85$, and hypertension was adequately controlled in 38% [5].

PATHOPHYSIOLOGY

While comorbid conditions that exacerbate hypertension such as increased arterial stiffness [6] and obstructive sleep apnea [7] are common in the CKD population, numerous mechanisms more specific to renal disease are proposed to contribute to hypertension. Sodium loading has long been clinically recognized as a major and essential contributor to hypertension both in those with normal renal function [8] and in those with renal disease [9]. As glomerular filtration rate (GFR) declines with progression of CKD, less sodium is filtered leading to sodium retention and an expanded extracellular fluid volume. Another classically recognized contributor is an inappropriately activated renin-angiotensin-aldosterone system (RAAS) [10], possibly provoked by renal ischemia in patients with renovascular disease.

More recently, sympathetic nervous system overactivity arising from renal efferent nerves has gained recognition as a significant contributor to hypertension in CKD as demonstrated by the finding of increased muscle sympathetic nerve activity in ESRD patients compared to normal controls or to ESRD patients status post bilateral nephrectomy [11]. Another unique contributor to sympathetic overactivity is reninase, a novel enzyme secreted by the kidney that metabolizes circulating catecholamines and which is deficient in CKD both in animal models and in humans [12].

CKD patients have additional causes of vasoconstriction including impaired nitric oxide synthesis from circulating inhibitors such as asymmetric dimethyl arginine [13]. Endothelin receptor activation contributes to vasoconstriction as elevated levels of endothelin-1 have been documented in various stages of CKD [14] and endothelin receptor blockade has

shown at least initial success in improving hypertension in humans [15]. More recently, phase II studies with endothelin-1 receptor antagonist that is highly selective for the type A receptor demonstrate between 35–40% lowering in albuminuria at 12 weeks of treatment and reduction in 24h ambulatory blood pressure of 4–6 mmHg over the same period [16].

Lastly, medications can provoke hypertension in the CKD population. While over the counter nonsteroidal anti-inflammatory drugs and decongestants can exacerbate hypertension, erythropoiesis stimulating agents are commonly prescribed for the anemia of CKD and resultant hypertension has been reported in up to 30% of patients [17]. The precise mechanism of how erythropoietin causes hypertension is unknown, but current evidence suggests that it is independent of hemoglobin level and more likely is mediated via vasoconstrictor effects, possibly through increased levels of endothelin-1 or sensitivity to that peptide [18].

NON PHARMACOLOGIC TREATMENT

Sodium Restriction

Given the central importance of volume overload in the pathogenesis of hypertension in kidney disease, restricting sodium intake is an important strategy for treating hypertension in CKD. While recent trials have shown low sodium to be efficacious for treating resistant hypertension without kidney disease [19] and for reduction of proteinuria and albuminuria [20], those studies examining low sodium diet for control of hypertension in CKD have been hampered by lack of randomization or blinding or a lack of gold standard BP measurements.

A recent elegantly designed randomized controlled 6 week trial demonstrated the efficacy of a low sodium diet in 20 patients with stage 3–4 CKD and elevated office BP [21]. Subjects were counseled on low sodium diet and were provided with samples of low sodium foods and after a run-in phase they were randomized to receive sodium tablets versus placebo before washout and cross over, with a goal sodium intake < 80 mmol per day in the low sodium group and 200 mmol per day in the high sodium group. At baseline subjects had an average 24 hour ambulatory BP of 151/82 mmHg and the improvement in average 24 hour ambulatory BP on the low sodium diet compared to high sodium diet was both statistically and clinically significant at 9.7/3.9 mmHg [21]. Both proteinuria and albuminuria were significantly improved on the low sodium diet. Importantly, questionnaires, pill counts, and 24 hour urine collections were used to confirm compliance with sodium content in the diets and a steady potassium intake between groups.

Animal studies demonstrate that reducing gut sodium absorption by inhibiting uptake of dietary sodium using the drug tenapanor, a non-absorbable inhibitor of the NHE3 transporter can reduce BP and protect the kidneys among animals with subtotal nephrectomy [22]. Among normal healthy volunteers the drug reduces sodium absorption in a dose-dependent manner by about 50 mmol per day without causing diarrhea. Clinical trials in diabetic nephropathy are in progress to evaluate the antihypertensive and antiproteinuric effects of this drug.

In the ESRD population, reducing total body sodium content is achieved by reducing the dry weight, where a 1 kg average reduction in dry weight has been shown to improve average 44 hour interdialytic ambulatory BP by 6.6/3.3 mmHg during an 8 week clinical trial, without extending the HD time or changing antihypertensive medications [23]. Achieving and maintaining an adequately low dry weight is a hands-on and iterative process that requires attention to details beyond only the prescribed dry weight [24]. This includes adherence to a low sodium diet and minimization of dialysate sodium content, both to reduce interdialytic weight gain [25]. Additionally, extending the dialysis time can make ultrafiltration easier to tolerate thus facilitating the achievement of an adequate dry weight, while shorter dialysis times have recently been shown to be associated both with higher BP and slower improvement in BP when dry weight is reduced [26]. Similarly, more frequent HD may also facilitate adequate ultrafiltration, and while the Frequent Hemodialysis Network trial didn't find a significant improvement in the trial's composite primary endpoint, the investigators did find significant reductions in weekly average pre-HD SBP and in the number of antihypertensive medications needed for the intervention group that dialyzed six times weekly [27].

Renal Artery Stenting

Atherosclerotic renal artery stenosis is common in CKD, with prevalence reported at high as 40% in patients initiating dialysis [28]. As renal artery stenosis leads to a state of elevated RAAS activity, it is attractive to consider angioplasty and stenting of the affected artery to relieve the ischemic stimulus promoting renin output. While prior randomized controlled trials failed to show significant benefit for angioplasty compared to medical therapy to treat hypertension, the subjects in those studies typically had only moderate renal artery stenosis and no CKD [29]. In contrast, the recently reported Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial recruited 931 subjects both with severe renal artery stenosis and with estimated GFR < 60 mL/min/1.73m² and then randomized them to medical therapy versus renal artery stenting plus medical therapy[30]. Over a median follow up of 43 months the CORAL trial did not find a benefit to renal artery stenting for the primary composite endpoint of cardiovascular and renal events. In a longitudinal analysis there was a statistically significant but clinically only modest improvement in SBP of 2.3 mmHg in the stented group, while the number of antihypertensive medications was no different between groups. The CORAL trial findings therefore echo the BP results of two other recent large randomized trials of renal artery stenting in CKD that both found no benefit for their primary renal outcomes and no improvement in BP as a secondary outcome [31;32]. It is likely that the consistent lack of antihypertensive efficacy for renal artery stenting in the setting of atherosclerotic renal artery stenosis is due to lesions that are too distal and diffuse within the renal arterial tree to be amenable to intervention.

Renal Denervation

Recent uncontrolled and unblinded trials of endovascular radiofrequency ablation of the renal nerves showed significant and dramatic BP improvement in patients with resistant hypertension, generating considerable enthusiasm for this novel therapy [33]. To address the methodological shortcomings of previous trials, the recently reported SYMPPLICITY HTN-3 trial randomized 535 subjects with resistant hypertension but without CKD to either

endovascular renal denervation or a sham procedure, and then followed these subjects for 6 months while their antihypertensive medications were held constant [34]. In contrast to the prior unblinded studies, the investigators found no significant improvement in either office BP or ambulatory BP in this trial. While these results call into question the efficacy of endovascular renal denervation, it remains possible that the negative results of the trial may have been due to lack of experience of the operators. More important, unlike angioplasty, there is no objective way to measure whether denervation has actually occurred. Short of performing cumbersome norepinephrine spillover there are few biomarkers to establish that the denervation procedure was effective.

Theoretically, patients with CKD represent a unique population that may benefit from this intervention in light of the known over-activity of the sympathetic nervous system in this disease. In fact a recent uncontrolled pilot trial of 12 subjects with ESRD and resistant hypertension treated with endovascular renal denervation found significant reductions in office BP and in the number of antihypertensive medications required [35]. However, the divergent findings between the initial open label studies without sham denervation and later blinded studies of renal denervation in patients without renal dysfunction require that caution be exercised and further blinded trials are needed before renal denervation can be deemed effective for treatment of hypertension in CKD.

PHARMACOLOGIC TREATMENT

As patients with substantial CKD and ESRD are commonly excluded from randomized controlled trials, there is a paucity of evidence to guide the choice of medications to treat hypertension in patients with renal disease. While acknowledging this limitation, the recently published clinical practice guidelines from the Eighth Joint National Committee (JNC 8) [36] and the Kidney Disease: Improving Global Outcomes (KDIGO) initiative [37] both emphasize the use of angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blocking (ARB) medications in the CKD population based on the results of older trials. However, dual use of ACEi and ARB medications is currently contraindicated in light of the recently reported results of the Veterans Affairs Nephropathy in Diabetes (NEPHRON-D) trial that enrolled 1448 patients with diabetic nephropathy, with or without hypertension [38]. Subjects were randomized to losartan plus lisinopril versus losartan plus placebo for prevention of a primary composite endpoint of renal events or death and the trial was halted early for lack of efficacy as well as for increased adverse events in the dual therapy group. Notably, BP was no different between groups.

While it is classically acknowledged that diuretic treatment is frequently necessary for hypertension control in CKD, the dogma has been to avoid thiazide-like diuretics in advanced CKD with GFR < 30 mL/min/1.73m² [39]. However, two recent uncontrolled trials challenge that paradigm. The first trial enrolled 14 patients with average estimated GFR 27 mL/min/1.73m² and average 24 hour ambulatory SBP 143 on a median of 4 antihypertensive medications, and after a run-in phase all patients were treated with chlorthalidone 25 mg daily with the dose titrated up unless not tolerated [40]. At the end of the 12 week intervention the subjects had a significant 10.5 mmHg reduction in 24 hour systolic ambulatory BP, and the treatment was generally well tolerated.

The second trial enrolled 60 CKD patients with average estimated GFR 39 mL/min/1.73m² and average office SBP 151 mmHg on 1.8 antihypertensive medications [41]. After a run-in phase all patients were started and maintained on chlorthalidone 25 mg daily and at the end of the 8 week intervention office SBP was significantly reduced by 20 mmHg. Notably, the 9 patients with estimated GFR < 30 mL/min/1.73m² had a similar significant reduction in office BP.

In the ESRD population on dialysis, two meta analyses of randomized controlled trials have shown nonspecific antihypertensive therapy to be associated with reduced risk of cardiovascular events[42;43], but there remains a dearth of clinical trial evidence available to guide the choice of medication class when treating hypertension in dialysis patients. The Hypertension in Hemodialysis Patients Treated with Atenolol or Lisinopril (HDPAL) trial begins to address that shortcoming. This trial randomized 200 HD patients both with hypertension defined as 44 hour interdialytic ambulatory BP 135/85 and with left ventricular hypertrophy to antihypertensive therapy with a regimen based on open label atenolol versus lisinopril for reduction in left ventricular hypertrophy as the primary endpoint [44]. Over the course of 1 year patients were treated with additional antihypertensives and dry weight reduction to maintain home BP 140/90 checked monthly. The trial was halted early for excess serious adverse events in the lisinopril group, and the primary endpoint was no different between groups at the time of the study's halt. Interestingly, the subjects in the lisinopril group had a higher home BP and required more antihypertensive drugs during the study, despite having more reduction in dry weight, suggesting that sympathetic overdrive may be a larger contributor to hypertension in ESRD than RAAS excess. Importantly, because there was no placebo group the HDPAL results do not necessarily indicate that lisinopril therapy is harmful, only that atenolol is superior in comparison.

Also recently reported, the Olmesartan Clinical Trial in Okinawa Patients Under Okinawa Dialysis Study (OCTOPUS) investigated the efficacy of ARB therapy for hypertension by recruiting 469 HD patients with hypertension defined as pre-HD BP 140/90 [45]. Subjects were randomized to open label treatment with an olmesartan based regimen or to therapy excluding ARB or ACEi drugs to achieve pre-HD BP < 140/90 for prevention of a primary composite endpoint of death plus cardiovascular events. After a mean follow up of 3.5 years the investigators found no difference in the primary outcome or in BP levels between groups. Taking the HDPAL and OCTOPUS results into account, we have begun to prescribe beta-blockers before ACEi or ARB medications when starting pharmacologic therapy for hypertension in our own HD patients.

GOAL BLOOD PRESSURE

A recent retrospective cohort study of over 650,000 veterans with CKD examined the relationship between BP and mortality, and with a median follow-up of 5.8 years the investigators found an increased risk of death for SBP < 130 mmHg or DBP < 70 mmHg [46]. While the findings in this predominantly white and elderly population may not be generalizable and causality cannot be determined from an observational study, these findings contribute to a trend of reanalyzing both the efficacy and potential harm of

previously tight BP goals in CKD. Based on randomized controlled trial data, the JNC 8 no longer recommends a BP goal < 130/80 in CKD patients [36] and the recommendations for a lower BP goal in the KDIGO guidelines are now heavily qualified [35]. The Systolic Blood Pressure Intervention Trial (SPRINT) is ongoing and its results will be informative. In this trial over 9,000 hypertensive patients with cardiovascular risk factors including CKD have been recruited and randomized to a standard office SBP goal of < 140 mmHg or an intensive goal of SBP < 120 mmHg with the intent to prevent the primary endpoint of cardiovascular events.

Owing to a lack of clinical trial evidence, goal BP levels in ESRD remain controversial with some observational studies finding a decreased risk of mortality associated with high peridialytic BP [47] however when the gold standard of ambulatory BP monitoring is employed, a strong and classical relationship emerges between high BP and mortality [48]. Ambulatory BP measurement is cumbersome to patients so we favor home BP monitoring as a convenient method that is superior to office or dialysis BP in correlating to ambulatory BP as well as for predicting prognosis in both HD and predialysis CKD patients [49].

CONCLUSION

While negative or harmful study outcomes can be frustrating, they may still offer valuable contributions to the accumulated knowledge in the field and afford providers new information on which to build their evidence based practice. Recent results in studies of CKD guide us away from routine use of renal artery stenting, renal denervation, dual ACEi and ARB therapy, ACEi or ARB medications as first line therapy in HD, and tight BP goals in CKD. Further, recent positive results make us question the old paradigm of avoiding thiazide-like diuretics in advanced CKD, reemphasize the efficacy of sodium restriction and among hemodialysis patients encourage us to use atenolol as first line antihypertensive therapy.

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