Strategies for Controlling Blood Pressure and Reducing Cardiovascular Disease Risk in Patients with Chronic Kidney Disease

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Patients with chronic kidney disease (CKD) suffer from an increased prevalence of cardiovascular disease (CVD) risk factors, and a high rate of premature CV morbidity and mortality. The confluence of CV risk factors, in the context of cardio-metabolic perturbations that vary as renal function declines, complicates strategies for the care of patients with CKD. Understanding the existing evidence for effective CVD treatment strategies can help providers better care for these patients, navigate the complex treatment guidelines, which often differ across major organizations, and minimize the conflicting recommendations that new studies may pose. A pragmatic approach is to target a BP <140/90 mm Hg, which frequently requires more than two or three antihypertensive agents. Most guidelines recommend a combination of diuretic and angiotensin converting enzyme inhibitor or angiotensin receptor blockers, along with a dihydropyridine calcium channel blocker, beta blocker or other agent based on co-existing medical conditions. Consideration for a lower BP goal and/or other therapeutic interventions should be based on the etiology of CKD, stage of CKD, and/or presence of proteinuria. Finally, most patients with CKD, not on dialysis, would benefit from treatment with statins and non-pharmacologic lifestyle interventions should be promoted for all patients with CKD. *Ethn Dis*. 2015;25(4):515-520; doi:10.18865/ed.25.4.515

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Introduction

Chronic kidney disease (CKD) is an emerging epidemic that is estimated to affect more than 25 million American adults,[1] with more than 600,000 Americans having progressed to end-stage renal disease (ESRD), many of whom receive renal replacement therapy with dialysis or kidney transplantation.[2] All patients with CKD are at a substantially increased risk for premature cardiovascular disease (CVD) and death that rises progressively as renal function declines, with the risk becoming even greater as the estimated glomerular filtration rate (eGFR) falls below 45 mL/min/1.73m^2.[3] The increased risk for CVD is in part related to a preponderance of major CV risk factors such as poorly controlled hypertension and diabetes,[4,5] as well as other complications associated with a progressive decline in renal function including anemia, secondary hyperparathyroidism and worsening vascular calcification.[6] The confluence of highly prevalent CV risk factors in the context of cumulative cardio-metabolic perturbations as renal function declines has led to many observational and randomized studies reporting mixed results. With growing emphasis on providing evidence-based healthcare,

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clinicians often feel trapped between guidelines that differ across major organizations and emerging studies that provide conflicting recommendations. Understanding the existing evidence in support of the most effective approaches to best orchestrate CVD strategies can assist providers in navigating the complexity of CV risk reduction and optimizing the care for their patients with CKD. In this report, we focus on trying to harmonize the major guidelines and supporting evidence for optimal blood pressure (BP) targets in patients with CKD as well as review the latest guidelines for treating lipid disorders to reduce CVD risk in the presence of CKD.

Epidemiology of Blood Pressure, CKD and Clinical Outcomes

The optimal BP goal for CVD risk reduction in patients with CKD remains elusive. Chronic kidney disease is a complex condition with degrees of severity characterized by the level of estimated glomerular filtration rate (eGFR) and proteinuria. Kovesdy and colleagues found the lowest risk for mortality among over 650,000 veterans when stratified by BP was at a systolic BP range of 130-149 mm Hg.[7] An analysis of more than 16,000 participants in the Kidney Early Evaluation Program (KEEP) with an eGFR <60 mL/min/1.73m^2 (mean 48 mL/min/1.73m^2) found that rates of end-stage renal disease (ESRD) stratified by BP level started to increase at a systolic BP 140 mm Hg and diastolic BP 90 mm Hg.[8] Older age may also influence this association as highlighted by Weiss et al. who reported a strong relationship between systolic BP and older patients existed only up to age 70 years after which the relationship disappeared.[9]

Several studies suggest as the level of eGFR declines, the association of BP level and clinical outcomes including mortality dissipates or may even reverse. Bansal et al reported no significant association between mortality and BP level in a cohort of over 1700 participants with a baseline eGFR <30 mL/min/1.73m^2,[10] while an analysis of more than 56,000 patients on dialysis (compared to earlier CKD stages) found a systolic BP <140 mm Hg was associated with a higher 3-year mortality risk compared to a systolic BP of 140-159 mm Hg and even 160-180 mm Hg.[11]

Randomized Trials of Blood Pressure, CKD and Clinical Outcomes

Two landmark studies, which advanced our understanding of the impact of inhibition of the renin angiotensin system (RAS) in diabetes-related CKD, did not compare different levels of BP.[12,13] The Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study found losartan was renoprotective compared to usual care in 1,513 patients with diabetes and CKD who were followed for >3 years with a target BP < 140/90 mm Hg and an achieved BP of 141/74 mm Hg.[12] Yet, in the Irbesartan Diabetic Nephropathy Trial (IDNT), irbesartan protected against the progression of diabetic nephropathy in patients with type 2 diabetes compared to usual care, with a target BP < 135/85 mm Hg (or a 10 mm Hg reduction in SBP if the value at screening was > 145 mm Hg) and achieved a mean BP of 142/83 mm Hg.[13] The African American Study of Kidney Disease and Hypertension (AASK) evaluated two different levels of BP control and three primary antihypertensive agents in one of the most difficult to treat populations. The study found no difference in major clinical outcomes randomized to usual (<140/90 mm Hg) or aggressive (<125/75 mm Hg) BP targets, but did find a significant reduction in clinical outcomes in the angiotensin converting enzyme inhibitor (ACEI) group vs beta blocker and calcium channel blocker (the calcium channel blocker arm was stopped early).[14,15] Extended follow-up of 9 years for all AASK participants at a goal BP 140/90 mm Hg found no difference in CV and mortality outcomes in either the subgroup originally randomized to the aggressive (<125/75 mm Hg) BP arm or the group randomized to usual (<140/90 mm Hg) target. However, there was a significant reduction in outcomes between groups in the subset of patients with baseline urinary protein excretion >300 mg/day.[16] Thus, the AASK study suggested RAS inhibition with a target BP <140/90 mm Hg was optimal, and a lower target may be warranted in the presence of proteinuria. In an analysis stratified of Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), participants treated with chlorthalidone, amlodipine, or lisinopril, there

was no difference in CV outcomes or mortality by eGFR according to class of antihypertensive therapy; BP levels were not compared.[17,18]

The addition of aldosterone blockers to ACEIs and/or angiotensin receptor blockers (ARBs) in CKD was shown to reduce proteinuria from baseline by 15%-54% and to significantly reduce BP. However, their effect on the risk of major CV events or ESRD is still unknown.[19,20] Importantly, side effects such as the increased risk of hyperkalemia and gynecomastia need to be closely monitored when aldosterone blockers are used in combination with RAS inhibition in the presence of CKD.[19,20] Finally, the combination of ACEI and ARB should not be used together as they have been associated with a trend toward increased risk of major clinical outcomes, as has the addition of a direct renin inhibitor to either ACEI or ARB.[21]

Guidelines for Blood Pressure Treatment in Patients with CKD

While the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) recommended a target BP goal <140/90 mm Hg for most patients, it was also recommended that high-risk groups such as those with CKD and diabetes should be treated to a lower BP target <130/80 mm Hg.[22] However, the recent report of the Panel Members Appointed to the Eighth Joint National Committee (JNC8) recommended raising the JNC7 BP targets for patients with CKD from 130/80 mm Hg to 140/90 mm Hg.[23] These recommendations are fairly consistent with the intent-to-treat goals of many major studies and are endorsed by recent meta-analyses and other clinical guidelines, although controversy still exists for a possible lower BP-target in CKD, especially in the presence of albuminuria based on secondary analyses of subgroups and outcomes related to achieved blood pressure (Table 1).

Pharmacological Cholesterol-Lowering Treatment in Adults with CKD

Statin treatment has been shown to be highly effective in reducing poor CV outcomes in many patients. Given the high CV event rate in CKD/ESRD, it was hypothesized that statin therapy would be highly effective in dialysis patients. The 4D trial, which was a multicenter, double-blind, randomized controlled trial, found no difference in composite of death from cardiac causes, nonfatal myocardial infarction, and stroke in atorvastatin given daily vs. placebo in

Table 1. Summary of select meta-analyses and clinical guidelines for treatment of high blood pressure in patients with chronic kidney disease[21,30]

Recommendations from the Panel Members Appointed to the Eighth Joint National Committee[23]	BP target of <140/90 mm Hg regardless of risk
The 2013 European Societies of Hypertension (ESH) and Cardiology (ESC) Guidelines.[31]	BP target of 140/90 mm Hg regardless of risk
The 2012 Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for BP Management in CKD[32]	CKD patients without albuminuria - target BP <140/90 mm Hg. If albuminuria >30mg/24hr, - target BP <130/80 mm Hg with RAS inhibition.
2014 Canadian Society of Nephrology and Canadian Diabetes Association [33]	CKD patients with DM with or without albuminuria should be treated to a BP target <130/80 mm Hg
Balamuthusamy et al (meta-analysis of 25 RCTs - 2008; N = 45,758) [34]	Evidence for improved CV outcomes in patients with CKD and proteinuria is stronger for use of RAS blockade than for a lower BP goal.
Upadhyay et al (meta-analysis MEDLINE and the Cochrane Central Register of Controlled Trials, July 2001 through January 2011; 2272 participants – none with DM)[35]	Did not find that a BP target <130/80 mm Hg improved clinical outcomes more than a target <140/90 mm Hg. Lower-quality evidence suggests a BP target <130/80 mm Hg may be beneficial in subgroups with proteinuria >300 mg/d.

BP, blood pressure; DM, diabetes; SBP, systolic blood pressure; CVD, cardiovascular disease; CKD, chronic kidney disease

Table 2. Strategies for controlling blood pressure and reducing cardiovascular disease risk in patients with chronic kidney disease (not on dialysis)[21,30]

BP Target	Target BP <140/90 mm Hg; the evidence for a lower target BP in patients with CKD is not consistent, although there is some evidence to target BP <130/80 mm Hg in patients with CKD and significant proteinuria (>300 mg/day).
Class of BP Agents	Diuretic and RAS inhibition have the best evidence for efficacy, although the role of RAS inhibition in patients with CKD and without proteinuria is less well defined. Class of diuretic needs to be appropriate for the level of eGFR. ACEI and ARB should not be used together, and direct renin inhibitors should not be used with ACEI/ARB.
Achieving BP Target	CKD patients often need more than two or three antihypertensive drugs including a diuretic to achieve target blood pressure control.
Treating Lipid Disorders	Add statins for patients with CKD, not on dialysis. For patients on dialysis do not add statins but if already taking statins do not discontinue. If a patient on dialysis has an acute vascular event, consider adding a statin (no data).
Assess CKD Severity (eGFR and Proteinuria)	Consider complications that arise as eGFR falls that may impact CVD risk such as anemia, use of erythrocyte stimulating agents, and mineral and bone disorders which can increase risk of calcification. Heavy proteinuria may necessitate more aggressive treatment with a lower BP goal and the addition of aldosterone blockade or non-dihydropyridine calcium channel blockers if traditional RAS inhibition alone is not effective.
Individualize Treatment	Take special account of CV co-morbidities, age, gender, race/ethnicity, sensitivity to and understanding of socio-cultural and economic factors, insurance profile, family support, and health beliefs/behaviors that may impede achieving optimal adherence to both pharmacologic and non-pharmacologic recommendations
Monitor for Side Effects	Assess for hyperkalemia, and postural dizziness/hypotension, particularly in elderly, diabetics and patients with arterial stiffness (increased pulse pressure).
Lifestyle Recommendations	Reinforcement of lifestyle recommendations including a healthy weight (BMI <30 kg/m^2, although increased BMI may be associated with increased survival for patients on dialysis, especially older patients),[36] limited alcohol intake, reduced salt intake to <90 mmol (<2g) per day unless contraindicated, and an exercise program compatible with CV health and tolerance, aiming for at least 30 minutes 5 times per week.

BP, blood pressure; CKD, chronic kidney disease; RAS, renin angiotensin system; eGFR, estimated glomerular filtration rate; CVD, cardiovascular disease; BMI, body mass index; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

1255 hemodialysis patients with type 2 diabetes followed for >4 years, despite a 42% reduction in the median LDL-C level compared to only 1.3% with placebo.[24] Similarly, the AURORA Study (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Dialysis: an Assessment of Survival and Cardiovascular Events) found no difference in CV-related death in >2700 dialysis patients who were randomized to rosuvastatin or placebo and followed for 3.8 years despite a 43% mean reduction in LDL-C with rosuvastatin.[25] Finally, the SHARP (Study of Heart and Renal Protection) found 4.9 years of treatment with simvastatin 20 mg plus ezetimibe 10 mg daily was more effective than placebo in 6247 CKD patients with a mean eGFR of 27 ml/min/1.73m^2, but not among the >3000 patients on dialysis.[26] Thus, adults aged >50 years with CKD and younger adults with CKD and increased CVD risk (eg, albuminuria >300mg/day, eGFR <45 ml/min/1.73m^2) but not receiving dialysis, should be treated with a statin or statin/ezetimibe combination. Individuals already on dialysis should continue their current statin therapy, but the initiation of statin therapy is generally not recommended.[27]

Lifestyle Recommendations of CVD reduction in Patients with CKD

In addition to optimal control of BP, CVD risk reduction in patients with CKD requires lifestyle modification, personalized tailoring to an individual patient with consideration of co-existing medical and socio-ecologic conditions (Table 2). In general CV risk reduction recommendations should include 30–45 minutes of moderate activity per day, 3–5 days per week, a low sodium diet intake, smoking cessation, weight reduction if needed and consideration for devel-

oping coping skills for specific stressors in work and home environments with meditation, relaxation, yoga, or biofeedback.[28] In addition, attention to nutritional intake consisting of a low dietary acid load has recently been suggested to be important for reducing the risk of ESRD progression.[29]

A prudent approach is to achieve a BP <140/90 mm Hg with a combination of diuretic and ACEI or ARB, and with simultaneous non-pharmacologic lifestyle intervention (Table 2).

Conclusion

In summary, the lack of harmonization of clinical guidelines for the treatment of high BP and CVD risk reduction in persons with CKD has created a challenge for many providers. Persons with earlier stages of CKD appear to have better outcomes with a SBP of <140 mm Hg or even lower, while at the later stages of CKD the relationship between BP level and mortality is much weaker. A prudent approach is to achieve a BP <140/90 mm Hg with a combination of diuretic and ACEI or ARB, and with simultaneous non-pharmacologic lifestyle intervention (Table 2). Consideration for a lower BP goal and/or other therapeutic interventions should be based on the etiology and stage of CKD, presence of proteinuria or other co-existing medical conditions. Patients with CKD and hypertension often require more than two or three antihypertensive medications to attain a target SBP <140 mm Hg. Thus, in addition to a diuretic and frequently an ACEI or ARB, the addition of non-dihydropyridine calcium channel blockers, beta blockers, alpha agonists or others are commonly required and the choice is often influenced by co-existing medical conditions. Finally, most patients with CKD, not on dialysis, would benefit from treatment with statins.

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