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Authors

Nicholas, Susanne B.
Vaziri, Nosratola D.
Norris, Keith C.

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What should be the blood pressure target for patients with chronic kidney disease?

Susanne B. Nicholas^{a,b,c,d}, Nosratola D. Vaziri^e, and Keith C. Norris^{a,d}

^aDivision of Nephrology, Diabetes and Hypertension, University of California, California

^bDivision of Endocrinology, Diabetes and Hypertension, University of California, California

^cDepartment of Medicine, David Geffen School of Medicine, University of California, California

^dCharles R. Drew University of Medicine and Science, Los Angeles, California

^eDivision of Nephrology and Hypertension, Departments of Medicine, Physiology and Biophysics, University of California, Irvine, Irvine, California, USA

Abstract

Purpose of review—Persons with chronic kidney disease (CKD) exhibit a disproportionate burden of elevated blood pressure (BP) with a high prevalence of premature end-stage renal disease and cardiovascular events.

Recent findings—Results of recent randomized controlled clinical trials suggest that most patients with reduced estimated glomerular filtration rate (eGFR) and hypertension experience optimal clinical outcomes when SBP is less than 140 mmHg and DBP is less than 90 mmHg. The benefit of additional lowering of SBP to less than 130 mmHg and DBP to less than 80 mmHg remains controversial, and appears to be of most benefit to the subset of CKD patients with proteinuria (>300 mg/day). The combination of a diuretic and an angiotensin receptor blocker (ARB) or angiotensin-converting enzyme inhibitor (ACEI) has demonstrated particular promise in patients with reduced eGFR and proteinuria.

Summary—A practical approach in clinical practice for the treatment of elevated BP in persons with CKD is to achieve a BP less than 140/90 mmHg with a combination of diuretic and an ARB or ACEI. Consideration for a lower BP goal and other therapeutic and nontherapeutic interventions can be made based on the cause of CKD, presence of proteinuria, or other coexisting medical conditions.

Keywords

chronic kidney disease; high blood pressure; hypertension

INTRODUCTION

Chronic kidney disease (CKD) is a major global health problem with an estimated one in nine adults afflicted [1,2]. The WHO had originally categorized diabetes, cardiovascular

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Correspondence to Keith C. Norris, MD, Department of Medicine, Charles R. Drew University of Medicine and Science, 1731 E. 120th Street, Los Angeles, CA 90059, USA. Tel: +1 310 249 5702; fax: +1 323 357 0747; keithnorris@cdrewu.edu.

Conflicts of interest

K.C.N. has declared associations with the following companies: Abbott, Amgen, Merck, and Pfizer. S.B.N. declared association with ConCERT and Janssen. N.D.V. declared no relevant competing interests.

disease, chronic lung disease, and cancer as the major chronic noncommunicable threats to public health in this century, accounting for the majority of deaths in high-income, middle-income, and low-income nations alike. In 2011, the WHO added CKD to the list of major chronic noncommunicable threats to public health because of its substantial impact on premature morbidity and mortality, as well as its cost to the healthcare system [1].

In the Chronic Renal Insufficiency Cohort (CRIC) study of a diverse group of adults ($n = 3612$) with a broad spectrum of renal disease severity, baseline data revealed that 87.5% had hypertension [3], a rate three times that of the estimated prevalence of hypertension (28.5%) in the US adult population [4]. Because of the high prevalence of elevated blood pressure (BP) levels in CKD populations, successful management of hypertension in CKD patients could have an enormous global impact. Although the control of hypertension among patients with CKD in the USA has improved from approximately 35% between 1988 and 1994 to approximately 45% between 2005 and 2010 [4], strategies to increase BP control further and agreement on the optimal level of BP control remain controversial. The scope of this review is focused on the recent studies assessing the optimal level of BP control in patients with CKD, the optimal class of therapeutic agents, and relevant nonpharmacologic recommendations.

DEFINITION OF CHRONIC KIDNEY DISEASE

In 2002, the National Kidney Foundation published the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines for the diagnosis and treatment of CKD, including the presence of markers of kidney damage such as albuminuria and five progressive stages of the disease based on a sustained reduction in estimated glomerular filtration rate (eGFR) (Table 1) [5]. The inclusion of the presence of markers of kidney damage such as albuminuria in the definition of CKD allows the clinical identification of CKD in its earliest stages when the eGFR might still be well within the normal limits, but increased rates of elevated BP may be present and early intervention helpful. The care of CKD represents a disproportionate burden on the US Medicare system. With increased rates of hypertension across the spectrum of the five stages of CKD, the mainstay of care for the patient with CKD is BP control and reduction of proteinuria with antihypertensive agents.

EPIDEMIOLOGY OF HYPERTENSION IN CHRONIC KIDNEY DISEASE

CKD is associated with increased rates of hypertension defined as physician-diagnosed hypertension or SBP of at least 140 mmHg and DBP of at least 90 mmHg, as well as prehypertension, SBP of at least 120 and less than 140 mmHg or DBP of at least 80 and less than 90 mmHg. It is estimated that CKD is present in only 9.9% of the US adult population with normal BP, but is present in 13.9% of the prehypertensive population, and 23.8% of the undiagnosed and 32.0% of the diagnosed hypertensive population [6]. Moreover, apparent treatment-resistant hypertension (uncontrolled BP despite 3 medications vs. all uncontrolled hypertensive patients) is 2.5–3 times as common among patients with CKD compared with those without CKD across three National Health and Nutrition Examination Survey (NHANES) periods, 1988–1994, 1999–2004, and 2005–2008 [7]. Finally, among the general US adult population with cardiovascular disease approximately 25% had an eGFR less than 60 ml/min/1.73 m² and a urinary albumin-to-creatinine ratio (ACR) greater than 30 mg/g [1]. The higher prevalence of hypertension in patients with CKD contributes to the high rates of end-stage renal disease (ESRD) and premature cardiovascular events [8,9].

THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM AND HYPERTENSIVE CHRONIC KIDNEY DISEASE

The renin-angiotensin-aldosterone system (RAAS) plays an important role in the modulation of hypertension and the mediation of hypertension-related complications. The documented role of RAAS as a facilitator of progression of CKD engenders the expectation of an attenuated risk of hypertension-related end-organ damage in patients treated with RAAS inhibition therapy. RAAS blockade can reverse endothelial dysfunction, attenuate proteinuria, and reduce renal injury independent of BP changes in animal models [10], making RAAS inhibition a rational therapeutic option for hypertension and proteinuria in CKD [11].

KEY TREATMENT TRIALS OF HYPERTENSIVE CHRONIC KIDNEY DISEASE

The African American Study of Kidney Disease and Hypertension (AASK) trial ($n=1094$) was a prospective study designed to focus on a high-risk cohort with hypertension-related CKD and examined the effects of two levels of BP control: intensive ($<120/80$ mmHg) and standard ($\sim 135\text{--}140/85\text{--}90$ mmHg), and three classes of initial antihypertensive therapy [angiotensin-converting enzyme inhibitor (ACEI), β -blocker, or calcium-channel blocker] on eGFR progression and combined clinical outcomes. Individuals with substantial proteinuria (>2.5 g per day) were excluded [12]. As the AASK study participants had substantial GFR reduction, it was implicit in the design that most, if not all, would require diuretic therapy. In fact, nearly 90% of AASK participants required concomitant diuretic therapy to achieve target BP levels. AASK demonstrated that clinical cardiorenal outcomes did not differ between intensive ($<120/80$ mmHg) and standard ($\sim 135\text{--}140/85\text{--}90$ mmHg) BP targets, and were improved with ACEI in comparison to β -blocker or calcium-channel blocker, with diuretics and other agents added as needed [13].

After completing the trial phase, patients were invited to enroll in a cohort phase in which the BP target was less than $130/80$ mmHg and primary therapy was diuretic with ACEI or angiotensin receptor blocker (ARB). During the cohort phase, corresponding intensive and standard group mean BP was $131/78$ and $134/78$ mmHg, respectively. With a combined follow-up period of 8.8–12.2 years across both phases, there remained no significant difference between the BP groups in clinical outcomes ($P=0.27$). However, the groups differed when stratified by baseline level of proteinuria ($P=0.02$ for interaction), with a potential benefit of original intensive BP treatment in patients with a protein-to-creatinine ratio of more than 0.22 ($P=0.01$), the equivalent of a urinary protein excretion rate of 300 mg/day [14].

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) enrolled over 33 000 high-risk hypertensive patients with a mean serum creatinine of 1 mg/dl and follow-up for up to 8 years. At year 5, mean BP was $135/75$ mmHg. In a secondary analysis of patients stratified by eGFR, normal (at least 90 ml/min/ 1.73 m²; $n=8126$), mild reduction ($60\text{--}89$ ml/min/ 1.73 m²; $n=18\,109$), or moderate–severe reduction (<60 ml/min/ 1.73 m²; $n=5662$), amlodipine, lisinopril, and chlorthalidone were equivalent, as initial monotherapy, in reducing the rate of composite endpoint of development of ESRD or 50% or greater decrement in eGFR [15]. An analysis of ALLHAT participants stratified into three baseline eGFR groups: normal or increased (>90 ml/min/ 1.73 m²; $n=8126$ patients), mild reduction ($60\text{--}89$ ml/min/ 1.73 m²; $n=18\,109$ patients), and moderate or severe reduction (<60 ml/min/ 1.73 m²; $n=5662$ patients) found no difference in the clinical outcomes by class of antihypertensive agent [16]. In addition, neither amlodipine nor lisinopril was superior to chlorthalidone in reducing the rate of development of ESRD or at least 50% decrement in eGFR in ALLHAT participants [17].

Exploring the relationship of BP goal to outcomes, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial [18], which included 4733 participants with type 2 diabetes mellitus and increased risk for cardiovascular disease including albuminuria followed for a mean of 4.7 years, found no benefit with regard to the primary composite outcome of major cardiovascular events with a SBP target of less than 120 mmHg versus less than 140 mmHg.

In a post-hoc analysis of the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study with 1513 patients followed for over 3 years with final BP of 141/74 mmHg, losartan was renoprotective compared with usual care [19]. In addition, there was no racial/ethnic difference in the renoprotective effect of ARB therapy, as assessed by albuminuria and development of ESRD.

A post-hoc analysis of the Irbesartan Microalbuminuria Type 2 Diabetes in Hypertensive Patients (IRMA-2) trial found no difference in the renal outcomes among the 531 study participants stratified to greater than or less than the median response in BP reduction of 11 mmHg over the initial 6 months. By contrast, a greater reduction in albuminuria achieved during the initial 6 months of RAAS blockade was associated with a significant reduction in the rate of decline in eGFR during 2 years of follow-up [20].

The optimism for enhanced efficacy with combination ARB/ACEI generated by the above findings of ARB or ACEI to improve clinical outcomes has recently been dampened. The Ongoing Telmisartan Alone and in Combination with Ramipril Global End Point Trial (ONTARGET) randomized 25 000 participants with vascular disease or diabetes with end-organ damage (13% with microalbuminuria) and followed them for 4.5 years. Baseline mean BP of 142/82 mmHg was reduced at 6 months by 6.4/4.3 mmHg in the Ramipril group, by 7.4/5.0 mmHg in the Telmisartan group, and by 9.8/6.3 mmHg in the combination-therapy group and continued at similar levels throughout the study. The composite primary outcome of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure did not differ between groups [21]. Also, although combination therapy reduced proteinuria to a greater extent than monotherapy, it worsened the major renal outcomes [22]. Thus, the ONTARGET trial did not demonstrate any cardiovascular benefit for dual RAAS blockade (with the ACEI Ramipril and the ARB Telmisartan), in a population at high risk of CVD, but did suggest an increased risk of major renal outcomes. Lambers Heerspink and de Zeeuw [23] suggested that the unanticipated results may have been because of the patient population studied, and that the result might have been different if the population had included a greater number of patients with CKD than the 13% with albuminuria. A parallel group of 5927 potential ONTARGET participants with known cardiovascular disease or diabetes with end-organ damage but without macroalbuminuria or heart failure who could not tolerate ACEIs were treated with Telmisartan, 80 mg/day ($n=2954$), or matching placebo ($n=2972$) plus standard treatment and followed for over 4.7 years [24]. The composite renal outcome of dialysis or doubling of serum creatinine, changes in eGFR, and changes in albuminuria did not differ between the groups.

The use of direct renin inhibitors (DRIs) has emerged as another potential therapeutic of value in treating hypertension in patients with CKD. The Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE) Trial randomized over 8600 participants with type 2 diabetes and nephropathy to either Aliskiren or placebo on top of standard therapy, ACEI or ARB [25]. Unfortunately, the ALTITUDE trial was stopped early because of a low likelihood of ever demonstrating clinical benefit and a trend toward increased risk of key adverse outcomes, casting doubt on the future use of DRIs in combination with ACEI or ARB [26].

RECENT GUIDELINES AND META-ANALYSES OF HYPERTENSION AND CHRONIC KIDNEY DISEASE

The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the management of blood pressure in chronic kidney disease indicated that the available evidence in CKD patients without albuminuria supports a target SBP of less than 140 mmHg and DBP less than 90 mmHg. However, in patients with an albumin excretion rate of greater than 30 mg per 24 h, the committee suggested a more aggressive SBP target of less than 130 mmHg and DBP less than 80 mmHg. In achieving BP control, the value of lifestyle changes (see list below) and the need for multiple pharmacological agents is acknowledged. RAAS inhibition therapy is suggested in patients with an albumin excretion rate of greater than 30 mg per 24 h. Importantly, recommendations are essentially identical in CKD patients with and without diabetes [27, 28]. Lifestyle modifications in patients with CKD to lower BP and improve long-term cardiovascular and related outcomes are as follows:

1. Individualize BP targets and agents according to age, coexistent cardiovascular disease, and other comorbidities, risk of progression of CKD, presence or absence of retinopathy (in CKD patients with diabetes), and tolerance of treatment.
2. Inquire about postural dizziness and check for postural hypotension regularly when treating CKD patients with BP-lowering drugs.
3. Lowering salt intake to less than 90 mmol/day (<2 g) of sodium (corresponding to 5 g of sodium chloride), unless contraindicated. Achieving or maintaining a healthy weight (BMI 20–25 and at least less than 30 kg/m²).
4. An exercise program compatible with cardiovascular health and tolerance, aiming for at least 30 min five times per week.
5. Limit alcohol intake to no more than two standard drinks per day for men and no more than one standard drink per day for women.

By contrast, Upadhyay *et al.* [29], using MEDLINE and the Cochrane Central Register of Controlled Trials (July 2001 through January 2011) of randomized controlled trials comparing lower versus higher BP targets in adult patients with CKD, did not find that a BP target less than 130/80 mmHg improved clinical outcomes more than a target less than 140/90 mmHg. Whether a lower target benefits patients with proteinuria requires further study.

A meta-analysis of 25 randomized controlled trials ($n=45\,758$) by Balamuthusamy *et al.* [30] found improved cardiovascular outcomes in patients with diabetic or nondiabetic CKD and proteinuria treated with RAAS blockade (ACEI/ARB) in comparison to placebo and control (β -blocker, calcium-channel blockers, and other antihypertensive-based therapy). Thus, the evidence is stronger for using RAAS blockade than it is for a lower BP goal in patients with CKD and proteinuria.

SPECIAL CONSIDERATIONS

Given the increased prevalence of CKD in older populations, special attention should be paid to tailoring BP treatment regimens in elderly patients with CKD. Careful consideration of age, comorbidities, and other therapies that may impact side-effect profile and therapeutic efficacy are even more significant in older patients. A more gradual escalation of treatment and close attention to adverse events related to BP treatment, including electrolyte disorders, acute deterioration in kidney function, orthostatic hypotension and drug side-effects, is required [27].

A recent study of 52 patients with nondiabetic nephropathy treated with ACEI found a low-sodium diet over a 6-week period (50 mmol Na⁺/day) reduced proteinuria ($P<0.001$) in comparison to the addition of ARB to ACEI, and was comparable to the reduction of proteinuria by the addition of both ARB and a low-sodium diet to ACEI [31]. By contrast, a low-sodium diet has been reported to paradoxically increase all-cause and cardiovascular mortality in persons followed for 10 years with either type 1 diabetic nephropathy (eGFR 85 ml/min/1.73 m² and over 30% with albuminuria) [32] or type 2 diabetes (eGFR 73 ml/min/1.73 m² and over 40% with albuminuria) [33]. Thus, even the traditional recommendation of sodium restriction in patients with CKD may not be as simple as previously considered.

It is well known that the initiation of RAAS inhibition therapy can lead to an acute reduction in GFR in patients with advanced CKD. In most instances, this is a physiologic hemodynamic effect that is reversed if the therapy is reduced or discontinued. An observational study by Ahmed *et al.* [34] showed that discontinuation of RAAS inhibition therapy in 52 patients with CKD stages 4–5 was followed by a greater than 25% increase in eGFR in over 60% of patients. However, the post-hoc analysis of the RENAAL trial found an initial fall in eGFR was a better predictor of long-term renoprotection [35], whereas a second smaller randomized trial reported patients with stage 4 CKD receiving benazepril had a lower risk of doubling of serum creatinine, kidney failure, or death compared with similar patients receiving placebo [36]. Thus, the current evidence does not support a stable reduction in eGFR as a rationale for the cessation of RAAS therapy in patients with later stages of CKD [37], although specific reasons for discontinuation such as hyperkalemia or hypotension may occur in some patients.

CONCLUSION

Persons with hypertension and kidney disease require a comprehensive approach to slow the progression of kidney disease and its complications, often necessitating aggressive care of the primary cause, assessment of lifestyle and sociocultural issues, and the use of two or more antihypertensive agents for control of BP (<140/90 mmHg) and proteinuria (Fig. 1). A lower target (<130/80 mmHg) can be considered in cases of CKD with proteinuria, although the evidence is less consistent (Table 2).

Looking forward, the National Institutes of Health (NIH)-funded Systolic Blood Pressure Intervention Trial (SPRINT), which will randomize over 7500 patients including significant numbers of patients over 75 years of age and patients with CKD to systolic BP targets of less than 140 mmHg or less than 120 mmHg over a period of 9 years, commenced 2010 and followed for cardiovascular, cognitive, and kidney endpoints deliberately, should yield additional evidence for optimizing BP treatment guidelines for many high-risk patients, including those with CKD [38].

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

of special interest

of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 489).

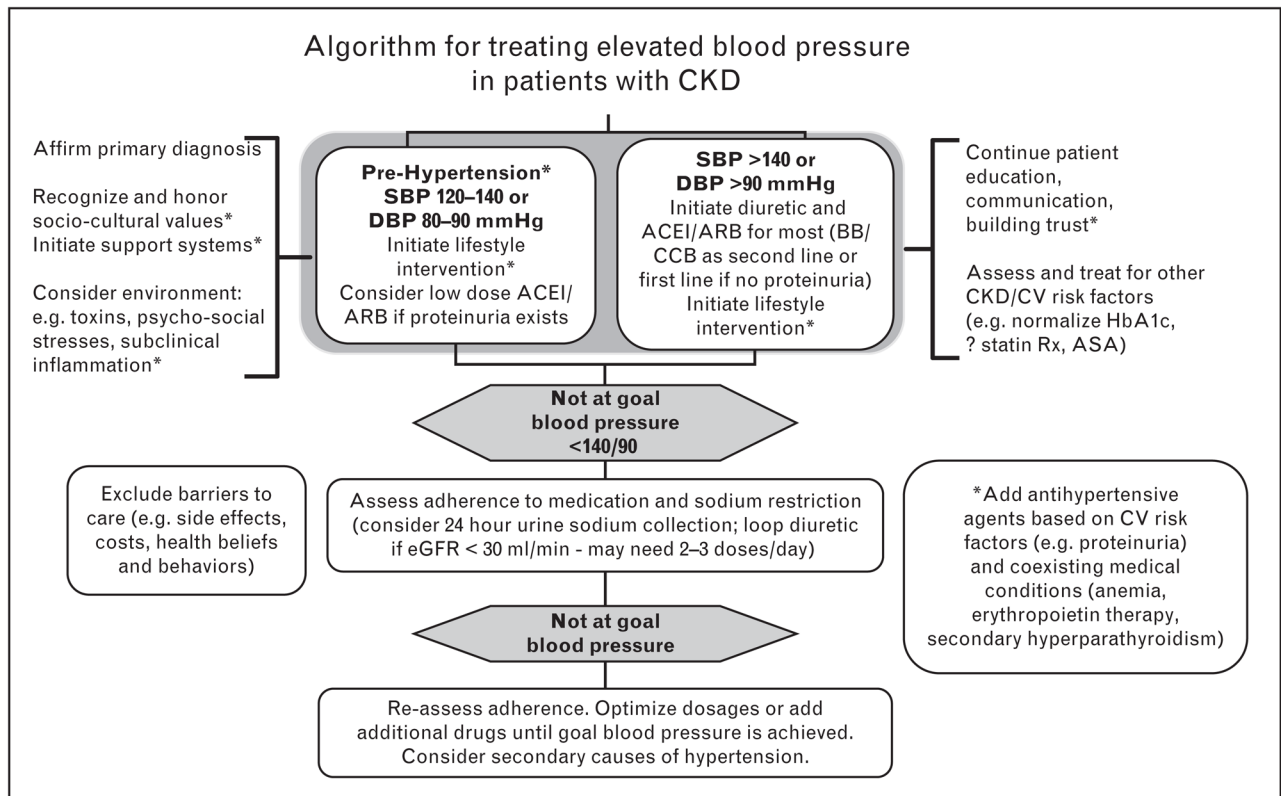
1. US Renal Data System. USRDS 2012 annual data report: atlas of end-stage renal disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Disease; 2012.
2. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. *JAMA*. 2007; 298:2038–2047. [PubMed: 17986697]
3. Muntner P, Anderson A, Charleston J, et al. Chronic Renal Insufficiency Cohort (CRIC) Study Investigators. Hypertension awareness, treatment, and control in adults with CKD: results from the Chronic Renal Insufficiency Cohort (CRIC) Study. *Am J Kidney Dis*. 2010; 55:441–451. [PubMed: 19962808]
4. Egan BM, Zhao Y, Axon RN. US trends in prevalence, awareness, treatment, and control of hypertension, 1988–2008. *JAMA*. 2010; 303:2043–2050. [PubMed: 20501926]
5. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis*. 2002; 39 (2 Suppl 1):S1–S266. [PubMed: 11904577]
6. Crews DC, Plantinga LC, Miller ER 3rd, et al. Centers for Disease Control and Prevention Chronic Kidney Disease Surveillance Team. Prevalence of chronic kidney disease in persons with undiagnosed or prehypertension in the United States. *Hypertension*. 2010; 55:1102–1109. [PubMed: 20308607]
7. Egan BM, Zhao Y, Axon RN, et al. Uncontrolled and apparent treatment resistant hypertension in the United States, 1988 to 2008. *Circulation*. 2011; 124:1046–1058. [PubMed: 21824920]
8. Van der Velde M, Matsushita K, Coresh J, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. *Kidney Int*. 2011; 79:1341–1352. [PubMed: 21307840]
9. Astor BC, Matsushita K, Gansevoort RT, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with mortality and end-stage renal disease. A collaborative meta-analysis of kidney disease population cohorts. *Kidney Int*. 2011; 79:1331–1340. [PubMed: 21289598]
10. Hayakawa H, Coffee K, Raij L. Endothelial dysfunction and cardiorenal injury in experimental salt-sensitive hypertension: effects of antihypertensive therapy. *Circulation*. 1997; 7:2407–2413. [PubMed: 9337217]
11. Norris KC, Tareen N, Martins D, Vaziri N. Implications of ethnicity for the treatment of hypertensive kidney disease, with an emphasis on African Americans. *Nat Clin Pract Nephrol*. 2008; 4:538–549. [PubMed: 18679391]
12. Wright JT Jr, Bakris G, Greene T, et al. African American Study of Kidney Disease and Hypertension Study Group. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA*. 2002; 288:2421–2431. Erratum in: *JAMA* 2006 295, 2726. [PubMed: 12435255]
13. Wright JT Jr, Agodoa L, Contreras G, et al. African American Study of Kidney Disease and Hypertension Study Group. Successful blood pressure control in the African American Study of Kidney Disease and Hypertension. *Arch Intern Med*. 2002; 162:1636–1643. [PubMed: 12123409]
14. Appel LJ, Wright JT Jr, Greene T, et al. AASK Collaborative Research Group. Intensive blood-pressure control in hypertensive chronic kidney disease. *N Engl J Med*. 2010; 363:918–929. [PubMed: 20818902]
15. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA*. 2002; 288:2981–2997. Erratum in *JAMA* 2004, 291, 2196. [PubMed: 12479763]
16. Rahman M, Pressel S, Davis BR, et al. ALLHAT Collaborative Research Group. Cardiovascular outcomes in high-risk hypertensive patients stratified by baseline glomerular filtration rate. *Ann Intern Med*. 2006; 144:172–180. [PubMed: 16461961]

17. Rahman M, Pressel S, Davis BR, et al. Renal outcomes in high-risk hypertensive patients treated with an angiotensin-converting enzyme inhibitor or a calcium channel blocker vs a diuretic: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med*. 2005; 165:936–946. [PubMed: 15851647]
18. Cushman WC, Evans GW, Byington RP, et al. Effects of intensive blood pressure control in type 2 diabetes mellitus. *N Engl J Med*. 2010; 362:1575–1585. [PubMed: 20228401]
19. De Zeeuw D, Ramjit D, Zhang Z, et al. Renal risk and renoprotection among ethnic groups with type 2 diabetic nephropathy: a post hoc analysis of RENAAL. *Kidney Int*. 2006; 69:1675–1682. [PubMed: 16572114]
20. Hellemons ME, Persson F, Bakker SJ, et al. Initial angiotensin receptor blockade-induced decrease in albuminuria is associated with long-term renal outcome in type 2 diabetic patients with microalbuminuria: a post hoc analysis of the IRMA-2 trial. *Diabetes Care*. 2011; 34:2078–2083. [PubMed: 21788629]
21. Yusuf S, Teo KK, Pogue J, et al. ONTARGET investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*. 2008; 358:1547–1559. [PubMed: 18378520]
22. Mann JF, Schmieder RE, McQueen M, et al. ONTARGET investigators. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. *Lancet*. 2008; 372:547–553. [PubMed: 18707986]
23. Lambers Heerspink HJ, de Zeeuw D. ONTARGET still OFF-TARGET? *Circulation*. 2011; 123:1049–1051. [PubMed: 21357820]
24. Mann JF, Schmieder RE, Dyal L, et al. TRANSCEND (Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease) Investigators. Effect of telmisartan on renal outcomes: a randomized trial. *Ann Intern Med*. 2009; 151:1–10. [PubMed: 19451556]
25. Parving HH, Brenner BM, McMurray JJ, et al. Baseline characteristics in the Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE). *J Renin Angiotensin Aldosterone Syst*. 2012; 13:387–393. [PubMed: 22333485]
26. US Food and Drug Administration. [Accessed 27 February 2013] FDA drug safety communication: new warning and contraindication for blood pressure medicines containing aliskiren (Tekturna). <http://www.fda.gov/Drugs/DrugSafety/ucm300889.htm>
27. KDIGO Blood Pressure Work Group. KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Int*. 2012; 2 (Suppl):337–414. A very comprehensive guideline for BP management in CKD. The guidelines support a target SBP of less than 140 mmHg and DBP less than 90 mmHg for CKD patients without albuminuria. However, in patients with an albumin excretion rate of greater than 30 mg per 24 h, the guidelines suggest a more aggressive SBP target of less than 130 mmHg and DBP less than 80 mmHg and RAAS inhibition therapy.
28. Wheeler DC, Becker GJ. Summary of KDIGO guideline. What do we really know about management of blood pressure in patients with chronic kidney disease? *Kidney Int*. 2013; 83:377–383. A nice summary of the KDIGO guidelines, and it is more clear that the potential benefit of a lower target of less than 130/80 mmHg for patients with proteinuria greater than 30 mg/day is based on lower-quality evidence from subgroup analyses. [PubMed: 23325075]
29. Upadhyay A, Earley A, Haynes SM, Uhlig K. Systematic review: blood pressure target in chronic kidney disease and proteinuria as an effect modifier. *Ann Intern Med*. 2011; 154:541–548. [PubMed: 21403055]
30. Balamuthusamy S, Srinivasan L, Verma M, et al. Renin angiotensin system blockade and cardiovascular outcomes in patients with chronic kidney disease and proteinuria: a meta-analysis. *Am Heart J*. 2008; 155:791–805. [PubMed: 18440325]
31. Slagman MC, Waanders F, Hemmelder MH, et al. Moderate dietary sodium restriction added to angiotensin converting enzyme inhibition compared with dual blockade in lowering proteinuria and blood pressure: randomised controlled trial. *BMJ*. 2011; 343:d4366. [PubMed: 21791491]
32. Thomas MC, Moran J, Forsblom C, et al. The association between dietary sodium intake, ESRD, and all-cause mortality in patients with type 1 diabetes. *Diabetes Care*. 2011; 34:861–866. [PubMed: 21307382]

33. Ekinci EI, Clarke S, Thomas MC, et al. Dietary salt intake and mortality in patients with type 2 diabetes. *Diabetes Care*. 2011; 34:703–709. [PubMed: 21289228]
34. Ahmed AK, Kamath NS, El Kossi M, et al. The impact of stopping inhibitors of the renin–angiotensin system in patients with advanced chronic kidney disease. *Nephrol Dial Transplant*. 2010; 25:3977–3982. [PubMed: 19820248]
35. Holtkamp FA, de Zeeuw D, Thomas MC, et al. An acute fall in estimated glomerular filtration rate during treatment with losartan predicts a slower decrease in long-term renal function. *Kidney Int*. 2011; 80:282–287. [PubMed: 21451458]
36. Hou FF, Zhang X, Zhang GH, et al. Efficacy and safety of benazepril for advanced chronic renal insufficiency. *N Engl J Med*. 2006; 354:131–140. [PubMed: 16407508]
37. Weir MR. Acute fall in glomerular filtration rate with renin–angiotensin system inhibition: a biomeasure of therapeutic success? *Kidney Int*. 2011; 80:235–237. [PubMed: 21760601]
38. National Heart Lung and Blood Institute. [Accessed 12 February 2013] NIH launches multicenter clinical trial to test blood pressure strategy. <http://public.nhlbi.nih.gov/newsroom/home/GetPressRelease.aspx?id=2667>

KEY POINTS

- The strongest evidence for the level of BP control to attenuate adverse renal and cardiovascular outcomes in patients with hypertension and CKD (either nondiabetic or diabetic nephropathy) is a target BP less than 140/ 90 mmHg.
- In patients with CKD and proteinuria, there is modest evidence that the first-line use of diuretics combined with a single class of RAAS inhibitor improves clinical outcomes. Dual RAAS inhibitor therapy has not been shown to improve clinical outcomes in patients with CKD.
- The evidence for a lower target blood pressure goal to improve clinical outcomes in patients with CKD and proteinuria is not consistent.
- Most patients with a reduced eGFR (<60 ml/min/ 1.73 m²) require 2–3 antihypertensive agents to achieve a BP less than 140/90 mmHg.
- Optimal care for patients with CKD necessitates an appropriate sensitivity to and an understanding of sociocultural factors such as education, socioeconomic status, family support, insurance profile, and health beliefs and behaviors that may act as barriers to achieving a BP less than 140/90 mmHg.

**FIGURE 1.**

Algorithm for a comprehensive approach to optimizing blood pressure control in persons with chronic kidney disease (CKD). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta blocker; CCB, calcium-channel blocker; CV, cardiovascular; eGFR, estimated glomerular filtration rate.

Table 1

Stages of chronic kidney disease

Stage	Description	eGFR (ml/min/1.73 m ²)
1	Slight kidney damage (as defined by urinary ACR 330 mg/g) with normal or increased kidney function	90
2	Slight kidney damage (as defined by urinary ACR 330 mg/g) with mild decrease in kidney function	60–89
3	Moderate decrease in kidney function	30–59
4	Severe decrease in kidney function	15–29
5	Kidney failure (dialysis or transplant imminent)	Less than 15

ACR, albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate.

Table 2

Pharmacological treatment recommendations for lowering blood pressure in chronic kidney disease patients with or without diabetes mellitus

Urine albumin excretion ^a	Target BP (evidence)	Preferred agent (evidence)
<30 mg per 24 h	SBP <140 mmHg DBP <90 mmHg (strong)	None (strong)
30–300 mg per 24 h	SBP <130 mmHg DBP <80 mmHg (weak)	ARB or ACEI (modest)
>300 mg per 24 h	SBP <130 mmHg DBP <80 mmHg (modest)	ARB or ACEI (strong)

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

^aUrine albumin excretion – mg per 24 h or equivalent.