Protecting Renal Function in the Hypertensive Patient: Clinical Guidelines

George L. Bakris

Both the incidence and prevalence of chronic kidney disease (CKD) are increasing in the United States and worldwide. Patients with both diabetes and hypertension have a dramatically increased risk of cardiovascular and renal events, particularly if both conditions are not effectively controlled. Failure to achieve the goals for blood glucose, blood pressure (BP), and lipids is associated with high morbidity from cardiovascular and renal events as well as the high costs of treating these morbid events. There is increasing evidence that cardiovascular events, renal failure, and premature death can be prevented or delayed by earlier identification and treatment of CKD, as well as by taking measures to prevent its onset. A large subgroup of hypertensive patients may be at increased risk for developing CKD and should be targeted for appropriate monitoring and treatment. Not all antihypertensive regimens are equally effective at preserving renal function. Clinical trials indicate that the primary clinical goal in the treatment of patients with CKD is to lower BP to the recommended goal as well as to reduce albuminuria and proteinuria to the lowest possible levels. This is achieved optimally by using agents that block the renin-angiotensin system in concert with other agents that reduce proteinuria and BP. Am J Hypertens 2005;18:112S–119S © 2005 American Journal of Hypertension, Ltd.

Key Words: Amlodipine besylate, benazepril hydrochloride, chronic kidney disease, hypertension, renin-angiotensin system.

There are approximately 20 million Americans currently living with chronic kidney disease (CKD).1 Patients with CKD have a significantly increased risk for cardiovascular disease (CVD), progression to end-stage renal disease (ESRD), and sudden death. Nondiabetic patients comprise the larger cohort of the Medicare population with CKD, although diabetic patients with CKD have higher mortality rates and more rapid progression to ESRD.1 The prevalence of CVD among patients with CKD is significantly higher than in individuals without CKD; for example, over a 2-year period, 80% of CKD patients in the Medicare database submitted CVD claims, compared with 45% of patients without CKD, and the prevalence of heart failure was four times as great.1

Considering the enormous growth of the elderly and diabetic populations, the United States Renal Data System estimates that, by the year 2030, more than 2.2 million individuals will require treatment for ESRD.1 This is a dire prediction; among patients on dialysis, the cost of treatment is enormous, and 5-year survival rates are only about 32%. In contrast, there is increasing evidence that cardiovascular events and progression of kidney disease can be delayed by earlier identification of CKD, as well as by taking measures to prevent its onset. In particular, appropriate treatment of hypertension is essential to reduce cardiovascular and renal morbidity and mortality among patients either with CKD or at risk for developing CKD.

This article reviews the essentials of treating hypertension in patients with or at high risk for CKD, with or without diabetes, based on evidence from randomized clinical trials and currently published expert clinical guidelines. The fundamental clinical goals in the treatment of hypertension in patients with or at risk for CKD include aggressive control of blood pressure (BP), prevention or reduction of albuminuria and proteinuria, and blockade of the renin-angiotensin system (RAS).

Definition of CKD

The definition of CKD is evidence of either kidney damage or decreased kidney function or both.2 Reduced kidney function starts at a glomerular filtration rate (GFR) of <89 mL/min/1.73 m² and is considered to be especially pronounced if the GFR is <60 mL/min for ≥3 months (Tables 1 and 2).2 Regardless of its etiology, CKD is staged according to the GFR and the presence or absence of kidney damage (Table 2),2 but its clinical features can be further described according to primary etiology (Table 3).2 A GFR of <60 mL/min/1.73 m² can be quantified using the Modification of Diet in Renal Disease (MDRD) formula, which can be found in Table 1.2

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1.73 m² corresponds to a serum creatinine level of >1.5 mg/dL in men or >1.3 mg/dL in women <60 years of age. Normal GFR varies according to age, sex, and body size and is generally about 8% lower in women than in men. Age-related declines in GFR begin at about age 50 years, at a rate of approximately 1 mL/min per year. However, age-related loss of renal function is directly proportional to BP level, and the rate of GFR decline can accelerate to 4 to 8 mL/min per year if systolic BP is not adequately controlled.

Risk Factors for CKD

Although the importance of assessing patients for CVD risk has become recognized as an important task in the primary care setting, too little emphasis has been placed on the need to assess patients for CKD risk and to take preventive action. Physicians are well aware that aggressive management of risk factors has a significant positive effect on the natural history of CVD, yet they appear to be less aware that management of risk factors can prevent the onset or delay the progress of CKD. Furthermore, the public may not associate hypertension and diabetes with risk for kidney failure; it is therefore incumbent upon medical providers to inform patients of the seriousness of this potential outcome.

There is a substantial overlap in the traditional risk factors for CVD and CKD. Epidemiologic data show that the development of CKD is associated with diabetes, hypertension, obesity, smoking, and low levels of high-density lipoprotein cholesterol. Clinical factors that are most predictive for CKD include a family history of renal disease and the presence of diabetes, hypertension, or autoimmune disease. Thus, a large subgroup of patients may be at increased risk for developing CKD and should be identified and targeted for appropriate monitoring and therapeutic interventions (Tables 4 and 5). Individuals at increased risk for CKD should have the following assessments at routine health examinations: BP; serum creatinine for estimation of GFR; albumin-to-creatinine ratio; and urinalysis to assess for protein, red blood cells, and white blood cells. Patients with CKD should also have routine evaluation of serum electrolytes (Table 6).

### Table 1. Criteria for the diagnosis of chronic kidney disease

<table>
<thead>
<tr>
<th>Kidney Damage With or Without Decreased Kidney Function</th>
<th>Decreased Kidney Function With or Without Kidney Damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration Criteria</td>
<td>≥3 months</td>
</tr>
<tr>
<td>GFR  &lt; 60 mL/min/1.73 m²</td>
<td>GFR &lt; 60 mL/min/1.73 m²</td>
</tr>
<tr>
<td>Any of the following:</td>
<td></td>
</tr>
<tr>
<td>Pathologic abnormalities noted on biopsy</td>
<td></td>
</tr>
<tr>
<td>Markers of kidney damage in blood or urine (albuminuria)</td>
<td></td>
</tr>
<tr>
<td>Abnormalities in imaging tests</td>
<td></td>
</tr>
</tbody>
</table>

GFR – glomerular filtration rate.

### Table 2. Stages of chronic kidney disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR Range (mL/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal or raised GFR</td>
<td>≥90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with mild drop in GFR</td>
<td>60–89</td>
</tr>
<tr>
<td>3</td>
<td>Moderate drop in GFR</td>
<td>30–59</td>
</tr>
<tr>
<td>4</td>
<td>Severe drop in GFR</td>
<td>15–29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt;15 (or dialysis)</td>
</tr>
</tbody>
</table>

GFR – glomerular filtration rate.

### Albuminuria

Albumin constitutes about 40% of total urinary protein excreted in most patients with CKD and diabetes. Both albuminuria and proteinuria are early markers of kidney damage, particularly in diabetic kidney disease. Moreover, they are very sensitive markers of cardiovascular risk and parallel findings with C-reactive protein. Thus, when present, these markers signal the presence of an inflammatory vascular process and the need for aggressive treatment to achieve recommended CVD risk reduction goals.

Measurements of urinary albumin excretion (UAE) are a valuable marker of renal function. The earliest clinical evidence of diabetic nephropathy is the appearance of microalbuminuria (UAE ≥30 to 299 mg/day); these levels are too low to be detected on routine urinalysis. Without intervention, 20% to 40% of patients with type 2 diabetes and microalbuminuria progress to overt nephropathy (UAE ≥300 mg/day), and about 20% of these patients will eventually develop ESRD. In addition to being the earliest manifestation of nephropathy, microalbuminuria is also...
a powerful independent risk factor for CVD and renal disease in both diabetic and nondiabetic individuals.\textsuperscript{8–10}

Although the risk factors for both CVD and CKD are essentially the same, screening high-risk hypertensive patients for microalbuminuria is frequently overlooked. The American Diabetes Association\textsuperscript{7} and the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)\textsuperscript{11} recommend that patients with diabetes—and others at high risk for CKD—be screened annually for microalbuminuria. This screening can be performed easily and accurately with an albumin-specific dipstick (microalbuminuria is \(>3\) mg/dL) or by measurement of albumin-to-creatinine ratio, using a random spot urine collection. By this method, microalbuminuria is defined as \(\geq 30\) and \(<300\) mg albumin/g creatinine.\textsuperscript{7} Patients with diabetes and microalbuminuria are considered to have incipient nephropathy; those with UAE \(>300\) mg/day are considered to have overt nephropathy.\textsuperscript{7} Patients at all stages of diabetic kidney disease are at increased risk for diabetic complications, including retinopathy, CVD, and nephropathy, and should be monitored for these complications. Monitoring of the ratio of protein-to-creatinine or albumin-to-creatinine in spot urine samples has been shown to be cost-effective\textsuperscript{12} and should be performed in all patients with CKD or diabetes.\textsuperscript{2}

**Goals for BP in CKD**

Large, population-based studies have shown that as BP increases, the risks of CVD events and ESRD increase continuously.\textsuperscript{13–17} Recent studies have also firmly established the importance of BP reduction as a means to slow the progression of different forms of renal parenchymal injury. Data from numerous randomized controlled trials indicate that the incidence of both CVD and CKD begins to increase at BP levels \(>127/83\) mm Hg in patients with or without diabetes.\textsuperscript{18–22}

Until recently, diastolic BP was the primary outcome variable studied in hypertension trials; however, the importance of controlling systolic BP is now recognized as the decisive factor for reduction of risk for cardiovascular and renal events (Fig. 1).\textsuperscript{23–25} Furthermore, the absolute level of BP reduction in patients with CKD is important. The initial stages of effective BP control in these patients can produce a relative hyperperfusion of the kidneys and a transient increase in serum creatinine. Clinicians should not become alarmed by this mild, transient rise in serum creatinine and inappropriate withdrawal of antihypertensive therapy. In these cases, serum creatinine will generally stabilize or decline over a few weeks. The JNC 7 report\textsuperscript{11} and the National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (K/DOQI) Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease\textsuperscript{24} state that at serum creatinine values of \(<3.0\) mg/dL and age \(<65\) years, a 30% to 35% increase in serum creatinine above the starting point is acceptable within the first 3 to 4 months of starting BP treatment, as long as hyperkalemia (potassium \(>6\) mEq/L) does not occur and the creatinine does not continue to rise.

The relationship between lower achieved BP levels and less rapid declines in GFR is well established.\textsuperscript{18} Hypertension-induced renal vascular injury can be prevented or delayed by lowering systolic BP to \(<140\) mm Hg in patients without renal disease. However, further reductions are required once signs of renal disease are present. Renal function declines at varying rates depending on the etiology of renal
disease (for example, diabetic nephropathy versus serum immunoglobulin A nephropathy), but earlier intervention in terms of BP reduction is invariably preferred to later intervention. The impact of early intervention is far more significant, compared with later interventions, in delaying the onset and progression of diabetic nephropathy.

Because of the weight of the evidence in favor of tight BP control, four important national publications recommend lower BP goals (130/80 mm Hg) for patients with diabetes and/or CKD: the JNC 7 report (Fig. 2); the NKF’s K/DOQI Clinical Practice Guidelines (Fig. 3, Table 7); a Consensus Paper of the Hypertension in African Americans Working Group; and a Position Statement from the American Diabetes Association.

Management of hypertension in patients with CKD or diabetes is challenging, and it generally requires a minimum of two and usually three medications that are different and complementary to achieve the recommended BP level. Controlling BP among all patients with pre-renal disease (patients with microalbuminuria or mild reductions in creatinine clearance) and achieving BP levels of <130/80 mm Hg in patients with CKD are required clinical strategies for limiting the risk of both CVD and renal events. Antihypertensive therapies used in patients with CKD should be evaluated for their ability to reduce albuminuria and proteinuria.

### Blocking the RAS

All randomized, adequately powered clinical trials to date have demonstrated that RAS blockade is the most effective antihypertensive therapy for preserving renal function and reducing CVD in patients with diabetic or nondiabetic disease.

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**Table 5.** Risk factors for chronic kidney disease and therapeutic interventions

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Clinical Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of CKD</td>
<td>Screen for family history</td>
</tr>
<tr>
<td>Diabetes/hyperglycemia</td>
<td>Glycemic control (pharmacologic and lifestyle measures)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>BP control (pharmacologic and lifestyle measures)</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>Exercise prescription</td>
</tr>
<tr>
<td>RAS overactivity</td>
<td>RAS suppression with ACE inhibitors or ARBs</td>
</tr>
<tr>
<td>Smoking or other tobacco use</td>
<td>Tobacco cessation (pharmacologic and nonpharmacologic measures)</td>
</tr>
<tr>
<td>Thrombogenic potential</td>
<td>Antiplatelet agents (daily low-dose aspirin)</td>
</tr>
<tr>
<td>Dyslipidemia (elevated LDL cholesterol and triglycerides)</td>
<td>Lipid-lowering therapy (pharmacologic and dietary)</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BP = blood pressure; CKD = chronic kidney disease; LDL = low-density lipoprotein; RAS = renin-angiotensin system.


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**Table 6.** Clinical evaluation of patients at increased risk of chronic kidney disease

<table>
<thead>
<tr>
<th>All patients</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Measurement of BP</td>
<td>Serum creatinine to estimate GFR</td>
</tr>
<tr>
<td>Protein-to-creatinine ratio or albumin-to-creatinine ratio in a first morning or random untimed “spot” urine collection</td>
<td>Examination of urine sediment for red blood cells or white blood cells</td>
</tr>
<tr>
<td>Ultrasound imaging (eg, in patients with symptoms of urinary obstruction or family history of polycystic kidney disease)</td>
<td>Serum electrolytes</td>
</tr>
<tr>
<td>Serum electrolytes</td>
<td>Urinary concentration</td>
</tr>
<tr>
<td>Urinary acidity</td>
<td></td>
</tr>
</tbody>
</table>

BP = blood pressure; GFR = glomerular filtration rate.


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This is also true in African Americans with kidney disease, as shown by the results of the African American Study of Kidney Disease (AASK) study. In this study, the benefits of angiotensin-converting enzyme (ACE) inhibitors in halting the progression of nondiabetic renal disease in African Americans with hypertension and CKD were demonstrated to be superior to those of amlodipine besylate or β-blockade. Angiotensin-converting enzyme inhibitors have also demonstrated substantial cardiovascular benefits in diabetic patients and in patients with heart failure and post-myocardial infarction. In the MICRO-HOPE substudy of the Heart Outcomes Prevention Evaluation (HOPE) trial, 3577 patients with diabetes and at least one additional cardiovascular risk factor, but without clinical proteinuria or heart failure at baseline, who received ACE inhibitor therapy versus placebo had a significant 24% reduction in the development of overt nephropathy after 4.5 years of follow-up; this effect was independent of BP reduction. Angiotensin receptor blockers (ARBs) have proved particularly beneficial in slowing the progress of renal disease in clinical trials of patients with diabetic nephropathy, although they have not been directly compared with ACE inhibitors in this population.

The recently published NKF practice guidelines make specific recommendations for pharmacologic therapy for all patients with CKD (Fig. 3, Table 7). Agents that block the RAS are considered the preferred agents in CKD because they have been shown to slow kidney disease progression and to reduce CVD by mechanisms in addition to BP reduction. The NKF guidelines recommend the use of either an ACE inhibitor or an ARB, regardless of BP, in all patients with diabetic kidney disease and in patients with nondiabetic kidney disease with spot urine total protein-to-creatinine ratio ≥200 mg/g. Furthermore, the guidelines recommend that moderate-to-high doses, rather than low doses, of RAS-blocking agents be used to achieve additional benefits. For example, there is evidence that using higher doses of RAS-blocking agents may achieve greater reductions in microalbuminuria and proteinuria. With regard to combination therapy, the NKF guidelines note that two or more agents will be needed to achieve BP goals. The NKF guidelines recommend that a diuretic be included in the regimen of most patients; however, selection of additional agents to reduce CVD risk and to achieve BP goals should be based on compelling indications as outlined in JNC 7.

Patients with CKD are at increased risk for complications from pharmacologic therapy and should be monitored more frequently than the general hypertensive population. In particular, all RAS-blocking agents, including ACE inhibitors, ARBs, and aldosterone receptor antagonists, may lead to hyperkalemia in patients with renal impairment. The NKF guidelines recommend that BP, GFR, and serum potassium be measured in all patients with CKD at the initiation of either ACE inhibitor or ARB therapy and also with each increase in dose of either agent. This is done either to establish a baseline or to set a new baseline for these values.
Combination Antihypertensive Therapy in Patients With Diabetes and CKD

Combination therapy plays an important role in quickly bringing high-risk patients to BP goal. The JNC 7 report has recently promulgated the “20/10” rule, which states that patients who present with BP levels >20 mm Hg systolic or >10 mm Hg diastolic over their appropriate BP goal should have therapy initiated with two agents, rather than with a single agent; this rule is also the recommendation of the NKF guidelines (Figs. 2 and 3, Table 7). Patients with CKD will almost always require combination antihypertensive therapy to achieve optimal BP levels of <130/80 mm Hg. A dihydropyridine calcium channel blocker (CCB) should not be used as monotherapy in patients with proteinuric kidney disease. The combination of a RAS-blocking agent with a diuretic or a CCB (or all three agents) is appropriate in this population; many patients will require a loop rather than a thiazide diuretic.

The complementary vasodilatory effects of an ACE inhibitor/CCB combination are clearly valuable for reducing BP more effectively compared with a traditional monotherapy approach. A recent study, the Study of Hypertension and the Efficacy of Lotrel in Diabetes (SHIELD), involving patients with diabetes compared combination ACE inhibitor/CCB therapy with ACE inhibitor monotherapy in terms of the ability of each regimen to bring patients to a BP level of <130/85 mm Hg over a 12-week period. In this study, 214 patients with diabetes were randomized to either amlodipine besylate/benazepril hydrochloride (HCl) or enalapril; hydrochlorothiazide (HCTZ) was added at week 8 if the BP target was not achieved. Patients receiving initial combination therapy showed a significantly greater reduction from baseline in systolic and diastolic BP at 12 weeks compared with patients receiving initial monotherapy (Fig. 4). To reach their target BP, 61% of participants treated with ACE inhibitor monotherapy required add-on therapy with HCTZ, compared with 44% of those treated with combination ACE inhibitor/CCB therapy. When the data were analyzed using the more current BP target of <130/80 mm Hg, by 12 weeks, 70% of patients initiated with combination therapy achieved this goal compared with 31% of patients receiving monotherapy.

In another 8-week, randomized, clinical trial, Systolic Evaluation of Lotrel Efficacy and Comparative Therapies (SELECT), combination therapy (amlodipine besylate/benazepril HCl) was compared with component monotherapy (amlodipine besylate or benazepril HCl) in 505 patients aged ≥55 years with stage 2 systolic hypertension (mean office baseline BP, 169/88 mm Hg). Ambulatory BP monitoring was used to assess the efficacy of the three treatments. After 8 weeks, combination therapy was significantly more effective than either monotherapy treat-

### Table 7. Hypertension and antihypertensive agents in chronic kidney disease

<table>
<thead>
<tr>
<th>Type of Kidney Disease</th>
<th>BP Target (mm Hg)</th>
<th>Preferred Agents for CKD With or Without Hypertension</th>
<th>Other Agents to Reduce CVD Risk and Reach Target BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic kidney disease</td>
<td>&lt;130/80</td>
<td>ACE inhibitor or ARB</td>
<td>Diuretic preferred, then BB or CCB</td>
</tr>
<tr>
<td>Nondiabetic kidney disease with spot urine total protein-to-creatinine ratio ≥200 mg/g</td>
<td>&lt;130/80</td>
<td>ACE inhibitor or ARB</td>
<td>Diuretic preferred, then BB or CCB</td>
</tr>
<tr>
<td>Nondiabetic kidney disease with spot urine total protein-to-creatinine ratio &lt;200 mg/g</td>
<td>&lt;130/80</td>
<td>None preferred</td>
<td>Diuretic preferred, then ACE inhibitor, ARB, BB, or CCB</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BB = β-blocker; BP = blood pressure; CCB = calcium channel blocker; CKD = chronic kidney disease; CVD = cardiovascular disease.

ment in reducing mean 24-h systolic BP and diastolic BP (Fig. 5).44

Many other studies clearly demonstrate that whether one uses an ACE inhibitor/diuretic, ARB/diuretic, or ACE inhibitor/CCB, all of the combinations lower BP more effectively than the monotherapy components. Thus, as recommended in the JNC 7 report, for a patient whose BP is >20/10 mm Hg above goal (>150/90 mm Hg for a patient with diabetes or CKD), combination therapy should be the initial therapy.11

Summary

Medical providers must diligently assess patients to determine their risk for CKD. The major clinical goals for treating hypertension in patients with or at risk for CKD are stringent BP control to <130/80 mm Hg, reduction or prevention of albuminuria, and introduction of RAS blockade, which has been shown to improve renal function beyond that received with BP reduction alone. Patients with diabetic kidney disease or nondiabetic CKD with a spot urine total protein-to-creatinine ratio ≥200 mg/g, as well as all patients with diabetes regardless of current renal status, should be prescribed an ACE inhibitor or an ARB, generally in combination with a diuretic, CCB, or both.

References


