

Hypertension and the Kidney

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Hypertension is an important and widely prevalent risk factor for the development of chronic kidney disease (CKD), which unfortunately may progress to end-stage renal disease. CKD is a progressive condition that causes significant morbidity and mortality. Diabetes is the leading cause of end-stage renal disease in the Western world. Both hypertension and diabetes are the causative factors for the occurrence of CKD and its consequences. Aggressive control of hypertension and diabetes is indicated to reduce the risk for kidney disease in the community. Certainly, effective control of hypertension is a proven modality to prevent renal disease. The concept of decreasing the systemic blood pressure as well as the intraglomerular pressure has led to the application of rational therapeutic options in patients with renal insufficiency. Although treatment of hypertension alone is critical, drugs that block the renin-angiotensin system have been shown to have special renal (and cardiovascular) benefits. Early detection and treatment of microalbuminuria is an integral part of disease management. This article reviews the pathophysiologic and therapeutic implications of the link between hypertension and the kidney. *Semin Nephrol* 25:236-245 © 2005 Elsevier Inc. All rights reserved.

In the United States it is estimated that approximately 50 million people have hypertension, about half either do not know they are hypertensive or have acknowledged but untreated hypertension, and only about a quarter have treated and adequately controlled their blood pressure (BP).¹ Furthermore, approximately 20 million adults have some degree of chronic kidney disease (CKD),² of whom 50% to 75% have hypertension. Importantly, the incidence of hypertension correlates directly with the degree of reduction in glomerular filtration rate (GFR).³ Conversely, there is a direct relationship between systolic blood pressure and the rate of decrease in renal function⁴ and development of end-stage renal disease (ESRD).⁵ The cardiovascular consequences of hypertension often are devastating, and in the presence of renal disease, the overall risk increases exponentially; in fact, patients with CKD are in the highest-risk group for cardiovascular disease.⁶ Despite recently published clinical practice guidelines recommending specific goals for patients with hypertension and chronic kidney disease (Table 1), data indicate that the blood pressure goal is achieved in only a small percentage of patients. Moreover, despite the widespread availability of an-

giotensin-converting enzyme inhibitors (ACEIs), angiotensin II-receptor blockers (ARBs), and other agents with proven renoprotective properties, the incidence of ESRD continues to increase steadily. Hypertension is now the second leading cause of ESRD in the United States⁷ after diabetes mellitus (DM), in which delaying progression to ESRD relies on rigorous control of blood pressure.⁸

Appropriate management of hypertension in patients with CKD includes decreasing both BP and proteinuria. For example, it is well established that microalbuminuria, defined as urine albumin/creatinine ratio of 30 to 299 mg/g albumin, is not only a sign of endothelial dysfunction but also of increased cardiovascular morbidity and mortality risk.⁹ This is pronounced especially in diabetic patients, in whom microalbuminuria constitutes a 2-fold higher risk for cardiovascular disease as compared with diabetic patients without microalbuminuria and microalbuminuric nondiabetic patients. Treating hypertension includes lifestyle modifications such as controlling obesity, stopping smoking, reducing alcohol intake, exercising, and eating a diet low in salt (Na < 2.5 g/d) but rich in vegetables, fruits, and low-fat dairy products.¹⁰ This review focuses on the pharmacologic treatment of hypertension in patients with established kidney disease based on data from randomized controlled clinical trials (RCTs).

Diabetes Mellitus

In the ESRD population, the most common diagnosis at present is diabetic nephropathy,⁷ with type 2 diabetes being

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Table 1 Treatment of Hypertension in CKD

Type of CKD	BP Goal	Preferred Agents for CKD ± HTN	Other Agents to Reduce CVD Risk and Reach BP Goal
Diabetic	<130/80	ACEI or ARB	Diuretic preferred, then β -blocker or CCB
Nondiabetic with spot urine total protein-to-creatinine ratio \geq 200 mg/g	<130/80	ACEI or ARB	Diuretic preferred, then β -blocker or CCB
Nondiabetic with spot urine total protein-to-creatinine ratio \geq 200 mg/g	<130/80	None preferred	Diuretic preferred, then ACEI, ARB, β -blocker, or CCB
Transplanted CKD	<130/80	None preferred	CCB, diuretic, β -blocker ACEI, ARB

Abbreviations: HTN, hypertension; CCB, calcium-channel blocker. Data from the National Kidney Foundation.⁶

the predominating cause because of its much higher prevalence. However, both types follow the same pathophysiologic sequence of (1) glomerular hyperfiltration (preclinical nephropathy), (2) microalbuminuria, typically with the onset of hypertension at this stage (incipient nephropathy), and (3) proteinuria with progressive and irreversible impairment of renal function. Surprisingly, not all (especially type 1) diabetic patients are hypertensive, and not all develop renal disease—what makes this group unique is unknown. Nevertheless, aggressive BP control is essential for all hypertensive patients with DM. In a large prospective study of type 2 diabetic patients, aggressive BP control proved superior to tight glycemic management in preventing death, stroke, and microvascular disease.⁸ ACEIs and ARBs are effective modulators of angiotensin-mediated hemodynamic (glomerular capillary hypertension and hyperfiltration) and nonhemodynamic effects (inflammation, cellular proliferation, and aldosterone release).¹¹ Since the initial landmark study by Lewis et al¹² establishing unequivocal benefits of ACEIs on the kidney beyond its BP lowering properties in type 1 diabetic patients with proteinuria, several RCTs have shown benefit of ACEIs in patients at risk for nephropathy including the Micro-Heart Outcomes Protection Evaluation (HOPE) study (3,577 diabetic patients randomized to placebo versus ramipril),¹³ the captopril primary prevention project (CAPPP) study (572 diabetic patients among 10,985 patients

with hypertension, randomized to captopril versus non-ACEI therapy),¹⁴ the appropriate blood pressure control in diabetes (ABCD) trial (470 patients with type 2 diabetes on enalapril versus nisoldipine),¹⁵ and Fosinopril and Amlodipine Cardiovascular Event Trial (FACET) (fosinopril versus amlodipine in 380 patients with type 2 diabetes).¹⁶ Moreover, a follow-up study of HOPE showed a reduced incidence of new-onset diabetes during treatment in patients receiving ACE inhibitor¹⁷ therapy.

With their specific angiotensin II–blocking properties, plus potentially enhanced stimulation of antiproliferative, anti-inflammatory type 2 angiotensin receptors, ARBs can be considered suitable for inhibition of the renin-angiotensin system. Angiotensin II (similar to aldosterone) escapes with ACEI therapy because of non-angiotensin-converting enzyme pathways (chymase and others), and although certainly attractive,¹⁸ the ultimate role of bradykinin remains speculative. The first 3 large RCTs investigating the renal effects of ARBs in the population with DM type 2 were both promising and disappointing. In diabetic patients with microalbuminuria, irbesartan reduced the incidence of progression to overt nephropathy, but normoalbuminuria was restored in only 34% of patients and only at the maximum dose of 300 mg (Fig 1).¹⁹ Although both irbesartan²⁰ and losartan²¹ (Fig 2) showed a reduced risk for developing ESRD in established

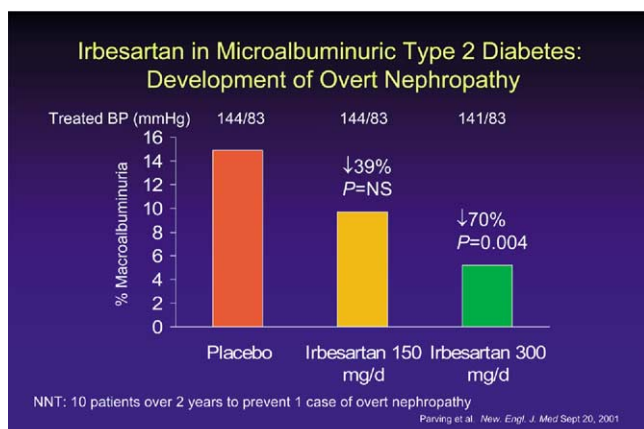


Figure 1 Irbesartan in microalbuminuric type 2 diabetes: the development of overt nephropathy. Number needed to treat: 10 patients over 2 years to prevent 1 case of overt nephropathy. Reprinted with permission from Parving et al.¹⁹

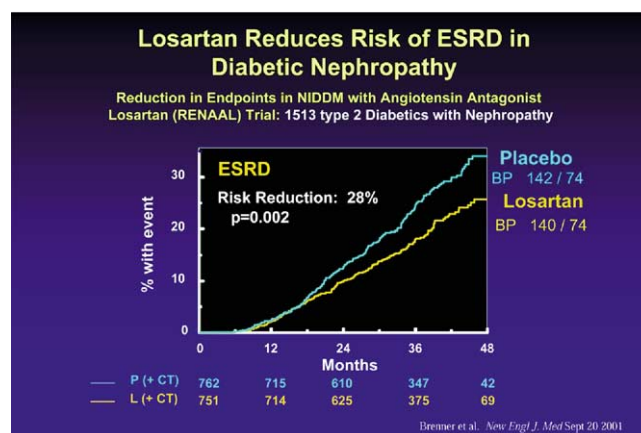


Figure 2 Losartan reduces the risk for ESRD in diabetic nephropathy. Reduction in end points in non-insulin-dependent diabetes mellitus with angiotensin antagonist losartan (RENAAL) trial, which included 1,513 type 2 diabetic patients with nephropathy. Reprinted with permission from Brenner et al.²¹

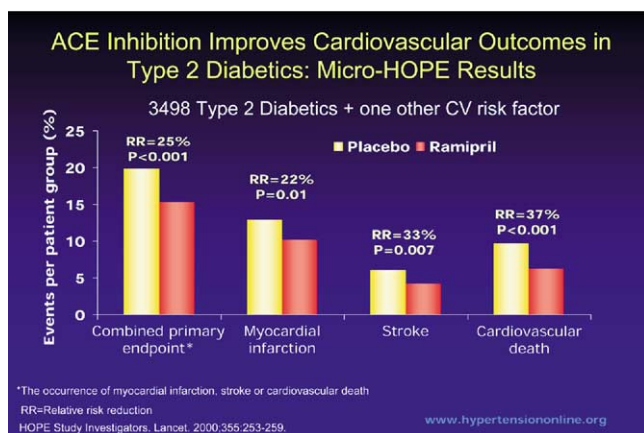


Figure 3 ACE inhibition improves cardiovascular outcomes in type 2 diabetic patients. The Micro-HOPE results are shown. The study consisted of 3,498 type 2 diabetic patients with 1 additional cardiovascular risk factor. □, Placebo; ■, ramipril. *The occurrence of myocardial infarction, stroke, or cardiovascular death. RR, relative risk reduction. Reprinted with permission from the HOPE Study Investigators.¹³ Available: www.hypertensiononline.org.

diabetic nephropathy, both agents fell short of showing a cardiovascular benefit (except for fewer hospitalizations for heart failure with losartan). However, it is important to note that none of these trials were powered to detect differences in cardiovascular outcomes. In contrast, the ACEI ramipril has been shown to provide cardiovascular benefit in diabetic participants in the HOPE trial (Fig 3).²² Similarly, greater cardiac benefits were seen with captopril versus losartan after acute myocardial infarction.²³ A cardiovascular benefit of losartan, as well as a reduced incidence of new-onset diabetes, was shown in the Losartan Intervention for Endpoint (LIFE) study²¹; however, the use of a β -blocker in the control arm has been criticized.^{24,25}

Combination therapy of ACEIs plus ARBs in both types of DM was investigated in some RCTs showing greater reduction in BP and albuminuria.²⁶⁻²⁸ The question of the optimal dose of the components remains unclear. Although the effect on BP has been inconsistent, strong evidence suggests superior efficacy for reducing albuminuria with combination therapy when compared with maximum-dose ACEI alone.²⁹⁻³¹

No RCT is available on the effect of aldosterone-receptor blockade in diabetic nephropathy. One small and unblinded study of only 8 patients with various nephropathies (5 DM type 2) and mean proteinuria of 3.8 g/d found that adding spironolactone to enalapril resulted in a further reduction of protein excretion by 54%, albeit with a decrease of 10 mm Hg in mean BP.³²

Primary Glomerular Disease

Because proteinuria per se induces cellular toxicity to podocytes, mesangial cells, and tubular epithelial cells, and leads to systemic hypertension caused by enhanced proximal tubular salt retention,³³ measures that decrease proteinuria—either pharmacologic or by dietary protein restriction—

should retard progression of renal disease, regardless of the underlying cause, as has been confirmed by Modification of Diet in Renal Disease (MDRD)³⁴ and Ramipril evaluation in nephropathy (REIN).³⁵ The decrease in renal function in patients with immunoglobulin A nephropathy, nephrosclerosis, autosomal-dominant polycystic kidney disease (ADPKD), or chronic interstitial nephritis is slower when compared with the diabetic population.³⁶ With the possible exception of ADPKD, ACEIs slow progression of nondiabetic nephropathy. This was shown in several RCTs, such as MDRD,³⁴ REIN,³⁵ HOPE,²² African American Study of Kidney Disease and Hypertension (AASK),³⁷ and others.^{38,39}

In ADPKD, progression to ESRD is more rapid if hypertension is present, however, improving BP has not been shown to influence deterioration of renal function significantly.^{34,40} Furthermore, to date, neither ACEI therapy^{36,38,41,42} nor protein restriction³⁵ has shown appreciable benefit in ADPKD. In a small study of 12 hypertensive patients with ADPKD, the ARB candesartan effectively decreased BP and microalbuminuria, but no long-term follow-up evaluation was available.⁴³ At this time, no RCTs have been conducted with ARBs in patients with AKPKD.

A synergistic renal effect of combining ACEIs and ARBs in nondiabetic renal disease was shown in some trials, and without any adverse effects.⁴⁴⁻⁴⁷ In patients with congestive heart failure, however, the combination led to worse mortality outcome or an increase in adverse effects in 2 recent trials.^{48,49} Monotherapy with eplerenone, a selective aldosterone inhibitor, reduced albuminuria to a greater extent than enalapril in a nondiabetic population (61.5% versus 25.7%, respectively), with similar effect on BP and a slightly more favorable side-effect profile.⁵⁰

Hypertensive Nephrosclerosis

Hypertensive nephrosclerosis is defined as nondiabetic CKD associated with chronic (often stage 2) hypertension with or without moderate proteinuria and a pathologic picture characterized by arteriosclerosis, arteriolosclerosis, glomerulosclerosis, and interstitial fibrosis in the absence of immune deposits. In the vast majority of patients the diagnosis of hypertensive nephrosclerosis is based on clinical (history, physical examination, urinalysis, and serologic testing criteria) rather than renal biopsy examination findings. Hypertension is an important cause of CKD and accounts for about one fourth of new cases of ESRD. The mechanisms by which increased BP causes kidney damage are understood incompletely and are the subject of intense investigation.

Approximately 6% of patients with hypertension may be at risk for permanent kidney damage and progressive disease (eg, hypertensive nephrosclerosis).⁵¹ Among Americans with end-stage kidney disease approximately 27% are believed to have primary hypertension as the underlying cause.⁵² Hypertensive nephrosclerosis is the second most common cause of all cases of ESRD in the United States and it is approximately 5-fold more common in African Americans as compared with non-African Americans.^{37,53} The Medicare costs to the ESRD program in the United States for care of patients with hyper-

Table 2 Risk Factors for Progression of Kidney Disease in Hypertensive Nephrosclerosis

Age
Sex
Race
Duration of hypertension
Proteinuria
Dyslipidemia
Family history
GFR <30 mL/min
Smoking
Lower socioeconomic status
Fewer nephrons

tensive nephrosclerosis exceed \$1 billion annually. End-stage kidney disease attributed to hypertension generally occurs at a younger age in African Americans as compared with non-African Americans.⁵² Moreover, epidemiologic and case-control studies show increased risk for hypertension as a cause of ESRD.^{5,54-58} Factors that may account for racial disparity in ESRD attributed to hypertension include a lack of access to medical care, socioeconomic status, severity of hypertension, duration of hypertension, educational level, alcohol and drug abuse, genetic factors, and nephron endowment.^{5,59-66} However, modifiable risk factors including sociodemographic, lifestyle, and clinical factors explain less than half of the increased risk for ESRD.⁶⁷ Therefore, other risk factors including genetic determinants may play an important role in predisposing African Americans to ESRD.

Risk Factors for Hypertensive Nephrosclerosis

Systolic hypertension is the most powerful predictor of development of progression of chronic kidney disease to ESRD (Table 2). For example, analysis of the impact of systolic hypertension among 334,000 men screened for the Multiple Risk Factor Intervention Trial indicated that systolic hypertension was an independent risk factor for all-cause ESRD. Moreover, the relationship between systolic BP and the development of ESRD was graded and consistent throughout the range of BPs recorded at the time of screening into the study.⁵ Observational studies and clinical trials also identified systolic BP as a predictor of renal outcomes in patients with hypertensive kidney disease. In addition to data from the Multiple Risk Factor Intervention Trial, data from the atherosclerosis risk in the communities observational study,⁶⁸⁻⁷¹ the Hypertension Detection and Follow-Up Study,⁵¹ the Systolic Hypertension in the Elderly Program trial,⁷² and the VA cooperative trial⁷³ reported that systolic BP is an independent risk factor for ESRD attributed to hypertension.

Proteinuria is a marker for the increased rate of decrease in kidney function in hypertensive patients with CKD.^{37,53,74-77} For example, those with a urine protein excretion rate of approximately 300 mg/d enrolled in the AASK study exhibited a 2-fold higher rate of decrease in GFR as compared with

those with lower protein excretion rates.⁵³ In hypertensive nephrosclerosis and glomerular diseases (eg, focal segmental glomerulosclerosis), proteinuria is associated with worse renal outcomes and reduction in proteinuria with improved outcomes. Moreover, antihypertensive strategies that reduce proteinuria and BP are more effective at slowing the decrease in GFR as compared with those that only decrease blood pressure.^{37,76,78}

Low GFR

Clinical trials indicated that lower GFR is a risk factor for subsequent development of ESRD and the rate of decrease in the GFR is faster among those with lower GFR levels.^{37,77,79}

Dyslipidemia

Approximately 60% of hypertensive patients have dyslipidemia and 40% of dyslipidemic individuals are hypertensive. Hypertriglyceridemia and low plasma levels of high-density lipoprotein are associated with the onset of hypertensive renal disease.⁶⁸ Also, hypercholesterolemia correlates with global glomerulosclerosis in patients with biopsy examination-proven hypertensive nephrosclerosis.⁸⁰ However, to date there are no clinical trials indicating that lipid-lowering therapy reduces the risk for onset or progression of hypertensive nephrosclerosis.

Cigarette Smoking

Smoking has been associated with an increased rate of decrease in renal function in diabetic patients and in those with hypertensive nephrosclerosis.^{81,82} Cigarette smokers with hypertensive nephrosclerosis and CKD have a markedly increased rate of progression of kidney disease despite similar levels of blood pressure control compared with nonsmokers.⁸¹

Cardiovascular Disease Risk

It is important to note that those with hypertension and CKD are at high risk for cardiovascular morbidity and mortality.⁵¹ For example, long-term follow-up evaluation of patients with hypertensive nephrosclerosis indicated that systolic BP increase is a strong predictor of development of heart failure.⁷³ Hypertensive patients with CKD are far more likely to have a myocardial infarction, stroke, or cardiovascular death than those without CKD.⁸³ After controlling for BP, those with kidney disease are at higher risk for these complications. Therefore, in addition to BP control, treatment should include identification and management of other cardiovascular risk factors in hypertensive nephrosclerosis.

Treatment

Assessment and Management Guidelines

Assessment of patients with hypertensive kidney disease should include complete medical history, physical examination, hemoglobin A1C, routine chemistries and urinalysis, urine protein/creatinine ratio, renal sonogram, and appropri-

Table 3 Recommended Treatment Plan for Hypertensive Nephrosclerosis

First Line	Alternative
Nonpharmacologic therapy	None
ACEI	Angiotensin II receptor blocker
Diuretic*	
Calcium-channel blocker	β -blocker
α -blocker	Clonidine
Minoxidil	Hydralazine

NOTE. Once-daily agents preferred for pharmacologic intervention.

*Thiazide for estimated GFR ≥ 50 mL/min/1.73 m², loop diuretic for estimated GFR < 50 mL/min/1.73 m².

ate serologic testing to look for auto-immune disorders (Table 3). This evaluation is aimed at identifying other causes of kidney disease such as familial diseases (eg, Alport's syndrome, Fabry's disease, focal segmental glomerulosclerosis) of the kidney as well as systemic lupus erythematosus, atheroembolic renal disease, multiple myeloma, systemic necrotizing vasculitides, hepatitis-associated glomerulonephritides, and cryoglobulinemia. Data from the AASK kidney biopsy examination pilot study indicated that these criteria correctly will identify patients with a pathologic picture consistent with hypertensive nephrosclerosis.⁸⁰ Further evaluation for causes other than hypertension including renal biopsy examination may be necessary in some cases depending on the results of serologic or renal imaging studies. The history and examination should include assessment of lifestyle and diet, with particular attention to smoking, exercise, and overweight stature. In addition, a lipid panel and measurement of hemoglobin level are important because both dyslipidemia and anemia may increase the risk for kidney disease progression in some patients.^{68,84}

Lifestyle modifications and pharmacologic decreasing of BP to less than 130/80 mm Hg with an ACE inhibitor-based regimen are recommended by the National Kidney Foundation for treatment of hypertensive CKD. Identifying additional modifiable risk factors beyond decreasing BP and inhibition of the renin-angiotensin-aldosterone system are an important aspect of ongoing studies.

Treatment Goals

There is an important interaction between BP levels, proteinuria, and kidney outcomes in patients with hypertension and CKD. There are 2 main treatment goals for those with hypertension and nondiabetic CKD: (1) lower the blood pressure and (2) block the renin-angiotensin-aldosterone system with an ACEI, or with an ARB in those with more than 300 mg protein/g creatinine on a random urine sample. The most important aspect of management of hypertensive CKD is to decrease BP. The National Kidney Foundation Clinical Practice Guidelines for Hypertension recommend a BP goal for all hypertensive patients with CKD of less than 130/80 mm Hg. In addition, for those with nondiabetic CKD the use of an ACEI as first-line treatment is recommended for those with a urine protein level of greater than 300 mg/g creatinine

whereas other first-line agents are acceptable for those with less than 300 mg/g creatinine.⁶ This BP level is based on results from AASK and other studies in hypertensive patients with nondiabetic kidney disease. In the AASK study, nearly 1,100 African Americans with hypertensive nephrosclerosis and reduced GFR were randomized to either ramipril, metoprolol, or amlodipine once daily and other antihypertensive medications to achieve 1 of 2 mean arterial pressure goals of mean BP less than 92 mm Hg or 102 to 107 mm Hg. The ACEI ramipril was found to be more effective in reducing the risk for rapidly decreasing GFR, ESRD, and death as compared with either amlodipine or metoprolol XL. In addition, ramipril treatment was associated with reduced proteinuria as compared with amlodipine. However, the AASK study did not find that a lower systolic BP decreased the risk for ESRD among those with hypertensive nephrosclerosis. Importantly, in treated patients, the average rate of decrease in GFR in patients with hypertensive nephrosclerosis (2 mL/min/y) is relatively slow as compared with diabetic nephropathy (6 mL/min/y). Meta-analyses of more than 1,800 nondiabetic proteinuric hypertensive patients support this BP goal.^{75,76,78} Systolic BP in the range of 120 to 130 is associated with a lower risk for ESRD in patients with more than 1 g/d of urine protein excretion, whereas for those with lesser degrees of proteinuria the lowering of systolic BP below 140 mm Hg was not. Taken together these data support the National Kidney Foundation recommendations as shown in Table 1. ACEI-based regimens are recommended as first-line therapy for all groups except in those with a very low level of proteinuria. Most patients with hypertensive nephrosclerosis have stage 2 hypertension; therefore, both nonpharmacologic and multi-drug therapy almost always are required.

Nonpharmacologic Treatment

First, all patients should be educated about lifestyle modification to include smoking cessation, regular aerobic exercise, moderate alcohol consumption, and weight loss for overweight individuals (>24 and >27 kg/m² for women and men, respectively). Smoking cessation may slow progression of kidney disease, and reduction in alcohol consumption, exercise, and weight loss also can lower BP markedly. Finally, for those with a high sodium intake, lowering dietary sodium intake may have a profound effect on systolic BP including in African Americans. Diets rich in fruits and vegetables (high fiber) and low-fat dairy products and low in saturated fat (Dietary Approaches to Stop Hypertension diet) are effective in lowering BP.¹⁰

Pharmacologic Treatment

Consistent with the Joint National Committee 7 recommendations, all patients should be assessed for any complications resulting from hypertension and those with a systolic blood pressure of 160 mm Hg or greater should begin with 2-drug therapy in addition to nonpharmacologic intervention. The use of once-daily ACEI combined with a diuretic is recommended by the National Kidney Foundation. For those with an estimated GFR of less than 50 mL/min, a loop diuretic

administered 2 or 3 times daily is preferable to a thiazide for those with hypertensive nephrosclerosis. If the BP goal is not achieved on this regimen, the addition of a once-daily calcium-channel blocker (or β -blocker) is reasonable. If 3 agents do not control BP then addition of a once-daily β -blocker (or calcium-channel blocker) is advisable. The subsequent addition of a long-acting α -blocker or a centrally acting α -2 sympathomimetic such as clonidine or guanfacine may be used. Finally, for selected individuals, the addition of a vasodilator such as hydralazine or minoxidil may be needed.

Monitoring BP Response

BP measurement should be performed frequently, preferably by the patient with a home BP monitor. The readings should be recorded by date and time and reviewed by the treating physician. The BP device should be tested and compared with office BP equipment to ensure that the office readings reflect home readings for accuracy. After initiation of antihypertensive therapy in those with CKD, the BP should be measured at least every 2 weeks until the target is reached and then monthly for 3 months to ensure stability and allow for titration of medications as needed. After establishment of the BP goal, quarterly office visits for BP measurements should be made to ensure maintenance of goal and to reassess renal function. Renal function monitoring should include measurement of serum creatinine level and urine protein level/creatinine level ratio. If BP control cannot be achieved with this sequence of adding agents, then consideration of secondary causes of hypertension including adrenal causes and renovascular hypertension is prudent and appropriate evaluation should be undertaken. However, review of diet and other lifestyle modifications, compliance with medication, and ability to afford antihypertensive agents are far more common and should be considered before extensive diagnostic studies are performed. AASK study was a prospective, double-blind, randomized, controlled trial in approximately 1,100 nondiabetic African Americans with hypertensive nephrosclerosis. The trial attempted to answer 2 key questions: (1) Does very aggressive lowering of blood pressure result in slower decrease in renal function? (2) Does the type of antihypertensive agent used to initiate BP lowering matter with regard to renal outcomes? Study participants were randomized to ramipril, amlodipine, or metoprolol XL administered once daily on the background of other antihypertensive medications and to 1 of 2 BP levels, either a mean arterial pressure of less than 92 or 102 to 107 mm Hg. There were no differences in the rate of decrease in GFR between groups; however, those treated with ramipril had a lower incidence of ESRD and death combined. Patients with a baseline protein excretion rate in excess of 300 mg/d or a urine protein creatinine ratio of greater than 0.22 had a rate of decrease in GFR of approximately 5 mL/min/y as compared with 2 mL/min/y in those with a baseline urine protein creatinine ratio of less than 0.22. Moreover, the composite clinical end point event rate was nearly 5 times higher in patients with proteinuria at baseline versus nonproteinuric participants. Ramipril lowered proteinuria to a greater extent as compared with amlo-

dipine. The results of these and other analyses from this landmark clinical trial likely will provide additional new insights and directions for future research into hypertensive nephrosclerosis.

In summary, hypertensive nephrosclerosis is an important public health problem. Similar to primary hypertension, it is a heterogeneous kidney disease that overall progresses slowly in comparison with other common renal diseases. Decreasing the BP to a level <130/85 mm Hg with a regimen containing an ACEI is effective in improving outcome in this disease. However, additional risk factors beyond BP are important in disease progression and future research should focus on these factors. The AASK cohort study will follow-up a substantial proportion of the original AASK study population and was designed for this purpose. Additional epidemiologic, histologic, pathophysiologic, and genetic studies also are needed before we optimally can treat and eventually prevent this devastating disease. Patients with hypertensive nephrosclerosis who smoke cigarettes should be encouraged to quit by enrollment in formal smoking cessation programs as soon as possible. Further, ATP III guidelines for lipid-lowering therapy should be applied to patients with hypertensive nephrosclerosis.⁸⁵

Treatment Guidelines

The key is to initiate treatment aggressively and in the early stages of disease. Once GFR reaches approximately 50% of normal, renal function usually deteriorates owing to glomerular hyperfiltration, proteinuria, and interstitial disease.⁸⁶ Although controversial, the exact sequence and type of BP medication probably is less important than actually reaching and maintaining the recommended BP goal. In United Kingdom Prospective Diabetes Study (UKPDS), among 758 patients with tightly controlled BP, 593 with DM type 2 who were followed-up for a median of 8.4 years showed no difference in long-term complications between the captopril and atenolol group.⁸⁷ In a study comparing enalapril and β -blocker in patients with nondiabetic disease, no difference was found in slowing progression to end-stage renal failure after 3 years.⁸⁸ Furthermore, the majority of patients with renal disease and hypertension will require 3 or more antihypertensive drugs.⁸⁹ It is imperative to tailor the drug regimen according to the side-effect profile, comorbid conditions, and response to treatment, thus maximizing compliance.

Substantial evidence suggests that using an ACEI or ARB in patients with CKD slows the progression of nephropathy. Side effects will need monitoring, in particular hyperkalemia, which is an issue in patients with impaired renal function, inadequate diuretic therapy, or DM (hyporeninemic hypoaldosteronism); changing from an ACEI to an ARB may or may not ameliorate the problem.⁹⁰ An increase in the serum creatinine level of 20% to 30% from baseline after starting ACEI or ARB therapy is common. Such increases may be less of a class-specific effect but rather the consequence of BP lowering per se in patients with nephropathy and impaired renal autoregulation.⁹¹ Importantly, several studies suggest that an increase in serum creatinine level in this setting is a favorable

prognostic sign, resulting in better long-term preservation of renal function.^{92,93}

Large and rigorously conducted RCTs have had a tremendous impact in our ability to improve disease and quality of life in our patients. Yet, what holds true for a large study population may not be true in a particular patient. In the future, investigation into genetic polymorphisms, for example, genes involved in activation of the renin-angiotensin system such as the DD isoform of the ACE gene,⁹⁴ will aid in identifying specific subgroups of patients particularly responsive to a certain regimen. This would help target therapy to maximum susceptibility and effect.

Hypertension in Hemodialysis Patients

Scope of the Problem

As noted earlier, the ESRD population is continuing to grow in the United States, and now nears 300,000 patients. Hypertension is present in 75% of patients on hemodialysis in the United States.⁹⁵ Hypertension is correlated independently with morbidity and mortality in the hemodialysis population.⁹⁶ Moreover, Foley et al⁹⁷ found that each increase of 10 mm Hg in mean arterial BP was associated independently with a progressive increase in concentric left ventricular hypertrophy and the development of de novo cardiac failure. These data strongly suggest that long-term hypertension is a major risk factor for cardiovascular events in the ESRD patient. Even though nephrologists recognize hypertension and commonly prescribe treatment, achieving a safe and optimal level of BP is a major challenge for patients and physicians.⁹⁸ There are many reasons for this poor BP control, including the following: (1) inconsistency in measuring BPs in ESRD patients because of the presence of a functioning access in one extremity that restricts BP measurement in the other extremity, or leg BP readings that are not well validated; (2) variable blood pressure depending on interdialytic weight gains in a given patient; (3) increased *white coat effect* caused by the anxiety associated with the anticipated cannulation of a fistula or graft; and (4) no consensus with regard to the optimal timing of BP measurement in hemodialysis patients.⁹⁸ Thus, it would seem prudent to standardize BP measurement somehow in hemodialysis units according to published guidelines.⁹⁹

The target BP in hypertensive ESRD patients also is not entirely clear. For instance, several studies have shown that low presystolic BP is associated with an increased mortality. Thus, the risk for mortality is U-shaped, being higher among patients who are markedly hypertensive (presystolic BP > 180 mm Hg) or markedly hypotensive (presystolic BP < 110 mm Hg) before dialysis or markedly hypotensive after dialysis.⁹⁵ Systolic BP is linked more strongly to cardiovascular risk than diastolic BP or mean arterial pressure, and needs to be well controlled in our ESRD patients.

Pathophysiology of Hypertension in ESRD

There are many reasons why hypertension is so prevalent in ESRD patients. Paramount among these is volume (extracel-

lular and intracellular) expansion, derangements of the renin-angiotensin system, and sympathetic overactivity. Other factors that may play a role include genetic factors, uremic toxins (such as homocysteine), the use of recombinant erythropoietin, secondary hyperparathyroidism, and the particular hemodialysis regimen. Accordingly, good BP control in an individual ESRD patient may involve different and combined strategies according to which of the earlier-listed mechanisms are involved.

An expanded extracellular fluid volume is the most consistent finding in hypertensive ESRD patients. Thus, the removal of excess volume is essential in controlling BP, and often other strategies fail until this goal is achieved. When BP remains increased despite achieving adequate volume control, then blocking increased sympathetic activity or modulating the renin-angiotensin system may be tried next.

In 20% to 30% of kidney failure patients the regular administration of recombinant human erythropoietin (rHu Epo) results in de novo hypertension or the aggravation of pre-existing hypertension.⁹⁵ This increase in BP often takes weeks to months to develop. There are multiple mechanisms involved, including an increase in whole-blood viscosity, endothelin release, activation of various neurohumoral systems, and a direct vasopressor effect of rHu Epo on renal resistance vessels. In these ESRD patients it is essential that the patient's anemia need not be corrected to normal values, and sometimes even modest anemia may be tolerated.

Treatment

The most effective way to control hypertension in dialysis patients is to restrict salt in the diet. Ideally, intradialytic weight gain can be kept at 2.5 to 3 kg in a 48-hour period, obviously allowing some flexibility depending on the size of the patient. In some dialysis centers where long or overnight dialysis therapy is used, patients often achieve normal BP without any medications. In these patients, the interdialytic weight gain is removed and the patient remains in relatively normal sodium balance.

Drug therapy for hypertension in ESRD patients includes all classes of antihypertensive drugs except for diuretics. In a few selected patients who have some residual renal function and thus significant urine output, a loop diuretic may help reduce interdialytic weight gain and help with better BP control. In a recent study, the pattern and use of antihypertensive drugs was reported in hemodialysis patients in the United States.¹⁰⁰ In this multicenter trial, 72% of the patients received antihypertensive medications: 48% were prescribed calcium-channel blockers, 24% were prescribed ACEIs, and 21% were prescribed β -blockers. ACEIs and angiotensin II-receptor blockers may decrease morbidity and mortality in ESRD patients by reducing the mean arterial pressure, aortic pulse wave velocity, and left ventricular hypertrophy.¹⁰¹

The potential downside to ACEI use includes hyperkalemia, anaphylactoid reaction with AN 69 membranes, and aggravation of renal anemia.¹⁰⁰ ACEIs exacerbate anemia in these patients by decreasing endogenous erythropoietin production and by blunting the erythropoietic response to epo-

etin. ACEIs are associated with a higher incidence of clinically important hyperkalemia by inhibiting residual renal potassium excretion and by blocking the colonic excretion of potassium.

β -blockers decrease BP, decrease some ventricular arrhythmias, and potentially improve left ventricular function in ESRD patients. Hypertensive patients who are noncompliant with their medications may benefit from the addition of transdermal clonidine therapy once a week. Minoxidil, a potent vasodilator, generally is reserved for dialysis patients with severe hypertension in whom BP cannot be controlled with the other classes of antihypertensive agents.

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