Preventing Chronic Kidney Disease in Special Populations

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Hypertension is a major risk factor for chronic kidney disease (CKD), cardiovascular disease, cerebrovascular events, and premature death. However, certain groups are known to be at higher risk for hypertensive end-organ damage, including diabetic patients, older patients with isolated systolic hypertension, and specific ethnic populations. Coexistent diabetes and hypertension dramatically increase the risk of developing CKD and other target-organ complications. The prevalence of hypertension, left ventricular hypertrophy, CKD, hypertensive renal disease, and end-stage renal disease (ESRD) is far greater in African Americans compared with white Americans. Identification of patients at increased risk for CKD offers the potential to prevent or delay ESRD and the cardiovascular events associated with CKD. Data from completed and ongoing controlled clinical hypertension trials will assist clinicians in creating optimal antihypertensive regimens for patients at increased risk for CKD. Am J Hypertens 2005;18:106S–111S © 2005 American Journal of Hypertension, Ltd.

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In 2001, the worldwide prevalence of end-stage renal disease (ESRD) was estimated to be 1.1 million individuals, with related annual per patient medical costs of about $66,000. This number is expected to exceed $2 million by the year 2010, with a predicted aggregate annual cost of approximately $1.1 trillion. Yet, despite the life-extending benefits of renal replacement therapy, a patient who started dialysis in the United States in 2001 had a life expectancy of only 31 months. Furthermore, many patients are not referred to hemodialysis units until they reach a very advanced stage of chronic renal failure, exacerbating their adverse clinical outcomes. Unquestionably, the most prudent alternative to this ominous scenario is to wage an effective campaign for the prevention of ESRD.

There is strong evidence that early detection of chronic kidney disease (CKD) and appropriate interventions can help prevent or delay the onset of ESRD. However, according to the National Kidney Foundation, most of the 20 million adults in the United States with CKD are unaware of it. In addition to the burdensome number of Americans with CKD, another 20 million may be at increased risk. Demographic and clinical factors that are associated with the development or progression of CKD are older age, diabetes, hypertension, a family history of kidney disease, and ethnic populations including African Americans, Hispanics, Pacific Islanders, and Native Americans.

The key treatment goals for patients with CKD are to achieve a blood pressure (BP) level <130/80 mm Hg, to monitor and reduce proteinuria, and to prescribe an antihypertensive regimen that includes an agent that blocks the renin-angiotensin system (RAS). An elevated serum creatinine level is an early indicator of CKD and is strongly related to inadequate treatment of high BP. An analysis of data from the National Health and Nutrition Examination Survey (NHANES) for 1988–1994 showed that an estimated 3.0% of Americans (5.6 million) had elevated serum creatinine levels, 70% of whom were hypertensive. Although 75% of individuals with hypertension and elevated serum creatinine levels were treated for hypertension, the mean BP level for this group was 147/77 mm Hg, and only 11% had BP levels <130/85 mm Hg.

A major area of opportunity for prevention of ESRD, as well as the cardiovascular events associated with CKD, depends upon early identification and treatment of populations at high risk of developing CKD and implementing prevention strategies throughout the course of CKD. This article describes populations at increased risk for CKD and outlines appropriate strategies for its prevention in these high-risk groups.
Preserving Renal Function in Patients With ISH

Isolated systolic hypertension is the most common form of hypertension among patients aged >50 years and is associated with a greater risk of development of CKD, compared with elevated diastolic BP.6,17 In Systolic Hypertension in the Elderly Program (SHEP),18 conducted in individuals with ISH aged ≥65 years, placebo-treated subjects in the highest quartile for systolic BP at baseline (range, 175 to 213 mm Hg) had an adjusted relative risk for decline in kidney function (defined as an increase in serum creatinine ≥0.4 mg/dL during 5 years of follow-up) of 2.44, compared with those in the lowest quartile at baseline (range, 158 to 163 mm Hg).19 Systolic BP had a far greater predictive power for decline in kidney function than did diastolic BP, pulse pressure, or mean arterial pressure. Elevated serum creatinine levels are common in older adults and are associated with increased risk of all-cause death, CVD, and heart failure.20 Isolated systolic hypertension is also associated with microalbuminuria. In a cross-sectional analysis for a population sample of 677 men and 890 women aged 45 to 64 years without diabetes or albuminuria, the risk of microalbuminuria was 4.95 for patients with ISH, compared with those without ISH.17

Isolated systolic hypertension should not be viewed as a normal result of aging. Patients with ISH should be brought to the same target BP goals as are recommended for all adults: <140/90 mm Hg for those with uncomplicated hypertension or <130/80 mm Hg for those with diabetes or CKD.6–8 To lower BP sufficiently and in a timely manner, combination antihypertensive therapy is recommended as initial therapy in patients with systolic BP >20 mm Hg above their recommended target systolic BP goal.1 However, caution is advised in initiating therapy with multiple agents in patients who may be at risk for orthostatic hypotension, such as some older patients or diabetic patients with autonomic dysfunction.7

The optimal treatment for preserving kidney function in patients with ISH remains uncertain. In SHEP,18 compared with placebo, diuretic-based treatment of patients with ISH prevented the development of CVD events in persons aged ≥60 years and did not affect the risk of creatinine levels becoming elevated during follow-up. However, hypokalemia occurred frequently among diuretic-treated participants, and the risk of a CVD event was about 50% greater in diuretic-treated subjects with hypokalemia than in treated subjects without hypokalemia.21 In the Systolic Hypertension in Europe (Syst-Eur) study,22 in 4695 patients aged >60 years with ISH (defined as systolic BP >160 mm Hg and diastolic BP <95 mm Hg), treatment with the dihydropyridine calcium channel blocker (CCB) nitren-
Dipine reduced all fatal and nonfatal cardiac endpoints by 26%. In patients assigned to active treatment, the incidence of mild renal dysfunction decreased by 64% and that of proteinuria by 33%. Active treatment reduced the risk of proteinuria more in diabetic (n = 455) than in nondiabetic patients (71% vs 20%).

Preserving Renal Function in Patients With Diabetes

Diabetic nephropathy is the most common cause of ESRD in the United States, accounting for 35% of all cases. Race is an important predisposing factor for the development of diabetic nephropathy: Australian aborigines, Polynesians and Maori, African and Native Americans, and Hispanics with type 2 diabetes are at a significantly higher risk for development of ESRD, compared with whites with type 2 diabetes. In patients with diabetes, both hyperglycemia and hypertension are independent risk factors for renal disease, and both should be controlled; however, tight control of BP has proven more beneficial than tight control of glucose in this population. Evidence is mounting that timely intervention can ameliorate the onset and course of diabetic nephropathy. However, the impact of intervention is greatest when instituted at the earliest point in the course of this complication, that is, at the stage of microalbuminuria. For this reason, patients with diabetes should be screened for microalbuminuria at least annually.

The appropriate BP target for all patients with diabetes is <130/80 mm Hg. The RAS-blocking agents have been shown to have favorable effects on cardiovascular and renal outcomes in patients with diabetes with or without nephropathy. Thus, a RAS-blocking agent should always be included in the antihypertensive regimen for all diabetic patients. Therapy with an angiotensin-converting enzyme (ACE) inhibitor has been shown to reduce the incidence of new-onset nephropathy, compared with placebo, whereas angiotensin receptor blockers (ARBs) have proven beneficial in slowing the progress of renal disease in patients with diabetic nephropathy and in reducing albuminuria in patients with diabetes and microalbuminuria.

In head-to-head comparisons, ACE inhibitors have proven superior to CCBs with respect to coronary event outcomes in patients with hypertension and diabetes. However, in one of these trials, Fosinopril versus Amlodipine Cardiovascular Events Randomized Trial (FACET), the combination of an ACE inhibitor and a CCB led to improved clinical outcomes compared with either component, and for several reasons may be a useful regimen in diabetic patients. This combination avoids the potential metabolic changes commonly associated with thiazide diuretics and β-blockers, and provides RAS blockade along with sufficient BP lowering for this high-risk population.

Preserving Renal Function in African Americans

It is notable that the major cause of death in the African American population is CVD, and both diabetes and nephritis are among the 10 leading causes of death among U.S. blacks. Almost one in three African Americans has high BP, and when compared with whites, African Americans are far more likely to develop CKD and ESRD. The burden of kidney failure caused by hypertension in African Americans is striking, with a rate 20 times higher among African Americans aged 25 to 44 years than among whites in the same age group. Furthermore, African Americans comprise 12% of the total U.S. population, but 33% of all dialysis patients.

The markedly greater prevalence of ESRD and hypertension among African Americans is clearly related to both biological and environmental factors. Some of the proposed biological factors that may differ among various ethnic groups include the relative influence of plasma renin activity, vascular reactivity, sodium sensitivity, and expanded plasma volume on both BP and end-organ damage. However, the impact of environmental factors is clearly in evidence as well. The confluence of biological and environmental risk factors among African Americans, compared with white Americans, was well demonstrated in the Atherosclerosis Risk in Communities (ARIC) study. Among men and women not reporting use of potassium-depleting medications during study visits during 1990 to 1993, the prevalence of low dietary potassium intake, renal dysfunction, hypertension, hypokalemia, and low income were significantly greater in African Americans compared with whites. The prevalence of obesity was significantly higher among African American women, compared with white women, although the difference in rates of obesity among both groups of men was nonsignificant.

In NHANES data for 1999 to 2000, the prevalence of obesity was also found to be highest among non-Hispanic black women, compared with non-Hispanic white women.
and Mexican American women.\textsuperscript{37} American Heart Association\textsuperscript{38} data show that in 2001, black women had a prevalence of diabetes that was twice that of white women (9.5\% and 5.4\%, respectively), although the highest prevalence was reported for Mexican American women (11.4\%). Furthermore, the impact of some dietary factors (ie, high-calorie and low-potassium intakes) may have greater impact than that of others (ie, high-sodium and high-alcohol intakes). In the ARIC study, white participants had higher dietary sodium intake and greater alcohol intake compared with African American participants. Notably, this study found a significant relationship between ethnicity and unprovoked hypokalemia (serum potassium <3.5 mmol/L in the absence of a potassium-depleting medication) that was five times higher in African Americans, compared with white Americans, and that may be an important factor involved in higher rates of hypertension, stroke, and CKD.\textsuperscript{39}

The regimen for treating hypertension in all high-risk patients should include a RAS-blocking agent. This is an important consideration in the treatment of African American patients, who are often presumed to have “low-renin” hypertension, and thus to potentially derive less benefit from RAS-blocking agents. In fact, the perception that African Americans do not benefit from RAS blockade is incorrect. This misperception is primarily based on a large database from the Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents\textsuperscript{40} that showed a lesser BP-lowering effect with ACE inhibitor monotherapy in hypertensive black men compared with hypertensive white men. Although this observation is valid for antihypertensive agents used as monotherapy, these data are obsolete, as monotherapy is not the treatment of choice for hypertension in the majority of African Americans.\textsuperscript{41} The use of a RAS-blocking agent is equally important in the treatment of all patients with indications for their use, regardless of ethnicity.

The African American Study of Kidney Disease and Hypertension (AASK)\textsuperscript{42,43} was designed to look at the optimal drug regimen for African Americans with hypertensive renal disease (glomerular filtration rate [GFR] 20 to 65 mL/min/1.73 m$^3$). The AASK study recruited 1094 nondiabetic African Americans with hypertension and impaired renal function, who were randomized to one of three drug regimens (metoprolol-based, amloidipine-based, or ramipril-based) and to one of two BP target levels (mean arterial pressure of 102 to 107 mm Hg or <92 mm Hg). The population was about 40\% female with an average age of 55 years and an average baseline BP of approximately 151/96 mm Hg. The results of AASK clearly indicate that ACE inhibitors are associated with improved renal outcomes in this patient population. Of note, patients assigned to the lower BP target did not experience greater reduction of progression of their renal disease compared with those assigned to the “usual” BP target. The amloidipine arm was halted prematurely after analysis indicated a relative excess rate of ESRD and death, compared with ramipril, particularly in patients with \textgeq 300 mg/day urinary protein excretion.\textsuperscript{42} Perhaps most significantly, results from AASK confirm that baseline proteinuria is highly predictive of clinical outcome.

The Lotrel and Enalapril in African Americans with Diabetes (LEAAD) study\textsuperscript{44} was a multicenter, double-blind, 24-week study conducted in 269 African Americans with hypertension and diabetes. The purpose of LEAAD was to compare initial monotherapy with initial combination therapy in terms of how quickly BP goals can be achieved. This is particularly relevant in African Americans with diabetes, who should always have a RAS-blocking agent included in their regimen. The mean age of patients was 55 years, and the mean baseline BP was 151/96 mm Hg. After 24 weeks of treatment, systolic BP was reduced from baseline to a significantly greater extent with combination therapy (–20.6 mm Hg) compared with monotherapy (–13.9 mm Hg). Furthermore, 60\% of patients receiving initial ACE inhibitor/CCB combination therapy achieved the target BP, compared with 44\% of patients receiving initial ACE inhibitor monotherapy. As noted previously, ACE inhibitor monotherapy is unlikely to lower BP sufficiently in African Americans, particularly those with diabetes or renal disease, who should achieve a target BP of <130/80 mm Hg. Thus, initial combination therapy is the only route to achieving RAS blockade and adequate BP reduction.

In conclusion, prevention of CKD is best accomplished by identifying individuals with increased risk for this event. Groups at increased risk for CKD include those with diabetes, older patients with ISH, and African Americans. The key clinical tasks in preventing CKD and delaying the progress of CKD are: identifying and appropriate screening of high-risk individuals; lowering BP to <130/80 mm Hg in patients with CKD; using a BP regimen that includes a RAS-blocking agent; and using combination therapy to achieve BP goals expediently.

References


