Prevention of Hypertension and Its Complications: Theoretical Basis and Guidelines for Treatment

JOHN M. FLACK,* ROSALIND PETERS,† TARIQ SHAFI,‡ HISHAM ALREFAI,§
SAMAR A. NASSER,* and ERROL CROOK¶

*Department of Internal Medicine, †College of Nursing, and Divisions of ‡General Internal Medicine, §Endocrinology, and ¶Nephrology, Department of Internal Medicine, Wayne State University, Detroit, Michigan.

Abstract. Hypertension is a nutritional-hygienic disease. Long-term caloric intake in excess of energy expenditures, chronic supraphysiological intake of dietary sodium, excessive alcohol consumption, and psychosocial stressors all contribute to the development of hypertension throughout the world. Elevated BP, particularly systolic BP, has been linked to multiple adverse clinical outcomes including stroke, heart failure, myocardial infarction, renal insufficiency/failure, peripheral vascular disease, retinopathy, dementia, and premature mortality. These undesirable clinical outcomes are typically, although not invariably, preceded by pressure-related target-organ injury such as left ventricular hypertrophy, renal insufficiency and proteinuria. The relation of BP and CKD and, in turn, the prevention of CKD or forestalling its progression by hypertension treatment, will be the focus of this manuscript. In hypertensive persons with reduced kidney function and/or proteinuria, lowering BP with multidrug therapy that is inclusive of pharmacologic modulators of the renin-angiotensin-aldosterone-kinin system is an effective strategy to forestall the progressive loss of kidney function. The totality of data support low therapeutic BP targets for persons with proteinuria >1 g/d. Nevertheless, in persons with CKD, even those with proteinuria below the dipstick positive level (approximately 300 mg/d or urine protein to creatinine ratio of 0.22), aggressive BP control also may be warranted because of the high risk of nonrenal cardiovascular disease. Multiple antihypertensive drugs will be required in the vast majority of patients with diabetes and/or reduced kidney function to attain BP goal. Renin-angiotensin system (RAS) modulator therapy is indicated among persons with diabetes mellitus and CKD. Available clinical data support the use of angiotensin receptor blockers in persons with type 2 diabetes and overt nephropathy for preservation of kidney function. Among persons with type 1 diabetes with or without overt nephropathy, type 2 diabetes without overt nephropathy and in nondiabetic CKD, the available clinical data support the use of angiotensin-converting enzyme inhibitors as the RAS modulator of choice. Low therapeutic target BP levels <130/80 mmHg in persons with type 2 diabetes mellitus also appear warranted based on available data mostly for reducing the risk of nonrenal cardiovascular disease and overall mortality.

Hypertension, like most cardiovascular conditions, is a nutritional-hygienic disease. The seeds of hypertension are rooted in physical inactivity, obesity, high caloric intake, and excessive dietary sodium intake as well as alcohol consumption. Genetic susceptibility to hypertension remains ill-defined; however, environmental exposures of gene-environment interactions can be favorably influenced by manipulation of lifestyle choices.

Prevention of hypertension-related complications such as reduced kidney function depends on population-wide control of known hypertension risk factors. Population-based hypertension prevention strategies would require widely implemented public health measures such as significant alterations to the food supply and effective strategies to significantly augment energy expenditure above current levels. The widespread failure in many countries to implement population-based public health approaches for hypertension/cardiovascular disease (CVD) prevention has heightened the importance of successful and efficient hypertension treatment strategies to prevent/forestall pressure-related complications and premature mortality.

Hypertension Risk Factors

Prolonged exposure to sedentary lifestyles and consumption of calories in excess of energy expenditures lead to a steep rise in BP, particularly systolic BP, with advancing age (1). Thus, the default approach in Western societies has been to rely on individuals, particularly high-risk or affected individuals, to voluntarily alter their lifestyle choices. Two hypertension risk factors, dietary sodium intake and obesity, will be highlighted because of their possible direct and substantive link not only to hypertension but to kidney disease as well.

Sodium. Daily requirements of dietary sodium for normal physiologic functioning, assuming normal kidney function, is less than 10 mmol of sodium per day. This amount, however,
is far less than the average daily intake in the United States as well as in many other countries (2). Among hypertensive African Americans, dietary sodium intake appears to be inversely related to education and household income and appears to exceed that of Caucasians (3,4).

A major focus of the influence of dietary sodium and its effect on cardiovascular disease has been on its pressor effect. Nevertheless, this does not completely characterize the mechanisms through which sodium causes cardiovascular-renal injury. Raising BP, particularly among persons who are overweight (5,6), and antagonizing the hypertensive effect of antihypertensives (ACE inhibitor > calcium antagonist) (7) are BP-related venues through which sodium causes target-organ injury. Sodium also can reversibly disrupt normal autoregulation of GFR, a mechanism that potentially exposes the glomerulus to inappropriately high systemic BP therefore predisposing to hemodynamic injury. There is also evidence that dietary sodium intake worsens proteinuria, especially among salt-sensitive persons (8,9) and, as well, increases left ventricular mass (10,11). Sodium also appears to be a direct vascular toxin. In experimental models sodium augments the production and release of vascular injury mediators such as TGF-beta (12). Sodium is also necessary for aldosterone to inflict fibrosis and scarring in target-organs (13).

**Obesity.** Obesity is a major risk factor for the two major causes of end-stage kidney disease (ESKD) in the United States—diabetes mellitus and hypertension. The major determinant of obesity in a given population appears to be energy expenditure over the long term that is less than habitual caloric intake. In the United States, African Americans, particularly women, are more obese than white women (14,15). Furthermore, African-American women residing in the southeastern United States have a significantly higher prevalence than African-American women residing outside this region (16,17). On average, within the United States, minority women are more likely to be obese than white women.

Obesity has been linked to raised BP (18,19), salt-sensitivity (5,6), as well as glucose intolerance (20,21), and dyslipidemia (22,23). In young adults, body size is the major determinant of left ventricular mass (24). In addition, obesity has been associated with higher levels of urinary protein excretion (25). There is emerging evidence that obesity may adversely affect kidney function possibly via activation of the local renin angiotensin and sympathetic nervous systems as well as by causing excessive renal sodium absorption, mesangial cell hypertrophy, matrix production, and glomerular hyperfiltration (26,27).

**BP and Kidney Disease**

**Epidemiology.** Epidemiological data have convincingly shown that BP is linked to CKD and proteinuria (28,29), and kidney disease-related mortality (30). The risk of ESKD, at least among African-American and white men, is inversely related to socioeconomic status and directly related to BP level (31). Approximately 85% of persons with CKD have hypertension. Also, persons with proteinuria superimposed on CKD have higher BP than persons with nonproteinuric CKD (32,33) and manifest an attenuated BP response to antihypertensive drug therapy (32,33).

**Physiological Basis for BP as a Mediator of Kidney Injury.** There is a compelling physiologic basis for the observations that sustained BP elevations cause CKD, as well as for the reasons that BP lowering slows the progressive loss of kidney function. A normal kidney can maintain a relatively constant GFR across a broad range of BP. This is termed renal autoregulation of the GFR. The glomerular afferent arteriole normally constricts when BP is high to prevent the transmission of systemic BP to the glomerulus. Conversely, when BP falls, the afferent arteriole dilates to stabilize GFR or to at least minimize its reduction. However, disordered autoregulation of GFR is known to occur in multiple clinical conditions such as diabetes mellitus, reduced renal mass, proteinuric kidney disease as well as during exposure to high levels of dietary sodium. For example, among persons with proteinuric kidney disease, systemic BP levels are high and are more efficiently transmitted to the glomerulus because of dysfunctional glomerular autoregulation. This is highly consistent with clinical studies showing that hypertensives, diabetics (types 1 and 2), and persons with CKD and proteinuria lose kidney function faster than those without proteinuria (32,35–40). Furthermore, proteinuria activates a multiplicity of cellular injury pathways that promote glomerulosclerosis and tubulointerstitial fibrosis (41–44).

When functioning kidney mass is reduced and global GFR falls, the hemodynamic stress on surviving glomeruli increase. One deleterious consequence of the increased hemodynamic stress is that intraglomerular pressure rises as a consequence of efferent arteriolar vasoconstriction coupled with afferent arteriolar dilation. The latter allows transmission of raised systemic BP into the glomerulus. Activation of the local renin angiotensin system constricts the efferent more than the afferent arteriole. These glomerular hemodynamic changes increase single nephron GFR in an attempt to maintain global GFR despite progressively fewer functioning nephrons. However, if these glomerular hemodynamic changes are sustained they will likely result in glomerular injury and an accelerated loss of kidney function over time.

**Evidence That BP Lowering Slows the Progressive Loss of Kidney Function**

**Type I Diabetes Mellitus.** Numerous studies in persons with type 1 diabetes mellitus (45–49) show that BP lowering, even without RAS modulator drugs, slows down the loss of kidney function. Another important consideration relates to the optimal treatment of patients with diabetic nephropathy. There is little controversy regarding the importance of RAS modulator therapy in persons with either type 1 or 2 diabetes mellitus. In type 1 diabetes mellitus with nephropathy and serum creatinine <2.5 mg/dl, there is very convincing evidence that the ACE inhibitor captopril, relative to placebo, reduces kidney disease progression as measured by changes in creatinine clearance and the incidence of ESRD (50). In this study, the risk of the composite primary endpoint of death, dialysis, and transplantation was reduced by 50%. Risk of doubling of serum
creatinine was reduced by 48% in the captopril group (P = 0.007). At present there are no corresponding clinical endpoint data available for angiotensin receptor blockers in persons with type 1 diabetes mellitus and nephropathy.

**Type 2 Diabetes Mellitus.** Multiple studies have shown the benefits of BP lowering on the preservation of kidney function (49,51). Other studies have shown that initial therapy with a multiplicity of antihypertensive drug classes—diuretics, beta-blockers, and calcium antagonists—reduce the risk of nonrenal CVD events compared with placebo (52–54). However, the major controversy in type 2 diabetes mellitus is whether ACE inhibitors or angiotensin receptor blockers provide optimal RAS modulator therapy. Another major question is not simply whether BP lowering is beneficial but rather how low should the minimal therapeutic target BP be set.

Two recently reported clinical trials in persons with type 2 diabetes mellitus and nephropathy showed the superiority of initial therapy with an angiotensin receptor blocker on the progressive loss of kidney function, proteinuria reduction, and first hospitalizations for heart failure relative to either initial treatment with amlodipine, a dihydropyridine calcium antagonist, and/or a treatment regimen containing neither an ACE inhibitor or an angiotensin receptor blocker (55,56). However, there was a trend toward higher stroke and nonfatal MI rates in the Irbesartan type II Diabetic Nephropathy Trial (IDNT) study with irbesartan, an angiotensin receptor antagonist, relative to amlodipine, a dihydropyridine calcium antagonist, despite similar levels of BP control and a more favorable effect of irbesartan on proteinuria.

The Hypertension Optimal Treatment (HOT) study was an important study that documented the benefits of low DBP targets among persons with type 2 diabetes mellitus (54). HOT randomized 50 to 80 yr old (mean age, 61.5 yr) hypertensives to one of three diastolic BP (DBP) targets: (1) ≤90, (2) ≤85, or (3) ≤80 mmHg. Initial therapy was with felodipine, a dihydropyridine calcium antagonist, followed by add-on therapy with an ACE inhibitor or beta-blocker, and last, a diuretic to attain the DBP target. In persons with type 2 diabetes over an average 3.8 yr, major cardiovascular events were incrementally lower 24.4, 18.6, and 11.9 per 1000 patient-years (P = 0.005) in highest to lowest DBP target groups, respectively. Likewise CVD mortality was lower with more aggressive therapy being 11.1, 11.2, and 3.7 per 1000 person-years (P = 0.016) in highest to lowest DBP target groups, respectively. The trend toward lower total mortality was in the same direction but did not attain statistical significance (P = 0.068).

A subgroup analysis of the Captopril Prevention Project (CAPP) found that persons with diabetes mellitus experienced 41% fewer composite primary events (myocardial infarction [MI], stroke, or cardiovascular death) than persons taking conventional therapy with diuretics or beta-blockers (57).

The data available for ACE inhibitors in persons with type 2 diabetes and nephropathy are less well developed (lack of clinical endpoint data) compared with those available for angiotensin receptor blockers. On the other hand, data support the use of ACE inhibitors among persons with type 2 diabetes mellitus without nephropathy. Data from persons with diabetes mellitus in the HOPE study were recently reported showing significant reductions in microvascular and macrovascular clinical events including the need for coronary revascularization with ramipril, an ACE inhibitor, compared with placebo, in persons with type 2 diabetes mellitus without nephropathy (58). The composite endpoint of MI, stroke, or death was lowered by 25% with ramipril (P = 0.0004) and the development of overt nephropathy was decreased by 24% (P = 0.027).

Two recent reports from the Appropriate BP Control in Diabetes (ABCD) trial provided support for low therapeutic BP targets in persons with type 2 diabetes, although not for preservation of kidney function (59). Some 470 persons with type 2 diabetes and hypertension (DBP ≥90 mmHg) were followed for an average of 5.3 yr. Participants were randomized either to intensive (DBP goal <75 mmHg) or moderate (DBP goal 80 to 89 mmHg) BP targets. Mean BP achieved in the two groups were 132/78 and 138/86 mmHg, respectively. Nisoldipine, a dihydropyridine calcium antagonist, was also compared with an ACE inhibitor, enalapril. There were no differences in the progression of nephropathy, retinopathy, or neuropathy between the intensive or moderate BP goals or between the nisoldipine and enalapril treatment arms. Nevertheless, total mortality was lower 5.5% versus 10.7% (P = 0.037) in the intensively treated group with target DBP <75 mmHg. In this same trial (60), normotensive (BP <140/90 mmHg) persons with type 2 diabetes controlled to 128/75 mmHg had less progression of normoalbuminuria to microalbuminuria and of microalbuminuria to overt albuminuria, fewer strokes, and less progression of diabetic retinopathy than those controlled to 137/81 mmHg. Again, there were no differences in clinical outcomes between the ACE inhibitor and the calcium antagonist.

**Nondiabetic Kidney Disease.** An important study in this regard is the Modification of Diet in Renal Disease Study (MDRD) in 585 persons with directly measured GFR between 13 to 55 ml/min per 1.73 m² aged 18 to 70 yr who were randomized to either a low goal BP (mean arterial pressure (MAP) ≤92 mmHg) or a usual goal BP (≤107 mmHg); these respective goals were adjusted upward for persons ≥61 yr of age to MAP ≤98 mmHg or ≤113 mmHg (34.61). Actual attained MAP in the low and usual BP groups was 93 and 97.7 mmHg, respectively, over the mean follow-up of 2.2 yr. No particular hypertension drugs were emphasized. Note that randomized to the low BP goal was not linked to an increase in adverse events or safety issues. The benefit of the low BP goal on slowing the decline in GFR was confined to persons with proteinuria >1.0 g/d. Nevertheless, despite the lack of benefit in the overall cohort on the decline in GFR, an important observation was made regarding overall hospitalizations. That is, higher on-treatment systolic but neither diastolic or MAP was associated with a greater risk of hospitalization during follow-up. The rate of hospitalizations was 9% per annum in the lowest on-treatment SBP quartile (<119 mmHg) and rose incrementally to 19.3% in the highest quartile (>138 mmHg). Hospitalizations in relation to DBP trended directly opposite of that for SBP. Hospitalizations were highest in the lowest DBP...
Pooled clinical endpoint data are available among persons with nondiabetic kidney disease showing the superiority of ACE inhibitors over non-ACE–containing regimens for the prevention of ESKD. In a meta-analysis reported by Giatritis and co-workers (62) the risk reduction for ESRD with ACE containing regimens versus non-ACE–containing treatments was 30% (95% CI, 0.51 to 0.97). No effect on mortality was observed. Patients taking ACE inhibitors did, however, experience greater BP lowering by approximately 5/1 mmHg. The African-American Study of Kidney Disease (AASK) recently reported that among African Americans with nondiabetic CKD, ramipril, an ACE inhibitor, was superior to a regimen that initiated therapy with either amloidipine, a dihydropyridine calcium antagonist, or metoprolol, a beta-blocker, for slowing the loss of kidney function and prevention of kidney-related clinical events (32). Furthermore, AASK study trial results were consistent with a large body of clinical trial data in nondiabetic CKD in that the greatest relative superiority of the ACE inhibitor was among those with the highest levels of proteinuria (63). Also, note that only kidney-related but not overall cardiovascular events were reported in AASK and that there was virtually no difference in BP lowering in the amloidipine and ramipril treatment arms (5). Clinical endpoint data for angiotensin receptor blockers in persons with nondiabetic kidney disease are not available. However, these agents will likely be the logical alternative RAS modulator for ACE-intolerant patients.

Goals of Antihypertensive Therapy in Persons with Reduced Kidney Function and/or Diabetes. The overall goals of antihypertensive therapy are to lower both systemic and intraglomerular BP. Lowering systemic BP can, but does not invariably reduce intraglomerular pressure. However, angiotensin converting enzyme inhibitors and angiotensin receptor blockers will lower intraglomerular pressure in a manner that is not directly dependent on reducing systemic BP (64,65). A logical third goal of therapy is to reduce urinary protein excretion. Lowering BP and use of RAS system modulating drugs will reduce urinary protein excretion. Other strategies to lower urinary protein excretion include dietary sodium restriction (66,67) as well cessation of cigarette smoking (68,69) and weight loss (70,71). Reductions in urinary protein excretion correlate with slower loss of kidney function (32,34,63). The clinician should be aware that attainment of low target BP levels (<130 to 135/80 to 85 mmHg) will be accomplished only with prescription of multiple (typically 3 to 4), not solitary, antihypertensive drugs (72).

BP control rates are poor for persons with diabetes and reduced kidney function. Coresh and co-workers (73) reported data from the NHANES III survey showing that only 11% of persons with serum creatinine ≥1.6 mg/dl (men) or ≥1.4 mg/dl (women) had BP <130/85 mmHg; only 27% had BP <140/90 mmHg; and an astounding 48% were prescribed only one antihypertensive drug. Hypertension control rates for persons with diabetes from the same NHANES III survey were similarly low. Only 12% of diabetics had BP <130/85 mmHg although 45% had BP <140/90 mmHg (74). Thus, these two high-risk populations have woefully inadequate BP control.

Kidney Function and RAS-Modulating Drugs
Angiotensin converting enzyme inhibitors or angiotensin receptor blockers have been recommended as initial therapy for patients with diabetic and nondiabetic kidney disease (72,75–77). When BP is lowered even without RAS modulators, but even more so when these agents are used, GFR often falls—at least initially. Furthermore, the initial decline in GFR appears to be more pronounced among persons with proteinuric kidney disease (32). This loss of GFR is attributable to disordered autoregulation of the GFR when systemic and/or intraglomerular pressure fall. This rise in creatinine after administration of RAS modulating drugs may cause the clinician to unjustifiably discontinue indicated treatment, especially if the creatinine stabilizes at a level higher than baseline. Consideration should be given to either reducing the RAS modulator drug dose or discontinuation when the rise in creatinine exceeds 30% or hyperkalemia develops (78). Diuretic-induced intravascular volume depletion is the most common avoidable reason for the rise in creatinine. Some data suggest that angiotensin receptor blockers may elevate the potassium less than angiotensin converting enzyme inhibitors among persons with EGFR <60 ml/min per 1.73 m² (72). Thus, the clinical conditions for which RAS modulator drugs are indicated also predispose to creatinine elevations when systemic and/or intraglomerular pressure fall because autoregulation of GFR is abnormal.

Summary
Persons with CKD, whether diabetic in origin or not, need aggressive BP control and use of RAS modulator drugs. Interestingly, the logic for low BP targets in some high risk populations such as persons with diabetes mellitus or CKD, may not always be preservation of kidney function but rather for reductions in nonkidney-related cardiovascular risk, fewer hospitalizations, and lower total mortality. Thus, treatment recommendations and clinical decisions for these high-risk patients should take into account global CVD risk not just kidney-related target-organ complications. Finally, the optimal RAS modulator drug class will depend on the type of CKD and, among persons with diabetes, the stage of nephropathy.

References


60. Sanchez RA, Traballi CA, Marco EJ, Gilbert BH, Ramirez AJ, Long G: Effects of ACE inhibition on renal haemodynamics in

Copyright © American Society of Nephrology. Unauthorized reproduction of this article is prohibited.
76. Standards of Medical Care for Patients with Diabetes Mellitus, Position Statement 2002