Hypertension affects almost 50 million people in the United States. Although the threshold of elevated blood pressure (BP) traditionally has been 140/90 mm Hg, recent recommendations for high-risk patients, such as those with kidney disease, heart failure, coronary artery disease, diabetes mellitus, and heavy proteinuria, target BP levels well below 140/90 mm Hg. In this article, the special populations of children, pregnant women, African-Americans, kidney disease patients, post-transplantation patients, and individuals with diabetes mellitus are discussed. Emphasis is placed on unique aspects of the epidemiology, diagnostic criteria, and therapeutic approaches.

Children

Epidemiologic studies have identified a link between elevated BP in childhood and hypertension in adults [1–3]. In addition, obesity, a major risk factor for hypertension among children and adults, has dramatically increased in prevalence over the last three decades according to the Centers for Disease Control and Prevention (CDC) [4]. The definition of hypertension is based on the age- and gender-specific distribution of BP in healthy children, clinical experience, and clinical consensus [5,6].

Blood pressure measurement

Children 3 years of age and older should have their BP measured at least twice and averaged, after a 5 minute rest, using the standard clinical sphygmomanometer, preferably in the right arm, with the stethoscope placed over the brachial artery approximately 2 cm above the cubital fossa [6]. Previously, diastolic BP (DBP) was determined by K₄ ("muffling") in children 12 years of age or younger and K₅ (disappearance of sound) in children 13 years of age and older [6,7]. An important change in the National High Blood Pressure Education Program (NHBPEP) 1996 update on the 1987 task force recommendations is that the fifth Korotkoff sound be used for all children, regardless of age [6]. In infants and children younger than 3 years of age Doppler ultrasound or oscillometric automated devices are more practical measurement modalities [6,8]. Ambulatory BP monitoring is predominantly a research tool in children because of a lack of standards in childhood despite some encouraging data regarding its benefits in detecting and managing childhood hypertension [9,10].

Etiology of hypertension in children

Primary, or essential hypertension, which refers to elevated BP without evident cause, is a diagnosis
that should not be applied in children until other potential causes have been excluded. Secondary hypertension is much more prevalent in children than among adults with hypertension. Therefore, attention must be given to identifying underlying disease processes contributing to the elevated BP.

Secondary hypertension occurs in 85% to 90% of all children with elevated BP. Renal artery obstruction secondary to thrombosis from umbilical artery catheterization is the most common cause of neonatal hypertension. Bronchopulmonary dysplasia, patent ductus arteriosus, and intraventricular hemorrhage are associated with neonatal hypertension [11]. Underlying renal disease is the most common cause of secondary hypertension in children younger than 13 years of age and is responsible for 70% to 80% of all cases of secondary hypertension in children [5,12]. Hypertension complicates almost 80% of all cases of acute post-streptococcal glomerulonephritis [5,12]. Chronic glomerulonephritis, reflux nephropathy, and renal artery stenosis are other renal causes of secondary hypertension in prepubertal children.

Coarctation of the aorta is the most common nonrenal secondary cause of hypertension, occurring in 5% to 15% of all cases of secondary hypertension in children [5]. Coarctation of the aorta, hyperthyroidism, and patent ductus arteriosus have been linked to isolated systolic hypertension, an uncommon BP phenotype in children [13]. Endocrinopathies—hyperthyroidism, hypercalceemia, adrenal cortical hyperplasia, or increased catecholamine production due to a pheochromocytoma—also must be considered as potential causes of elevated BP in children. Oral contraceptive use should be considered as a potential cause of elevated BP in adolescent girls. In older children, ingestion of sympathomimetics such as cocaine, amphetamines, or pseudoephedrine should be considered, particularly when there is concurrent evidence of sympathetic nervous system overactivity.

Primary or essential hypertension is rarely found in children younger than 10 years of age but is more frequent in later childhood and adolescence. Primary hypertension accounts for about 10% to 15% of all cases of hypertension in prepubescent children, but information regarding its incidence and overall prevalence in later childhood is lacking [12,14].

Body size is a major determinant of BP among children [6], with obesity being a major modifiable risk factor for essential hypertension in children.

According to data from the National Health and Nutrition Examination Survey III (NHANES), 13% of children age 6 to 14 years and 14% of adolescents aged 12 to 19 years are overweight. This is double the number in NHANES II (1976–1980) and nearly triple the number who were overweight prior to 1976 [4].

In contrast to adults, among children there are minimal differences in BP between African-Americans and whites. A review of eight large epidemiologic studies in children and adolescents (N = 47,196) found few substantive differences in either systolic BP (SBP) or DBP [15]. Other risk factors such as low birth weight and exposure to environmental lead may predispose to development of premature onset hypertension. As with adults, socioeconomic status may be a factor in childhood hypertension especially as it relates to dietary and exercise patterns, probable body size, exposure to environmental toxins such as lead, and access to as well as utilization of health care.

**Diagnostic evaluation**

Patient history should include attention to measures of growth and development (e.g., failure to thrive, precocious puberty, delayed secondary sexual development), dietary intake, physical activity, recurrent urinary tract infections, exposure to nephrotoxic drugs (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], amphetamines, cocaine), and oral contraceptive use in girls. Family history of premature onset of hypertension, with or without early onset hemorrhagic stroke, is suggestive of glucocorticoid remedial aldosteronism (GRA). The physical examination should include abdominal assessment for flank masses or abdominal bruits, thyroid bruits, and comparison of lower extremity BP with arm BP as a screen for coarctation of the aorta.

For obese children with mild hypertension (at or just above 95th percentile) and a family history of hypertension, the NHBPEP guidelines recommend few diagnostic studies beyond urinalysis, blood urea nitrogen, and serum creatinine levels. Others have recommended additional studies such as uric acid and lipid levels [5,12]. Pregnancy tests should be considered for adolescent girls. When BP elevations are severe, priority is given to detailed assessment of the kidney anatomy and functioning, because as many as 80% of the children with hypertension have kidney parenchymal disease [5]. The plasma aldosterone:renin ratios as a screening test for mineralocorticoid hyperten-
sion may be useful in selected cases. Elevated urinary 18-hydroxycorticosteroid excretion and/or genetic testing for the chimeric 11-beta-hydroxylase-aldosterone synthase gene can make the diagnosis of GRA. The serum metanephrine : creatinine ratio is a useful screening test for suspected pheochromocytoma. Echocardiograms are helpful in the diagnosis of coarctation of the aorta and can also show a left ventricular mass/hypertrophy.

Treatment of childhood hypertension

Weight reduction and aerobic exercise are recommended for children with BP levels at the 90th percentile or higher [5,12,13]. Results of low sodium diets have been mixed [16–18], and potassium supplementation does not appear to lower BP effectively in children [19,20]. Nevertheless, dietary sodium intake in the United States far exceeds recommended physiologic requirements; thus, a reduction in dietary sodium is advisable. Aerobic exercise is an important adjunct to weight loss and BP reduction and can be safely instituted in asymptomatic children with uncomplicated hypertension. If there is insufficient response to lifestyle interventions, or if the child has severe hypertension, then antihypertensive drug therapy should be considered. The goal is to reduce the BP to below the 95th percentile [6]. Angiotensin-converting enzyme (ACE) inhibitors, β-blockers, diuretics, and calcium antagonists are options for initial therapy. ACE inhibitors and angiotensin receptor blockers may be particularly useful in children with kidney disease but, because of their teratogenic effects (after the first trimester), these drugs should be used with extreme caution in older girls who may be sexually active [6]. β-blockers may reduce exercise tolerance in physically active children and also can cause bronchospasm in patients with reactive airway disease [5,14]. Nevertheless, there is a lack of long-term outcome studies on the effects of antihypertensive drug therapy initiated during childhood [6].

Pregnancy

Hypertension is an important cause of maternal and fetal morbidity and mortality and complicates 6% to 8% of all pregnancies [21]. Severe, adverse complications of hypertension in pregnancy are cerebral hemorrhage, disseminated intravascular coagulation, hepatic failure, acute renal failure, and abruptio placentae. The underlying cause of the elevated BP appears to be more important to the pregnancy outcome than the elevated BP per se.

BP readings should be taken in the seated position at heart level with an appropriately sized cuff. Measurement of BP in the left, lateral recumbent position is no longer recommended as BP measurement in this position can produce spuriously low readings [22]. DBP should be reported as Korotkoff Phase V sound [21], as more recent work indicates that K5, not K4, is closer to the true DBP [23–25]. Although ambulatory BP monitoring has been used increasingly in pregnancy [26], its role in the routine management of pregnant women remains to be established.

Blood pressure in normal pregnancy

Profound changes in circulatory physiology occur during pregnancy. Peripheral resistance decreases by 25%, blood volume increases by approximately 50% by the end of the second trimester, and cardiac output increases by about 35% to 50% above nonpregnant values during the first trimester [27,28]. Also, renal blood flow and the glomerular filtration rate rise significantly, and the renin-angiotensin-aldosterone system is activated, although there is resistance to the vasoconstrictive effects of angiotensin II [29]. The result of these changes is that first BP falls, with diastolic BP averaging 10 mm Hg lower than nonpregnant values by midtrimester, and then increases slowly to nongravid levels during the third trimester [30].

Classification of hypertension

The US NHBPEP advocates the use of four categories: chronic hypertension; preeclampsia-eclampsia; preeclampsia superimposed on chronic hypertension; and gestational (transient) hypertension. Chronic hypertension is defined as elevated BP (SBP ≥ 140 and/or DBP ≥ 90 mm Hg) that was either present prior to conception or was detected before the 20th week of gestation and does not resolve after delivery. Preeclampsia-eclampsia is a systemic syndrome characterized by hypertension occurring after the 20th week of gestation and is usually, though not invariably, accompanied by proteinuria. Eclampsia is the convulsive phase of the disorder. Preeclampsia superimposed on chronic hypertension has a prognosis that is much worse than for either condition alone and can cause severe maternal and fetal complications [21]. It can be difficult to distinguish superimposed preeclampsia from an exacerbation.
of chronic hypertension with underlying kidney disease. Nevertheless, it is better to err on the side of caution and overdiagnose pre-eclampsia rather than to miss it [21]. Superimposed preeclampsia hypertension is highly likely in previously hypertensive women who have a new-onset of proteinuria ($\geq 0.3$ g protein in 24-hour urine specimen); in women with hypertension and proteinuria before 20 weeks’ gestation; a sudden, precipitous increase in BP ($>30$ mm Hg systolic or $>15$ mm Hg diastolic) in women with previously controlled hypertension; thrombocytopenia ($<100,000$ cells/mm$^3$) or abnormal alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels [21].

Gestational (transient) hypertension, a relatively benign condition, is elevated BP occurring without proteinuria with onset late in pregnancy or the early puerperium that resolves within 12 weeks of delivery.

**Management of chronic hypertension in pregnancy**

Generally, neither maternal nor fetal risks are increased in uncomplicated mild chronic hypertension. Most of the increased risk is associated with severe hypertension (50% fetal loss for women with stage III hypertension) [31] or preeclampsia superimposed on the chronic hypertension [32]. There is some evidence that antihypertensive drug treatment may forestall progression to severe hypertension during pregnancy [33,34]; however, one retrospective study did not find that antihypertensive medications reduced the frequency of superimposed preeclampsia, preterm delivery, or abruptio placentae in treated versus untreated women [35], and there is no evidence that drug therapy improves neonatal outcomes [21]. Women with chronic hypertension may paradoxically experience an exaggerated fall in BP during the first two trimesters, which may permit discontinuation of their antihypertensive medication; however, antihypertensive therapy should be restarted if BP reaches 150 to 160 mm Hg systolic and/or 100 to 110 mm Hg diastolic [21].

**Antihypertensive medications during pregnancy**

Medication choices in pregnancy are more limited because of their potential teratogenic effects and the lack of randomized clinical trials in pregnant women. Many studies have initiated antihypertensive drug therapy in midgestation after the greatest risk of significant fetal deformity had passed. Thus, there are a small number of drugs qualifying for the Food and Drug Administration’s Category A designation [36].

Methyldopa, a central adrenergic inhibitor, is the drug of choice for initial therapy in pregnancy. In addition to its long history of safety and effectiveness, it has been prospectively evaluated in randomized trials, including one 7-year follow-up of the children exposed in utero [37–39]. Hydralazine is the vasodilator of choice in acute hypertensive crises and also has been used successfully in the management of chronic hypertension. Calcium antagonists, particularly nifedipine, appears to be an effective, safe antihypertensive agent. Beta blockers are second line drugs and are mostly used late in pregnancy and have been linked to fetal growth retardation [40]. Alpha blockers are not recommended except in the rare case of hypertension secondary to pheochromocytoma [36]. Diuretics are not recommended as first-line therapy [21]. These agents may attenuate the normal increase in blood volume to normal pregnancy levels and therefore may retard fetal growth. Nevertheless, a meta-analysis found diuretics to be safe and efficacious except in cases in which uteroplacental blood flow is already reduced [21]. Thiazide diuretics are primarily used when they have been initiated prior to pregnancy. Furosemide, a loop diuretic, should be avoided because of potential embryotoxicity [41]. There are little data on antihypertensive medications during lactation. Animal studies suggest that these drugs are excreted through breast milk, and short-term studies have not found adverse effects from methyldopa or hydralazine on infants. ACE inhibitors and angiotensin receptor blockers are contraindicated in pregnancy [21] because they are associated with growth restriction, oligohydramnios, irreversible fetal/neonatal renal failure, and neonatal death [21,42,43].

**Preeclampsia**

Clinicians should have a high index of suspicion for preeclampsia in women considered to be at greater risk for developing the condition. Risk factors include (1) nulliparity, (2) >40 years of age, (3) African-American race, (4) preexisting cardiovascular disease (CVD) (e.g., chronic hypertension, renal disease, diabetes mellitus), (5) multifetal pregnancy, (6) family history of pregnancy-induced hypertension, (7) previous preeclampsia if a multipara, (8) increased body size, and (9) higher prepregnancy level of SBP, DBP, or both.
**Pathophysiology of preeclampsia**

Preeclampsia is a pregnancy-specific, multisystem disorder with both maternal and fetal manifestations that can be life-threatening even in the setting of modest BP elevations. Plasma volume is reduced, which can lead to decreased regional perfusion and hemoconcentration. Abnormal vascular responses appear to be related to increased sensitivity to pressor substances (eg, AII and endothelin), decreased endogenous vasodilators, and cytokine-induced endothelial cell damage [44]. Organ-selective vasoconstriction resulting in widespread microvascular cerebral changes and ischemia within the brain, not just the BP elevation per se, are believed to cause the seizures. Thrombocytopenia, probably attributable to platelet aggregation and deposition at sites of endothelial damage, has been observed [45]. Renal blood flow, glomerular filtration rate, and serum uric acid clearance all are reduced. Serum urate levels also may be elevated [21]. Liver injury as evidenced by elevated serum enzymes (aminotransferase and lactate dehydrogenase) or the HELLP syndrome (hemolysis, elevated liver enzymes, low platelets) may be present.

**Management of preeclampsia**

Virtually all interventions are designed to protect the mother while allowing time for fetal maturity and cervical ripening. Although delivery cures preeclampsia, its effect is not immediate and women remain at risk for continuing problems such as seizures up to 5 days postpartum. Hypertension and proteinuria may not remit for weeks. Nonpharmacologic interventions for preeclampsia include restricted physical activity. Close maternal and fetal surveillance is required. Initial in-patient management and evaluation is usually advisable [21]; however, home care and outpatient management may be acceptable for a select group of patients with mild preeclampsia who are remote from term [46–48]. Pharmacologic interventions for preeclampsia include antihypertensive and antiseizure medications. There are data that do and others that do not support the use of calcium supplementation [49,50], antihypertensive medication [39,51], and aspirin [52–54] for the prevention of preeclampsia [21]. Magnesium sulfate is effective in reducing the incidence of eclampsia in women with severe preeclampsia [55]; however, in women treated with calcium antagonists, precipitous falls in BP may occur after administration of magnesium sulfate [21].

**African-Americans**

African-Americans, as a group, have an earlier onset of hypertension, higher age-adjusted hypertension prevalence, and more BP-related target-organ damage (ie, left ventricular hypertrophy, kidney disease) than age- and sex-matched whites [56,57]. The relative race differential in hypertension prevalence is most pronounced among those with the highest BP levels—almost 9% of African-Americans but fewer than 1% of whites having Joint National Committee (JNC) stage 3 hypertension (≥180/110 mm Hg). An important point of emphasis, however, is that most differences in hypertension and pressure-related complications between African-Americans and whites appear to be quantitative not qualitative. That is, there is a higher burden of hypertension and pressure-related complications among African-Americans compared to whites. The relationship of BP to demographic characteristics such as age and to CVD-renal endpoints over a wide range of BP, however, is remarkably similar [57,58]. Among African-Americans, hypertension accounts for a greater proportion of the overall mortality burden than it does in the white population. Nevertheless, in NHANES-1, the SBP logistic regression coefficient for total mortality was similar among African-American and white men but was slightly higher in white women than African-American women [59]. Additional analyses from this same longitudinal data set showed the higher relative risks of death associated with an SBP ≥140 mm Hg in African-Americans relative to whites was attributable to the greater prevalence of African-Americans with BP levels at or above this SBP level. The excess hypertension prevalence, in turn, accounted for 10% of the African-American mortality excess. Finally, heterogeneity in the risk for hypertension [60], the response to antihypertensive drug therapy [61], and the occurrence of pressure-related complications such as stroke [62,63] and kidney disease [64] have been described within race and ethnic groups when these groups have been stratified either by geography, socioeconomic status, or dietary habits. These within-race differences are typically larger than previously described inter-race differences in these same outcomes.

**Treatment**

There appears to be no compelling reason(s) to believe that drug selection for African-Americans differ from other race or ethnic group unless
dictated by clinical characteristics that can vary at the individual level. Therapeutic recommendations for African-American patients typically have been guided by overreliance on whether initial monotherapy with diuretic and calcium antagonist lowered BP more than other drug therapies such as ACE inhibitors and beta blockers. This therapeutic paradigm is flawed for at least two reasons. First, in trials in which diuretics and calcium antagonists have lowered BP more than other drugs, say ACE inhibitors, the average attained BP in all of the treatment groups typically remained significantly above 140/90 mm Hg. Accordingly, typically three to four drugs are needed to attain low therapeutic BP targets in high-risk hypertensive patients. Second, the “only BP matters” therapeutic paradigm ignores the fact that antihypertensive drug therapy has been shown to protect target organs and reduce clinical events over and above what realistically can be attributed to BP lowering [65–67].

Another issue has been the utilization of known/perceived racial (group level) differences that are extrapolated in blanket fashion to virtually all individuals in that group. Known or perceived pathophysiologic tendencies in hypertensive African-Americans have led to overinterpretation of differences in BP responsiveness of African-Americans and whites to drugs with their primary locus of action on the renin-angiotensin-aldosterone kinin (RAAK) system. For example, hypertensive African-Americans more so than whites manifest suppressed circulating renin activity. Many hypertensive African-Americans, however, have normal to high circulating renin activity. In addition, hypertensive African-Americans compared to whites do not appear to be plasma volume expanded [68]. Also, the control of renin secretion is complex and is not necessarily linked to plasma volume expansion in African-Americans with hypertension [69].

The linkage of lesser average BP responsiveness in African-Americans relative to whites to drugs primarily affecting the RAAK system because of the tendency toward suppressed circulating renin activity is flawed on several accounts. First, the implicit assumption that African-Americans and white hypertensive study volunteers are similar is often incorrect. Prior to randomized treatment assignment in clinical trials, racial differences often exist—including different distributions of BP levels, different duration of BP, differences in smoking status, and kidney function—all of which potentially confound the observed BP response differentials. These differences are rarely, if ever, adjusted for in the contrasts of BP responses between African-Americans and whites. Furthermore, racial contrasts on BP response are virtually always post hoc comparisons of convenience samples that are outside the usual protections (ie, balancing of confounders) of the randomization procedure. Second, the differences in BP response, for example with ACE inhibitors, are most prominent at relatively low doses and either diminish markedly or disappear altogether with titration of the drug dose into the middle or upper part of the dosing range [70,71]. Third, relatively smaller differences in mean BP responsiveness between African-American and white hypertensive patients have inexplicably overshadowed the much greater heterogeneity of BP response within racial groups. Moreover, some African-Americans have greater reduction in BP than whites to drugs such as ACE inhibitors and beta blockers despite that, on average, whites respond better at the group level. This paradox at the level of the individual occurs because the race-specific BP response distributions overlap each other. Finally, at least with ACE inhibitors, the pretreatment renin level does not predict BP response in African-Americans [72]. Thus, the totality of evidence provides compelling, albeit to a degree circumstantial, rationale against the long-held treatment paradigm of avoiding antihypertensive agents that primarily act on the renin-angiotensin system on the presumption of lack of efficacy in either BP lowering or target-organ protection. Data from the ongoing ALLHAT trial [73] will likely provide even more answers regarding relative benefits of antihypertensive drugs, attained BP levels, and modifiers of these effects in African-American hypertensive patients.

The recent interim analysis of the African-American Study of Kidney Disease (AASK) trial provides important insights regarding the therapeutic selections and clinical characteristics influencing preservation of kidney function in African-Americans who have reduced kidney function attributable to hypertensive nephrosclerosis [74]. AASK was a 3 × 2 factorial design trial that randomized 1094 African-Americans with glomerular filtration rates (GFR) between 20 and 65 mL/min/1.73 m² to treatment with amlo-dipine (n = 217, 5–10 mg/d), ramipril (n = 436, 2.5–10 mg/d), or metoprolol (n = 441, 50–200 mg/d) with a usual mean arterial pressure (MAP) goal of 102 to 107 mm Hg or to a low MAP goal of ≤92 mm Hg. Unblinded drug therapy was se-
The primary trial outcome was the rate of change in GFR and the main secondary outcome was the composite of a reduction in GFR >50% or 25 mL/min/1.73 m², end-stage renal disease (ESRD), or death. After the initial 3 months of the trial, BP averaged 134.5/82 (MAP = 99.8) and 132.9/81.4 (MAP = 98.8) mm Hg, respectively, in the ramipril and amlodipine treatment arms. Each group took an average of 2.75 drugs.

Although there was no difference among the treatment groups in the mean change in GFR over 3 years, compared to the amlodipine treatment arm, ramipril had a 36% slower decline in GFR after 3 months (P = 0.002) and a 38% lower risk of the composite clinical endpoint (P = 0.005), and less proteinuria (P < 0.001). These observations were accentuated in participants with urinary protein:creatinine ratio >0.22 (~300 mg/dl). Over the entire 3 years the ramipril group had a 2.02 mL/min/1.73 m² slower mean decline in GFR (P = 0.006) and a 48% lower risk of the composite clinical endpoint. GFR remained higher over the 3 year follow-up in the amlodipine arm in participants with baseline urinary protein:creatinine ratio ≤0.22 and among persons with baseline GFR ≥40 mL/min/1.73 m².

What is the clinical meaning of these results? First, these data confirm the previously reported benefits [75] in other populations of pharmacologic targeting of the RAAK system with ACE inhibitors in patients with reduced kidney function. In fact, AASK provides the first such tangible data to support of the previous speculations that we have previously put forth [76]. The relative superiority of the ACE inhibitor as initial therapy in African-Americans with kidney disease is somewhat ironic given the long held belief that calcium antagonists were preferred antihypertensive agents for African-Americans. This widely held treatment paradigm existed because among individuals treated with monotherapy, calcium antagonists lowered BP, on average, more effectively than ACE inhibitors. Third, these data provide evidence in African-Americans that the drug selection paradigm should clearly move away from solely being based on BP lowering efficacy of antihypertensive drugs. It is reasonable to ask if monotherapy with amlodipine, and by implication other dihydropyridine calcium antagonists, is contraindicated in African-Americans and other persons with hypertensive kidney disease?

There are, we believe, two important caveats regarding the interpretation of this study. Amlodipine was used without simultaneous pharmacologic targeting of the RAAK system. Also, the in-study average BP levels remained relatively high despite prescription of almost three antihypertensive drugs. Although AASK could not directly address the impact of amlodipine with concurrent pharmacologic targeting of the RAAK system, in at least one other study the ACE inhibitor was superior as monotherapy to amlodipine, but the combination of the ACE inhibitor and amlodipine was even better [77,78]. Thus, until more data become available, a reasonable integration of the AASK data with the totality of evidence is that dihydropyridine calcium antagonists can be used in patients with kidney disease along with simultaneous pharmacologic blockade of the RAAK system. A further interpretation would be that aggressive BP lowering, even lower than that attained in AASK, should be the goal of therapy.

Kidney disease

Elevated BP commonly occurs in persons with kidney disease and, in turn, hypertension per se can cause a spectrum of mild-to-moderate kidney dysfunction that, if unabated, can ultimately result in ESRD and mortality attributable to kidney disease. Hypertension and diabetes mellitus are the two major causes of ESRD accounting for almost 60% of new ESRD cases per annum. ESRD rates are currently increasing 5% to 6% per annum. Type 2 diabetes mellitus has recently replaced hypertension as the primary cause of ESRD among African-Americans. Interestingly, obesity is a major risk factor both for hypertension and diabetes mellitus and, perhaps not coincidentally, has been linked to a multiplicity of changes in kidney neurohumoral and hemodynamic function that may contribute to the pathogenesis of kidney injury [79].

There are several important concepts for the practitioner who will be responsible for the care of patients with hypertension and kidney disease. First, the positive association of BP with risk of kidney failure and kidney disease mortality begins well within the so-called “normal” BP range [58,64]. Second, prospective pharmacologic BP lowering interventions with various combinations of antihypertensive drugs can slow the decline in GFR. BP levels as low as approximately 90 mm
Hg MAP have been shown to provide incremental protection against the loss of kidney glomerular filtration [80]. It is patently unrealistic to think of attainment of low therapeutic BP targets (<130/80–85 mm Hg) with antihypertensive monotherapy—combination therapy or “therapeutic cocktails” are the rule. The most recent BP target for persons with kidney disease [80] from the National Kidney Foundation (NKF) is <130/80 mm Hg. The DBP target is more aggressive than the <85 mm Hg target recommended in the JNC VI report.

There are almost 6 million persons with serum creatinine levels ≥1.6 mg/dL or ≥1.4 mg/dL in men and women, respectively [81]. Usually serum creatinine levels have been used in clinical practice to identify person with reduced kidney function; however, moderate kidney dysfunction (estimated GFRs <60 mL/min/1.73 m²) is easily missed, particularly in women, when relying solely on serum creatinine levels as an estimate of kidney function (Fig. 1). Arguably, the practitioner should be able to readily diagnose milder kidney dysfunction (estimated GFR 60–90 mL/min/1.73 m²). Unquestionably, the lack of recognition of moderate kidney dysfunction leads to uninformed clinical decision making. As a consequence, less than optimal therapeutic decisions are made, resulting in incomplete BP lowering and, ultimately, less than maximal preservation of kidney function. Box 1 displays the ways that lack of recognition of kidney dysfunction impedes optimal clinical decision making, therapeutic choices, and clinical outcomes. Importantly, the practitioner will set therapeutic BP targets higher than is recommended (<130/80–85 mm Hg) when kidney dysfunction (≤60 mL/min/1.73 m²) remains undetected, a frequent occurrence when the serum creatinine level is used as the primary indicator of kidney function.

<table>
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<table>
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Fig. 1. Agreement between serum crea and EGFR.

**Treatment**

Patients with elevated BP and reduced kidney function are less often controlled to their goal BP than persons without kidney disease [82]. In
addition, it is quite clear that multidrug therapy is required to achieve the low therapeutic goal BP levels. Diuretics are an indispensable component of the multidrug cocktail used to treat these patients, particularly when the patient is on more than two other antihypertensive drugs [83,84]. ACE inhibitors have been shown to slow the progressive loss of kidney function among people with either diabetic or nondiabetic kidney disease [85]. The protective effect appears to be most evident among persons with the most pretreatment proteinuria and the lowest level of kidney function [86,87]. These agents are profoundly antiproteinuric. Among individuals with milder reductions in kidney function, the risk of ischemic coronary and other cardiovascular events is significantly elevated. In the HOPE trial, individuals with serum creatinine ≥1.4 to 2.3 mg/dL and without dipstick proteinuria had greater risk for CVD death (11.4% versus 6.6%) and total mortality (17.8% versus 10.6%). Among these patients, CVD, all-cause mortality, and heart failure hospitalizations were increased by twofold in persons with kidney insufficiency compared to those without reduced kidney function. Treatment with ramipril, an ACE inhibitor, reduced risk of the combined primary study endpoint—CVD death, myocardial infarction, or stroke—by 20% (95% CI, −41%, +9%) among persons with kidney insufficiency [88]. There is emerging evidence that angiotensin receptor blockers provide similar kidney protection, at least in the setting of diabetic nephropathy. It should be remembered, however, that while drug selection is important, at the very minimum, the attainment of the goal BP also must be achieved to provide maximal protection against progressive loss of kidney function and to minimize nonkidney CVD sequelae.

**Therapeutic caveats**

Dietary sodium restriction is important because reduced kidney function leads to impaired natriuretic capacity. This combined with the use of vasodilator drugs can augment salt and water retention and, coupled with the relatively high amounts of sodium in the typical American diet, can lead to poor BP control and less than optimal reductions in proteinuria. Potassium-containing salt substitutes should be avoided in most patients with reduced kidney function. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) can further reduce glomerular filtration, leading to salt and water retention, poor BP control, and even a tendency toward hyperkalemia, especially when other drugs that impair potassium secretion, such as ACE inhibitors, heparin, potassium-sparing diuretics, and to a lesser degree, angiotensin receptor blockers, are used simultaneously. The use of diuretics is essential in patients with kidney disease. Selection of the appropriate diuretic, however, is not always easy. When the estimated GFR is 50 mL/min/1.73 m² or less, we avoid thiazide diuretics and use either zaroxolyn or furosemide. Furosemide, because of its short half-life, is most effective when used at least twice daily. Zaroxolyn is a long-acting drug and can be effectively dosed once daily.

**Kidney function changes with treatment**

To put these recommendations into practice, clinicians should not let predictable changes in kidney function prevent them from choosing and maintaining the most appropriate therapy for persons with reduced kidney function. If BP elevations, the reduction in kidney function, or both are severe, a reduction in BP after initiation of pharmacologic therapy, even if ACE inhibitors or angiotensin receptor blockers are not used, will likely cause a transient rise in creatinine. ACE inhibitors initially cause a measurable fall in GFR [74]; however, over the long term, these agents markedly slow the progressive loss in kidney function. Bakris and Weir [86], in their excellent review of the subject, point out that the major reason for a rise in creatinine after initiation of ACE inhibitor therapy is volume depletion attributable to overdiuresis. In persons with critical bilateral renal artery stenosis, the use of ACE inhibitors or angiotensin receptor blockers are not used, will likely cause a transient rise in creatinine. ACE inhibitors initially cause a measurable fall in GFR [74]; however, over the long term, these agents markedly slow the progressive loss in kidney function. Bakris and Weir [86], in their excellent review of the subject, point out that the major reason for a rise in creatinine after initiation of ACE inhibitor therapy is volume depletion attributable to overdiuresis. In persons with critical bilateral renal artery stenosis, the use of ACE inhibitors also can cause a rise in creatinine. This is an infrequent cause, however, of rising creatinine levels after initiation of ACE therapy. Angiotensin receptor blockers can cause both elevations in creatinine and hyperkalemia similar to the ACE inhibitors but are less likely to do so.

**Posttransplantation**

Hypertension is quite common after solid organ transplantation and is more likely to be present if BP was elevated before transplantation. In fact, the relationship of elevated BP with transplantation is due in part to the fact that many transplants (eg, kidney) are performed in patients who were hypertensive prior to transplantation. A major reason for posttransplantation hypertension, however, is immunosuppressive therapy with the calcineurin inhibitors, cyclosporine and tacrolimus.
Epidemiology

Since the advent of calcineurin use for posttransplant immunosuppression, the occurrence of posttransplant hypertension has risen. For example, posttransplant hypertension now complicates 67% to 90% of kidney transplants as compared to a 45% to 50% occurrence during the precyclosporine era [89,90]. Similar trends have been noted in recipients of bone marrow, livers, and hearts. Similar to the general population, hypertension is an important risk factor for CVD in kidney transplant recipients. The level of BP after transplant has been identified as an important determinant of kidney graft survival. Accordingly, in more than 29,000 kidney transplant recipients, Opelz and coworkers [91] found that 1-year graft survival was incrementally worse at SBP levels >139 mm Hg. The 24-hour BP burden also appears to be increased given the lack of nocturnal decline in BP; however, this abnormal diurnal variability in BP has been observed in persons with chronic kidney disease and therefore may antedate transplantation [92].

Overall mortality, CVD, or coronary risk is markedly increased in kidney transplant recipients. CVD accounts for almost 75% of posttransplantation mortality in kidney transplant recipients [93]. The 1997 USRDS data system [93] reports that kidney transplant recipients are 2.2 times more likely to die of CVD than the general population. Thus, the necessity of controlling BP as well as comprehensive management of other CVD risk factors to improve clinical outcomes is obvious.

Causes of posttransplant hypertension

Posttransplant hypertension can occur as a consequence of a broad range of causes. Obviously calcineurin inhibitors raise BP in the posttransplant period. Tacrolimus also causes posttransplant hypertension, although the data suggest that cyclosporine produces greater renal vasoconstriction and resultant systemic hypertension at an earlier onset than tacrolimus [94,95]. Furthermore, one study found higher serum creatinine and cholesterol levels among African-Americans taking cyclosporine versus tacrolimus 1 year after cadaveric kidney transplantation [96]. Concurrent use of corticosteroids also augments the risk of posttransplant hypertension. Other important causes, however, must be considered such as acute/chronic graft rejection, glomerulonephritis, renal artery stenosis, and hypertension attributable to the native kidney. Critical renal artery stenosis at the suture line in the grafted kidney occurs in about 1 in 50 transplants [97] and should be suspected when there is an abrupt rise in BP after transplantation. Atherosclerotic renal artery obstruction occurs many months to years after transplantation. Pretransplant hypertension has been linked to an increased risk of chronic graft rejection, which is a major cause of graft loss during the first year after transplantation. Focal glomerulosclerosis, a cause of kidney failure and transplantation, can recur in approximately 40% of kidney grafts [98]. In addition, focal sclerosis has been detected de novo in 30% of patients with chronic allograft nephropathy [99]. Many patients will have reduced kidney function as evidenced by estimated GFRs <60 mL/min/1.73 m^2. Thus, they will have reduced natriuretic capacity and will likely be highly sensitive to dietary sodium. In addition, the median number of antihypertensive drugs required to achieve BP control after kidney transplantation is two when serum creatinine is <1.3 mg/dL and increases to four when serum creatinine is between 1.3 and 2.0 mg/dL [90].

Mechanisms of calcineurin hypertension/cardiovascular toxicity

These agents increase sympathetic nervous system activity [100], blunt the natriuretic response to volume expansion, cause vasoconstriction, and augment the effect of other endogenous vasoconstrictors. Cyclosporine augments proximal tubular reabsorption of sodium. Cyclosporine appears to unfavorably alter the balance of endogenous vasodilators and vasoconstrictors as it decreases cyclic guanosine monophosphate (cGMP) production [101] either via decreased nitric oxide (NO) production and/or disturbed signal transduction from NO to cGMP [102]. Furthermore, cyclosporine causes dose-related increases in the potent vasoconstrictor endothelin [103] along with increased urinary excretion of thromboxane A_2, a vasoconstrictor prostaglandin [104,105].

Cyclosporine can cause kidney damage at multiple foci: the arterioles, glomeruli, and interstitium. Glomerulonephritis, interstitial fibrosis, and arteriopathy all have been described [106]. Cyclosporine also causes in intense constriction of the glomerular afferent arteriole, a potentially important consideration in the selection of drugs, lifestyle modifications, and therapeutic BP targets in this high-risk patient population.
Treatment

In patients with functioning kidney transplants it seems prudent to control BP aggressively to levels that are at least as low those recommended for persons with kidney disease (<130/80–85 mm Hg). One important consideration is that these patients have only a solitary functioning kidney. There are, in addition, several important therapeutic caveats to consider. Sodium restriction can augment BP response to most antihypertensive drugs, particularly in the setting of reduced kidney function, ad lib sodium intake, and vasodilator therapy, as the latter augments salt and water retention by the kidney. One must be careful with the transplant patient on cyclosporine, however, to avoid excessive sodium restriction and/or diuresis, both of which can lead to further reductions in GFR as well as augment cyclosporine nephrotoxicity. Cyclosporine-treated patients also are prone to developing hyperkalemia. Calcium antagonists are attractive antihypertensive agents in this population because they cause glomerular afferent arteriolar dilatation thus reversing the intense vasoconstriction caused by cyclosporine. Some calcium antagonists can, however, significantly raise cyclosporine levels, whereas others do not appear to. Amlodipine, diltiazem, nicardipine, and verapamil can cause substantial increases in cyclosporine levels; isradipine, nifedipine, and nitrendipine do not appear to do so. An additional theoretic concern with the calcium antagonists is that glomerular afferent arteriolar dilatation can result in direct transmission of systemic BP to glomeruli, resulting in damage, dysfunction, and over time, premature senescence. Thus, it is critically important to lower systemic BP to relatively low levels in the posttransplant population, particularly when using these agents. Finally, ACE inhibitors, angiotensin receptor blockers, and aldosterone receptor antagonists all have theoretic appeal in the posttransplant population because these drug classes antagonize/reverse target-organ injury responses (ie, fibrosis) as well as because of the favorable effects of ACE inhibitors and angiotensin receptor blockers on intraglomerular hemodynamics. Nevertheless, there are several important considerations when using ACE inhibitors and angiotensin receptor blockers. In transplant patients on cyclosporine with intense glomerular afferent arteriolar constriction, these agents can further depress GFR and elevate serum creatinine levels. Also, ACE inhibitors and angiotensin receptorblockers should be discontinued in patients with posttransplant renal artery stenosis because of the potential for deterioration in kidney function.

Diabetes mellitus

Epidemiology

Almost 16 million Americans have diabetes mellitus; 10.2 million of them are aware of their diagnosis [107]. Diabetes prevalence increases with advancing age and disproportionately affects racial and ethnic minority groups in the United States. Persons with type 2 diabetes have striking increases in absolute risk for micro- and macro-vascular CVD–renal disease complications, with the relative increase compared to persons without diabetes being greater in women than men [108]. The risk of heart disease for people with diabetes mellitus increases approximately two to four fold over that for people without diabetes mellitus [107,108]. Approximately 75% of deaths among persons with diabetes are attributable to CVD. Lifetime risk of ESRD is increased relative to the general population at approximately 8%, although the risk is much less than among persons with type 1 diabetes mellitus.

Hypertension in persons with diabetes mellitus is defined as BP ≥130/85 mm Hg. People with diabetes mellitus are more likely to have hypertension than the general population in part because of common risk factors such as obesity, physical inactivity, and advanced age. Fifty-five percent to 65% of people with diabetes mellitus also have hypertension. Although most hypertension among persons with diabetes mellitus is “essential,” the clinician should be aware of the potential superimposition of critical renal artery stenosis (of atherosclerotic origin) or renovascular hypertension upon long-standing essential hypertension because of the propensity to develop atherosclerosis in this high-risk population. The lower BP threshold for the diagnosis of diabetes mellitus is more than justified by the higher absolute CVD and mortality risks in persons with type 2 diabetes mellitus [109–111] and the proven benefit of BP lowering in placebo-controlled trials with both diuretic-based [108] and dihydropyridine calcium antagonist-based therapeutic regimens [111–113] in reducing the risk of microvascular and macrovascular complications. In addition, the diuretic-based Hypertension Detection and Follow-up Program (HDFP) documented a reduction in CVD risk among persons with diabetes in those
treated with the diuretic-based stepped care regimen compared to referred care [110]. Nevertheless, many if not most patients with diabetes mellitus require combination drug therapy to achieve target BP levels irrespective of the initial therapy chosen [109,112,114,115]. BP control rates to <130/85 mm Hg are abysmally low at 11%.

Active drug treatment trials

There has been considerable debate and controversy regarding which drug class conferred the greatest risk reduction to hypertensive persons with type 2 diabetes mellitus. Furthermore, the published data in this area have been conflicting, at least to a degree. The landmark United Kingdom Prospective Diabetes Study Group study [115] over a median follow-up of 8.4 years found no difference in BP lowering efficacy or frequency of hypoglycemic events or in the incidence of diabetes-related complications, myocardial infarction, stroke, or total mortality between antihypertensive drug regimens starting with captopril, 25 mg twice a day, or atenolol, 50 mg once daily [115]: however, atenolol-treated patients gained more weight and more often required additional glucose lowering therapy than those treated with captopril. The Hypertension Optimal Treatment (HOT) trial of hypertension provided important information regarding the importance of low target BP levels for persons with type 2 diabetes mellitus on active antihypertensive drug therapy [112]. HOT randomized more than 19,000 patients aged 50 to 80 years with DBPs of 100 to 115 mm Hg to one of three target DBP levels: <90, <85, or ≤80 mm Hg. Follow-up averaged 3.8 years. All patients received treatment initially with felodipine, 5 mg once daily, with ACE inhibitors, beta-blockers, and diuretics used as add-on therapy to achieve target DBP levels. Amongst those with diabetes mellitus, major cardiovascular events and CVD mortality were incrementally and significantly lowered across the DBP strata. There was a 51% reduction in major CVD events at the lowest target DBP level of ≤80 as compared to the CVD events at ≤90 mm Hg. Low dose aspirin was effective in reducing both myocardial infarction and major CVD event rates. Thus, these data with dihydropyridine-based therapy conclusively show the value of lower therapeutic target BP levels among hypertensive persons with diabetes mellitus. The Captopril Prevention Project (CAPP) study compared a captopril-based regimen to conventional therapy with diuretics and/or beta blockers in almost 11,000 men and women aged 25 to 66 years with DBP ≥100 mm Hg [116]. Add-on therapy in the captopril group after attainment of the maximal dose of 100 mg/d was a diuretic. Calcium antagonists were used as add-on therapy in both groups. Follow-up averaged 6.1 years. Among individuals with diabetes mellitus, there were 66% fewer myocardial infarctions, 33% fewer cardiac events, and 41% lower rates of the aggregate primary endpoint of myocardial infarction, stroke or CVD death in the captopril group compared to the conventional therapy group. A fascinating observation was made regarding the influence of captopril, an ACE inhibitor, on the incidence of diabetes mellitus. There were 21% fewer new cases of diabetes mellitus in the captopril group compared to the conventional therapy group. Data from CAPP suggests that ACE inhibitor–based therapy might be superior to initial therapy with diuretics and beta blockers and further suggests that ACE inhibitors might prevent new cases of diabetes mellitus.

The data supporting the role of ACE inhibitors as the preferred drug therapy among individuals with diabetes mellitus has come from both placebo-controlled trials and trials comparing ACE inhibitors to other active therapies. Several studies have contrasted the ACE inhibitors and dihydropyridine calcium antagonists as initial therapy in persons with type 2 diabetes mellitus and hypertension. These studies, Fosinopril versus Amlodipine Cardiovascular Events trial (FACET) [78] and the Appropriate Blood Pressure Control in Diabetics (ABCD) [117] trial, both showed that initial therapy with ACE inhibitors conferred greater protection against CVD morbidity and mortality than initial therapy with a dihydropyridine calcium antagonist. In the ABCD trial, risk of myocardial infarction was 9.5-fold higher with nisoldipine than enalapril, although there was no difference observed in stroke, heart failure, CVD mortality, or all-cause mortality incidence. Data from the placebo-controlled MICRO-HOPE study were quite compelling [118]. Almost 3600 persons with diabetes mellitus (plus one other CVD risk factor or a prior CVD event) aged 55 years and older were enrolled in the HOPE trial and randomly allocated to ramipril, an ACE inhibitor, or placebo. Follow-up averaged 4.5 years. BP was 2.4/1.1 mm Hg lower in the ramipril compared to the placebo group. The risk of the combined primary outcome of myocardial infarction, stroke, or CVD death was 25% lower in the ramipril group. Adjustment for the BP difference between the ramipril and placebo groups did not
change this risk reduction. Persons with and without microalbuminuria as well as with and without hypertension appeared to benefit from ramipril treatment. Incidence of myocardial infarction, stroke, CVD death, revascularization, total mortality, and overt nephropathy all were lower, to a statistically significant degree, in the ramipril group. These data strongly suggest that ACE inhibitor treatment reduced the incidence of micro- and macro-vascular events in people with diabetes mellitus to a degree that was unexplained by lower BP in the ramipril group.

Studies in normotensive individuals

In addition to studies previously mentioned that enrolled at least some normotensive people, there are other studies suggesting benefit of ACE inhibitor therapy among normotensive persons with diabetes mellitus. Although conducted among individuals with type 1 diabetes mellitus, the administration of captopril compared to placebo appeared to lower the risk of ESRD and mortality among normotensive patients given captopril compared to placebo [66]. Other studies in normotensive persons with type 2 diabetes have documented that ACE inhibitor therapy can prevent the development of microalbuminuria in persons initially free of microalbuminuria prior to treatment [119] and can retard the progression from microalbuminuria to overt nephropathy [64]. ACE inhibitors administered after myocardial infarction also appear to reduce 6-week mortality in persons with type 2 diabetes mellitus [120]. These data provide some support for the use ACE inhibitors in normotensive persons with diabetes mellitus for the secondary prevention of target-organ damage.

Therapeutic recommendations

ACE inhibitors are preferred drugs in diabetic patients with hypertension and even merit strong consideration among those who are normotensive. Angiotensin receptor blockers are gaining favor, particularly for patients with diabetic nephropathy. Attainment of goal BP levels, at the very minimum, is a critical means of protection against the excess morbidity and mortality associated with diabetes mellitus; however, BP control is unlikely to occur in most persons with diabetes without combination drug therapy. The data regarding the benefit of dihydropyridine calcium antagonist in persons with type 2 diabetes are compelling in placebo-controlled trials. In relative terms, however, ACE inhibitors appear to provide better CVD protection than dihydropyridine calcium antagonists and conventional therapy with diuretics and beta blockers when directly compared. Angiotensin receptor blockers also appear to protect the kidney better than dihydropyridine calcium antagonists. A reasonable interpretation of the available data seems to be that long-acting dihydropyridine calcium antagonists are safe and effective in diabetes mellitus. Their biggest use, however, will be in persons already treated with ACE inhibitors or angiotensin receptor blockers. Another compelling lesson from the clinical trials in hypertensive persons with type 2 diabetes mellitus has been that risk reduction observed with a wide variety of mechanistically dissimilar drug classes highlights the important role of BP reduction in reducing risk in this high-risk population.

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