

Uric Acid and Hypertension in Adolescents

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Hypertension is the most common form of cardiovascular disease. Although it is less common in adolescents than in adults, hypertension and the associated organ damage can and often does begin early in life. Consequently, for many with high blood pressure (BP), measures directed at the long-term prevention of cardiovascular morbidity may need to be started in adolescence to achieve maximal effectiveness. This article discusses some of the problems unique to hypertension in the young, as well as recent discoveries regarding the likely role played by increases in serum uric acid level in the development of adolescent-onset essential hypertension.

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Hypertension, present in nearly 25% of adults, is the most prevalent form of cardiovascular disease. The American Heart Association's Heart Disease and Stroke Statistics—2004 Update, which compiled data through 2001, documented a cardiovascular death rate of nearly 1 million per year, which is consistent with prior reports.^{1,2} Hypertension leads to morbidity and mortality by dramatically escalating the risk for myocardial infarction, congestive heart failure, stroke, peripheral vascular disease, and renal failure.³⁻⁶ Normalization of blood pressure (BP) by using antihypertensive agents and lifestyle modification significantly decreases morbidity and mortality but has not reduced the risk to zero, nor has it completely ameliorated end-organ damage.⁷⁻⁹ Consequently, the only completely effective treatment for the complications of hypertension is prevention of hypertension itself.

Although hypertension is less common in children and adolescents, evidence suggests that the roots of adult hypertension are present in childhood.¹⁰ The presence of increased BP in childhood is an excellent predictor of hypertension in adults.¹¹ Other factors that predict hypertension are diabetes, obesity, hyperlipoproteinemia, and a family history of hypertension or early cardiovascular disease.¹² These particular risk factors are much the same as those for cardiovascular morbidity in adults. Although modification of these risk factors is somewhat effective in decreasing morbidity in adults, early risk reduction, such as in childhood, should be considerably more efficacious.

Numerous studies also have shown that the initiation of

end-organ damage occurs during childhood. Left ventricular hypertrophy,¹³ electrocardiographic changes,¹⁴ microalbuminuria,¹⁵ and atherosclerotic plaque development¹⁴ all have been shown in hypertensive children with a prevalence, at the time of diagnosis, ranging from 10% to 40%. Data from the National Health and Nutrition Examination Survey (NHANES) III study showed that BPs in the 90th percentile or greater is associated with decreases in cognitive function as measured by the Wechsler Intelligence Scale for Children and the Wide Range Achievement test.¹⁶ These data suggest that increased BP, even levels below our current definitions of hypertension, may contribute to intellectual impairment and decreased school and developmental performance. The accumulation of potentially irreversible organ injury and impaired neurocognitive function in hypertensive children makes an understanding of hypertension and its prevention in children a public health priority.

The American Heart Association recently published guidelines for the primary prevention of atherosclerotic cardiovascular disease beginning in childhood.¹⁷ These include dietary, weight, body mass index, and BP screening at all well-child visits and behavioral modification, laboratory evaluation, and follow-up evaluation for certain high-risk individuals. The goals of these guidelines are to decrease the prevalence and severity of cardiovascular disease by early intervention. Although these recommendations are of critical importance, we do not yet have a sufficient understanding of the early steps in the development of hypertension and obesity to address all relevant risk factors adequately.

Definition and Prevalence of Hypertension in Children

Because of the rarity in children of myocardial infarction, stroke, and other overt cardiovascular outcomes that are used

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to define morbidity and success of treatment in adults, hypertension in children is defined statistically. The Task Force on High Blood Pressure in Children and Adolescents developed normative BP tables based on data from over 70,000 children; they define the 90th and 95th percentile BPs for boys and girls stratified by age and height percentile.^{18,19} The current recommendation for the diagnosis of hypertension in children is a BP greater than or equal to the 95th percentile systolic or diastolic BP measured at 3 separate clinic visits. Recent data on the decreases in neurocognitive function in children with BPs above the 90th percentile¹⁶ and the high prevalence of left ventricular hypertrophy at the time of diagnosis in hypertensive adolescents^{13,14,20} suggest that the current definitions of hypertension may prove to be too conservative.

The use of a statistical definition of hypertension in children allows for predictions of the expected prevalence. Use of BP above the 95th percentile for age, gender and height on 3 consecutive visits leads to a statistically predicted prevalence of hypertension in the adolescent population of between 2 and 3%. Screening studies in school populations have supported this estimate.²⁰ The actual rate of diagnosis, however, is much lower, suggesting a poor case identification rate, most likely owing to inadequate screening efforts.

Ambulatory blood pressure monitoring (ABPM) uses portable belt monitors connected to an oscillometric blood pressure cuff worn by the patient for 24 to 72 hours. In this way, the patient's blood pressure is measured 2 to 3 times an hour during normal activities, including sleep periods. ABPM provides mean and extreme blood pressure readings as well as BP load (fraction of readings above the threshold of hypertension). These data can be compared with normative data stratified for sex and height to determine if a child is hypertensive.²¹

ABPM offers several advantages over casual measurements in the assessment and management of childhood hypertension. First, it avoids the problem of *white coat hypertension*, the transient increase of BP caused by the stress associated with the context of its measurement.²² Second, ABPM provides both the mean blood pressure over time periods and the hypertensive load, which is the fraction of blood pressure readings above the threshold for hypertension. Both of these measurements have better correlation with the risk for end-organ injury than casual BP measurements.²³ Finally, ABPM identifies nondippers, individuals who lack the greater than 10% decrease in blood pressure associated with sleep. Nondippers are at higher risk for end-organ damage.^{24,25}

Classes of Hypertension in Children

Hypertension in children often results from underlying renal, cardiovascular, or endocrinologic disease. Thirty percent to 60% of hypertensive children have an identifiable cause^{18,19,26} and are therefore classified as having secondary hypertension. The most common causes are renal parenchymal disease resulting from urinary tract infections, glomeru-

Table 1 Major Problems in the Field of Pediatric Hypertension

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| Definition of hypertension |
| Optimal methods for diagnosis |
| Goals of treatment |
| Method/medication for treatment |
| Mechanism of disease |

lonephritis, complications during the neonatal period, or congenital renal diseases such as polycystic kidney disease or obstructive uropathy. The presence of renal parenchymal disease can lead to renal insufficiency or to activation of the renin-angiotensin-aldosterone system with resulting vasoconstriction, or, more commonly, sodium and fluid retention. Cardiovascular causes of hypertension include renal artery stenosis and coarctation of the aorta. Endocrinologic causes such as mineralocorticoid excess, hyperthyroidism, and catecholamine excess²⁷ are less common. Because pediatric hypertension frequently is secondary to renal or other organ disease, hypertensive children frequently undergo detailed diagnostic evaluation²⁸ to assist in both management and prognosis.

Primary, or essential, hypertension is the diagnosis given to children when a reasonably comprehensive work-up for secondary causes has been exhausted. Depending on the population, 40% to 70% of hypertensive children will have essential hypertension. The likelihood is greater among children presenting during adolescence or those with a significant family history for hypertension.²⁶ Children with essential hypertension frequently are obese (50%), often salt sensitive (50%), and almost universally progress to adult hypertension.²⁹

The third class of hypertension seen in children is white coat hypertension. In theory, white coat hypertension is quite simple, increased blood pressures only in the presence of a medical professional. In practice, however, identifying such individuals can be quite difficult. The most common way to determine white coat hypertension is by using ABPM. Digital blood pressure monitors for home use also have been used to identify white coat hypertension and some groups have reported good correlation with ABPM.³⁰ It is likely that not all children need ABPM to confirm hypertension. Sorof et al³¹ estimated the probability of white coat hypertension in the pediatric population as a function of blood pressure index (the ratio of the child's casual BP to the 95th percentile for the child's age, height, and sex). As the blood pressure index increased from 1.0 to 1.2, the probability of white coat hypertension decreased from 87% to 15%, and was less than 5% at a blood pressure index of 1.3.

Major Problems in Pediatric Hypertension

Several fundamental questions regarding hypertension in adolescents remain unanswered (see Table 1). The first relates to the use of a statistical definition of hypertension. Such a definition provides diagnostic criteria, however, it provides

little guidance in regard to whom to treat and what the BP targets should be when treatment is introduced. In the absence of solid outcome measurement, it is impossible to assess the short-term or long-term morbidity associated with BPs currently considered hypertensive. Identification of specific noninvasive measures of end-organ damage or intermediate end points that directly tie to the risk for hypertension in adulthood and risk for future cardiovascular morbidity and mortality would allow a more evidence-based design of antihypertensive therapy for children. The second problem is one of accuracy of measurement. With a high incidence of white coat hypertension, seated right-arm BP measurement, as recommended by the Report of the Second Task Force on Blood Pressure on Children and Adolescents, may be inferior to ABPM that generally is not as available. Consequently, debate remains on the optimal techniques for pediatric BP measurement and diagnosis. The third problem is related to the definition of hypertension. Without an outcome-based definition of hypertension, establishing goals for effective treatment of hypertension is difficult. The current practice is to maintain blood pressures below the 95th percentile, but whether this is therapeutically necessary, or adequate, is not clear. The fourth problem is caused by the paucity of clinical pharmaceutical trials performed in children. Most of the available antihypertensive medications have not been tested formally for dosing, safety, and efficacy in children and adolescents. Finally, very little data are available on the physiology and biochemistry of early onset essential hypertension.

The Correlation Between Uric Acid and Essential Hypertension

The hypothesis that uric acid level may be important in the development of primary hypertension has been suggested repeatedly over the past 130 years. An association of gout with hypertension was first noted in 1879.³² Twenty-five percent to 40% of adult patients with untreated hypertension have hyperuricemia (>6.5 mg/dL) and many more have a high normal serum uric acid level (5.0–6.5 mg/dL).^{33,34} The relationship between uric acid level and BP is continuous and is observed in both African Americans and in Caucasians.³⁵ Furthermore, hyperuricemia predicts the development of, and is an independent risk factor for, hypertension.^{36,37}

In adolescents, the association between increased serum uric acid level and the onset of essential hypertension is even more striking. The Moscow Children's Hypertension Study found hyperuricemia (>8.0 mg/dL) in 9.5% of children with normal BP, in 49% of children with borderline hypertension, and in 73% of children with moderate and severe hypertension.³⁸ The Hungarian Children's Health Study followed-up all 17,624 children born in Budapest in 1964 for 13 years and found that significant risk factors for the development of hypertension were increased heart rate, early sexual maturity, and hyperuricemia.³⁹ These 2 studies do not separate the hypertensive children by underlying diagnosis so the relationship between serum uric acid level and hypertension may be skewed by ascertainment bias. In a small study, Gruskin⁴⁰

compared adolescents (13–18 years of age) with essential hypertension to age-matched healthy controls with normal BPs. The hypertensive children had both increased serum uric acid level (mean, >6.5 mg/dL) and higher peripheral renin activity. In a racially mixed population referred for the evaluation of hypertension, Feig and Johnson⁴¹ observed that the mean serum uric acid level (\pm SD) in controls and children with white coat hypertension were nearly identical (3.6 ± 0.8 mg/dL and 3.6 ± 0.7 mg/dL, respectively, $P = .80$), but slightly higher in secondary hypertension (4.3 ± 1.4 mg/dL, $P = .008$), and significantly increased in children with primary hypertension (6.7 ± 1.3 mg/dL, $P = .000004$). There was a tight linear correlation between the serum uric acid levels and the systolic and diastolic BPs in the population referred for evaluation of hypertension ($r = .8$ for systolic BP and $r = .6$ for diastolic BP).⁴¹ Among patients referred for evaluation of hypertension, a serum uric acid level greater than 5.5 mg/dL had an 89% positive predictive value for essential hypertension whereas a serum uric acid level less than 5.0 mg/dL had a negative predictive value for essential hypertension of 96%.⁴¹

This close a correlation between serum uric acid level and BP has not been seen in all populations. Goldstein and Manowitz⁴² evaluated the NHANES III database for BP and serum uric acid level in adolescents while controlling for age, height, weight, and sexual maturity. They reported a positive association for boys but not girls. The observed difference likely is owing to population selection. The NHANES, although extremely large, contains few hypertensive children and even fewer with essential hypertension. If uric acid truly is associated with the onset of essential hypertension and less so with normal BP regulation (for which there are no data to support), then any effect germane to this small subset of the population is likely to be lost in the population at large. Interestingly, the association between hypertension and serum uric acid level is less strong in adults. In the Framingham data, it attenuates with subsequent examinations.^{43,44} This suggests that an increase in uric acid level may be more important in the development of hypertension rather than in its maintenance.

Evidence that Increased Serum Uric Acid Level May Cause Hypertension

The strong association between hyperuricemia and hypertension does not prove a causal link. Hyperuricemia has been considered as a surrogate for decreased renal function because it increases in correlation with decreased glomerular filtration rate,⁴⁵ and serum uric acid level is increased in groups of adults with increased cardiovascular risk including African Americans,⁴⁶ men,⁴⁷ and individuals with obesity or insulin resistance.⁴⁸ Many have argued that this association is an epiphenomenon.

The search for a mechanistic link between hyperuricemia and hypertension required a reliable model in which the effects of uric acid could be isolated and studied. Previously

described hyperuricemic mice have been generated by the targeted knock out of the uric acid oxidase gene or pharmacologic blockade of uric acid oxidase with high-dose oxonic acid. These mice develop severe hyperuricemia, resulting in marked uricosuria, intratubular crystal deposition, and acute renal failure.^{49,50} In contrast, low-dose administration of oxonic acid results in a dose-responsive increase in serum uric acid level that is not associated with intrarenal crystal deposition. This serves as an excellent model to investigate the effect of mild hyperuricemia on BP and target organ injury.

The hyperuricemic rats develop hypertension⁵¹ and preglomerular arteriopathy.⁵² The induced hypertension can be prevented or corrected by inhibition of uric acid production with allopurinol (a xanthine oxidase inhibitor). The early hypertension is dependent on the renin-angiotensin system and nitric oxide pathways;⁵¹ however, once preglomerular vascular disease develops, hypertension is driven by the kidney and decreasing the uric acid level is no longer protective.⁵³ These findings suggest that the development of hypertension is a multistep process. First is the induction of increased blood pressure by the action of a stimulus, such as uric acid, which is followed by the development of renal vascular disease that perpetuates the hypertension, even if the initial insult is removed. If substantiated in humans, prevention of the renal microvascular lesions during childhood may decrease the incidence of long-term hypertension.

One of the major criticisms of the hypothetical role of uric acid in hypertension has been the lack of a plausible mechanism. To address this concern, renal histology specimens from oxonic acid-treated and control rats were evaluated by using immunohistochemical stains for renin and nitric oxide synthase. Hyperuricemic rats exhibited a marked increase in juxtaglomerular renin expression, and a marked decrease in macula densa, neuronal nitric oxide synthase expression. All of these effects were blocked by the concomitant administration of allopurinol or benzydaronone (a xanthine oxidase inhibitor and a uricosuric agent, respectively). In addition, in a hyperuricemic remnant kidney model, Kang et al⁵⁴ showed the induction of cyclooxygenase-2 in vascular smooth muscle cells of the interlobular arteries. Because cyclooxygenase-2 is a major regulator of renin expression,⁵⁵ increased serum uric acid level may result in activation of cortical cyclooxygenase-2, and with the development of an afferent arteriopathy, both of which activate renin expression. Increased activity of the renin-angiotensin-aldosterone system would lead to vasoconstriction and the activation of profibrotic cytokines such as transforming growth factor- β .

Proof that uric acid may be involved in the pathogenesis of hypertension in humans requires studies examining the effect on BP of decreasing the uric acid level. In an open-label pilot study, adolescents with newly diagnosed essential hypertension were treated with allopurinol for 1 month followed by a 4-week washout period. The resulting decrease of serum uric acid level from a mean of 6.9 mg/dL to 3.3 mg/dL with allopurinol significantly decreased casual BP measurements and led to normalization of BP by ABPM criteria in 4 of 5 patients.⁵⁶ One must be careful in the interpretation of the pilot study owing to a potential placebo effect; nevertheless,

Table 2 Major Theories and Supporting Data to Explain Essential Hypertension

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| Renal arteriopathy |
| Biopsy data |
| Decreased nephron number |
| Birth weight and gestational age |
| Autopsy studies |
| Altered vasoactive tone |
| sympathetic nervous system activity studies |
| Endothelial dysfunction studies |
| Genetic |
| Family history |
| Tubular channel defects leading to hypertension |
| Polymorphisms in renin-angiotensin system components |

the initial results provide a support for a causative role in adolescent-onset essential hypertension.

Possible Causes of Essential Hypertension

Despite being the most common disease on earth, a complete understanding of the cause of essential hypertension remains elusive. Table 2 reviews the major prevailing theories on the cause(s) of essential hypertension. These theories are not mutually exclusive and, in fact, some of the difficulty of identifying the precise cause of hypertension may be its multifactorial cause and that different populations are subject to different relative contributions of the major causative pathways.

The preeminence of the kidney in essential hypertension has been known for many years. In an animal model, either hypertension or normal BP could be transferred by kidney transplant.⁵⁷ In humans, recipients of kidneys from donors who had essential hypertension universally developed hypertension posttransplant even if they were previously normotensive. These observations may be explained in part by the presence of renal arteriosclerosis. This pathologic lesion is present in the kidneys of 98% of hypertensive individuals⁵⁸ and although similar lesions are seen in other organs, only arteriosclerosis in the kidneys correlates with increased BP.⁵⁹ The degree of arteriosclerosis in a renal biopsy sample can predict the degree of BP increase accurately⁶⁰ and, at least in some individuals, the lesion precedes hypertension.⁶¹ Arteriosclerosis would alter autoregulation and single-nephron hemodynamics, leading to an induction of the renin-angiotensin system.

Congenital decrease of total nephron mass also is related closely to the risk and development of essential hypertension. This fetal programming theory has been championed by Barker et al^{62,63} based on an observed inverse relationship between birth weight and adult BP. If one evaluates birth weight and risk for onset of hypertension in early adolescence,⁶⁴ the correlation is not present, but this does not refute a possible long-term risk. In an autopsy study in which the total numbers of nephrons were compared in age-matched adults with and without a history of essential hypertension,

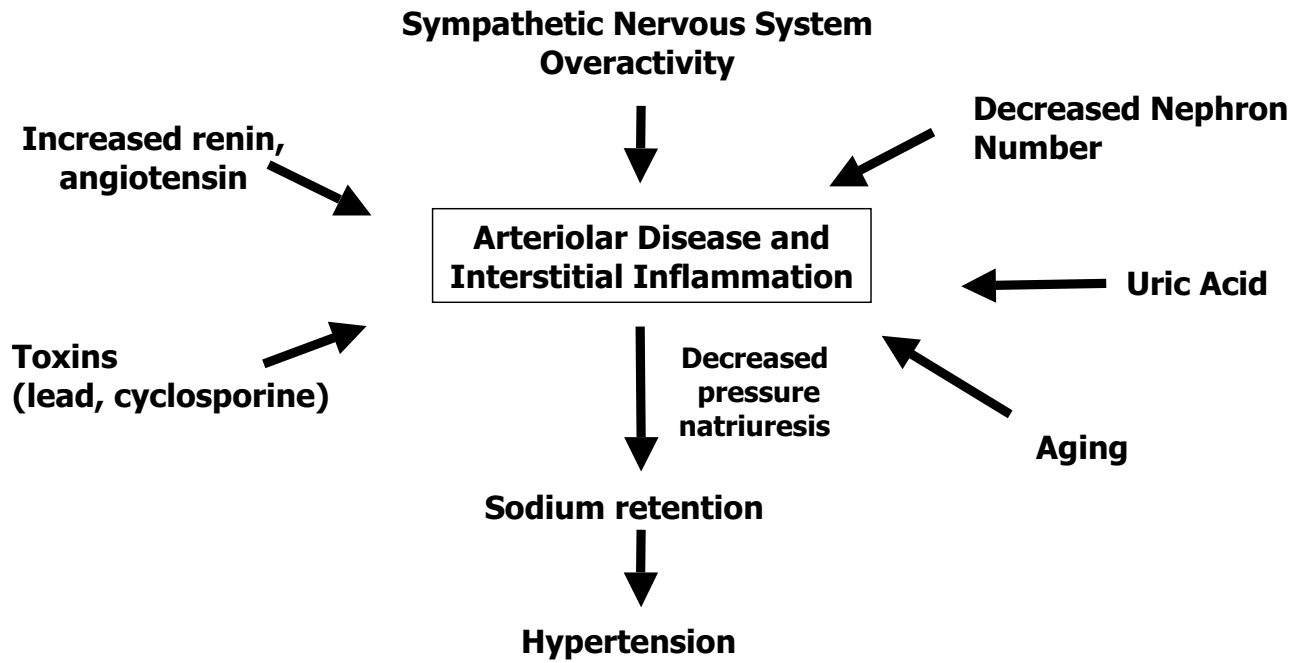


Figure 1 A possible pathway leading to essential hypertension. The renal arteriosclerotic lesion, associated with renal parenchymal hypoxia and inflammation, leads to chronic alteration of the pressure natriuresis curve such that renal sodium excretion is decreased at any given blood pressure. This leads to sodium retention and salt-sensitive hypertension. This common pathway could be triggered by a variety of insults including increased serum uric acid levels, sympathetic nervous system hyperactivity, nephrotoxicity, or compensatory hyperperfusion triggered by nephron hypoplasia.

hypertensive individuals had, on average, 40% fewer nephrons than controls.⁶⁵

Vasoactive dysfunction leading to essential hypertension also has considerable support. Hyperactive resting tone of the sympathetic nervous system has been observed in many patients with new-onset hypertension. It consists of increased sympathetic nerve firing rates,⁶⁶ altered norepinephrine reuptake,⁶⁷ decreased arterial baroreflex buffering of sympathetic nerve traffic,⁶⁸ or norepinephrine-mediated release of other vasoactive compounds such as angiotensin II.⁶⁹ Many patients with essential hypertension also have significant impairment of their endothelium-mediated vasodilatation as measured by forearm phethysmography,⁷⁰⁻⁷³ which may lead to an increase in resting vascular tone.

The final class of potential causative factors for essential hypertension is genetic cause. Essential hypertension, or the propensity to develop hypertension, clearly runs in families, but extensive genetic screening has not yielded specific genetic loci. This may be because of variable penetrance, but it is more likely that essential hypertension is controlled by several genes, the combination of which defies simple genetic analysis. There are several forms of genetic hypertension that are caused by defects in renal sodium handling. Polymorphisms in the renin-angiotensin system also have been implicated in the hypertension observed in certain populations.

The various possible mechanisms leading to essential hypertension are not mutually exclusive. More than one mechanism may be present in a given individual or family, or, alternatively, several mechanisms can cause initiation of a

common pathway that yields hypertension. **Figure 1** shows one hypothetical pathway leading to essential hypertension. The renal arteriosclerotic lesion is associated with renal parenchymal hypoxia and inflammation and leads to chronic alteration of the pressure natriuresis curve such that renal sodium excretion is decreased at any given BP. This leads to sodium retention and salt-sensitive hypertension.^{74,75} This common pathway could be triggered by a variety of insults including increased serum uric acid levels, sympathetic nervous system hyperactivity, nephrotoxicity, or compensatory hyperperfusion triggered by nephron hypoplasia. There are even data to suggest that some of the triggers may lead to one another, for example, increased uric acid levels could lead to endothelial dysfunction,⁷⁶ activation of the renin-angiotensin system,⁵² and, potentially could contribute to decreased nephron number.⁵⁶

Clinical and Research Implications

The enormous complexity and morbidity of essential hypertension are both very strong arguments to both study and manage hypertension at its earliest roots, the adolescent population. From a clinical perspective, early identification and treatment will at least arrest and possibly reverse end-organ damage that begins quite early in life. For individuals whose increased BP is at least in part caused by acquisition of renal arteriopathy, early intervention may hold the promise of primary prevention of

essential hypertension. If the support for increase of serum uric acid level as a trigger of renal arteriopathy and early onset essential hypertension continue to mount, this pathway will have significant implications for the management of essential hypertension in the young.

The current recommendation for the first-line treatment of essential hypertension is the initiation of diuretic therapy. This recommendation is based in large part on the findings of the Antihypertensive and Lipid Lowering to Prevent Heart Attacks Trial (ALLHAT) trial that in adults with hypertension, diuretics were superior to calcium channel blockade and angiotensin-converting enzyme inhibition in prevention of cardiovascular morbidity and mortality.⁷⁷ Some degree of caution must be used in extrapolating these results to adolescents. First, in a lower-risk population that was of a less diverse ethnic make-up, the Second Australian National Blood Pressure Study Group, found angiotensin-converting enzyme inhibitors to be superior to diuretics in cardiovascular outcomes, especially in older men.⁷⁸ Second, neither of these large studies included young adults or children, so generalization is not possible. Third, the goals for therapy in children cannot be a short-term decrease of cardiac mortality, instead there will need to be reversal or prevention of detectable end-organ damage or prevention of hypertension in adulthood. Finally, diuretics impair renal uric acid clearance. For adolescents in whom uric acid possibly could contribute to the development or maintenance of hypertension, short-term BP control with diuretics may be counterproductive in the long term.

From a research perspective, the adolescent hypertensive population offers unique and critical insights. In contrast to older and more infirmed populations, adolescents with hypertension have few other illnesses that confound the outcome measures and consequently may provide greater clarity to the physiology and treatment study outcomes. Most importantly, any interventions to prevent the future development of hypertension and its comorbid conditions will need to be investigated and tested in the young, prior to the onset of high blood pressure.

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