Screening for Hypertension in Children and Adolescents to Prevent Cardiovascular Disease

abstract

BACKGROUND AND OBJECTIVE: The prevalence of hypertension is increasing in children, and may persist into adulthood. This systematic review was conducted for the US Preventive Services Task Force recommendation on the effectiveness of screening asymptomatic children and adolescents for hypertension in order to prevent cardiovascular disease.

METHODS: Eligible studies were identified from Medline and the Cochrane Library (through July 2012). We included trials and controlled observational studies in asymptomatic children and adolescents on the effectiveness and harms of screening and treatment, as well as accuracy of blood pressure measurement. One author extracted study characteristics and results, which were checked for accuracy by a second author.

RESULTS: No studies evaluated the effects of screening for hypertension on health outcomes. Two studies of screening tests for elevated blood pressure reported moderate sensitivities (0.65, 0.72) and specificities (0.75, 0.92). Sensitivities and specificities of child hypertension for the later presence of adult hypertension (7 studies) were wide ranging (0–0.63 and 0.77–1.0, respectively), and associations between child hypertension and carotid intima media thickening and proteinuria in young adults (3 studies) were inconsistent. Seven studies reported that drug interventions effectively lowered blood pressure in adolescents over short follow-up periods. No serious treatment-related adverse effects were reported.

CONCLUSIONS: There is no direct evidence that screening for hypertension in children and adolescents reduces adverse cardiovascular outcomes in adults. Additional studies are needed to improve diagnosis and risk stratification of children with elevated blood pressure and to quantify risks and benefits of interventions. Pediatrics 2013;131:490–525
Between 1% and 5% of children and adolescents have hypertension, and its prevalence has risen in the United States by 1% to 2% over recent decades. Hypertension is usually asymptomatic, and a significant proportion of children with hypertension are undiagnosed. Screening children and adolescents for elevated blood pressure could identify hypertension at an early stage where interventions could be initiated, potentially decreasing the rate of progression of hypertension from childhood to adulthood and reducing the clinical consequences of hypertension in adulthood.

The strongest risk factor for primary hypertension in children of all ages and both genders is elevated BMI; children who are overweight or obese have a two- to threefold increased risk of hypertension. This increased risk is particularly concerning given that ~17% of children and adolescents in the United States are now obese and have higher risk of other cardiovascular risk factors such as an adverse lipid profile and insulin resistance.

Other risk factors for primary hypertension include low birth weight, gender, ethnicity, and a positive family history. Secondary hypertension is most commonly related to underlying renal parenchymal or renovascular disease; less common causes include aortic coarctation and endocrine disorders. Elevated blood pressure is usually only 1 clinical manifestation of the underlying disorder, and treatment is typically directed at correcting the underlying cause.

For the majority of children and adolescents, the rationale for identifying elevated blood pressure lies in the potential to stratify risk of future cardiovascular disease. There is convincing evidence that structural and functional changes in the cardiovascular system, which indicate early atherosclerosis, can be detected in adolescents and young adults. What is less clear are the nature and magnitude of the relationship between elevated blood pressure and other cardiovascular risk factors in children or adolescents and cardiovascular risk in adults. Cohort studies that have followed children to young adulthood suggest that adiposity, insulin resistance, and an adverse lipid profile progress at an increased rate in prehypertensive and hypertensive children and adolescents compared with normotensive children.

AIMS OF THIS REVIEW

The purpose of this systematic review is to provide the US Preventive Services Task Force (USPSTF) with evidence to update their 2003 recommendation on screening for high blood pressure in children and adolescents. The larger review is available at www.uspreventiveservicestaskforce.org. With the input of members of the USPSTF, we developed an analytic framework (Fig 1) and key questions to guide our literature search and review.

1. Is screening for hypertension in children/adolescents effective in delaying the onset or reducing adverse health outcomes related to hypertension?
2. What is the diagnostic accuracy of screening tests for elevated blood pressure in children/adolescents?
3. What is the association between hypertension in children/adolescents and hypertension and other intermediate outcomes in adults?
4. What are the adverse effects of screening for hypertension in children/adolescents, including labeling and anxiety?
5. What is the effectiveness of drug, non-drug, and combination interventions?
for treating primary hypertension in children/adolescents?

6. What is the effectiveness of drug, nondrug, and combination interventions initiated for the treatment of primary hypertension in children/adolescents for reducing blood pressure and other intermediate outcomes in adults?

7. What is the effectiveness of drug, nondrug, and combination interventions initiated for the treatment of primary hypertension in children/adolescents for reducing adverse health outcomes in adults related to primary hypertension?

8. What are the adverse effects of drug, nondrug, and combination interventions for treating primary hypertension in children/adolescents?

**METHODS**

This review was developed by the Oregon Evidence-Based Practice Center under contract with the Agency for Healthcare Research Quality (contract 290-2007-10057-I) and follows the systematic review methods of the USPSTF.26,27

**Search Strategies**

We searched the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews (through July 2012) and MEDLINE (1946 to July 9, 2012) for relevant studies and systematic reviews, and manually reviewed reference lists for relevant citations (Appendix 1).

**Study Selection and Processes**

Papers were selected for full review if they met predefined inclusion criteria (Appendix 2). Controlled studies of screening for hypertension in asymptomatic children and adolescents were included. For studies of diagnostic accuracy, eligible studies included a reference standard comparison and provided adequate data to reproduce contingency tables. Evidence from randomized placebo-controlled trials was used to assess the efficacy of treatments on multiple outcomes, including blood pressure, other intermediate health outcomes, and final health outcomes, in childhood, adolescence, and adulthood. Studies with <30 participants and studies of interventions for the treatment of obesity and lipid disorders in children were excluded, because these populations are considered in other USPSTF recommendations.26,29 To assess harms of treatment, studies without a comparison or a placebo group were included. Studies of secondary hypertension were excluded, although some studies included proportions of participants with secondary hypertension.

All citations identified through searches and other sources were independently reviewed by 2 authors for inclusion and exclusion. Discrepancies at the full-text level were resolved through consensus. One author extracted data on the patient population, study design, testing methods, analysis, follow-up, and results, and a second author checked data extraction for accuracy.

**Quality Assessment and Synthesis**

By using predefined criteria developed by the USPSTF,26 2 authors rated the quality of studies (good, fair, poor) and resolved discrepancies by consensus. Authors assessed the overall strength of the body of evidence for each key question as good, fair, or poor by using methods developed by the USPSTF on the basis of the number, quality, and sample size of studies, as well as the consistency of results among studies and directness of the evidence.26 The limited number of studies and the heterogeneity of study designs, interventions, and diagnostic tests precluded meta-analyses; results are therefore summarized qualitatively as means or as ranges, as appropriate.

**RESULTS**

Our literature search identified a total of 6435 citations, of which we reviewed 1059 full-text publications and included 34 studies (Fig 2).

**Key Question 1: Is Screening for Hypertension in Children/Adolescents Effective in Delaying the Onset or Reducing Adverse Health Outcomes Related to Hypertension?**

No randomized trials compared health outcomes related to hypertension in screened versus nonscreened child or adolescent populations.

**Key Question 2: What Is the Diagnostic Accuracy of Screening Tests for Elevated Blood Pressure in Children and Adolescents?**

We identified 2 fair-quality studies that provided data on the diagnostic accuracy of screening tests (Appendix 3).30,31 Compared with a reference standard of 24-hour ambulatory measurement, office-based blood pressure measurement (3 measurements at each of 2 clinic visits) had a sensitivity of 0.65 (95% confidence interval [CI], 0.45–0.80) and a specificity of 0.75 (95% CI, 0.63–0.84).31 The positive predictive value was 0.37 (95% CI, 0.28–0.47) and the negative predictive value was 0.63 (95% CI, 0.53–0.72). All 105 participants (mean age, 13 years) had been referred for evaluation at a specialty clinic, so they may not have been representative of screened populations of asymptomatic children. In addition, ambulatory measurement is not yet an internationally accepted reference standard in children and adolescents. A second study examined a random sample of 9017 eighth graders, of whom about 10% (900/9017) had blood pressure >95th percentile on initial screening, whereas the remainder (8117/9017) were normotensive.30 At follow-up in 10th grade, the sensitivity
and specificity of initial elevated blood pressure for persistent elevation of blood pressure were 0.72 (95% CI, 0.65–0.78) and 0.92 (95% CI, 0.91–0.92), respectively; however, the positive predictive value was low (0.17 [95% CI, 0.15–0.20]). This study primarily followed only the sample of children whose initial screening test was positive rather than the entire population, which may have biased the diagnostic accuracy in this study.

In addition, 12 studies compared 1 measurement of blood pressure with subsequent reference measurements but did not meet our inclusion criteria because either they failed to apply the reference tests to participants who initially screened negative or they did not use an acceptable reference standard. Positive predictive values among these studies ranged from 0.04 to 0.53. The reasons for this heterogeneity were unclear but did not appear to be related to varying prevalence of hypertension, method or device used for testing, or thresholds used to define positive tests.

Key Question 3: What Is the Association Between Hypertension in Children/Adolescents and Hypertension and Other Intermediate Outcomes in Adults?

Ten longitudinal studies provided evidence on the association between elevated blood pressure or hypertension in childhood and elevated blood pressure, hypertension, or intermediate outcomes in adults (Appendix 4). Positive predictive values (i.e., the probability of adult hypertension given the presence of elevated blood pressure or hypertension in childhood) ranged from 0.19 to 0.65. Five studies reported significant associations between elevated blood pressure in childhood and hypertension in adults, with odds ratios (ORs) ranging from 1.1 to 4.5 and relative risks ranging from 1.5 to 9. Two studies reported conflicting findings on the association between childhood hypertension and carotid intima media thickness in young adults. Systolic blood pressure (SBP) > 80th percentile in adolescence was mildly associated with carotid intima media thickness in adulthood in 1 study (regression coefficient, 0.013; P < .001). A second study, however, found no increased risk of carotid intima media thickness in adulthood related to
elevated systolic blood pressure in childhood (highest quartile versus lower 3 quartiles: OR, 1; 95% CI, 0.80–1.25), although the level of SBP elevation is not defined in this study. Childhood hypertension was significantly associated with microalbuminuria in black but not white adults in a single study. We found no evidence for associations between diagnosed hypertension in childhood and other intermediate or final health outcomes.

Key Question 4: What Are the Adverse Effects of Screening for Hypertension in Children and Adolescents, Including Labeling and Anxiety?

One small good-quality study compared 85 children (10–18 years of age) with elevated blood pressure identified by screening to children matched by age and gender from the same community. The only outcome reported was rates of school absenteeism, which did not differ significantly between the 2 groups.

Key Question 5: What Is the Effectiveness of Drug, Nondrug, and Combination Interventions for Treating Primary Hypertension in Children and Adolescents?

Fourteen fair-quality randomized controlled trials (RCTs) (in 15 publications) of treatment of hypertension in children and adolescents met inclusion criteria (Table 1; Appendix 5). The proportion of children with primary hypertension ranged from 31% to 56%; however, most studies did not report the proportion of participants with secondary hypertension.

Drug Interventions

All seven included trials of drug interventions examined different drugs. Most compared active drug (in different doses) to placebo, with follow-up of only 4 weeks. The magnitude of effects on SBP and diastolic blood pressure (DBP) varied and were not consistently different from changes in blood pressure in the placebo group (or these differences were not reported).

Five studies reported the percentage of participants achieving target blood pressure at the end of the follow-up period, and all noted an increase in those who achieved target levels with the active drug (range 15–86% of subjects). However, 26% to 47% of children in the placebo groups also achieved normal blood pressure at the end of the study period. Most studies reported significant reductions in mean SBP (range, 1.9–10.2 mm Hg) and DBP (range, 0.4–8.1 mm Hg). Eplerenone (50 mg/day) produced a small increase in mean SBP and no change in DBP. Most studies had limitations, most notably the failure to report the statistical significance of differences between treatment groups in addition to within-group treatment differences. Also, comparison among studies was difficult because of varying drug dosages.

Drug Plus Lifestyle Interventions

The school-based A Dietary/Exercise Alteration Program Trial (ADAPT) examined the effectiveness of a multi-component, school-based intervention, including nutrition education for and promotion of diet modification to children and parents; expanded community availability of low-sodium foods in grocery stores, restaurants, and school lunches; a school-based exercise program; and propranolol and chlorthalidone compared with no intervention group. This complex intervention resulted in a significant decrease in both SBP and DBP at the 6-month follow-up (mean SBP change: −7.6 mm Hg [P < .0001]; mean DBP change: −6.9 mm Hg [P < .01]) compared with the control group. At 30 months, however, SBP increased from baseline in both the intervention (1.4 mm Hg) and control groups (3.5 mm Hg), although DBP remained below baseline levels (mean change: −4.2 mm Hg in the intervention group and −3.3 mm Hg in the control group).

Lifestyle Interventions

Most of the six trials examining lifestyle interventions included support related to the interventions (eg, regular check-ins) in addition to diet, exercise, or meditation. Only 1 study demonstrated statistically significant reductions in blood pressure compared with untreated controls. This small, school-based RCT compared the effects of 5 versus 3 weekly physical education classes in hypertensive children and reported that blood pressure decreased significantly more in participants receiving 5 weekly classes over the 8-month follow-up period (mean between-group difference in SBP = −4.9 mm Hg and DBP = −3.8 mm Hg; P < .05 for both outcomes). In another trial, a low-sodium diet combined with personalized support from a nutritionist and/or potassium chloride supplementation was effective in reducing blood pressure compared with usual care plus placebo at 36 months among girls but not among boys. Other studies of meditation, relaxation, and dietary changes reported no significant differences between intervention and control groups.

Key Question 6: What Is the Effectiveness of Drug, Nondrug, and Combination Interventions Initiated for the Treatment of Primary Hypertension in Children/Adolescents for Reducing Blood Pressure and Other Intermediate Outcomes in Adults?

No RCTs examined the effectiveness of interventions for hypertension in children or adolescents for reducing blood pressure or other intermediate outcomes in adults.
<table>
<thead>
<tr>
<th>Author, Year, Duration</th>
<th>Interventions</th>
<th>Baseline (mm Hg)</th>
<th>Follow-up (mm Hg)</th>
<th>Mean Difference: Follow-up Versus Baseline (mm Hg)</th>
<th>Mean Difference at Intervention Versus Placebo (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug interventions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Batisky et al 2007⁷⁻⁸ (4 wk)</td>
<td>Metoprolol 0.2 mg/kg</td>
<td>131.4 76.3</td>
<td>126.2 73.2</td>
<td>−5.2 3.1</td>
<td>−4.6 −6.1</td>
</tr>
<tr>
<td></td>
<td>Metoprolol 1.0 mg/kg</td>
<td>135.0 81.0</td>
<td>127.3 76.1</td>
<td>−7.7 4.9</td>
<td>−3.5 −3.2</td>
</tr>
<tr>
<td></td>
<td>Metoprolol 2.0 mg/kg</td>
<td>130.60 76.7</td>
<td>124.3 69.2</td>
<td>−6.3 7.5</td>
<td>−0.2 −10.1</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>132.7 81.4</td>
<td>130.8 79.3</td>
<td>−1.9 2.1</td>
<td>— —</td>
</tr>
<tr>
<td>Flynn et al 2004⁴⁻⁵ (4 wk)</td>
<td>Amlodipine 2.5 mg</td>
<td>137.9ᵃ 74.2ᵃ</td>
<td>Not reported</td>
<td>— —</td>
<td>— —</td>
</tr>
<tr>
<td></td>
<td>Amlodipine 5 mg</td>
<td>135.0 81.0</td>
<td>127.3 76.1</td>
<td>−7.7 4.9</td>
<td>−3.5 −3.2</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>132.7 81.4</td>
<td>130.8 79.3</td>
<td>−1.9 2.1</td>
<td>— —</td>
</tr>
<tr>
<td>Li et al 2010⁴⁻⁵ (4 wk)</td>
<td>Eplerenone 25 mg</td>
<td>125.0 71.3</td>
<td>124.1 70.7</td>
<td>−0.9 0.6</td>
<td>−5.4 0.8</td>
</tr>
<tr>
<td></td>
<td>Eplerenone 50 mg</td>
<td>125.7 70.9</td>
<td>126.2 70.9</td>
<td>0.5 0.0</td>
<td>−3.3 1.0</td>
</tr>
<tr>
<td></td>
<td>Eplerenone 100 mg</td>
<td>128.1 70.3</td>
<td>127.0 69.4</td>
<td>−1.1 0.9</td>
<td>−2.5 −0.5</td>
</tr>
<tr>
<td></td>
<td>Placebo (mean, all arms)</td>
<td>128.7 70.4</td>
<td>129.5 69.9</td>
<td>0.8 0.5</td>
<td>— —</td>
</tr>
<tr>
<td>Sorof et al 2002⁵⁻⁶ (4 wk)</td>
<td>Bisoprolol + hydrochlorothiazide (all doses)</td>
<td>133.8 83.0</td>
<td>124.0 76.0</td>
<td>−9.8 7.0</td>
<td>−4.5 −3.5</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>133.8 81.8</td>
<td>128.5 79.5</td>
<td>−5.3 2.3</td>
<td>— —</td>
</tr>
<tr>
<td>Trachtman et al 2003⁵⁻⁶ (3 wk)</td>
<td>Felodipine 2.5 mg</td>
<td>Not reported</td>
<td>Not reported</td>
<td>— —</td>
<td>— —</td>
</tr>
<tr>
<td></td>
<td>Felodipine 5 mg</td>
<td>Not reported</td>
<td>Not reported</td>
<td>— —</td>
<td>— —</td>
</tr>
<tr>
<td></td>
<td>Felodipine 10 mg</td>
<td>Not reported</td>
<td>Not reported</td>
<td>— —</td>
<td>— —</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>132.0 79.0</td>
<td>123.0 71.3</td>
<td>−9.7 8.1</td>
<td>−3.6 −4.2</td>
</tr>
<tr>
<td>Wells et al 2010⁵⁻⁶ (4 wk)</td>
<td>Candesartan (all doses)</td>
<td>Not reported</td>
<td>Not reported</td>
<td>−10.2 6.6</td>
<td>— —</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>Not reported</td>
<td>Not reported</td>
<td>−3.7 1.8</td>
<td>— —</td>
</tr>
<tr>
<td>Drug plus lifestyle interventions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berenson et al 1983⁹⁻¹⁰ (6 mo)</td>
<td>ADAPT program</td>
<td>116.6 77.7</td>
<td>109.0 70.8</td>
<td>−7.6 6.9</td>
<td>−6.5 −3.6</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>118.5 78.3</td>
<td>115.5 74.4</td>
<td>−3.0 3.9</td>
<td>— —</td>
</tr>
<tr>
<td>Berenson et al 1990¹⁻² (30 mo)b</td>
<td>ADAPT program</td>
<td>116.6 77.7</td>
<td>118.0 73.5</td>
<td>1.4 4.2</td>
<td>−3.6 −1.7</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>118.5 78.5</td>
<td>122.0 75.2</td>
<td>3.5 3.3</td>
<td>— —</td>
</tr>
<tr>
<td>Lifestyle interventions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Couch et al 2008¹⁻² (6 mo)</td>
<td>DASH diet</td>
<td>128.4 80.4</td>
<td>120.1 75.2</td>
<td>−9.3 5.2</td>
<td>0.1 −1.2</td>
</tr>
<tr>
<td></td>
<td>Routine care</td>
<td>124.3 81.5</td>
<td>120.0 76.4</td>
<td>−4.3 5.3</td>
<td>— —</td>
</tr>
<tr>
<td>Ewart et al 1987¹⁻² (8 mo)</td>
<td>Relaxation training</td>
<td>127.0 79.1</td>
<td>118.6 72.9</td>
<td>−8.4 6.2</td>
<td>−2.3 −3.1</td>
</tr>
<tr>
<td></td>
<td>No intervention</td>
<td>126.5 80.4</td>
<td>120.3 78.0</td>
<td>−6.2 4.4</td>
<td>— —</td>
</tr>
<tr>
<td>Gregoski et al 2011¹⁻² (3 mo)</td>
<td>Meditation</td>
<td>119.4 68.1</td>
<td>116.8 68.3</td>
<td>−2.8 1.8</td>
<td>−4.4 −2.4</td>
</tr>
<tr>
<td></td>
<td>LifeSkills training</td>
<td>118.6 68.0</td>
<td>119.8 68.2</td>
<td>0.2 0.2</td>
<td>−1.2 −0.5</td>
</tr>
<tr>
<td></td>
<td>Regular health education</td>
<td>121.4 69.3</td>
<td>121.0 68.7</td>
<td>−0.4 0.6</td>
<td>— —</td>
</tr>
<tr>
<td>Hansen et al 1991¹⁻² (3 mo)</td>
<td>Extra physical education classes</td>
<td>Not reported</td>
<td>Not reported</td>
<td>— —</td>
<td>— —</td>
</tr>
<tr>
<td></td>
<td>No extra classes</td>
<td>— —</td>
<td>— —</td>
<td>— —</td>
<td>— —</td>
</tr>
<tr>
<td>Howe et al 1991¹⁻² (4 wk)</td>
<td>Low sodium diet</td>
<td>115.0ᵃ 60.1ᵃ</td>
<td>112.6 59.1</td>
<td>Not reported</td>
<td>−1.2 −0.9</td>
</tr>
<tr>
<td></td>
<td>High sodium diet</td>
<td>113.8 60</td>
<td>— —</td>
<td>— —</td>
<td>— —</td>
</tr>
</tbody>
</table>

DASH, Dietary Approaches to Stop Hypertension; —, indicates that data is not available.  
ᵃ Values for total cohort; data not stratified according to treatment group.  
b Continuation of Berenson et al 1983 study.
Key Question 7: What Is the Effectiveness of Drug, Nondrug, and Combination Interventions Initiated for the Treatment of Primary Hypertension in Children/Adolescents for Reducing Adverse Health Outcomes in Adults Related to Primary Hypertension?

No RCTs examined the effectiveness of interventions for hypertension in children or adolescents for reducing clinical outcomes in adults.

Key Question 8: What Are the Adverse Effects of Drug, Nondrug, and Combination Interventions for Treating Primary Hypertension in Children and Adolescents?

Drug Interventions

Twelve trials reported adverse events with drug therapy (Appendix 6).55–59,67–71 One study was rated good quality67; the remainder were of fair quality.53–55,57–67,68–71 Four of the studies included children with primary hypertension,53,57–59 whereas the remainder included children with primary or secondary hypertension.54,55,67–71 The number of children enrolled in the studies ranged from 76 to 304, the mean age ranged from 12 to 14 years, and the duration of follow-up for reporting adverse events ranged from 4 weeks to 1 year.

Serious adverse events were rarely reported, and there were no deaths in any of the studies. One study of metoprolol reported 1 case each of pneumonia and metemorrhagia.55 Another study reported a case of near syncope and an elevated creatinine in a patient who received an incorrect dose of telmisartan. A third study reported 8 serious adverse events among 304 patients, although none were considered to be treatment related.55

Adverse event data were often poorly reported, and most studies reported noncomparative data from open-label extensions of RCTs. Five studies of monotherapy reported similar rates of adverse events in the intervention (range, 27–77%) and placebo groups (range, 25–66%).55,57,59,67,68 Children taking a combination of bisoprolol plus hydrochlorothiazide had lower overall rates of adverse events compared with placebo (53–75%, P = .05) after 12 weeks of follow-up.56 Withdrawals caused by adverse events ranged from 0% to 7% in children receiving active treatments53,54,56–59,67–71 and 0% to 6.2% in placebo groups.53,56,58,59,67,68

Headache was the most common specific adverse event in most studies: rates ranged from 2% to 33% in children receiving active treatments53,56,57,59,68,71 but only 2 studies reported rates for the placebo group. One study reported that no headaches occurred in the placebo group compared with 11% of active treatment patients,59 whereas in a second study, headache was reported in 31% versus 26% (placebo versus combination treatment, significance not reported).56 Other commonly reported adverse events associated with active treatments were cough, upper respiratory infections, and gastrointestinal events, including nausea and diarrhea, although specific rates were not always reported.53,54,56–58,59,68–71

Two studies pooled adverse event data from selected drug trials submitted to the Food and Drug Administration over a 7-year period; however, neither study used standard systematic review methods.72,73 Pooled patient-level data from 1707 children from 10 placebo-controlled RCTs of 10 different active agents72 revealed similar rates of adverse events between active treatment (0.83 events per patient) and placebo groups (0.76 per patient) after 2 to 4 weeks of follow-up (between-group P = .37). Pooled data from 8 RCTs of hypertensive children revealed no difference in the incidence of cough between active treatment and placebo groups (3% in both groups; P = .86).73

Other Interventions

The fair-quality ADAPT of a propranolol and chlorthalidone/lifestyle intervention described in key question 54 reported no adverse events.60,61 No studies of lifestyle modification alone reported adverse events.

DISCUSSION

Direct evidence linking screening of children and adolescents for hypertension and delaying the onset or reducing the risk cardiovascular outcomes in adults is not available, and indirect evidence is sparse and of variable quality. We did not identify evidence for the effectiveness of interventions used to treat primary hypertension in children on lowering blood pressure levels or reducing adverse health outcomes in adults. A summary of the evidence is provided in Table 2.

High-quality data on the diagnostic accuracy of blood pressure measurement to detect hypertension were also sparse and suggest moderate sensitivities (0.65 and 0.72), with somewhat higher specificities (0.75 and 0.92). These data suggest that many children who have elevated blood pressure on screening will not have hypertension. There are also some data to suggest that hypertension in childhood is associated with hypertension in young adults (OR range, 1.1–4.5; relative risk range, 1.5–9) or has low to moderate sensitivities (0 and 0.65) and specificities (0.77 and 1) for predicting adult hypertension. Moreover, the association between childhood hypertension and carotid intima media thickness and microalbuminuria in young adults was also inconclusive, and direct evidence on other intermediate or final health outcomes was lacking.

The effectiveness of antihypertensive medications in children and adolescents has been examined in 7 trials, all of which were small and of short duration, and each examined a different
### TABLE 2 Summary of Evidence

<table>
<thead>
<tr>
<th>Key question</th>
<th>Number of Studies (Overall Quality)</th>
<th>Limitations</th>
<th>Consistency</th>
<th>Applicability to Primary Care</th>
<th>Summary of Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Key question 1: Is screening for hypertension in children/adolescents effective in delaying the onset or reducing adverse health outcomes related to hypertension?</td>
<td>No studies</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>No studies</td>
</tr>
<tr>
<td>Key question 2: What is the diagnostic accuracy of screening tests for elevated blood pressure in children/adolescents?</td>
<td>2 trials (poor)</td>
<td>Studies were flawed or not directly applicable to an asymptomatic US population. Only 1 included a comparison with a gold standard of ambulatory monitoring.</td>
<td>Consistent</td>
<td>Low</td>
<td>Sensitivity and specificity of office-based screening for hypertension was 0.65 and 0.75 (positive predictive value, 0.37) compared with ambulatory screening in 1 study of a referred population. A second, school-based study comparing an initial positive screen to subsequent diagnosis of hypertension had sensitivity (0.72) and specificity (0.92), but the positive predictive value was lower (0.17).</td>
</tr>
<tr>
<td>Key question 3: What is the association between hypertension in children/adolescents and hypertension and other intermediate outcomes in adults?</td>
<td>10 cohort studies (poor)</td>
<td>Studies used different thresholds for defining elevated blood pressure and hypertension in children and different definitions of hypertension in adults. Studies had methodologic shortcomings.</td>
<td>Inconsistent</td>
<td>Moderate</td>
<td>Sensitivities and specificities of elevated blood pressure or hypertension from childhood to adult hypertension ranged from 0.77 to 1. PPs ranged from 0.19 to 0.85. Five studies reported significant associations between elevated blood pressure in childhood and hypertension in adults, with ORs ranging from 1.1 to 4.5 and RRs of 1.5 to 9. Two studies reported associations between childhood hypertension and carotid intima media thickness in young adults, with conflicting findings. One study reported a significant association between childhood hypertension and microalbuminuria only in black individuals.</td>
</tr>
<tr>
<td>Key question 4: What are the adverse effects of screening for hypertension in children/adolescents, including labeling and anxiety?</td>
<td>1 study (poor)</td>
<td>Evidence limited to results from 1 good-quality study</td>
<td>NA (1 study)</td>
<td>High</td>
<td>Children labeled as hypertensive did not miss more days of school in the year after diagnosis compared with prelabeling or compared with nonhypertensive children. Other harms associated with screening were not reported.</td>
</tr>
<tr>
<td>Key question 5: What is the effectiveness of drug, nondrug, and combination therapies for treating primary hypertension in children/adolescents?</td>
<td>14 RCTs (poor)</td>
<td>Longest drug study duration was only 4 wk</td>
<td>Consistent</td>
<td>Moderate</td>
<td>Children achieving normotensive status (on the basis of varying definitions) ranged from 15% to 86% in patients taking drug treatments and 11% to 48% in patients taking placebo. There were significant reductions of mean SBP (range 2–10 mm Hg), and mean DBP (range 0.4–8 mm Hg) with some drugs and dosages. The difference between intervention and placebo groups ranged from 0 to 9 mm Hg for SBP and 0.5 to 10 mm Hg for DBP. However, reductions were often only at higher doses of active treatments, and studies only lasted for 4 wk. One school-based study of a drug plus lifestyle intervention reported a significant, sustained reduction in blood pressure in the combination group versus the control group. Studies of nondrug therapies were limited, and only 1 study examining the effect of additional physical education classes in school reported a sustained mean reduction in blood pressure in for both boys and girls.</td>
</tr>
</tbody>
</table>

For many studies, the proportion of children with secondary hypertension was unclear.
agent. Most importantly, their antihypertensive effects varied in magnitude, were not consistently present for a given agent for both SBP and DBP, and were not consistently different from placebo or from baseline. Blood pressures in placebo groups often improved along with those of the intervention group, suggesting regression to the mean. From the limited data we identified, medications appeared to be well tolerated, with no serious adverse effects.

Interventions for treating elevated blood pressure that involve lifestyle interventions alone or in combination with an antihypertensive medication found inconsistent results. Of the 3 studies that had positive results, increased physical education at school was effective at reducing blood pressure in 1 study, whereas in a second longer-term school-based study, the effects of an antihypertensive combined with a complex lifestyle program (the ADAPT program) were not sustained, and finally, a low sodium diet combined with personalized support was only effective in girls.

The most important potential limitation of this review was the absence of any evidence to address several of the key questions and the limited quantity and quality of evidence for others. This lack of evidence inevitably limits the conclusions that can be drawn from this review. Second, our search strategy, although rigorous, may have failed to identify relevant studies. We used citation searching of included articles and reviewed all articles identified by the expert reviewers to augment our search strategy. We limited our search to English language publications, which could have limited eligible studies. We cannot exclude the possibility of publication and selective reporting biases, but we were not able to formally test for this. In addition, by including only studies where the interventions were directed against treatment of hypertension (eg, rather than obesity), indirect evidence was excluded. Finally, identified studies had multiple deficiencies in reporting and methodology, which limited the data available for analysis and interpretation. Limitations included the lack of studies that examined an intervention in >1 trial or obvious clinical heterogeneity, precluding the use of meta-analyses.

Future research in this area needs to address the following major gaps in the current state of evidence.

- Diagnostic accuracy of blood pressure measurement in primary care and community settings for screening children of varying ages and characteristics. This includes

<table>
<thead>
<tr>
<th>Number of Studies (Overall Quality)</th>
<th>Limitations</th>
<th>Consistency</th>
<th>Applicability to Primary Care</th>
<th>Summary of Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Key question 6: What is the effectiveness of drug, nondrug, and combination therapies initiated for the treatment of primary hypertension in children/adolescents for reducing blood pressure and other intermediate outcomes in adults?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No studies</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Key question 7: What is the effectiveness of drug, nondrug, and combination therapies initiated for the treatment of primary hypertension in children/adolescents for reducing adverse health outcomes in adults related to primary hypertension?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No studies</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Key question 8: What are the adverse effects of drug, nondrug, and combination therapies for treating primary hypertension in children/adolescents?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 studies (13 RCTs, 2 FDA analyses) (fair)</td>
<td>Numerous trials from key question 5 did not report comparative events rates between active treatment and placebo arms, and adverse event rates overall are not well-reported in most studies.</td>
<td>Consistent</td>
<td>Moderate</td>
<td>Studies of antihypertensive drugs in children and adolescents generally reported no significant difference between active treatments and placebo in adverse event rates or in withdrawals due to adverse events. In one study, a combination of bisoprolol and hydrochlorothiazide was associated with lower adverse event rates than placebo. Four studies reported serious adverse events, although with the exception of 1 case of syncope due to a dosing error, serious adverse events were generally not deemed treatment related. Analysis of FDA data revealed no significant difference between drug treatments and placebo in the incidence of specific adverse events, including headache (the most commonly reported adverse event), cardiac events, gastrointestinal events, and cough. No studies reported on harms associated with nondrug treatments.</td>
</tr>
</tbody>
</table>

FDA, Food and Drug Administration; NA, not applicable; PPV, positive predictive value; RR, relative risk.
identifying the number, frequency, and timing of readings needed to confirm or rule out hypertension.74

- Adverse effects of screening, including health care utilization, burden on the family, and discomfort and anxiety for the child and family.

- Epidemiologic studies to describe the natural history of elevated blood pressure and hypertension in children and adolescents, identifying factors that predict persistence into adulthood, and regression to normal based on baseline characteristics such as age, BMI, and pattern of blood pressure. Such studies need to use current definitions of hypertension and be of sufficient duration to draw clinically useful conclusions.74,75

- Epidemiologic studies to better define thresholds used to define hypertension in children and adolescents and their association with both structural (eg, carotid intima media thickening, left ventricular mass) and functional (eg, arterial stiffness) markers of target organ damage related to hypertension.

- Longer-term trials of benefits and risks of all antihypertensive agents (as monotherapy and in combination) and evidence for both short- and long-term safety. Given the expected duration of antihypertensive therapy, the absence of long-term safety data is a significant limitation.

- Large, controlled, good-quality trials of feasible nondrug interventions for children and adolescents using more sophisticated approaches to complex interventions to identify components that provide the greatest benefit over prolonged periods.

CONCLUSIONS

The prevalence of hypertension in children and adolescents is increasing in the United States, largely driven by increased BMI. Screening children for elevated blood pressure or hypertension has the potential to shift the management of hypertension to younger age groups and potentially reduce future cardiovascular disease risk in adults. However, at present, the evidence needed to support these practices is limited. Although it would be logistically (and ethically) very challenging to demonstrate the effects of interventions in children and adolescents with elevated blood pressure on cardiovascular outcomes occurring many decades later in adults, there are clearly a number of outstanding research gaps that can be addressed by feasible research designs in a much shorter time frame. Increasingly, blood pressure is being viewed within a paradigm of overall cardiovascular risk stratification, along with other risk factors, such as lipid profiles, insulin resistance, and BMI.16 We anticipate that addressing these current gaps in the evidence for blood pressure will be critical to add to clinicians’ ability to identify children and adolescents with increased cardiovascular risk and also to offer a balanced assessment of the overall benefit of interventions to reduce this risk and prevent future cardiovascular disease.

ACKNOWLEDGMENTS

The authors thank the responsible Medical Officer at the Agency of Healthcare Research and Quality, Iris Mabry-Hernandez, MD, MPH, and US Preventive Services Task Force members Kirsten Bibbins-Domingo, PhD, MD, David Grossman, MD, MPH, Bernadette Melynky, PhD, RN, CPNP/NPP, and Wanda Nicholson, MD, MPH. We also thank Matthew Gillman, MD, for providing clinical expertise.

REFERENCES

10. Sorof JM, Lai D, Turner J, Poffenbarger T, Portman RJ. Overweight, ethnicity, and the


47. Juhola J, Magnussen CG, Viikari JSA, et al. Tracking of serum lipid levels, blood pressure, and body mass index from childhood to adulthood: the Cardiovascular Risk in


APPENDIX 1 Search Strategies

**Screening**

Database: Ovid Medline(R) and Ovid OLDMEDLINE(R)

1 Hypertension or hypertension.mp.
2 prehypertension.mp.
3 pre-hypertension.mp.
4 2 or 3
5 high blood pressure.mp.
6 or/1–5
7 Mass screening
8 6 and 7
9 Limit 8 to (English language and humans)
10 Limit 9 to “all child (0 to 18 years)”
11 9 and (child$ or pediatr$ or adolescen$ or school-age).mp.
12 10 or 11

Database: EBM Reviews: Cochrane Central Register of Controlled Trials

1 Hypertension/ or hypertension.mp.
2 prehypertension.mp.
3 pre-hypertension.mp.
4 2 or 3
5 high blood pressure.mp.
6 or/1–5
7 Mass screening/
8 6 and 7
9 8 and (child$ or pediatr$ or school or adolescen$ or teen$).mp.

**Diagnostic accuracy**

Database: Ovid Medline(R) and Ovid OLDMEDLINE(R)

1 Hypertension/
2 prehypertension.mp. or Prehypertension/
3 1 or 2
4 Blood pressure determination/
5 sensitivity.mp.
6 specificity.mp.
7 5 and 6
8 “Sensitivity and specificity”/
9 7 or 8
10 3 and 9
11 4 and 9
12 10 or 11
13 Limit 12 to “all child (0 to 18 years)”

Database: EBM Reviews: Cochrane Central Register of Controlled Trials

1 Hypertension/
2 prehypertension.mp. or Prehypertension/
3 1 or 2
4 Blood pressure determination/
5 sensitivity.mp.
6 specificity.mp.
7 5 and 6
8 “Sensitivity and specificity”/
9 7 or 8
10 3 and 9
11 4 and 9
12 10 or 11
13 12 and (child$ or pediatr$ or school or adolescen$ or teen$).mp.

**Tracking**

Database: Ovid Medline(R) and Ovid OLDMEDLINE

1 “cardiovascular risk in young finns”.mp.
2 “bogalusa heart”.mp.
3 muscatine.mp.
4 (“childhood determinants of adult health” or cdah).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
5 or/1–4
6 5 and (child$ or pediatr$ or adolescen$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
APPENDIX 1

Continued

Screening

7 blood pressure.mp. or Blood Pressure/
8 Hypertension/ or hypertension.mp.
9 or
10 9 and (child$ or pediatric$ or adolescent$).mp.
11 10 and adult$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
12 Longitudinal studies/
13 11 and 12
14 6 or 13
15 “Amsterdam Growth and Health Longitudinal Study” mp.
16 15 and (child$ or pediatric$ or adolescent$).mp.
17 14 or 16
18 17 not pregnancy.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
19 17 not infant$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
20 18 or 19
21 Limit 20 to (English language and humans)
22 Atherosclerosis/
23 Vascular diseases/
24 Albuminuria/
25 Cerebrovascular disorders/
26 Hypertrophy, Left ventricular/
27 Hypertension/
28 or/22–27
29 21 and 28

Interventions

Database: Ovid Medline(R) and Ovid OLDMEDLINE(R)

1 Hypertension/dh, de, dt, pc, rt, rh, su, th [Diet Therapy, Drug Effects, Drug Therapy, Prevention & Control, Radiotherapy, Rehabilitation, Surgery, Therapy]
2 Wt Loss/
3 Exercise/
4 dietary modification.mp. or Food Habits/
5 Diet, sodium-restricted/
6 Angiotensin-Converting Enzyme Inhibitors/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
7 Angiotensin II Type 1 Receptor Blockers/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
8 Labetalol/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
9 Adrenergic β-Antagonists/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
10 Atenolol/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
11 Bisoprolol/ad, ae, tu [Administration & Dosage, Adverse Effects, Therapeutic Use]
12 Metoprolol/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
13 Propranolol/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
14 Calcium Channel Blockers/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
15 Amlodipine/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
16 Felodipine/ad, ae, tu, to [Administration & Dosage, Adverse Effects, Therapeutic Use, Toxicity]
17 Isradipine/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
18 Nifedipine/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
19 Clonidine/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
20 Diuretics/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
21 Hydrochlorothiazide/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
22 Chlorothalidone/ad, ae, tu, to [Administration & Dosage, Adverse Effects, Therapeutic Use, Toxicity]
23 Furosemide/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
24 Spironolactone/ad, ae, tu, to [Administration & Dosage, Adverse Effects, Therapeutic Use, Toxicity]
25 Triamterene/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
26 Amiloride/ad, ae, tu, to [Administration & Dosage, Adverse Effects, Therapeutic Use, Toxicity]
27 Adrenergic α-Antagonists/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
28 Doxazosin/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
29 Prazosin/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
30 Vasodilator Agents/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
31 Hydralazine/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
32 Minoxidil/ad, ae, po, tu [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use]
33 Captopril/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
34 Enalapril/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
Screening

35 Fosinopril/ad, ae, tu, to [Administration & Dosage, Adverse Effects, Therapeutic Use, Toxicity]
36 Lisinopril/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
37 Losartan/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
38 (benazepril or quinapril or irbesartan or terazosin).mp.
39 or/2–38
40 Hypertension/
41 39 and 40
42 1 or 41
43 Limit 42 to (English language and humans)
44 Limit 43 to “all child (0 to 18 years)”

Database: EBM Reviews: Cochrane Central Register of Controlled Trials

1 Wt Loss/
2 Exercise/
3 dietary modification.mp. or Food Habits/
4 Diet, Sodium-Restricted/
5 Angiotensin-Converting Enzyme Inhibitors/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
6 Angiotensin II Type 1 Receptor Blockers/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
7 Labetalol/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
8 Adrenergic β-Antagonists/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
9 Atenolol/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
10 Bisoprolol/ad, ae, tu [Administration & Dosage, Adverse Effects, Therapeutic Use]
11 Metoprolol/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
12 Propranolol/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
13 Calcium Channel Blockers/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
14 Amlodipine/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
15 Felodipine/ad, ae, tu, to [Administration & Dosage, Adverse Effects, Therapeutic Use, Toxicity]
16 Isradipine/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
17 Nifedipine/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
18 Clonidine/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
19 Diuretics/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
20 Hydrochlorothiazide/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
21 Chlorothalidone/ad, ae, tu, to [Administration & Dosage, Adverse Effects, Therapeutic Use, Toxicity]
22 Furosemide/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
23 Spironolactone/ad, ae, tu, to [Administration & Dosage, Adverse Effects, Therapeutic Use, Toxicity]
24 Triamterene/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
25 Amiloride/ad, ae, tu, to [Administration & Dosage, Adverse Effects, Therapeutic Use, Toxicity]
26 Adrenergic α-Antagonists/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
27 Doxazosin/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
28 Prazosin/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
29 Vasodilator Agents/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
30 Hydralazine/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
31 Minoxidil/ad, ae, po, tu [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use]
32 Captopril/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
33 Enalapril/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
34 Fosinopril/ad, ae, tu, to [Administration & Dosage, Adverse Effects, Therapeutic Use, Toxicity]
35 Lisinopril/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
36 Losartan/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
37 (benazepril or quinapril or irbesartan or terazosin).mp.
38 or/1–37
39 Blood Pressure/
40 38 and 39

Systematic reviews

Database: EBM Reviews: Cochrane Database of Systematic Reviews

1 hypertension.ti.
2 blood pressure.ti.
3 or 2
4 3 and (child$ or pediatric$ or school or adolescent$ or teen$).mp.
5 4 not (neonat$ or newborn or infant$).ti.
6 5 not (pregnан$ or postpartum).ti.
<table>
<thead>
<tr>
<th>Key Questions</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Settings</td>
<td>All</td>
<td>Pediatric specialty/subspecialty clinics, inpatient, or long-term care settings, emergency or urgent care facilities</td>
</tr>
<tr>
<td>Populations</td>
<td>1, 2, and 4</td>
<td>Pregnant adolescents</td>
</tr>
<tr>
<td></td>
<td>3 and 5–8:</td>
<td>Majority of study population included secondary hypertension</td>
</tr>
<tr>
<td>Interventions</td>
<td>1–4:</td>
<td>24-h, ambulatory, or home-based blood pressure measurements. Diagnostic tests or investigations used to identify or confirm possible causes of secondary hypertension</td>
</tr>
<tr>
<td></td>
<td>5–8:</td>
<td>Interventions for treatment of secondary hypertension</td>
</tr>
<tr>
<td></td>
<td>Drug:</td>
<td>Interventions where reduction in blood pressure was not a primary objective of the study (eg, weight loss studies)</td>
</tr>
<tr>
<td></td>
<td>Lifestyle:</td>
<td>Measures of cognitive function</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Blood pressure</td>
<td>Blood pressure variability, such as diurnal variations or nocturnal blood pressure dipping</td>
</tr>
<tr>
<td></td>
<td>Left ventricular hypertrophy (defined using left ventricular mass index and/or measures of left ventricular geometry)</td>
<td>Arterial wall dysfunction, including measures of arterial stiffness, pulse wave velocity, or augmentation index</td>
</tr>
<tr>
<td></td>
<td>Urinary albumin excretion (microalbuminuria)</td>
<td>Metabolic measures, eg, measures of impaired glucose tolerance, levels of insulin, lipid profiles, homocysteine levels</td>
</tr>
<tr>
<td></td>
<td>Intima-medial thickness (measured at carotid and/or femoral arteries)</td>
<td>Uric acid levels</td>
</tr>
<tr>
<td></td>
<td>Retinal vascular changes</td>
<td>Inflammatory markers including C-reactive protein</td>
</tr>
<tr>
<td></td>
<td>Body changes in weight or BMI</td>
<td>Body changes in weight or BMI</td>
</tr>
<tr>
<td>Study designs</td>
<td>1</td>
<td>Studies reporting intermediate outcomes</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Studies that do not provide enough data to recreate 2 × 2 tables or calculate sensitivity and specificity</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Studies that do not use a true reference standard for comparison</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Studies not reporting measures of association</td>
</tr>
<tr>
<td></td>
<td>Randomized controlled trials, controlled clinical trials, observational studies with a comparison group (eg, comparative cohort and case-control studies), and systematic reviews</td>
<td>Study designs other than those specified</td>
</tr>
<tr>
<td></td>
<td>Studies of predictive validity that compare with a reference standard (eg, ambulatory monitoring)</td>
<td>Study designs other than those specified</td>
</tr>
<tr>
<td></td>
<td>Longitudinal cohort and epidemiology studies</td>
<td>Study designs other than those specified</td>
</tr>
<tr>
<td></td>
<td>Randomized controlled trials, controlled clinical trials, observational studies with a comparison group (eg, large cohort and case-control studies), and systematic reviews. If none were identified, uncontrolled before-after studies were examined.</td>
<td>Study designs other than those specified</td>
</tr>
<tr>
<td></td>
<td>Randomized controlled trials, controlled clinical trials, observational studies with a comparison group (eg, large cohort and case-control studies), and systematic reviews</td>
<td>Study designs other than those specified</td>
</tr>
</tbody>
</table>
### APPENDIX 3 Diagnostic Accuracy of Screening for Elevated Blood Pressure in Children and Adolescents

<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Screening Test</th>
<th>Reference Standard</th>
<th>Definition of a Positive Screening Examination</th>
<th>Population</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
<th>Quality Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixler and Laird 1983</td>
<td>Three measures with mercury manometer measured at least 4 wk apart</td>
<td>Initial screening results compared with subsequent measures</td>
<td>SBP or DBP ≥95th percentile based on normative levels for the study population</td>
<td>n = 9017; eighth graders with follow-up at 10th grade; mean age not reported; all were in eighth grade at time of initial screening: 53% male, 44% black, 42% white, 14% Hispanic</td>
<td>Initial positive screen versus subsequent screens: 0.72 (95% CI, 0.65–0.78)</td>
<td>Initial positive screen versus subsequent positive screening test: 0.92 (95% CI, 0.91–0.92)</td>
<td>Initial positive screen versus subsequent positive screening test: 0.17 (95% CI, 0.15–0.2)</td>
<td>Initial positive screen versus subsequent positive screening test: 0.993 (95% CI, 0.991–0.994)</td>
<td>Fair</td>
</tr>
<tr>
<td>Stergiou et al 2008</td>
<td>Three averaged measurements with mercury sphygmomanometer, measured in nondominant arm in sitting position after 5 min at rest</td>
<td>24-h ambulatory blood pressure measurements</td>
<td>SBP or DBP ≥95th percentile based on US normative blood pressure tables</td>
<td>N = 102; 100% referred for screening; mean age 13 y (SD, 3; range, 6–18); 63% male; race not reported</td>
<td>Positive ambulatory result versus positive clinic result: 0.85 (95% CI, 0.45–0.90)</td>
<td>Positive ambulatory result versus positive clinic result: 0.75 (95% CI, 0.63–0.84)</td>
<td>Positive ambulatory result versus positive clinic result: 0.37 (95% CI, 0.29–0.47)</td>
<td>Positive ambulatory result versus positive clinic result: 0.63 (95% CI, 0.53–0.72)</td>
<td>Fair</td>
</tr>
</tbody>
</table>
### APPENDIX 4  Studies Tracking Hypertension From Childhood to Adulthood

<table>
<thead>
<tr>
<th>Author, Year, and Study Name (Follow-up)</th>
<th>Definition of HTN in Childhood</th>
<th>Definition of HTN in Adulthood</th>
<th>Outcomes</th>
<th>Quality Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood pressure outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bao et al 1995⁴³; Bogalusa Heart Study (15 y)</td>
<td>SBP &gt;140 mm Hg or DBP &gt;90 mm Hg or ever treated for hypertension</td>
<td>Hypertension at follow-up, baseline highest SBP quintile versus other SBP quintiles: 18% (54/301) vs. 5% (90/1204); risk ratio 3.6; 95% CI, 2.5–5.1. Hypertension at follow-up, baseline highest DBP quintile versus other DBP quintiles: 15% (45/301) vs. 8% (72/1204); risk ratio 2.5, 95% CI, 1.8–3.6.</td>
<td>Unclear; data from 1505 subjects who completed baseline and follow-up surveys (of 3965 at baseline)</td>
<td>No loss (Cohort selected based on availability of data, 39% of original cohort completed both surveys)</td>
</tr>
<tr>
<td>Beckett et al 1992⁴⁴; Fels Longitudinal Study (20 y)</td>
<td>DBP not defined</td>
<td>DBP &gt;90 mm Hg</td>
<td>DBP 80 vs. 60 mm Hg at age 15 and presence of hypertension at age 35: Males: risk ratio 5.0; females: risk ratio 4.5. DBP 85 vs. 60 mm Hg at age 15 and presence of hypertension at age 35: Males: risk ratio 3.9; females: risk ratio 6.6. DBP 90 vs. 60 mm Hg at age 15 and presence of hypertension at age 35: Males: risk ratio 4.9; females: risk ratio 3.0</td>
<td>Unclear; data from 523 subjects who completed baseline and follow-up surveys (of 976 at baseline)</td>
</tr>
<tr>
<td>Author, Year, and Study Name (Follow-up)</td>
<td>Definition of HTN in Childhood</td>
<td>Definition of HTN in Adulthood</td>
<td>Outcomes</td>
<td>Quality Considerations</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>-------------------------------</td>
<td>-------------------------------</td>
<td>----------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Gillman et al 1983&lt;sup&gt;45&lt;/sup&gt;; Study not named (12 y)</td>
<td>&gt;90th percentile (SBP: 113 mm Hg, within study)</td>
<td>&gt;90th percentile (SBP: 139 mm Hg, within study)</td>
<td>Positive predictive value, sensitivity, and specificity of BP at age 10 predicting BP &gt; 90th percentile at age 20</td>
<td>Children from a single school in East Boston, MA, sampling method unclear</td>
</tr>
</tbody>
</table>

**SBP, males:**
- >75th percentile (108 mm Hg): 0.26, 0.59, 0.80
- >90th percentile (113 mm Hg): 0.35, 0.33, 0.93
- >95th percentile (117 mm Hg): 0.44, 0.17, 0.97
- >99th percentile (123 mm Hg): 0.58, 0.04, >0.99

**SBP, females:**
- >75th percentile (108 mm Hg): 0.27, 0.66, 0.79
- >90th percentile (114 mm Hg): 0.39, 0.36, 0.94
- >95th percentile (118 mm Hg): 0.48, 0.20, 0.98
- >99th percentile (125 mm Hg): 0.65, 0.04, >0.99

**DBP, males:**
- >75th percentile (68 mm Hg): 0.21, 0.34, 0.82
- >90th percentile (71 mm Hg): 0.24, 0.16, 0.93
- >95th percentile (73 mm Hg): 0.27, 0.08, 0.97
- >99th percentile (77 mm Hg): 0.34, 0.01, >0.99

**DBP, females:**
- >75th percentile (67 mm Hg): 0.19, 0.49, 0.77
- >90th percentile (71 mm Hg): 0.24, 0.23, 0.92
- >95th percentile (74 mm Hg): 0.30, 0.10, 0.98
- >99th percentile (78 mm Hg): 0.38, 0.02, >0.99
<table>
<thead>
<tr>
<th>Author, Year, and Study Name (Follow-up)</th>
<th>Definition of HTN in Childhood</th>
<th>Definition of HTN in Adulthood</th>
<th>Outcomes Quality Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Juhola et al 201147; Cardiovascular Risk in Young Finns Study (27 y)</td>
<td>≥95th percentile</td>
<td>Unclear</td>
<td>Prehypertension or hypertension in adulthood and BP ≥95th percentile in childhood: Female, ages 6 and 9: OR 2.4 (95% CI, 1.1–3.2) Female, ages 12, 15, and 18: OR 2.3 (95% CI, 1.6–3.5) Males, ages 6 and 9: OR 2.8 (95% CI, 1.5–5.1) Males, ages 12, 15, and 18: OR 2.1 (95% CI, 1.5–3.1) PPV, sensitivity, specificity of BP ≥95th percentile in childhood and hypertension in adulthood All ages 6–18: 0.44; 0.1; 0.97</td>
</tr>
<tr>
<td>Other publication: Juonala et al 200477</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lauer et al 199348, Muscatine Study (unclear)</td>
<td>Unclear; results reported for &gt;90th percentile</td>
<td>SBP or DBP &gt;90th percentile (cohort specific)</td>
<td>24% of children with BP &gt;90th percentile had BP &gt;90th percentile in adulthood; risk ratio 2.4 (P &lt; .001) 39% of children with SBP &gt;90th percentile had SBP &gt;90th percentile in adulthood; risk ratio 1.9 (P &lt; .001) 17% of children with DBP &gt;90th percentile had DBP &gt;90th percentile in adulthood; risk ratio 1.7 (P &lt; .001) 32% of children with DBP &gt;90th percentile had DBP &gt;90th percentile in adulthood; risk ratio 1.5 (P &lt; .001)</td>
</tr>
<tr>
<td>Author, Year, and Study Name (Follow-up)</td>
<td>Definition of HTN in Childhood</td>
<td>Definition of HTN in Adulthood</td>
<td>Outcomes</td>
</tr>
<tr>
<td>-----------------------------------------</td>
<td>-------------------------------</td>
<td>-------------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Shear et al 1987; Bogalusa Heart Study (8 y)</td>
<td>Not reported</td>
<td>140/90 mm Hg</td>
<td>SBP ≥80th percentile at years 1, 4, and 6 and hypertensive at follow-up: Sensitivity: 0.27; Specificity: 0.95 DBP ≥80th percentile at years 1, 4, and 6 and hypertensive at follow-up: Sensitivity: 0.33; Specificity: 0.98</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recruitment</th>
<th>Attrition: % with complete data, % of original N at follow-up</th>
<th>Measurement Method Stated for Both Time Periods?</th>
<th>Statistical Analysis and Adjusted Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>not applicable</td>
</tr>
<tr>
<td>Author, Year, and Study Name (Follow-up)</td>
<td>Definition of HTN in Childhood</td>
<td>Definition of HTN in Adulthood</td>
<td>Outcomes</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>---------------------------------</td>
<td>---------------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Sun et al 2007; Fels Longitudinal Study (unclear)</td>
<td>Least-squares means determined according to age and gender (absolute values not reported)</td>
<td>SBP &gt; 130 mm Hg and/or DBP &gt; 85 mm Hg</td>
<td>Odds of hypertension at &gt; 30 y of age given SBP exceeding criterion values at single examination in childhood: Males 5–7 y old males: 3.8 (95% CI, 1.5–9.7) 8–13 y old males: 3.5 (95% CI, 1.5–8.3) 14–18 y old males: 1.1 (95% CI, 0.5–2.4) Females 5–7 y old females: 4.5 (95% CI, 1.1–17.7) 8–13 y old females: 2.7 (95% CI, 1.0–7.1) 14–18 y old females: 3.8 (95% CI, 1.2–12.7)</td>
</tr>
</tbody>
</table>

Other outcomes
<table>
<thead>
<tr>
<th>Author, Year, and Study Name (Follow-up)</th>
<th>Definition of HTN in Childhood</th>
<th>Definition of HTN in Adulthood</th>
<th>Outcomes</th>
<th>Quality Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoq et al 2002[46], Bogalusa Heart Study (16 y)</td>
<td>$\geq 90$th percentile for age, ethnicity, and gender</td>
<td>$\geq 90$th percentile for age, ethnicity, and gender</td>
<td>Annual change in BP on adulthood urinary albumin/creatinine ratio by ethnicity: Childhood SBP by ethnicity: Blacks: regression coefficient 0.016 ($P = .05$) Whites: regression coefficient $-0.002$ ($P = .78$) Annual change in SBP from childhood to adulthood by ethnicity: Blacks: regression coefficient 0.315 ($P = .002$) Whites: regression coefficient $-0.045$ ($P = .55$) Childhood DBP by ethnicity: Blacks: regression coefficient 0.026 ($P = .012$) Whites: regression coefficient $-0.002$ ($P = .791$) Annual change in DBP from childhood to adulthood by ethnicity: Blacks: regression coefficient 0.292 ($P = .016$) Whites: regression coefficient 0.083 ($P = .5$)</td>
<td>Unclear; data from 2122 subjects who completed baseline and follow-up surveys (of 3865 at baseline)</td>
</tr>
<tr>
<td>Li et al 2003[49], Bogalusa Heart Study (22 y)</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Odds of carotid intima media thickness in upper quartile given SBP risk factor (not defined): childhood (14–17 y): 1.00 (95% CI, 0.80–1.20)</td>
<td>Unclear; data from 486 subjects who completed baseline and follow-up surveys and carotid artery ultrasound (of 3865 at baseline)</td>
</tr>
</tbody>
</table>
### APPENDIX 4  Continued

<table>
<thead>
<tr>
<th>Author, Year, and Study Name (Follow-up)</th>
<th>Definition of HTN in Childhood</th>
<th>Definition of HTN in Adulthood</th>
<th>Outcomes</th>
<th>Quality Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raitakari et al 2003&lt;sup&gt;50&lt;/sup&gt;; Cardiovascular Risk in Young Finns Study (21 y)</td>
<td>≥80th percentile</td>
<td>≥80th percentile</td>
<td>Relationship between SBP ≥80th percentile at age 12–18 (mean age 14.9 y) and carotid intima media thickness 21 y later: regression coefficient 0.013 (SE 0.003); <em>P</em> &lt; .001</td>
<td>Finnish children and adolescents aged 3, 6, 9, 12, and 15 y randomly sampled from 5 cities; 38% (1367/3596) lost to follow-up at 21 y; Yes Logistic regression; age, sex</td>
</tr>
</tbody>
</table>

BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; NR, not reported; PPV, positive predictive value; SBP, systolic blood pressure.
### APPENDIX 5 Interventions for Hypertension in Children and Adolescents

<table>
<thead>
<tr>
<th>Author, Year (Quality Rating)</th>
<th>Study Design and Setting Duration</th>
<th>N</th>
<th>Demographic Characteristics</th>
<th>Intervention</th>
<th>Proportion of Patients Achieving ≤95th Percentile of Blood Pressure for Age, Gender, and Height</th>
<th>Blood Pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug interventions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Batisky et al 2007 (fair)</td>
<td>RCT 28 sites United States 4 wk</td>
<td>140</td>
<td>Mean age 13 (SD 2.8) y</td>
<td>Group A: Metoprolol ER 0.2 mg/kg Groups A–C pooled: 48% (95% CI, 37–55)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>70% male</td>
<td>Group B: Metoprolol ER 1.0 mg/kg Group B: 29% (95% CI, 8–44)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>25% black</td>
<td>Group C: Metoprolol ER 2.0 mg/kg Group C: 26% (95% CI, 8–44)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean SBP: 132 mm Hg</td>
<td>Group A: 25.2 (95% CI, 27.7 to 22.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean DBP: 78 mm Hg</td>
<td>Group B: 27.7 (95% CI, 21.1 to 24.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>74% BMI ≥95th percentile</td>
<td>Group C: 26.3 (95% CI, 28.7 to 23.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Group D: Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean change from baseline, SBP:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Group A: −5.2 (95% CI, −7.7 to −2.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Group B: −7.7 (95% CI, −11.3 to −4.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Group C: −6.3 (95% CI, −8.7 to −3.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Group D: −5.1 (95% CI, −5.5 to 1.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flynn et al 2004 (fair)</td>
<td>RCT crossover 49 sites in North and South America 4 wk</td>
<td>268</td>
<td>Mean age 12 (SD 3.3) y</td>
<td>Study Phase 2 (included placebo comparison)</td>
<td>Study Phase 2 results</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean SBP: 137.9 (SD 12.7) mm Hg</td>
<td>Group A: 40%</td>
<td>Mean change from baseline, SBP:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean DBP: 74.2 (SD 11.8) mm Hg</td>
<td>Group B: 35%</td>
<td>Group A: −6.9 ± 12.5 (P = NS) (P = .05 versus placebo)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>31.3% (84/268) primary hypertension</td>
<td>Group C: 30%</td>
<td>Group B: −8.7 ± 13.3 (P = NS) (−3.6 ± 12.7, P = .01 versus placebo)</td>
<td></td>
</tr>
<tr>
<td>Li et al 2010 (fair)</td>
<td>RCT 43 sites in the US, South Africa, Russia, and Dominican Republic 4 wk</td>
<td>304</td>
<td>Mean age not reported (53% &lt;12 y)</td>
<td>Study Phase B (included placebo comparison)</td>
<td>Phase B results</td>
<td>Least squares mean change from baseline, SBP:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>63% male</td>
<td>Group A: Eplerenone 25 mg once daily</td>
<td>Group A: P = NS</td>
<td>Group A: P = NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>35% black</td>
<td>Group B: Eplerenone 25 mg twice daily</td>
<td>Group B: 2.76 (95% CI, −5.5 to 0; P = 0.048 versus placebo)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>57% white</td>
<td>Group C: Eplerenone 25 mg bid for 2 wk followed by 50 mg bid for 4 wk</td>
<td>Group C: P = NS</td>
<td>Least squares mean change from baseline (any group), DBP: P = NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>11% Hispanic</td>
<td>Group D: Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8% Asian</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>56% primary hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author, Year (Quality Rating)</td>
<td>Study Design and Setting Duration</td>
<td>N</td>
<td>Demographic Characteristics</td>
<td>Intervention</td>
<td>Proportion of Patients Achieving ( \leq )95th Percentile of Blood Pressure for Age, Gender, and Height</td>
<td>Blood Pressure (mm Hg)</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>----------------------------------</td>
<td>----</td>
<td>-----------------------------</td>
<td>--------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Sorof et al 2002(^{20}) (fair)</td>
<td>RCT</td>
<td>94</td>
<td>Mean age 14 y</td>
<td>Group A: Bisoprolol fumarate 2.5+ hydrochlorothiazide 6.25</td>
<td>NR</td>
<td>Least squares mean change from baseline, SBP: Groups A–C pooled: (-9.3 \ (P &lt; .05)) versus placebo Group D: (-.49)</td>
</tr>
<tr>
<td></td>
<td>Clinical trial from 22 sites in United States and Brazil 4 wk</td>
<td></td>
<td>57% male</td>
<td>Group B: Bisoprolol 5 mg + hydrochlorothiazide 6.25 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>43% white</td>
<td>Group C: Bisoprolol fumarate 10 mg + hydrochlorothiazide 6.25 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>41% black</td>
<td>Group D: Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>14% Hispanic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1% Asian</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1% multiracial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean BMI = 28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trachtman et al 2003(^{37}) (fair)</td>
<td>RCT</td>
<td>133</td>
<td>Mean age 12 y (SD 3)</td>
<td>Group A: 2.5 mg felodipine ER</td>
<td>BP ( \leq )90th percentile</td>
<td>Mean difference SBP at follow-up versus placebo (95% CI): Groups A–C pooled: (-0.71 \ (4.8 \text{ to } 3.38; P = \text{NS})) Group D: (-0.06 \ (4.6 \text{ to } 3.3; P = \text{NS}))</td>
</tr>
<tr>
<td></td>
<td>Clinical trial at 30 sites in the United States 3 wk</td>
<td></td>
<td>60% male</td>
<td>Group B: 5 mg felodipine ER</td>
<td>Group A: 15%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>39% black</td>
<td>Group C: 10 mg felodipine ER, titrated to target dose</td>
<td>Group B: 18%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Group D: Placebo</td>
<td>Group C: 19%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Group D: 11%</td>
<td></td>
</tr>
<tr>
<td>Trachtman et al 2008(^{36}) (fair)</td>
<td>RCT</td>
<td>240</td>
<td>Mean age not reported (29% (&lt;12\ y; 71% \geq12\ y)</td>
<td>Group A: Candesartan 2/4 mg</td>
<td>Group A: 54%</td>
<td>Least squares mean change from baseline, SBP: Groups A–C: (-10.22 \ (P &lt; .0001)) versus placebo Group D: (-.36)</td>
</tr>
<tr>
<td></td>
<td>Clinical trial at 42 sites in United States and Europe 4 wk</td>
<td></td>
<td>71% male</td>
<td>Group B: Candesartan 8/16 mg</td>
<td>Group B: 62%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>69% BMI ( \geq )95th percentile</td>
<td>Group C: Candesartan 16/32 mg</td>
<td>Group C: 65%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>47% black</td>
<td>Group D: Placebo</td>
<td>Group D: 31%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>45% white</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author, Year (Quality Rating)</td>
<td>Study Design and Setting Duration</td>
<td>N</td>
<td>Demographic Characteristics</td>
<td>Intervention</td>
<td>Proportion of Patients Achieving ≤95th Percentile of Blood Pressure for Age, Gender, and Height</td>
<td>Blood Pressure (mm Hg)</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>----------------------------------</td>
<td>----</td>
<td>-----------------------------</td>
<td>--------------</td>
<td>-----------------------------------------------------------------------------------------------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Wells et al 2010 (fair)</td>
<td>RCT</td>
<td>77</td>
<td>Mean age: 14 y (SD 3 y)</td>
<td>Group A: Telmisartan 1 mg/kg/day (low-dose group)</td>
<td>Group A: 50% (6–&lt;12 y), 68% (12–&lt;18 y)</td>
<td>Adjusted mean difference SBP at follow-up versus placebo (95% CI): Group A: −3.6 (−9.2 to 1.3, P = NS)</td>
</tr>
<tr>
<td></td>
<td>Clinical trial at 16 sites in United States, Brazil, and Mexico</td>
<td></td>
<td>57% male</td>
<td>Group B: Telmisartan 1 mg/kg/day, titrated up to 2 mg/kg/day after 1 wk (high-dose group)</td>
<td>Group B: 88% (6–&lt;12 y), 79% (12–&lt;18 y)</td>
<td>Group B: −8.5 (−14.0 to −3.0, P &lt; 0.0027)</td>
</tr>
<tr>
<td></td>
<td>4 wk</td>
<td></td>
<td>51% white 37% black</td>
<td>Group C: Placebo</td>
<td>Group C: 33% (6–&lt;12 y), 27% (12–&lt;18 y)</td>
<td>Group B: −4.8 (−9.7 to 0, P = 0.051)</td>
</tr>
<tr>
<td>Drug plus lifestyle interventions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berenson et al 1983 (fair)</td>
<td>RCT</td>
<td>150</td>
<td>NR</td>
<td>ADAPT Program</td>
<td></td>
<td>Mean change from baseline, SBP: Group A: −7.6</td>
</tr>
<tr>
<td></td>
<td>School-based in United States</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other publication:</td>
<td>Frank et al 1982 (fair)</td>
<td>6 mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berenson et al 1990 (fair)</td>
<td>RCT</td>
<td>150</td>
<td>Mean age 12 y 53% male</td>
<td>Same as above</td>
<td></td>
<td>Adjusted mean difference, SBP: Group A versus Group B: −3.6 (SD 1.12; P &lt; 0.01)</td>
</tr>
<tr>
<td></td>
<td>School-based in United States</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adjusted mean difference DBP: Group A versus Group B: −1.7 (SD 0.82; P &lt; 0.05)</td>
</tr>
<tr>
<td>Continuation of</td>
<td>Berenson et al 1983 (fair)</td>
<td>30 mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifestyle interventions</td>
<td>Diet</td>
<td>57</td>
<td>Mean age 14 y 63% male</td>
<td>Group A: DASH-type diet modified for adolescent population + counseling</td>
<td>Group A versus Group B: 0.1</td>
<td>Mean difference at follow-up, SBP: Group A versus Group B: 0.1</td>
</tr>
<tr>
<td></td>
<td>Cincinnati Children’s Hospital Medical Center, United States</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Howe et al 1991 (fair)</td>
<td>RCT crossover</td>
<td>103</td>
<td>Mean age 13 y (range 11–14 y)</td>
<td>Group A: Low-sodium diet (&lt;75 mmol/day) + counseling</td>
<td>Group A: 61% versus Group B 44%, P = NS</td>
<td>No significant differences in SBP or DBP between diets; baseline values not reported</td>
</tr>
<tr>
<td></td>
<td>School-based Adelaide, Australia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 phases of 4 wk each</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author, Year (Quality Rating)</td>
<td>Study Design and Setting, Duration</td>
<td>N</td>
<td>Demographic Characteristics</td>
<td>Intervention</td>
<td>Proportion of Patients Achieving ≤95th Percentile of Blood Pressure for Age, Gender, and Height</td>
<td>Blood Pressure (mm Hg)</td>
</tr>
<tr>
<td>------------------------------</td>
<td>----------------------------------</td>
<td>---</td>
<td>-----------------------------</td>
<td>--------------</td>
<td>------------------------------------------------------------------------------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Sinaiko et al 1993&lt;sup&gt;66&lt;/sup&gt; (fair)</td>
<td>RCT St. Paul and Minneapolis public schools, United States</td>
<td>210</td>
<td>Mean age 13 y 50% male</td>
<td>Group A: Low sodium diet (&lt;70 mmol/day)</td>
<td>NR</td>
<td>Changes in SBP: Boys: No significant differences in rates of increase in SBP between low sodium, potassium supplement, and placebo groups. Girls: Significant difference in SBP between low sodium group (slight overall decrease) and the placebo group (significant increase from baseline). No other differences between groups. Changes in DBP: Boys: No significant differences in rates of increase in BP between low sodium, potassium supplement, and placebo groups. Girls: The low sodium group was the only group that had rates of increase in DBP compared with placebo that were significantly greater than zero.</td>
</tr>
<tr>
<td>Hansen et al 1991&lt;sup&gt;69&lt;/sup&gt; (fair)</td>
<td>RCT Odense, Denmark School-based 8 mo</td>
<td>137</td>
<td>Age range 9–11 y Other demographic characteristics: NR</td>
<td>Group A: 3 extra lessons per week of an ordinary school physical education program Group B: No extra physical education lessons</td>
<td>NR</td>
<td>Mean difference at follow-up, SBP: Group Aversus Group B: −4.9; P &lt; .05 Mean difference at follow-up, DBP: Group Aversus Group B: −3.8; P &lt; .05</td>
</tr>
<tr>
<td>Author, Year (Quality Rating)</td>
<td>Study Design and Setting Duration</td>
<td>N</td>
<td>Demographic Characteristics</td>
<td>Intervention</td>
<td>Proportion of Patients Achieving 95th Percentile of Blood Pressure for Age, Gender, and Height</td>
<td>Blood Pressure (mm Hg)</td>
</tr>
<tr>
<td>------------------------------</td>
<td>----------------------------------</td>
<td>----</td>
<td>-----------------------------</td>
<td>--------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Gregoski et al 2011 (fair)</td>
<td>RCT</td>
<td>166</td>
<td>Mean age 15 y</td>
<td>Group A: Breathing awareness meditation Group B: LifeSkills training (weekly 30-min sessions focusing on training in problem-solving skills, reflective listening, conflict resolution, anger management to enhance social skills and assertiveness) Group C: Health education control</td>
<td>NR</td>
<td>Mean 24-h SBP at 3 mo follow-up: Group A versus Group B versus Group C: 116.6 vs 119.8 vs 121.0 Group A versus Group B: $P = NS$ Group A versus Group C: $P = .05$ Mean 24-h DBP at 3 mo follow-up: Group A versus Group B versus Group C: 66.3 vs 68.2 vs 68.7; $P = NS$ for all comparisons</td>
</tr>
<tr>
<td>Ewart et al 1987 (fair)</td>
<td>RCT</td>
<td>159</td>
<td>BMI range: 19.0–31.2</td>
<td>Group A: Progressive muscle relaxation (12 wk, 15–20 min, 4 d/wk) provided in school</td>
<td>NR</td>
<td>No significant differences between SBP and DBP between treatment and control groups</td>
</tr>
</tbody>
</table>

BP, blood pressure; DASH, Dietary Approaches to Stop Hypertension; ER, extended release; NR, not reported; NS, not significant.
### APPENDIX 6 Harms of Interventions for Hypertension in Children and Adolescents

<table>
<thead>
<tr>
<th>Author, Year (Quality Rating)</th>
<th>Relevance</th>
<th>Type of Study Setting and Duration</th>
<th>Mean Age (SD) (y)</th>
<th>Number Randomized or Analyzed</th>
<th>Intervention</th>
<th>AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug interventions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Batisky et al 2007 (fair)</td>
<td>All participants had primary hypertension</td>
<td>RCT 28 centers</td>
<td>12.5 (2.8)</td>
<td>144 randomized in dosing study, 100 analyzed in safety study</td>
<td>ER metoprolol succinate 0.2–2.0 mg/kg</td>
<td>4-wk dose-ranging study: 1 withdrawal due to AEs</td>
</tr>
<tr>
<td></td>
<td>United States</td>
<td>4-wk dose-ranging study</td>
<td></td>
<td></td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>52-wk open-label study:</td>
<td></td>
<td></td>
<td>Fatigue noted by 1 patient each in the 0.2, 1.0, and 2.0 mg/kg groups</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>52-wk safety study:</td>
<td></td>
<td></td>
<td>5 withdrawals due to AEs (1 each of fatigue, nightmares, anxiety, dizziness, asthma)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>25 mg or 12.5 mg once daily at investigator discretion; increase every 2 wk until maximum of 200 mg once daily</td>
<td></td>
<td></td>
<td>Serious AEs: 2/100 (2%; 1 pneumonia and 1 menometrorrhagia)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 4-wk phases</td>
<td></td>
<td></td>
<td>Other AEs:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Headache: 30%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Upper respiratory tract infection: 20%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cough: 19%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nasopharyngitis: 13%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pharyngolaryngeal pain: 12%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fatigue: 9%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diarrhea: 7%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dizziness: 6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flynn et al 2004 (fair)</td>
<td>31% with primary hypertension</td>
<td>RCT crossover</td>
<td>12.1 (3.3)</td>
<td>268 randomized; 84 with primary hypertension</td>
<td>Amlodipine 2.5–5.0 mg/day</td>
<td>5 withdrawals due to AEs: 12/268 (??%), of which 6 considered by study investigators to be study drug related (3 worsening hypertension, 1 facial edema, 1 finger edema and rash, 1 premature ventricular contractions)</td>
</tr>
<tr>
<td></td>
<td>Clinical trial from 49 centers in North and South America</td>
<td>2 4-wk phases</td>
<td></td>
<td></td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Serious AEs: 5/268 (2%; 1 each: urinary tract infection, gastroenteritis and hypovolemia, pulmonary edema, pneumonia, pancreatitis)</td>
<td></td>
</tr>
</tbody>
</table>
### APPENDIX 6 Continued

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Relevance</th>
<th>Type of Study Setting and Duration</th>
<th>Mean Age (SD) (y)</th>
<th>Number Randomized or Analyzed</th>
<th>Intervention</th>
<th>AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazan et al 2010&lt;sup&gt;67&lt;/sup&gt; (good)</td>
<td>Primary hypertension 75% (225/302); Patients with clinically significant medical condition or chronic disease, malignant or severe hypertension excluded</td>
<td>RCT</td>
<td>12.2 (2.97)</td>
<td>422 screened 302 randomized</td>
<td>Olmesartan medoxomil</td>
<td>Any adverse event: olmesartan 33/93 (36%) versus placebo 27/89 (30)</td>
</tr>
<tr>
<td>Li et al 200&lt;sup&gt;46&lt;/sup&gt; (fair)</td>
<td>Hypertensive (20.9% with renal etiology, otherwise not reported), or high-normal blood pressure in the presence of associated clinical condition such as diabetes mellitus</td>
<td>Dose-ranging RCT; 78 clinical centers in United States, Russia, Israel</td>
<td>12.1 (2.8)</td>
<td>376 screened</td>
<td>Fosinopril</td>
<td>Overall study withdrawals across all 4 phases of study due to AEs: 5/253 (2%)</td>
</tr>
</tbody>
</table>

#### Details:
- **Phase A**: 10-day run-in 255 eligible
- **Phase B**: 4-wk dose-ranging
- **Phase C**: 2-wk withdrawal versus placebo
- **Phase D**: 1-y open-label safety phase

- **Incidence of specific AEs not reported; headache most common**
- **Phase C**: Incidence of AEs similar between placebo (33.9%) and combined fosinopril treatment groups (34.3%)
- **Phase D**: Specific AEs:
  - Headache: 51/253 (20%)
  - Nasopharyngitis: 24/253 (10%)
  - Cough: 23/253 (9%)
  - Pharyngitis: 22/253 (9%)
  - Abdominal pain: 16/253 (6%)
<table>
<thead>
<tr>
<th>Author, Year (Quality Rating)</th>
<th>Relevance Type of Study Setting and Duration</th>
<th>Mean Age (SD) (y)</th>
<th>Number Randomized or Analyzed</th>
<th>Intervention</th>
<th>AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li et al 2010 (fair) 55% primary hypertension</td>
<td>RCT</td>
<td>Age &lt; 12 y: 52.6%</td>
<td>304 randomized</td>
<td>Eplerenone 25 mg once daily, 25 mg twice daily, or 25 mg twice daily for 2 wk then 50 mg twice daily for 4 wk</td>
<td>Phase A: Placebo: Any AE: low dose 38% versus middle dose 31% versus high dose 40%</td>
</tr>
<tr>
<td></td>
<td>17% renal-related hypertension</td>
<td>Phase A: 6-wk dosing study (no placebo)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phase B: 4-wk placebo-controlled study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shahinfar et al 2005 (fair) 69% Hypertension; &quot;more than 50% had underlying kidney disease&quot; (secondary hypertension) but no additional details reported</td>
<td>Dose-ranging RCT: phase 1 randomized to 3 different doses, phase 2 randomized washout; 43 clinical centers in North and South America (including United States), Europe, Africa, 38 days</td>
<td>12 (3.1)</td>
<td>175 randomized</td>
<td>Losartan</td>
<td>Withdrawals due to AEs: 1/175 (&lt;1%) Drug-related AEs: 14/175 (8%), of which headache (5) was most common event Comparison of AE in Phase 2 between active drug and control not reported</td>
</tr>
</tbody>
</table>
### APPENDIX 6 Continued

<table>
<thead>
<tr>
<th>Author, Year (Quality Rating)</th>
<th>Hypertension; unclear severity of underlying kidney disease (study entry required glomerular filtration rate ≥ 30 mL/min/1.73 m²)</th>
<th>Dose-ranging RCT</th>
<th>Phase 1 randomized to 3 different doses, phase 2 randomized washout</th>
<th>Multisite (number and location not reported); 29 days</th>
<th>Mean Age (SD) (y)</th>
<th>Number Randomized or Analyzed</th>
<th>Intervention</th>
<th>AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soffer et al 2003 (fair)</td>
<td></td>
<td>Mean not reported 47% &lt;6–12 y, 53% 13–16 y</td>
<td>115 randomized</td>
<td>Lisinopril</td>
<td>Withdrawals due to AEs: 1/115 (&lt;1%) Drug-related AEs: 14/115 (12%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sorof et al 2002 (fair)</td>
<td>Excluded severe hypertension and correctable secondary hypertension</td>
<td>RCT</td>
<td>13.8 (3.1) 94 randomized (62 treatment + 32 placebo)</td>
<td>B/HT (n = 62): B/HT group had fewer overall AEs than placebo group, 33/62 (53%) vs 24/32 (75%) (P = .047) and fewer serious AEs, 1/62 (2%) vs 5/32 (16%) (P = .016)</td>
<td>B/HT group: Most common AE was headache (29%) 1 patient had severe hypertension, and discontinued the study Placebo group: Most common AE was headache (31%) 2 patients had severe hypertension, and discontinued the study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trachtman et al 2003 (fair)</td>
<td></td>
<td>RCT</td>
<td>12.1 (2.7) 133 randomized</td>
<td>ER felodipine 2.5 mg (n = 33), 5 mg (n = 34), or 10 mg (n = 31), titrated to target dose over 2–3 wk, depending on dosage Placebo (n = 35)</td>
<td>1 withdrawal due to “heart racing”; heart rate was 98 bpm and ECG normal, and 1 withdrawal due to vomiting the first dose (5 mg) % reporting AEs: placebo 66% and 64%, 56%, and 77% in the felodine ER 2.5 mg, 5.0 mg, and 10 mg groups, respectively Most common AEs were headaches (33%), respiratory infections (12%), and nausea (10%) Pedal edema was noted in 2 (2%) of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author/Year (Quality Rating)</td>
<td>Relevance</td>
<td>Type of Study Setting and Duration</td>
<td>Mean Age (SD) (y)</td>
<td>Number Randomized or Analyzed</td>
<td>Intervention</td>
<td>AEs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------------</td>
<td>-----------</td>
<td>-----------------------------------</td>
<td>------------------</td>
<td>-------------------------------</td>
<td>-------------</td>
<td>-----</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trachtman et al 2008 (fair)</td>
<td>Excluded secondary hypertension</td>
<td>RCT % Age &gt;12 y: 70.8%</td>
<td>240 randomized</td>
<td>4 wk trial: 3/240 patients in the 4 wk trial and 5/233 patients in the 52 wk study discontinued due to AEs, specifically hypotension, arm fracture, dizziness, headache, low white blood cell count, and progression of underlying renal disease (2 patients)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wells et al 2002 (fair)</td>
<td>Severe or symptomatic hypertension excluded</td>
<td>Dose-ranging RCT 2-wk dose ranging phase and 2-wk placebo controlled washout phase</td>
<td>Median 12 y</td>
<td>110 enrolled</td>
<td>Enalapril</td>
<td>Drug-related AEs: 12/110 (11%) Dizziness: 4/110 (4%) Headache: 2/110 (2%) Cough: 3/110 (3%) No incidence of renal failure, angioedema or hyperkalemia 5 laboratory AEs possibly, probably or definitely related to study drug</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author, Year (Quality Rating)</td>
<td>Relevance</td>
<td>Type of Study Setting and Duration</td>
<td>Mean Age (SD) (y)</td>
<td>Number Randomized or Analyzed</td>
<td>Intervention</td>
<td>AEs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------</td>
<td>------------</td>
<td>-----------------------------------</td>
<td>------------------</td>
<td>------------------------------</td>
<td>--------------</td>
<td>-----</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wells et al 2010 (fair)</td>
<td>Excluded secondary hypertension</td>
<td>RCT</td>
<td>14 (2.5)</td>
<td>115 enrolled</td>
<td>Telmisartan low dose (1 mg/kg/day) (n = 30) and high dose (1 mg/kg/day titrated up to 2 mg/kg/day after 1 wk) (n = 3)</td>
<td>Any AE: Low dose patients: 41.7% Placebo patients: 31.3% Significance not reported 2 patients discontinued due to AEs, both in the high dose group: 1 patient who experienced a serious AE (near syncope and moderate increase in blood urea nitrogen and serum creatinine) who received an excessive dose in error; and 1 patient due to moderate-intensity dizziness, weakness, and headache</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berenson et al 1983 (fair)</td>
<td>BP &gt;90th percentile for height control group with blood pressure &lt;80th percentiles and the 50–60th percentile for comparison (based on percentiles derived from study) Excluded children with evidence of secondary hypertension</td>
<td>“Close to clinical trial” 8 mo</td>
<td>12 150 (50 high blood pressure treatment group, 50 high blood pressure comparison group, 50 medium blood pressure comparison group)</td>
<td>Group A: 50 high blood pressure treatment group, 50 high blood pressure comparison group, 50 medium blood pressure comparison group</td>
<td>Propranolol: 20 mg/day for children &lt; 40 kg, 40 mg/day for those &gt; 40 kg + chlorthalidone 625 mg per day for children &lt; 40 kg, 125 mg/day for those &gt; 40 kg + nutrition education and promotion of dietary modification to children and parents Group B (high BP elevation at baseline): No treatment Group C (medium BP elevation at baseline): No treatment</td>
<td>AEs reported as very low incidence with no major complications 1 temporary withdrawal from active treatment due to nightmares</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## APPENDIX 6

### Other clinical studies (FDA analyses)

<table>
<thead>
<tr>
<th>Author, Year (Quality Rating)</th>
<th>Relevance</th>
<th>Type of Study Setting and Duration</th>
<th>Mean Age (SD) (y)</th>
<th>Number Randomized or Analyzed</th>
<th>Intervention</th>
<th>AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baker-Smith et al 201073 (not rated)</td>
<td>Mild to moderate hypertension, analysis of data from 8 trials submitted to FDA between 1998 and 2005 (original studies not cited)</td>
<td>13</td>
<td>1289 analyzed (42% placebo + 58% active drug)</td>
<td>ACEs (6 datasets) and ARBs (2 datasets), including benazepril (n = 85), enalapril (n = 101), fosinopril (n = 222), lisinopril (n = 104), quinapril (n = 112), ramipril (n = 217), losartan (n = 235), losartan (n = 168)</td>
<td>Subjects who reported cough in the cohort receiving active drugs (21/748, 2.8%) vs placebo (14/551, 2.5%), P = .86</td>
<td></td>
</tr>
<tr>
<td>Smith et al 200872 (not rated)</td>
<td>Unclear; severe hypertension, and significant renal disease excluded</td>
<td>12.1</td>
<td>1707 analyzed (885 placebo, 1022 active treatments)</td>
<td>Active treatments (n = 1022; mean doses not reported): amlodipine (n = 258), benazepril (n = 85), enalapril (n = 101), felodipine (n = 133), fosinopril (n = 235), losartan (n = 295), lisinopril (n = 104), losartan (n = 168), quinapril (n = 112), ramipril (n = 219) placebo (n = 685)</td>
<td>No significant difference between groups for any AEs Any AE: 235/885 (34%) vs 382/1022 (37%) Hypertension: 3/885 (4%) vs 1/1022 (1%) Hypotension: 0/235 (0%) vs 3/1022 (1%) Cardiac: 8/885 (1%) vs 16/1022 (2%) Neuropsychological: 15/885 (2%) vs 26/1022 (3%) Headache: 115/885 (17%) vs 179/1022 (18%) Syncope: 15/885 (2%) vs 31/1022 (3%) Gastrointestinal: 54/885 (6%) vs 90/1022 (9%) Asthma: 11/885 (2%) vs 12/1022 (1%) Elevated LFT: 7/885 (1%) vs 7/1022 (1%) Muscle aches: 11/885 (2%) vs 17/1022 (2%)</td>
<td>Placebo versus active treatment: Subjects who reported cough in the ACE group: (17/524, 3.2%); ARB group: (4/224, 1.8%), P = .34</td>
</tr>
</tbody>
</table>

ACE, angiotensin-converting enzyme inhibitors; AE, adverse event; ARB, angiotensin receptor blockers; bpm, beats per minute; B/H, bisoprolol fumarate/hydrochlorothiazide; ECG, electrocardiograph; ER, extended release; FDA, Food and Drug Administration; LFT, liver function test.
Screening for Hypertension in Children and Adolescents to Prevent Cardiovascular Disease
Matthew Thompson, Tracy Dana, Christina Bougatsos, Ian Blazina and Susan L. Norris

Pediatrics 2013;131;490
DOI: 10.1542/peds.2012-3523 originally published online February 25, 2013;

Updated Information & Services
including high resolution figures, can be found at:
http://pediatrics.aappublications.org/content/131/3/490

References
This article cites 74 articles, 22 of which you can access for free at:
http://pediatrics.aappublications.org/content/131/3/490.full#ref-list-1

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Cardiology
http://classic.pediatrics.aappublications.org/cgi/collection/cardiology_sub
Cardiovascular Disorders
http://classic.pediatrics.aappublications.org/cgi/collection/cardiovascular_disorders_sub

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
https://shop.aap.org/licensing-permissions/

Reprints
Information about ordering reprints can be found online:
http://classic.pediatrics.aappublications.org/content/reprints

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since . Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2013 by the American Academy of Pediatrics. All rights reserved. Print ISSN: .
Screening for Hypertension in Children and Adolescents to Prevent Cardiovascular Disease
Matthew Thompson, Tracy Dana, Christina Bougatsos, Ian Blazina and Susan L. Norris
Pediatrics 2013;131;490
DOI: 10.1542/peds.2012-3523 originally published online February 25, 2013;

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/131/3/490