Clinical and Demographic Characteristics of Children With Hypertension

Joseph Flynn, Ying Zhang, Susan Solar-Yohay, Victor Shi

Abstract—Most information describing hypertension in the young comes from single-center reports. To better understand contemporary demographic and clinical characteristics of hypertensive children and adolescents, we examined baseline data on 351 children aged 1 to <17 years old who were enrolled in 2 multicenter trials of valsartan. Anthropometric, laboratory, and demographic information at randomization was extracted from the clinical trials databases. Summary variables were created and compared for 3 age groups: <6 years (n=90), 6 to <12 years (n=131), and 12 to <17 years (n=130). Comparisons were also made between different etiologies of hypertension and for different anthropometric categories. Children <6 years old were significantly more likely to have secondary hypertension and were significantly less likely to have weight or body mass index >95 percentile compared with older children. Estimated glomerular filtration rate was significantly lower in children <6 years old (90.9±31.8 mL/min per 1.73 m²) than in the other 2 age groups (6 to <12 years, 141.4±42.1 mL/min per 1.73 m²; 12 to <17 years, 138.3±46.0 mL/min per 1.73 m²). Frequency of total cholesterol >95 percentile was significantly lower in children aged <6 years. Frequency of total cholesterol >95 percentile was significantly lower in children aged <6 years. Diastolic blood pressure index (subject blood pressure÷95 percentile) was significantly higher in children <6 years old (1.1 versus 1.0 in both the 6 to <12 years and 12 to <17 years groups; both P<0.0001). We conclude that hypertensive children <6 years are more likely to have secondary hypertension and to have higher diastolic blood pressure and lower glomerular filtration rate and are less likely to be obese or to have elevated cholesterol than school-aged children or adolescents. These findings emphasize unique aspects of childhood hypertension that should be considered when evaluating children and adolescents with elevated blood pressure and in designing future clinical trials. (Hypertension. 2012;60:1047-1054.)

Key Words: children ■ adolescents ■ clinical trial ■ obesity ■ secondary hypertension ■ primary hypertension ■ pediatric hypertension

Few contemporary data are available that provide an accurate description of the clinical and demographic characteristics of hypertensive children and adolescents. Most recent studies have been retrospective, single-center reports from referral centers that focus on highlighting specific aspects of the referred patient populations.1–4 Even the available multicenter data5 are affected by referral bias, small sample size, and other issues that limit the conclusions that can be drawn about hypertensive children in general.

Two multicenter studies of the efficacy and safety of valsartan in hypertensive children and adolescents were conducted by Novartis Pharmaceuticals in the late 2000s.6,7 In this report we have pooled the baseline clinical and demographic data on the subjects enrolled in those trials to better describe the characteristics of such patients in the current era.

Study Design

This analysis of demographic and clinical characteristics of children with hypertension was conducted using data from 2 randomized, double-blind, multicenter valsartan trials sponsored by Novartis Pharmaceuticals. Study A23076 was performed at 36 centers in 7 countries, and Study A23027 was performed at 55 centers in 9 countries. Institutional review boards/ethics committees at each participating center reviewed and approved the study protocols; written informed consent/assent was obtained for all of the study participants according to local requirements.

Subjects

Detailed inclusion and exclusion criteria for the 2 trials have been published previously.6,7 Study A2307 enrolled children aged <6 years with seated systolic blood pressure (BP; SBP) ≥95th percentile for age, sex, and height8 who were not receiving antihypertensive treatment or who had inadequately controlled hypertension on current treatment. Minimum patient weight was 8 kg. Key
exclusion criteria included seated SBP ≥25% above the 95th percentile; clinically significant laboratory abnormalities; estimated creatinine clearance <30 mL/min per meter squared; aortic coarctation with gradient ≥30 mm Hg; bilateral renal artery stenosis; organ transplantation other than renal or heart transplantation; known sensitivity to valsartan or other angiotensin II receptor blockers; or use of any investigational drug within 30 days before study drug administration. Study A2302 enrolled children and adolescents aged 6 to 16 years with seated SBP ≥95th percentile for age, sex, and height but <5% above the 99th percentile. Minimum patient weight was 18 kg. Key exclusion criteria were similar to those in study A2307.

Assessments
Assessments at the baseline visit included review of inclusion/exclusion criteria and documentation of concomitant medications and physical examination, including seated BP measurement (supine BP measurement was allowed in children <6 years of age, as appropriate). The study visit BP was the mean of 3 measurements obtained in the right arm by auscultation using a cuff with adequate bladder length to cover between 80% and 100% of the upper arm circumference; oscillometric BP measurement was allowed in children <6 years of age and in older children if auscultatory BP measurement was unavailable. Laboratory studies, including serum chemistries, complete blood count, and urinalysis, were obtained at the screening visit and sent to a central laboratory for analysis.

Definitions
Hypertension severity was categorized according to the recommendations of the Fourth report as stage 1 hypertension, ≥95th to 99th percentile for age, sex, and height plus 5 mm Hg, or stage 2 hypertension, >99th percentile for age, sex, and height plus 5 mm Hg. Obesity status was categorized using the Centers for Disease Control and Prevention clinical growth charts as nonobese, body mass index (BMI) <95th percentile for age and sex, or obese, BMI ≥95th percentile for age and sex. Subjects were categorized as having secondary hypertension if the local investigator reported a specific disorder as the cause of the hypertension and were categorized as having primary hypertension if no such underlying condition was identified.

Statistical Analysis
Demographic, anthropometric, BP, and laboratory data at the time of randomization were extracted from the clinical trials database of the 2 studies. Summary variables were created and compared for 3 age groups, <6 years, 6 to <12 years, and 12 to <17 years. Comparisons across these age groups were also performed in subgroups based on hypertension cause (primary versus secondary hypertension), anthropometric variables (obese versus nonobese at baseline), race (black versus nonblack), treatment history (previous versus no previous antihypertensive therapy), and hypertension severity (stage 1 versus stage 2 hypertension). To allow for additional comparison of hypertension severity across age groups, systolic and diastolic BP index was calculated as the patient’s systolic or diastolic BP divided by the 95th percentile value for a child of the same age, sex, and height. For categorical variables, differences between groups were analyzed using χ² testing. For continuous variables, differences across groups were analyzed using an ANOVA model, and differences between pairs of groups were analyzed using t tests. Similar analyses were performed within the 3 age groups for selected variables. All of the statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

Results
A total of 351 children aged 1 to 16 years were enrolled in the combined studies (6 to <12 years [n=131], and 12 to <17 years [n=130]). Information on country of origin of the enrolled children is presented in Table S1 of the online-only Data Supplement.

Demographic and baseline anthropometric and clinical characteristics according to age group are summarized in Table 1. Approximately 60% of the total population were male (212 of 351); 44% were black (154 of 351); and 34% were Hispanic (118 of 351). There were lower percentages of black and Hispanic children in the youngest age group compared with the 2 other groups. The majority of randomized patients (65%) had received previous antihypertensive therapy, including 71% (64 of 90) of young children, 59% (77 of 131) of school-aged children, and 67% (87 of 130) of adolescents.

Other notable age-related observations in the total population included a greater prevalence of secondary hypertension among young children (<6 years) than in school-aged children (6 to <12 years) and adolescents (12 to <17 years); 83.3% versus 38.2% and 40.0%, respectively (both P<0.0001); higher mean sitting diastolic BP (DBP) index in young children than in school-aged children and adolescents (1.1 versus 1.0 and 1.0, respectively; both P<0.0001); and lower prevalence of elevated cholesterol (>95th percentile for age and sex) among young children than among school-aged children or adolescents (7.8% versus 21.4% [P=0.064] and 16.2% [P=0.038], respectively).

Primary Versus Secondary Hypertension
Approximately one half of enrolled patients had primary hypertension (50% [174 of 351]), including 17% of young children (15 of 90), 62% of school-aged children (81 of 131), and 60% of adolescents (78 of 130). There was a significant age-related increase in BMI in both the primary and secondary hypertension subgroups (Table 2). Within each age group, BMI was significantly higher in those with primary hypertension compared with those with secondary hypertension (1 to <6 years, 19.5±3.7 versus 16.2±2.5 kg/m², P=0.0049; 6 to <12 years, 26.4±8.3 versus 19.5±5.8 kg/m², P<0.0001; ≥12 years, 35.1±11.1 versus 22.9±5.2 kg/m², P<0.0001).

Mean sitting SBP index and DBP index were similar across age groups for those with secondary hypertension, but mean sitting SBP index was significantly higher in school-aged children and adolescents than in young children for those with primary hypertension (P=0.0012; Table 2). Within each age group, mean seated SBP was significantly higher in those with secondary hypertension versus those with primary hypertension only among children 1 to <6 years old (115.9±7 versus 111.9±7.1 mm Hg; P=0.0476). SBP index was significantly higher in those with secondary hypertension in children 1 to <6 years old (1.1±0.06 versus 1.0±0.05; P=0.0001) and in children 6 to <12 years old (1.1±0.09 versus 1.1±0.05; P<0.0004) but not in children ≥12 years old. Mean seated DBP and DBP index were both significantly higher in those with secondary hypertension in all 3 of the age groups (data not shown).

In the primary hypertension subgroup, statistically significant age-related differences in mean calculated glomerular filtration rate (GFR11; P=0.0002; lowest in young children) and mean serum total cholesterol (P=0.02; highest in school-aged children) were present. In the secondary hypertension subgroup, only mean calculated GFR (P<0.0001; lowest in young children) varied significantly across age groups.
Within each age group, mean calculated GFR was significantly lower in those with secondary hypertension than in those with primary hypertension (data not shown). Other laboratory values, including serum potassium, triglycerides, and urinalysis results, did not vary significantly between age groups for either those with primary or secondary hypertension (data not shown). Within the age groups, mean serum potassium was significantly higher in children with secondary hypertension compared with those with primary hypertension only in the ≥12-year age group (4.4 ± 0.5 versus 4.1 ± 0.4 mEq/L; P = 0.002).

**Obese Versus Nonobese**

Of the 341 patients for whom BMI percentile could be calculated (not calculated for patients ≤2 years of age), 44% (n=150) were obese (BMI ≥95th percentile for age and sex). Young children were less likely to be obese than school-aged children and adolescents (17.5% versus 51.9% and 52.3%, respectively; both P<0.0001; Table 3).

In both obese and nonobese patients, mean sitting SBP index and mean sitting DBP index were similar across age groups. Within each age group, there was no difference in either mean seated SBP or SBP index when comparing obese versus nonobese patients. However, both mean seated DBP and DBP index were significantly higher in nonobese than obese children in the 6 to <12 and ≥12-year age groups (see Table S2). Significant age-related differences in mean calculated GFR (P=0.0002; lowest in young children) and mean serum total cholesterol (P=0.0027; highest in young children) were observed in obese patients (Table 3). Significant age-related differences in mean calculated GFR (P<0.0001; lowest in young children), mean serum potassium (P=0.043; highest in young children), and mean serum triglycerides (P=0.030; highest in young children) were observed in nonobese patients. When analyzed within age groups, mean calculated GFR was significantly higher

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**Table 1. Demographic and Baseline Anthropomorphic and Clinical Characteristics of the Randomized Population, by Age Category**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>&lt;6 y (n=90)</th>
<th>6 to &lt;12 y (n=131)</th>
<th>12 to &lt;17 y (n=130)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (range) age, y</td>
<td>3.0 (1.0–5.0)</td>
<td>9.0 (6.0–11.0)</td>
<td>14.0 (12.0–16.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td>54 (60.0)</td>
<td>73 (55.7)</td>
<td>85 (65.4)</td>
<td>0.28</td>
</tr>
<tr>
<td>Male</td>
<td>36 (40.0)</td>
<td>58 (44.3)</td>
<td>45 (34.6)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>28 (31.1)</td>
<td>56 (42.7)</td>
<td>34 (26.2)</td>
<td>0.015</td>
</tr>
<tr>
<td>Hispanic</td>
<td>62 (68.9)</td>
<td>75 (57.3)</td>
<td>96 (73.8)</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>63 (70.0)</td>
<td>75 (57.3)</td>
<td>59 (45.4)</td>
<td>0.0014</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>27 (30.0)</td>
<td>56 (42.7)</td>
<td>71 (54.6)</td>
<td></td>
</tr>
<tr>
<td>Nonblack</td>
<td>16.8 (2.95)*</td>
<td>23.8 (18.87)</td>
<td>30.2 (10.97)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean (SD) BMI, kg/m²</td>
<td>&lt;0.0001</td>
<td>115.2 (7.18)</td>
<td>127.5 (8.86)</td>
<td></td>
</tr>
<tr>
<td>Previous antihypertensive therapy, n (%) yes</td>
<td>64 (71.1)</td>
<td>77 (58.8)</td>
<td>87 (66.9)</td>
<td>0.14</td>
</tr>
<tr>
<td>Mean (SD) sitting SBP, mm Hg</td>
<td>1.1 (0.07)</td>
<td>1.1 (0.07)</td>
<td>1.1 (0.07)</td>
<td>0.80</td>
</tr>
<tr>
<td>Mean (SD) sitting DBP, mm Hg</td>
<td>69.3 (8.15)</td>
<td>75.9 (10.47)</td>
<td>79.2 (12.45)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean (SD) sitting DBP index (DBP÷95th percentile)</td>
<td>1.1 (0.15)</td>
<td>1.0 (0.14)</td>
<td>1.0 (0.16)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean (SD) sitting pulse, bpm</td>
<td>103.1 (15.56)</td>
<td>91.3 (14.09)</td>
<td>81.2 (12.64)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Severity of hypertension, n (%)</td>
<td>0.94</td>
<td>58 (64.4)</td>
<td>86 (66.7)</td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>32 (35.6)</td>
<td>43 (33.3)</td>
<td>44 (34.6)</td>
<td>0.038</td>
</tr>
<tr>
<td>Stage 2</td>
<td>10 (11.1)</td>
<td>63 (48.1)</td>
<td>79 (60.8)</td>
<td></td>
</tr>
<tr>
<td>Acetabular (&lt;75th percentile)</td>
<td>1 (1.1)</td>
<td>38 (29.0)</td>
<td>29 (22.3)</td>
<td></td>
</tr>
<tr>
<td>Borderline (75th to 95th percentile)</td>
<td>7 (7.8)</td>
<td>28 (21.4)</td>
<td>21 (16.2)</td>
<td></td>
</tr>
</tbody>
</table>

*Data show the BMI for children 1 to >6 y of age: n=80, since patients ≤2 y of age are not included in the calculation. BMI indicates body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.
Table 2. Baseline Blood Pressure and Selected Laboratory Parameters in Pediatric Patients With Primary Hypertension and Pediatric Patients With Secondary Hypertension, by Age Category

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Age Category</th>
<th>Patients with primary hypertension (n=174)</th>
<th>Patients with secondary hypertension (n=177)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt;6 y</td>
<td>6 to &lt;12 y</td>
</tr>
<tr>
<td>n</td>
<td></td>
<td>15</td>
<td>81</td>
</tr>
<tr>
<td>Mean (SD) body mass index, kg/m²</td>
<td>19.5 (3.7)</td>
<td>26.4 (8.3)</td>
<td>35.1 (11.1)</td>
</tr>
<tr>
<td>Mean (SD) sitting SBP, mm Hg</td>
<td>111.9 (7.12)</td>
<td>126.8 (7.48)</td>
<td>137.4 (7.12)</td>
</tr>
<tr>
<td>Mean (SD) sitting SBP index (SBP÷95th percentile)</td>
<td>1.0 (0.05)</td>
<td>1.1 (0.05)</td>
<td>1.1 (0.05)</td>
</tr>
<tr>
<td>Mean (SD) sitting DBP, mm Hg</td>
<td>66.1 (5.11)</td>
<td>72.8 (8.50)</td>
<td>76.4 (10.91)</td>
</tr>
<tr>
<td>Mean (SD) sitting DBP index (DBP÷95th percentile)</td>
<td>1.0 (0.10)</td>
<td>0.9 (0.11)</td>
<td>0.9 (0.13)</td>
</tr>
<tr>
<td>Mean (SD) calculated GFR (Schwartz formula), mL/min per 1.73 m²</td>
<td>113.8 (25.77)</td>
<td>155.1 (35.09)*</td>
<td>156.9 (40.64)</td>
</tr>
</tbody>
</table>

GFR indicates glomerular filtration rate; DBP, diastolic blood pressure; SBP, systolic blood pressure.

* n=80.
† n=73.
‡ n=51.

in obese compared with nonobese patients in all 3 of the age groups (data not shown). There was also a trend toward higher total cholesterol in obese patients ≥12 years old (172.8±38.4 versus 162±32.7 mg/dL; P=0.09) and significantly higher triglycerides in obese patients 6 to <12 years old (149.2±102 versus 113.1±70.4 mg/dL; P=0.02).

Black Versus Nonblack

Blacks composed less than one half (44%) of the total randomized population. Approximately 30% of young children (27 of 90), 43% of school-aged children (56 of 131), and 55% of adolescents (71 of 130) were black.

There was a significant age-related increase in BMI in both the black and nonblack subgroups (Table 4). Within the age groups, BMI was significantly higher only in nonblack patients ≥12 years of age (32.9±11.2 versus 27±9.8 kg/m²; P=0.002), not in those 1 to <6 years (17.6±2.8 versus 16.4±3 kg/m²; P=0.07) or in those 6 to <12 years (23.9±8.2 versus 23.7±8.2 kg/m²; P=0.85).

In black patients, mean sitting SBP index was similar across age categories, but mean sitting DBP index was higher in young children (P=0.0010; Table 4). In nonblack patients, mean sitting DBP index was also higher in young children (P=0.0015). Within the age groups, mean seated SBP was significantly higher in nonblack patients compared with black patients only in children aged ≥12 years old (139.3±10.5 versus 135.7±6.9 mm Hg; P=0.03), whereas mean SBP index was significantly higher in nonblack patients compared with black patients in both the 6- to <12-year (1.1±0.08 versus 1.1±0.05; P=0.02) and ≥12-year (1.1±0.09 versus 1.1±0.04; P=0.007) groups. No differences were seen within any age group for either mean DBP or DBP index when comparing nonblack with black patients.

Significant age-related differences in mean calculated GFR (P<0.0001; lowest in young children) were observed in both the black and nonblack subgroups. No other significant age-related differences in laboratory values were seen in either the black or nonblack subgroups. Within the age groups, mean calculated GFR was significantly higher in black children compared with nonblack children for all 3 of the age groups (see Table S3). In addition, mean serum potassium was significantly higher in nonblack children aged ≥12 years (4.3±0.5 versus 4.1±0.4 mEq/L; P=0.04), and serum triglycerides were significantly higher in nonblack children aged ≥12 years (154.3±92.0 versus 114.3±53.2 mg/dL; P=0.004).

Patients With Stage 1 Versus Stage 2 Hypertension

The majority of randomized patients (66%) had stage 1 hypertension, including 64% (58 of 90) of young children,
67% (86 of 129) of school-aged children, and 65% (83 of 127) of adolescents. As in the other comparisons discussed above, there was a significant age-related increase in BMI within the stage 1 and stage 2 hypertension groups, with children ≥12 years having the highest values, but there were no significant differences in BMI for those with stage 1 versus those with stage 2 hypertension within any of the age groups (data not shown). Mean sitting SBP index was similar across age categories, but mean sitting DBP index was highest in young children for both those with stage 1 and stage 2 hypertension (data not shown).

Mean calculated GFR was significantly lower in the youngest age group among those with both stage 1 and stage 2 hypertension (data not shown). In addition, within the 1- to <6-year age group itself, mean calculated GFR was significantly lower among those with stage 2 hypertension compared with those with stage 1 hypertension (80.3±27.1 versus 96.6±32.9 mL/min per 1.73 m²; P=0.02). This difference was not seen in any of the other 2 age groups.

### Table 3. Baseline Blood Pressure and Selected Laboratory Parameters in Obese (BMI ≥95th Percentile) and Nonobese (BMI <95th Percentile) Pediatric Patients With Hypertension, by Age Category

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>&lt;6 y</th>
<th>6 to &lt;12 y</th>
<th>12 to &lt;17 y</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Obese patients (n=150)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>14</td>
<td>68</td>
<td>68</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean (SD) sitting SBP, mm Hg</td>
<td>118.3 (5.20)</td>
<td>129.0 (7.68)</td>
<td>137.3 (9.50)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean (SD) sitting SBP index (SBP÷95th percentile)</td>
<td>1.1 (0.06)</td>
<td>1.1 (0.06)</td>
<td>1.1 (0.08)</td>
<td>0.58</td>
</tr>
<tr>
<td>Mean (SD) sitting DBP, mm Hg</td>
<td>68.9 (6.33)</td>
<td>73.3 (9.28)</td>
<td>76.8 (12.82)</td>
<td>0.026</td>
</tr>
<tr>
<td>Mean (SD) sitting DBP index (DBP÷95th percentile)</td>
<td>1.0 (0.14)</td>
<td>0.9 (0.12)</td>
<td>0.9 (0.16)</td>
<td>0.35</td>
</tr>
<tr>
<td>Mean (SD) calculated GFR (Schwartz formula), mL/min per 1.73 m²</td>
<td>107.9 (18.37)*</td>
<td>158.0 (37.56)</td>
<td>156.5 (44.90)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Mean (SD) serum total cholesterol, mg/dL</td>
<td>233.0 (158.39)</td>
<td>177.8 (35.99)†</td>
<td>172.8 (38.42)</td>
<td>0.0027</td>
</tr>
<tr>
<td>Mean (SD) serum triglycerides, mg/dL</td>
<td>298.4 (483.91)</td>
<td>149.2 (102.01)†</td>
<td>141.3 (83.55)</td>
<td>0.0065</td>
</tr>
<tr>
<td><strong>Nonobese patients (n=191)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>66</td>
<td>63</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>Mean (SD) sitting SBP, mm Hg</td>
<td>115.4 (6.69)</td>
<td>126.0 (9.80)</td>
<td>137.3 (8.11)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean (SD) sitting SBP index (SBP÷95th percentile)</td>
<td>1.1 (0.06)</td>
<td>1.1 (0.09)</td>
<td>1.1 (0.06)</td>
<td>0.90</td>
</tr>
<tr>
<td>Mean (SD) sitting DBP, mm Hg</td>
<td>69.6 (8.61)</td>
<td>78.7 (11.02)</td>
<td>81.9 (11.55)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean (SD) sitting DBP index (DBP÷95th percentile)</td>
<td>1.1 (0.13)</td>
<td>1.0 (0.15)</td>
<td>1.0 (0.15)</td>
<td>0.093</td>
</tr>
<tr>
<td>Mean (SD) calculated GFR (Schwartz formula), mL/min per 1.73 m²</td>
<td>88.6 (33.53)‡</td>
<td>123.1 (39.44)§</td>
<td>118.0 (38.38)‖</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean (SD) serum total cholesterol, mg/dL</td>
<td>165.1 (39.12)‡</td>
<td>174.8 (30.90)§</td>
<td>162.0 (32.74)‖</td>
<td>0.10</td>
</tr>
<tr>
<td>Mean (SD) serum triglycerides, mg/dL</td>
<td>151.0 (106.11)‡</td>
<td>113.1 (70.42)§</td>
<td>122.9 (65.68)‖</td>
<td>0.030</td>
</tr>
</tbody>
</table>

Body mass index percentile was not calculated for patients ≤2 y of age; therefore, these very young patients were excluded from this analysis. GFR indicates glomerular filtration rate; DBP, diastolic blood pressure; SBP, systolic blood pressure.

* n=13.
† n=67.
‡ n=65.
§ n=62.
‖ n=61.

### Discussion

Previous studies of hypertensive children and adolescents have been characterized by small patient numbers, referral bias, and other issues that have limited the insights that they might provide into the demographic and clinical characteristics of these patients. In this report, we have overcome many of the limitations of previous reports by pooling data from 2 multicenter clinical trials, including the first trial of an antihypertensive agent conducted in children <6 years of age. The relatively large patient number, wide age range, and large number of contributing centers should make our findings more generalizable than data found in currently available reports.

A notable finding in this study is the significantly higher prevalence of secondary hypertension in young children <6 years of age compared with school-aged children and adolescents. In addition, estimated GFR was significantly lower in the youngest age group, which is consistent with the high percentage of children with underlying renal disease enrolled in the study conducted in the <6-year old age group.
Also of note is the finding that estimated GFR was significantly lower in children aged 1 to <6 years with stage 2 hypertension. Together, these findings provide objective evidence to support consensus recommendations to conduct a more extensive evaluation for secondary causes of persistent hypertension in younger children. The high prevalence of primary hypertension among older patients is consistent with recent reports from referral centers and supports performing a limited diagnostic evaluation in hypertensive children >6 years of age.

Children <6 years of age in this study tended to display higher DBP than children ≥6 years when BP was indexed to adjust for age and height. This difference was seen in the overall group, as well as in the black and nonblack subgroups, but was not seen when subjects were categorized as obese or nonobese. This difference is likely explained by the higher prevalence of secondary hypertension in the youngest age group and reinforces the widely held notion that diastolic hypertension indicates that a secondary cause is more likely to be present. The failure to see this effect when subjects were sorted by obesity status may be a consequence of the relatively small number of obese subjects in the youngest age group.

Although diastolic BP index was highest in the youngest group of children, systolic BP index was similar across all of the age groups. This suggests that SBP and/or DBP criteria could be considered for eligibility for enrollment in a hypertension trial in young children, but SBP criteria alone would be appropriate for trials enrolling school-aged children and adolescents. Perhaps the reliance on SBP alone in trial A2307 played a role in this trial’s failure to show a dose-response effect of valsartan in children <6 years old, a point that has been made by some authors. However, the similar severity of SBP elevation across all of the age groups and the demonstration of a dose-response effect in trial A23027 supports the use of SBP in hypertension trials enrolling older children.

The impact of the obesity epidemic on childhood hypertension is reflected in several findings of this study. The mean BMI of adolescents 12 to <17 years of age was 30.2 kg/m², which is the cut point for the diagnosis of obesity in adults, and ≈50% of children 6 to <12 years old and adolescents 12 to <17 years old were classified as obese. This confirms trends reported in recent single-center and multicenter referral series, as well as findings from school screening studies indicating a higher prevalence of hypertension among obese children. In addition, nonobese children aged ≥6 years had higher DBP than obese children, which is consistent with reports demonstrating a higher prevalence of isolated systolic hypertension in obese children. Although total cholesterol was similar in the obese and nonobese groups, triglycerides were higher, consistent with the dyslipidemia frequently seen in obese

Table 4. Baseline Blood Pressure and Selected Laboratory Parameters in Black and Nonblack Pediatric Patients With Hypertension, by Age Category

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Age Category</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;6 y</td>
<td>6 to &lt;12 y</td>
</tr>
<tr>
<td>Black patients (n=154)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>27</td>
<td>56</td>
</tr>
<tr>
<td>Mean (SD) body mass index, kg/m²</td>
<td>17.6 (2.8)</td>
<td>23.9 (8.2)</td>
</tr>
<tr>
<td>Mean (SD) sitting SBP, mm Hg</td>
<td>115.4 (7.38)</td>
<td>126.3 (7.47)</td>
</tr>
<tr>
<td>Mean (SD) sitting SBP index (SBP÷95th percentile)</td>
<td>1.1 (0.07)</td>
<td>1.1 (0.05)</td>
</tr>
<tr>
<td>Mean (SD) sitting DBP, mm Hg</td>
<td>70.2 (8.34)</td>
<td>77.1 (8.83)</td>
</tr>
<tr>
<td>Mean (SD) sitting DBP index (DBP÷95th percentile)</td>
<td>1.1 (0.15)</td>
<td>1.0 (0.12)</td>
</tr>
<tr>
<td>Mean (SD) calculated GFR (Schwartz formula), mL/min per 1.73 m²</td>
<td>99.6 (27.73)</td>
<td>150.4 (33.84)*</td>
</tr>
<tr>
<td>Nonblack patients (n=197)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>63</td>
<td>75</td>
</tr>
<tr>
<td>Mean (SD) body mass index, kg/m²</td>
<td>16.4 (3)</td>
<td>23.7 (8.2)</td>
</tr>
<tr>
<td>Mean (SD) sitting SBP, mm Hg</td>
<td>115.1 (7.15)</td>
<td>128.5 (9.71)</td>
</tr>
<tr>
<td>Mean (SD) sitting SBP index (SBP÷95th percentile)</td>
<td>1.1 (0.07)</td>
<td>1.1 (0.08)</td>
</tr>
<tr>
<td>Mean (SD) sitting DBP, mm Hg</td>
<td>69.0 (8.12)</td>
<td>75.1 (11.54)</td>
</tr>
<tr>
<td>Mean (SD) sitting DBP index (DBP÷95th percentile)</td>
<td>1.1 (0.15)</td>
<td>1.0 (0.16)</td>
</tr>
<tr>
<td>Mean (SD) calculated GFR (Schwartz formula), mL/min per 1.73 m²</td>
<td>87.1 (32.90)‡</td>
<td>134.8 (46.38)</td>
</tr>
</tbody>
</table>

GFR indicates glomerular filtration rate; DBP, diastolic blood pressure; SBP, systolic blood pressure.

*n=55.
†n=70.
‡n=61.
children with or without hypertension.16 Excluding patients who were <6 years old, estimated GFR was higher in obese hypertensive children and adolescents, which reflects glomerular hyperfiltration, a known risk factor for obesity-related renal damage.17 Taken together, these findings highlight the significance of obesity-related hypertension in the young and support increased efforts aimed at reducing the prevalence of childhood obesity.

Few consistent race-related differences were seen in this study. It is worth noting, however, that SBP was higher in nonblack patients in the 2 older age groups and that GFR was lower in nonblack patients in all of the age groups. Similarly, there were few differences noted according to severity of hypertension, with the exception of significantly lower calculated GFR in the youngest patients with stage 2 hypertension, which was discussed above.

Limitations of this study include a lack of detailed medical history information, which could have affected the classification of subjects as having secondary versus primary hypertension, and also the use of diverse BP measurement equipment at different local sites and in different age groups. Subjects for both studies were recruited from centers specializing in childhood hypertension, which might have contributed to selection bias. However, given the large number of participating centers and large number of children enrolled in the 2 trials, we do not believe that these issues would have had significant impact on our primary conclusions. A more significant limitation is that selection of study subjects was guided by the inclusion/exclusion criteria of the 2 clinical trials, which would have led to exclusion of children and adolescents with more severely elevated BP and/or known significant renal disease, resulting in a bias toward primary hypertension in the study subjects and a bias toward obese subjects,1 along with overemphasis of the known comorbidities of obesity, such as dyslipidemia.16 Screening logs kept by the individual sites were not available for review, so we were unable to determine whether there were significant differences between children who enrolled in the studies and those who failed to meet study entry criteria. Thus, our findings may not be generalizable beyond otherwise healthy children with mild-to-moderate hypertension. However, it should be noted that recent school screening data have shown that children with even stage 2 hypertension are fairly uncommon, accounting for only ≈3% of children with an initially elevated BP.16 We, therefore, believe that our findings actually do accurately reflect the characteristics of most hypertensive children and adolescents.

Perspectives
Although there are consensus recommendations for evaluation of children and adolescents with elevated BP, the published evidence describing the characteristics of such children has been limited to date. This report provides objective data that demonstrate that very young children are more likely to have secondary hypertension than older children and that obesity and its complications continue to exert significant influence on the characteristics of hypertensive children. These data may also be useful to inform the design of future trials of antihypertensive agents in children and adolescents so that past trial failures can be avoided.

Acknowledgments
We thank all of the participating local investigators and study coordinators for their contributions to the trials and all of the patients and families for their participation.

Sources of Funding
This work was supported by Novartis Pharmaceuticals.

Disclosures
J.F. was a paid consultant to Novartis Pharmaceuticals at the time of the 2 trials and is currently participating as a local investigator in another trial sponsored by Novartis. Y.Z., S.S.-Y., and V.S. are employees of Novartis.

References


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**Novelty and Significance**

**What Is New?**

- Previous studies of hypertensive children have been limited to single centers, but this study includes children from a large variety of centers.
- Our data clearly show that young children with hypertension are more likely to have underlying causes than older children.
- We also show that obese hypertensive children have metabolic abnormalities, such as elevated lipids.

**What Is Relevant?**

- When evaluating children with elevated BP, it is important to do a thorough evaluation for underlying causes if the child is 6 years of age.

**Summary**

Young children with hypertension are more likely to have secondary causes than older children; this has implications for both the clinical evaluation of hypertensive children and for the design of clinical trials.
Clinical and Demographic Characteristics of Children with Hypertension

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Seattle, WA 98105
Phone: 206.987.2524
Fax: 206.987.2636
E-mail: joseph.flynn@seattlechildrens.org
<table>
<thead>
<tr>
<th>Country</th>
<th>1-&lt;6 yrs (N=90)</th>
<th>6-&lt;12 yrs (N=131)</th>
<th>&gt;=12 years (N=130)</th>
<th>Total (N=351)</th>
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<td>Argentina</td>
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<tr>
<td>Belgium</td>
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<td>5</td>
<td>14</td>
<td>19</td>
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<tr>
<td>Brazil</td>
<td>24</td>
<td>44</td>
<td>26</td>
<td>94</td>
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<tr>
<td>Chile</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3</td>
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<tr>
<td>France</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Germany</td>
<td>0</td>
<td>4</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>India</td>
<td>20</td>
<td>0</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Netherlands</td>
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<td>0</td>
<td>2</td>
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</tr>
<tr>
<td>Poland</td>
<td>11</td>
<td>10</td>
<td>9</td>
<td>30</td>
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<td>Senegal</td>
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<td>1</td>
<td>3</td>
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<tr>
<td>United Kingdom</td>
<td>0</td>
<td>2</td>
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<td>4</td>
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<tr>
<td>United States</td>
<td>16</td>
<td>61</td>
<td>69</td>
<td>146</td>
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Table S2. Comparison of Mean Seated DBP and DBP index within age groups for obese vs. non-obese children

<table>
<thead>
<tr>
<th>Obesity status</th>
<th>1 - &lt; 6 years</th>
<th>6 - &lt; 12 years</th>
<th>&gt;= 12 years</th>
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<tbody>
<tr>
<td>N</td>
<td>14</td>
<td>66</td>
<td>68</td>
</tr>
<tr>
<td>Non-obese</td>
<td>68</td>
<td>63</td>
<td>68</td>
</tr>
<tr>
<td>Obese</td>
<td>68</td>
<td>62</td>
<td>62</td>
</tr>
<tr>
<td>Mean (SD) Seated DBP, mm Hg</td>
<td>68.9 (6.3)</td>
<td>69.6 (8.6)</td>
<td>73.3 (9.3)</td>
</tr>
<tr>
<td>P value, Non-obese vs. obese</td>
<td>0.78</td>
<td>0.003</td>
<td>0.02</td>
</tr>
<tr>
<td>Mean (SD) DBP index</td>
<td>1.0 (0.14)</td>
<td>1.1 (0.13)</td>
<td>0.9 (0.12)</td>
</tr>
<tr>
<td>P value, Non-obese vs. obese</td>
<td>0.09</td>
<td>0.0001</td>
<td>0.02</td>
</tr>
</tbody>
</table>
Table S3. Comparison of serum creatinine and calculated GFR within age groups in black vs. non-Black children

<table>
<thead>
<tr>
<th>Age Group</th>
<th>1 - &lt; 6 years</th>
<th>6 - &lt; 12 years</th>
<th>&gt;= 12 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Racial group</td>
<td>Black</td>
<td>Non-black</td>
<td>Black</td>
</tr>
<tr>
<td>N</td>
<td>27</td>
<td>61</td>
<td>55</td>
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<tr>
<td>Mean (SD) serum creatinine, mg/dL</td>
<td>0.6 (0.19)</td>
<td>0.7 (0.31)</td>
<td>0.5 (0.14)</td>
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<tr>
<td>P value, Non-black vs. black</td>
<td>0.03</td>
<td>0.006</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean (SD) calculated GFR, ml/min/1.73m²</td>
<td>99.6 (27.7)</td>
<td>87.1 (32.9)</td>
<td>150.4 (33.8)</td>
</tr>
<tr>
<td>P value, Non-black vs. black</td>
<td>0.09</td>
<td>0.03</td>
<td>0.002</td>
</tr>
</tbody>
</table>