

## Pediatric trials of antihypertensive agents: impact of trial design and unique pediatric factors on efficacy end points

There is an increasing prevalence of pediatric hypertension worldwide due to the growing epidemic of childhood obesity. Recent regulatory changes in the USA and Europe have stimulated major pediatric clinical trials of 16 different antihypertensive agents, leading to US FDA labeling of 10 of these drugs. With increased pediatric hypertension trial experience, trial designs have been refined and we now better understand factors associated with trial success, including the ability to differentiate a dose–response relationship. The use of weight-based dosing and liquid formulation of study drug, selection of an appropriate dose range and appropriate blood pressure end points all increase the likelihood of pediatric trial success.

**Keywords:** clinical trials • pediatric exclusivity • pediatric hypertension • trial design • written request

Nations throughout the developed world are facing an emerging epidemic of pediatric hypertension [1]. It is estimated that one out of every seven US children and adolescents demonstrate prehypertension with 3–4% meeting diagnostic criteria for hypertension [2]. Reported prevalence trends are similar in other nations.

As the prevalence of pediatric hypertension has increased, so has the need for pediatric specific data supporting safety and efficacy of antihypertensive drugs. Although numerous antihypertensive drugs have been studied in clinical trials in adults, in the past, there has been a paucity of evidence to support safety and efficacy in children and adolescents. As a consequence, providers have used drugs ‘off-label’, extrapolating dosing and efficacy from adult data [3]. This practice is common in pediatrics but is potentially harmful, as unique developmental physiology can affect drug dosing, safety and efficacy. Recognizing this, regulatory initiatives in both the USA and Europe have created incentives and/or mandates to conduct clinical trials of drugs in children and adolescents. Pediatric trials of antihypertensive agents have been specifically

prioritized and over the preceding 15 years more than 20 clinical trials have been conducted to evaluate safety, efficacy and dosing of pediatric antihypertensive agents. These trials have resulted in FDA labeling of 10 new pediatric antihypertensive drugs (Figure 1). The purpose of this review is to summarize trials completed for these various antihypertensive agents and to review lessons learned along the way with regard to trial design and conduct.

### Written request criteria & clinical trial design

In the USA, trials conducted for pediatric drug labeling are developed in close cooperation between the study sponsor and the FDA. The FDA ‘written request’ is the formal mechanism for drug labeling and sponsors must comply with written request criteria in order to be eligible for incentives. The strategy for FDA drug approval typically calls for: a dose-ranging trial in hypertensive pediatric patients; pharmacokinetic trials in four pediatric age groups: infants and toddlers, pre-school children, school-age children and adolescents; and safety data with a summary

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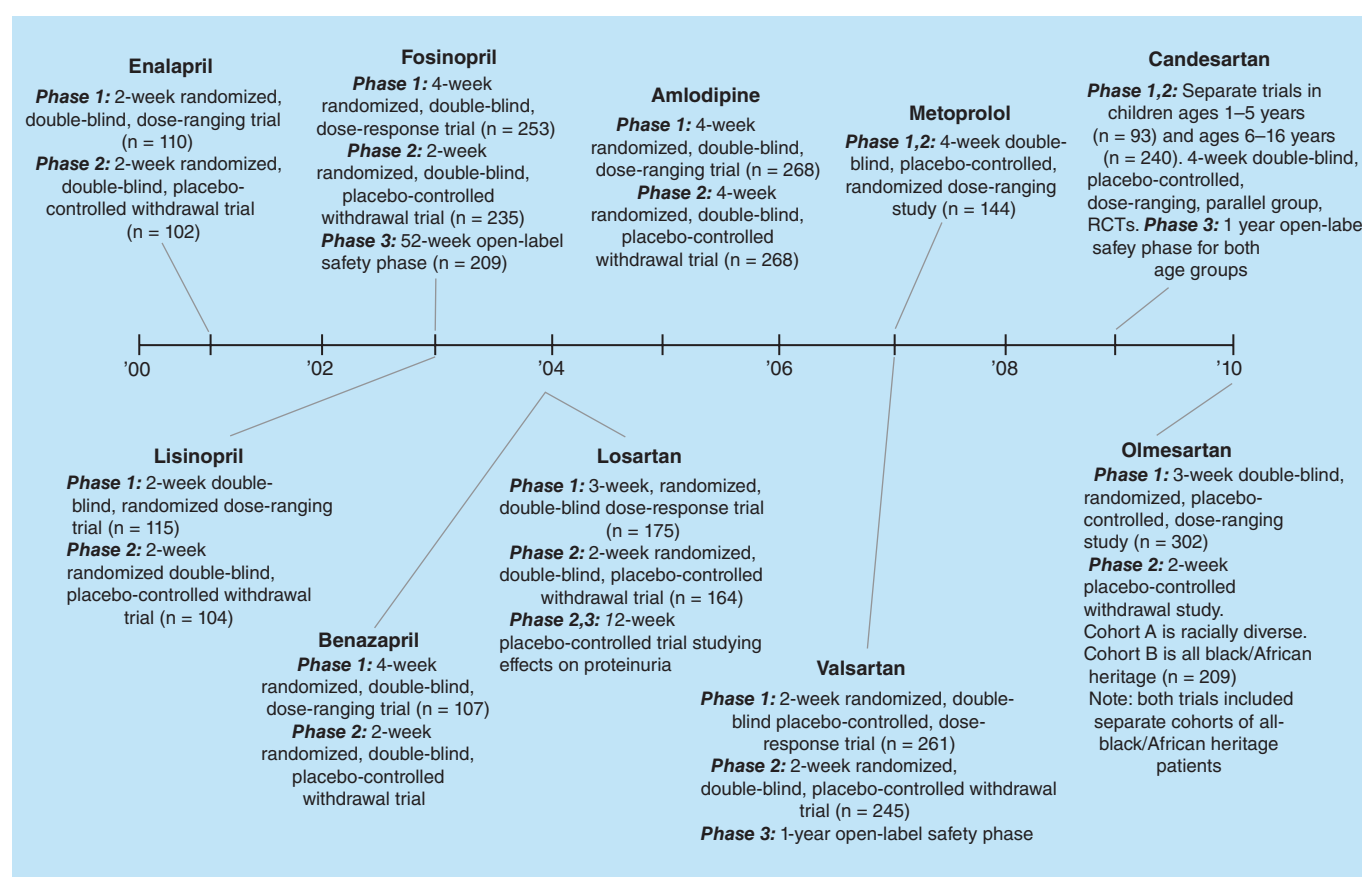
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**Figure 1. Timeline for completion of trials that have resulted in US FDA labeling for treatment of hypertension in children and adolescents.**

of all available information on the safety of the drug in pediatric patients. The FDA written request contains the required elements of the requested studies, including indication, number of studies, sample sizes, trial design and age ranges required to effect a labeling change (Table 1). These criteria have undergone several amendments aimed at improving trial standards and ensuring a meaningful and generalizable trial outcome. The written request also outlines four potential efficacy trial designs (Figure 2) [4].

### Trial design A

In this design, patients are randomized to placebo or several different dosages of study drug (Figure 2). The trial is analyzed based on the slope of the placebo-corrected change in blood pressure. An effective drug and successful trial would demonstrate a negative slope indicating that blood pressure decreases as drug dosage increases. The advantage of this trial type is that both successful and unsuccessful (“failed”) trials are interpretable, and therefore responsive to the FDA written request. A major disadvantage is the need for a placebo group. Some have questioned the ethics of conducting placebo-controlled trials in children in

general [5,6]. Prior analyses have demonstrated that short-term exposure to placebo in pediatric trials of antihypertensive medications is safe with no increased risk of adverse events in those randomized to placebo [7]. Furthermore the written request allows these trials to employ a 3:1 randomization scheme thereby limiting randomization to placebo. Nonetheless some parents will still have concerns about their child’s participation and this may delay recruitment.

### Trial design B

This trial design avoids the issues associated with a placebo-controlled trial by randomizing to one of two or three dosages of the test drug (Figure 2). The trial is considered successful and responsive to the written request if there is a negative slope of the dose–response curve. However, the trial is uninterpretable if the slope is zero because it is not possible to determine if there is no drug effect, or if all doses were too low or too high resulting in a similar effect in all arms. Thus, a negative trial would be unresponsive to the written request and consequently this design involves significant risk for manufacturers compared with the other trial designs. Moreover, the lack of controls does not allow adequate assessment of safety.

Table 1. Elements typically required to satisfy US FDA written request criteria for pediatric hypertension trials.

Definition of hypertension	<p>≥95th percentile for age/gender/height</p> <p>or</p> <p>≥90th percentile if concurrent conditions present</p>
Demographic criteria	<p>&gt;50% pre-adolescent subjects</p> <p>40–60% black subjects</p> <p>Male and female subjects</p>
Formulation criteria	Age-appropriate formulations (liquid formulation required)
Dose range	Blood levels should range from less than those achieved with the lowest approved adult dose to more than those achieved with the highest generally used adult dose
Primary efficacy end points	<p>Absolute or percent change in systolic or diastolic blood pressure</p> <p>Trial design A/B – change from baseline to the end of the treatment period + inter-dosing interval (trough)</p> <p>Trial design C/D – change in blood pressure from the last on-treatment visit to the end of withdrawal period</p>
Primary pharmacokinetic end points	Bioavailability half-life, $C_{max}$ and $T_{max}$ in the various age groups and for parent and metabolites
Trial duration	Typically 2 weeks but longer if a period of dose titration is needed
Safety criteria	<p>Follow patients at least weekly for adverse events and to detect unacceptable increases in blood pressure</p> <p>Trials should include an independent Data Safety and Monitoring Committee</p> <p>Trials should include a 1-year open-label treatment period to evaluate adverse events, growth (change in head circumference, weight, length or height) and development (milestones, school performance, neurocognitive testing)</p>
Statistical considerations	<p>≥80% power to detect a 3mmHg change in blood pressure of conventional (<math>p &lt; 0.05</math>, two-sided) statistical significance</p> <p>Interim analyses allowed to assess variability following a pre-specified rule to adjust sample size to achieve target power</p>

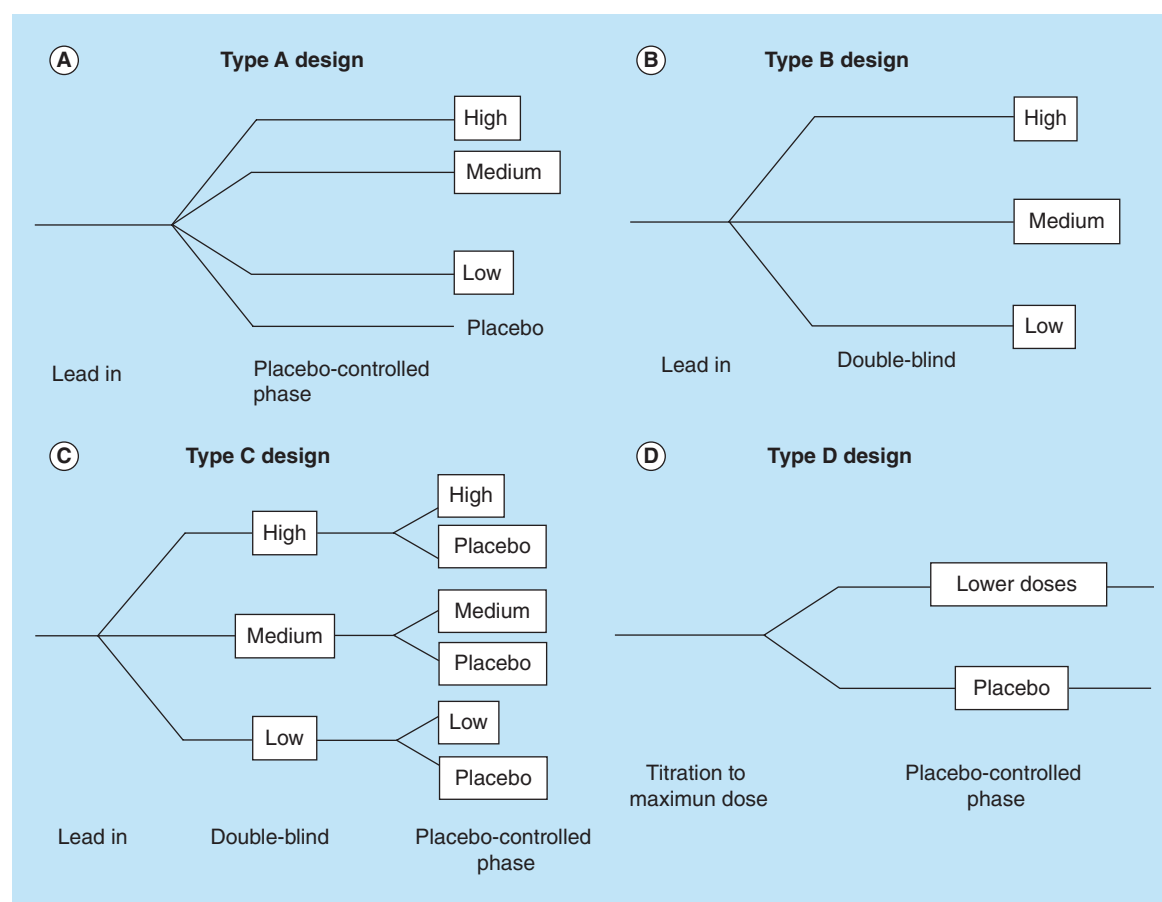
### Trial design C

This design is initially similar to 'B' with randomization to one of three dosages of study drug. However, after an active treatment phase, the study switches to a placebo-controlled phase and patients are re-randomized to either continue on their assigned drug or switched to placebo. Advantages of this design are that it avoids use of a true placebo arm but, because patients act as their own controls, there is increased power to obtain interpretable results regardless of the trial outcome. If the slope of the dose–response curve during the treatment phase is negative, the trial is successful and responsive to the written request. If the slope is zero during the treatment phase then further analysis of the placebo-controlled phase allows interpretation. If the treatment phase dose–response curve slope were zero, but the withdrawal phase demonstrated a rise in

blood pressure, this would indicate that the low-end doses were too high. Alternatively, if blood pressure did not change during the withdrawal phase, this would suggest that the drug was ineffective, the dosages were too low, or the withdrawal period was too short to completely wash out the drug effect. Thus a major advantage of this trial design is that the trial is interpretable regardless of outcome.

### Trial design D

In this design, patients are force-titrated to maximal tolerated drug doses, and then randomly withdrawn to lower dosages, including placebo. Similar to design C, this design avoids the use of a placebo arm. Analysis is similar to that of trial design C and the trial is interpretable regardless of outcome. However, titration to maximal tolerated doses increases the



**Figure 2. Pediatric antihypertensive trial designs.**

Trial design: **(A)** involves randomization to placebo, low, medium or high dose with analysis of the placebo-corrected change in blood pressure; **(B)** involves randomization without a placebo control and therefore a successful trial requires a negative dose-response curve; Trial design **(C)** is initially similar to B but after an active treatment phase, the study switches to a placebo controlled phase. This design allows interpretation even if the slope of the dose response curve for the initial phase is zero. In Trial design **(D)** patients are force titrated to maximal tolerated drug doses and then randomly withdrawn to lower doses including placebo.

risk of adverse events – a major disadvantage of this design.

### Pediatric antihypertensive drug trials

Since 2000, 16 drugs have been studied for out-patient treatment of pediatric hypertension in response to a FDA written request. Ten of these drugs have been labeled for use in pediatric populations. Of the remaining six drugs, two trials resulted in negative labeling changes noting lack of efficacy (eplerenone and irbesartan) while trials for bisoprolol, felodipine, quinapril and ramipril did not result in labeling changes (Table 2).

#### Enalapril

Enalapril was the first pediatric antihypertensive labeled by the FDA in 2002 [8]. The enalapril trials employed trial design C with a 2-week dose-response phase ( $n = 110$ ) and a 2-week placebo-controlled withdrawal phase ( $n = 102$ ). Compared to children

treated with placebo, those treated with moderate or high doses (2.5 or 20 mg for children  $<50$  kg and 5 mg or 40 mg for children  $>50$  kg) demonstrated significantly lowered diastolic blood pressure (DBP) and systolic blood pressure (SBP). However, the low-dose group (0.625 mg/1.25 mg) did not demonstrate lowering of DBP or SBP. There was no significant difference in antihypertensive effects across race, age, sex or Tanner stage. Enalapril was well tolerated and safe in the 4-week trial. The most common side effects were dizziness (3.6%) and headache (1.8%), and there was only one drug discontinuation ( $<1\%$ ) due to adverse events. The enalapril FDA label is unique in that the drug has a pediatric indication for all children with the exception of neonates.

#### Fosinopril

Fosinopril was labeled for treatment of pediatric hypertension by the FDA in 2003 [9,10]. The pivotal

Table 2. Summary of trial designs and outcomes for pediatric antihypertensive trials completed in response to a US FDA written request.

Drug	Trial design	Sample size	Dose response	Label change
Amlodipine	C	268	No	Yes
Benazepril	D	107	No	Yes
Bisoprolol	A	94	Yes 1–5/No 6–17	No
Candesartan	A	240	Yes	Yes
Enalapril	C	110	Yes	Yes
Eplerenone	C	304	No	Yes (negative)
Felodipine	D	133	No	No
Fosinopril	C	253	No	Yes
Irbesartan	C	318	No	Yes (negative)
Lisinopril	C	118	Yes	Yes
Losartan	C	175	Yes	Yes
Metoprolol	A	140	No	Yes
Quinapril	A	112	No	No
Ramipril	D	219	No	No
Valsartan	C	351	No 1–5/Yes 6–16	Yes
Olmesartan	C	302	Yes	Yes

fosinopril pediatric trial followed trial design C, including a 4-week dose-ranging phase ( $n = 253$ ) and a 2-week placebo-controlled withdrawal phase ( $n = 235$ ). There was also a 52-week open-label extension phase ( $n = 209$ ) to assess the safety profile. In the clinical trials, all three dose levels (0.1, 0.3 and 0.6 mg/kg) of fosinopril were equally effective at reducing SBP and DBP with no dose response in the overall cohort. Further analysis showed that fosinopril was effective at reducing SBP in a dose-responsive manner in black children; however, blacks required a higher dose per body weight to achieve adequate control. Fosinopril was well tolerated with no serious adverse events in the 52-week open-label extension study. Discontinuation of fosinopril secondary to adverse events during the dose-ranging and withdrawal phase was rare (1.6%). In the open-label extension phase, 83% successfully reached target blood pressure with headache (20.1%), nasopharyngitis (9.6%), cough (9.1%), pharyngitis (8.6%) and abdominal pain (6.2%) being the most common adverse events.

### Lisinopril

Lisinopril was labeled for pediatric hypertension by the FDA in 2003 [11]. Pediatric trials consisted of a 2-week dose-ranging study ( $n = 115$ ) and a 2-week placebo-controlled withdrawal study ( $n = 104$ ). In the pivotal trial (design C), lisinopril demonstrated a dose-response reduction in SBP and DBP

that was consistent across age groups, Tanner stages and ethnicity. Lisinopril was safe and well tolerated with no serious adverse events and few discontinuations (<1%). The most common adverse events were headache (3.5%), dizziness from hypotension (1.7%) and abdominal pain (1.7%).

### Benazepril

Pediatric trials for benazepril have not been published in the literature, but the FDA labeled it for pediatric hypertension in 2004 and the trials are summarized on the FDA label [12]. Benazepril significantly lowered SBP but did not exhibit a dose response. Benazepril was well tolerated. The FDA label does not specifically list the adverse event profile or report if any patients discontinued the trial due to drug-related adverse events.

### Ramipril & quinapril

Clinical trials were conducted in response to FDA-issued written requests for both ramipril and quinapril [13]. Both drugs failed to demonstrate a dose response and therefore neither drug received a labeled indication for treatment of pediatric hypertension. To our knowledge the results of these trials have not been published in the medical literature. The FDA website includes information summarizing the results of the ramipril trials [13]. Ramipril was studied in a pharmacokinetic trial, a dose-escalation, randomized double-blind withdrawal study (enrolling 219 children and adolescents ages 6–16 years) and in a 1-year safety extension trial. Ramipril

was demonstrated to be safe but failed to demonstrate a dose response during the withdrawal phase and therefore was considered non-efficacious.

### Losartan

Losartan was the first angiotensin receptor blocker labeled for pediatric hypertension by the FDA in 2004 [14]. The pivotal clinical trial (trial design C) included a 3-week dose-response study (n = 175) and a 2-week placebo-controlled withdrawal study (n = 164). Losartan demonstrated a dose-response reduction in SBP and DBP with efficacy demonstrated for the moderate and high dose groups (2.5 or 25 mg for children <50 kg and 5.0 or 50 mg for children ≥50 kg) but no significant difference in blood pressure during withdrawal from the low dose losartan group. There were too few non-white patients to evaluate race-related differences in dose response. Losartan was well tolerated with few discontinuations due to adverse events (<1%). Losartan was also studied in a clinical trial focused on reduction of proteinuria in hypertensive (n = 60) and normotensive (n = 246) children with chronic kidney disease [15]. Losartan reduced proteinuria by 35.9% (95% confidence interval: 27.6–43.1%) and was superior to both placebo (normotensive cohort) and amlodipine (hypertensive cohort). Additionally, losartan reduced SBP and DBP in both cohorts and was superior to amlodipine, although the authors postulated that a lack of change in blood pressure in children on amlodipine was due to titration effect. There were no serious adverse events in this trial and 0.7% of subjects discontinued losartan due to adverse events.

### Valsartan

Valsartan was labeled for pediatric use by the FDA in 2007 [16]. Pediatric clinical trials (trial design C) included a 2-week dose-ranging study (n = 261) followed by a 2-week placebo-controlled withdrawal study (n = 245) and a 1-year open-label extension study. Valsartan demonstrated a dose-response reduction in SBP and DBP but no statistically significant difference in blood pressure between the low- or medium-dose groups (10, 20 mg for children <35 kg and 20, 40 mg for children ≥35 kg). Valsartan's antihypertensive effects were observed across all subgroups including sex, age, Tanner stage and race (black and non-black). During the dose response and withdrawal phase of the study, there were no serious adverse events and few subjects (1.6%) discontinued therapy due to adverse events. Headache (11.6%) and dizziness (2.7%) were the most commonly reported adverse events in the dose-response phase. In the 52-week open-label trial, 3.6% of subjects discontinued valsartan due to adverse events. Gastroenteritis (<1%) and hyperkalemia (<1%) were the only adverse events considered to be drug-related.

### Candesartan

Candesartan was labeled for pediatric use by the FDA in 2009 following separate trials in children ages 1 to less than 6 years of age and children ages 6–17 years [17,18]. Candesartan demonstrated a dose response only in the trial in younger study subjects. In the dose-ranging study in subjects ages 6–17 years (trial design A), candesartan demonstrated a significant decrease in SBP and DBP compared with placebo at all dose levels but not a dose response. The lack of dose response was attributed to a narrow dose range. In the extension study, the 1-year response rate (SBP <95%) was 52%. Black children had a lesser reduction in SBP and DBP, and a lower response rate compared with white children (response rate in black vs white, 43 vs 61%). Drug discontinuation due to adverse events was rare (1% in dose-ranging study and 2.1% in open-label study), and there were no serious adverse events. The most common adverse events were headache, upper respiratory infection, dizziness, cough and sore throat.

### Olmesartan

Olmesartan was labeled for pediatric hypertension by the FDA in 2010 [19]. Pediatric clinical trials (trial design C) consisted of a 3-week dose-ranging study (n = 302) followed by a 2-week placebo-controlled withdrawal study (n = 289). Olmesartan demonstrated a dose-response reduction in SBP and DBP, but the blood pressure reduction was smaller in blacks. Olmesartan was well tolerated and drug discontinuation due to adverse events was rare (<1%) with no serious adverse events. The most commonly experienced side effects in the 6-week period were headache (1.7%) and dizziness (1.3%).

### Irbesartan

Irbesartan was not labeled for pediatric hypertension due to lack of efficacy [20,21]. The irbesartan pediatric efficacy trial (trial design C) included a 3-week double-blind dose-response study and a 2-week placebo-controlled withdrawal study. A 6-month open-label extension trial was performed for safety assessment. There was no dose response in the irbesartan trial. Although the difference in blood pressure at the end of the withdrawal phase was statistically significant, the effect size (-2.3 mmHg reduction in SBP) was small and was not felt to be clinically meaningful. Adverse events were more frequent than in other angiotensin receptor blocker trials and 2.5% discontinued study drug. There was also one case of erythema multiforme possibly related to irbesartan use.

### Amlodipine

Amlodipine was labeled for pediatric hypertension by the FDA in 2004 [22]. It is the most commonly prescribed



calcium channel blocker for pediatric hypertension. The pediatric amlodipine efficacy trial (trial design C) included a dose-ranging study (n = 268) and a placebo-controlled withdrawal study (n = 268). Amlodipine did not demonstrate a dose-response reduction in SBP and DBP. SBP reduction was slightly greater in females compared with males; otherwise, SBP reduction across race, age and etiology of HTN (hypertension) did not differ significantly. Amlodipine was generally well tolerated with few discontinuations due to adverse events (2.2%). Reasons for discontinuation included worsening hypertension (1.1%), facial edema (<1%), edema of the fingers with rash (<1%) and premature ventricular contractions (<1%). Peripheral edema, an adverse event commonly seen in adults, was reported in 3.8% of children in dose-ranging phase and 2.3% of children in placebo-withdrawal phase.

#### Felodipine extended release

Felodipine is a long acting calcium channel blocker that was not approved for pediatric hypertension by the FDA due to lack of efficacy [23]. The felodipine pediatric trial (trial design D) included a 3-week dose-response trial (n = 128). A 14-week open-label extension trial was performed to assess safety. Felodipine was well tolerated (0.8% discontinued due to adverse event) and there were no serious adverse events.

#### Metoprolol

Metoprolol was labeled for pediatric hypertension by the FDA in 2007 after completion of a 4-week placebo-controlled dose-ranging study (n = 144) and a 52-week open-label extension study (n = 85) of the extended release formulation [24]. In the dose-ranging phase (trial design A), metoprolol significantly reduced SBP compared with placebo, but with no dose-response effect. Only high doses of XR metoprolol (2 mg/kg) demonstrated significant reductions in DBP compared with placebo. Authors postulated that the lack of dose-response reduction in SBP may have been due to a flattening of the dose-response curve or a limitation of the study design. At the end of the dose-ranging study, the response rate for metoprolol was 46% (95% CI: 37%–55%). Metoprolol's antihypertensive effects were independent of age, Tanner stage and race. Authors note that overweight patients (BMI >95%) tended to have less pronounced SBP reductions. Metoprolol was safe and well tolerated with a maximum decrease in heart rate of only 6.5 beats per minute. Drug discontinuation was rare in all trial phases (0.7% in the dose-response phase and 5.9% in the open-label trial). The most commonly reported adverse events in trial participants receiving

metoprolol were headache (30%), upper respiratory tract infection (20%), cough (19%), nasopharyngitis (13%), pharyngolaryngeal pain (12%), fatigue (9%), diarrhea (7%) and dizziness (6%).

#### Bisoprolol fumarate/hydrochlorothiazide

Bisoprolol fumarate/HCTZ (B/HT) is a combination hypertensive that failed to gain FDA labeling for pediatric hypertension due to lack of efficacy [25]. In a placebo-controlled dose-ranging pediatric trial (n = 94) (trial design A), the percentage of patients in the B/HT group that achieved blood pressure control (SBP and DBP <90th percentile) was not significantly different from placebo (45% for B/HT, 34% for placebo). Discontinuation of B/HT due to adverse events was rare (1.6%) and overall fewer adverse events were reported for the B/HT group compared with placebo.

#### Eplerenone

Eplerenone is a selective aldosterone antagonist that was not labeled for pediatric hypertension by the FDA due to lack of efficacy [26,27]. The pediatric trial (trial design C) consisted of a 6-week dose-ranging study (n = 304) and a 4-week dose withdrawal study (n = 277). Children on concomitant therapy with a potent CYP3A4 inhibitor (clarithromycin, ketoconazole), potassium supplement, or potassium level >5.5 mEq/l were excluded and eplerenone is considered contraindicated under such circumstances. In children ages 4–17 years old, eplerenone did not demonstrate a dose-response effect and reduced SBP was only seen for the high dose level (50 mg twice a day for children >20 kg). There was no significant difference in DBP compared with the placebo group. Eplerenone was well tolerated with few serious adverse events (2.6%) or discontinuations in the 10-week trial (<1%).

#### Failure to demonstrate a dose response

Overall, 9 of the 16 pediatric antihypertensive drug trials failed to show a dose response, a critical trial end point in terms of dosing recommendations. In a meta-analysis of these trials, we determined that several factors were predictive of success [28]. These factors are discussed below.

#### Dose range

The difference between low- and high-dosage groups was extremely variable between trials. For example, in the failed amlodipine, fosinopril and irbesartan trials, the difference between low- and high-dosage groups was twofold, sixfold and ninefold, respectively. By comparison, the successful enalapril, lisinopril and losartan trials (which all demonstrated a dose response) had 32-, 32- and 20-fold differences, respectively. In

general, unless contraindicated for safety concerns, the lowest dose should be lower than the lowest approved dose in adults, and the highest dose should at least be twofold higher than the highest approved dose in adults [28]. The selection of wide dosage ranges is important because closely spaced dosages will be more likely to yield overlapping exposures among dose groups. This will make it more difficult for a trial to demonstrate a significant dose–response relationship.

### Dose by weight

Weight-based dosing strategies were inconsistent in trials. Flaws in dosing strategies sometimes resulted in paradoxical dosing such that heavier children assigned to a high-dosing group could actually receive lower doses on a per kg basis than lighter children assigned to low dosing group. For example, the amlodipine trial did not incorporate individual subject weight in dosing but rather gave all children in the low-dosage arm 2.5 mg of product and all children in the high-dosage arm 5 mg of product. Paradoxical dosing was also possible in the fosinopril trial. Although this trial did use a weight-based strategy, the highest allowable dose was 40 mg. Thus a child weighing <30 kg in the medium-dose arm could receive a higher dose on a per kg basis than a heavier child in the high-dose arm. In both the amlodipine and fosinopril trials blood pressure did not show a dose response as randomized; however, increased dosage on a milligram per kilogram basis was associated with a decrease in blood pressure [28,29]. Problems associated with weight-based dosing are likely exacerbated in pediatric hypertension trials as study subjects are often obese. Although the effects of obesity on drug dosing in children are not well defined, it is certainly possible that obese children might require higher drug doses for some drugs, particularly those with higher lipophilicity [30–32]. Indeed a common flaw across pediatric hypertension trials is that all have capped dosing at the maximum approved adult dose. For trials to optimally evaluate drug dosing in children the lowest clinical trial dose should be lower than the lowest approved adult dose and the highest clinical trial dose should be at least twofold higher than the maximum approved adult dose unless contraindicated for safety reasons [28].

### Development & use of a liquid formulation

Trials that did not develop a pediatric (e.g., liquid) formulation often exhibited a wide range in exposure within each weight stratum because precise dosing is not feasible using a limited number of tablets. As a result of exposure-related concerns in these trials, pediatric formulations are now required by the FDA written request (see requirements outlined in [Table 1](#)).

### Primary end point

Most successful trials used change in DBP as the primary end point, while several unsuccessful trials (amlodipine, fosinopril and irbesartan) used sitting SBP as the primary end point. We evaluated the reduction in systolic and DBPs related to several agents and found that a reduction in DBP was more closely related to the dosage of agent administered [29]. One plausible explanation for this finding might be because DBP has less physiological variability among observations within a subject than SBP. Significant within subject variability of a study end point can contribute to difficulties detecting a dose response. Systolic hypertension is however more than threefold more common than diastolic hypertension in children and adolescents [33,34]. Therefore, use of SBP as an end point has greater clinical applicability and also improves subject recruitment. To overcome these limitations, we have previously suggested using mean arterial blood pressure, which incorporates both SBP and DBP, as the primary end point. SBP and DBP could still be assessed as secondary trial end points [28].

### Blood pressure measurement

There is heterogeneity in methodology used to measure blood pressure for clinical trials. Some trials have relied on oscillometric devices while others used auscultation. The two methods do not always agree and significant differences have been detected in certain patient populations [35]. Auscultation is considered the gold standard for direct measurement of systolic and DBP, and is recommended as the preferred method of blood pressure measurement in children [36,37]. Oscillometric devices directly measure mean arterial pressure and then compute systolic and diastolic pressures using an algorithm. Potentially these devices might be best used in clinical trials for assessment of mean arterial pressure, although this has not been specifically studied.

Even when using standardized equipment, there will be variability in blood pressure measurements. Although not specified in the written request, most trials completed for pediatric exclusivity have complied with current guidelines requiring that elevated SBP and DBP be measured in triplicate with the mean of the three measurements reported. This can sometimes create difficulties when highly discordant blood pressure measurements are obtained. A consideration for future trials is the use of ambulatory blood pressure measurement which allows for a more comprehensive assessment of circadian blood pressure control, correlates better with end-organ damage in hypertension and has demonstrated lower cost in adult hypertension trials [35,37]. For these reasons ambulatory blood pressure measurement is gaining increased acceptance in pediatric clinical practice and in adult



as well as pediatric clinical trials. As evidence accrues with respect to normative values in children, feasibility, reproducibility and cost, we anticipate that ambulatory blood pressure monitoring might be an important trial end point and perhaps eventually the measurement of choice for future hypertension trials.

### Study population

It is likely that the pathophysiology underlying hypertension impacts treatment effects. Successful trials of lisinopril, olmesartan and enalapril enrolled >50% of study subjects with glomerular or urogenital hypertension (with glomerular filtration rate > 30ml/min/1.73<sup>2</sup>) [8,11,19]. Patients with glomerular or urogenital hypertension are more resistant to antihypertensive management but might also be more sensitive to renin–angiotensin–aldosterone modulation. These factors would likely improve the likelihood of demonstrating a dose–response relationship due to a greater discrimination between low- and high-dose effects. The candesartan trials provide evidence to support this as they were conducted separately in two age groups – children ages 1–6 years and children ages 6–17 years. In the younger age range, 80% of trial subjects had glomerular or

urogenital hypertension and the trial was positive, demonstrating a dose response [18]. In the older age range, less than 10% of trial subjects had renovascular hypertension and the trial was considered negative with no dose response [17]. The fosinopril trials provide another example of this but with respect to racial differences. Overall the fosinopril trials did not demonstrate a dose–response; however, in subgroup analysis there was a dose response in black subjects only. This was because black subjects were less sensitive to low-dose fosinopril which made it possible to discriminate a dose response with higher doses [9,10]. Whenever possible trials should enroll homogeneous patient populations or use power calculations to stratify based on underlying disease pathophysiology, racial differences or other factors that might affect the dose response.

### Conclusion

Legislative incentives and an emerging epidemic of pediatric hypertension have stimulated numerous pediatric antihypertensive drug trials in children and adolescents over the last 15 years. As a result of these trials, much has been learned about safety and efficacy of antihypertensive agents in children, and also about strategies for successful

#### Executive summary

##### Pediatric hypertension

- Prevalence of pediatric hypertension is increasing and currently affects ~3–4% of children in the developed world.
- Historically drugs have been used off-label to treat pediatric hypertension, extrapolating dosing, safety and efficacy from adult studies. This practice is now considered unsafe.
- Recent regulatory initiatives in the US and Europe have stimulated recent pediatric trials of antihypertensive drugs.

##### Written request criteria & trial design

- The FDA ‘written request’ is the formal mechanism for drug labeling and outlines trial design and other pediatric specific trial requirements.
- A classic placebo-controlled trial.
- A trial with randomization to several different dosages with no placebo.
- A trial with randomization to several dosages in the active phase followed by re-randomization to placebo versus continuation of study drug.
- A trial involving force titration to maximal tolerated dosages followed by withdrawal to lower dosages or placebo.

##### Pediatric antihypertensive drug trials

- Since 2000, 16 different drugs have been studied in response to a FDA issued written request.
- Ten drugs have been approved for use in children and adolescents:
  - amlodipine, benazapril, candesartan (ages 1–5 years), enalapril, fosinopril, lisinopril, losartan, metoprolol, valsartan (ages 6–16 years), and olmesartan.

##### Factors associated with failure to demonstrate a dose–response

- Only 7/16 efficacy trials have demonstrated a dose–response, a critical end point for determining the most appropriate recommended treatment dose.
- Factors associated with successful demonstration of a dose response include:
  - Use of weight-based dosing
  - Use of a liquid formulation of study drug
  - Appropriate dose range selection
  - Appropriate blood pressure end points
  - Study population.

pediatric trial design. Recurrent themes have emerged from both successful and unsuccessful drug trials that should be considered in future trials in children. Involvement of pediatric pharmacology experts assisting in weight-based dosing strategies, liquid formulations and consideration of special populations (e.g., obese children) is likely to increase trial success. For pediatric antihypertensive trials in particular, close attention should be paid to the end point selection of SBP or DBP and the study population should be stratified by race and underlying disease pathophysiology. Results and experiences from past trials have already resulted in changes to the FDA written request template that will improve trial design in children.

### Future perspective

Moving forward, it is critical that our community not only learn from past experiences but also that we anticipate future directions so as to design and implement trials that optimally meet the needs of our patients. Studies of the comparative effectiveness, long-term safety and effects of antihypertensive drugs on growth and development are needed. It is important to recognize that blood pressure is a surrogate end point associated with long-term target organ damage. Target-organ changes

have been documented in children with hypertension including retinal damage, left ventricular hypertrophy, microalbuminuria, increased carotid intima media thickness and increased cerebrovascular resistance [38–42]. At present, we have a limited understanding of the long-term implications and potential reversibility of these findings in children. However, as we gain further knowledge and insight, it will be important for trials to consider whether assessment of target-organ damage might improve our understanding of drug efficacy. With these changes and a continued commitment to developing safe and effective drugs in children, future trials will continue to not only improve pharmacotherapy of hypertension in children but also lead the way for successful pediatric drug trials in general.

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