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# Anti-hypertensive drugs in children and adolescents

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## Abstract

Worldwide the prevalence of essential hypertension in children and adolescents continues to increase. Traditionally providers have used "off-label" drugs to treat pediatric hypertension, meaning that rigorous clinical trials of these drugs have not been specifically performed in pediatric patient populations. Consequently providers have extrapolated dosing, safety and efficacy from trials in adults. This practice is sub-optimal as children demonstrate unique differences in drug metabolism and response. Use of unstudied or understudied drugs increases risk of adverse events and/or can lead to sub-optimal efficacy. Recognizing these concerns, regulatory agencies have created financial incentives for industry to conduct pediatric clinical trials. These incentives, coupled with the emerging pediatric hypertension epidemic, have spurred over 30 clinical trials of anti-hypertensive drugs over the past 15 years and have resulted in labeling of 10 new drugs by the United States Food and Drug Administration for treatment of hypertension in children and adolescents. Unfortunately the financial incentive structures focus on newer drugs and drug classes. Consequently there is now a relative dearth of trial data for older but sometimes commonly

prescribed pediatric antihypertensive drugs. This article reviews recent pediatric antihypertensive drug trials with a focus on trial design and endpoints, drug dosing, safety, efficacy and specific drug indications. We also review the available data and experience for some of the more commonly prescribed, but less well studied "older" pediatric antihypertensive drugs.

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**Key words:** Hypertension; Children; Clinical trials; Dosing; Safety

**Core tip:** This review focuses on the major clinical trials of anti-hypertensive drugs that have been completed over the past 15 years in response to regulatory initiatives by the United States Food and Drug Administration and the European Medicines Agency. These trials have changed the landscape of anti-hypertensive drug management in children.

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## INTRODUCTION

Nations throughout the developed world are facing an emerging epidemic of pediatric hypertension that has paralleled an increasing prevalence of childhood obesity<sup>[1-5]</sup>. In recent cross-sectional studies, greater than one out of every seven United States children and adolescents demonstrate prehypertension with over 3% meeting diagnostic criteria for hypertension<sup>[6]</sup>. Prevalence trends are similar in population-based assessments in numerous other nations<sup>[7-11]</sup>. Elevated blood pressure during childhood and adolescence is associated with end organ damage<sup>[12,13]</sup>, most commonly left ventricular hypertrophy, and

is predictive of hypertension in early adulthood<sup>[5,14,15]</sup>.

With increasing prevalence of pediatric hypertension, there is a need for data supporting safety and efficacy of antihypertensive drugs. While a wide variety of antihypertensive drugs have been studied in clinical trials in adults, traditionally there has been a paucity of evidence to support safety and efficacy of antihypertensive drugs in children and adolescents. Consequently, providers were forced to use drugs “off-label”, extrapolating dosing and efficacy from adult data<sup>[16]</sup>. This practice is sub-optimal as children demonstrate unique physiology and pathology, and off-label drug use risks inadequate disease treatment and/or safety events. Furthermore most drugs designed for use in adults do not have pediatric specific tablets or formulations, which can complicate dosing. Recognizing these concerns, regulatory agencies in both the United States and Europe have passed recent regulatory initiatives aimed at stimulating pediatric clinical trials<sup>[17,18]</sup>. These initiatives have been very successful and over the preceding 15 years, more than 20 clinical trials of antihypertensive agents have been completed in children leading to approval of 10 drugs by the United States Food and Drug Administration (FDA) for treatment of hypertension in children and/or adolescents (Figure 1).

This review summarizes the available data and experience supporting the use of antihypertensive drugs in children and adolescents diagnosed with essential hypertension with a particular focus on recent pediatric clinical trials. Angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, calcium channel blockers, beta blockers and diuretics will be covered with a critical appraisal of available clinical trial data supporting dosing, efficacy, safety, and treatment in specific patient populations. Approval of drugs for pediatric use by the United States FDA will be used as a meaningful benchmark of adequate drug study, reflecting the stringent standards required for FDA approval.

## IDENTIFICATION OF CLINICAL TRIAL DATA

To identify anti-hypertensive drug trials in children and adolescents, we used four principle sources: the United States FDA website (<http://www.accessdata.fda.gov/>), the FDA approved drug label, the European Medicines Agency (EMA) website (<http://www.ema.europa.eu/>) and PubMed. The FDA website and drug label include detailed information summarizing clinical trials completed in response to an FDA issued written request (a requirement for trials completed for drug labeling) including trial design, drug dosing, efficacy and safety data. Similarly the EMA publishes the results of reviews conducted for EMA pediatric drug approval. We also reviewed publications cited on PubMed for relevant clinical trials. Publications were identified following a PubMed search restricted to children and adolescents  $\leq 18$  years and using MeSH terms “Hypertension” and “clinical trial”.

## ANGIOTENSIN CONVERTING ENZYME INHIBITORS

ACE inhibitors target the renin-angiotensin-aldosterone-system (RAAS). ACE converts angiotensin I to angiotensin II (Ang II), a peptide that causes vasoconstriction and stimulates aldosterone production, itself a potent vasoconstrictor. ACE inhibitors lower blood pressure by decreasing Ang II and mitigating its downstream effects. In adults, ACE inhibitors are commonly used antihypertensives and have the additional benefit of reducing cardiovascular and renal events<sup>[19]</sup>. In pediatric populations, ACE inhibitors are the most commonly prescribed antihypertensive for both primary and secondary hypertension<sup>[20,21]</sup>. ACE inhibitors have anti-proteinuric effects and are particularly beneficial in children with chronic kidney disease<sup>[22-24]</sup> (Table 1). However, similar to adult trials, pediatric trials provide evidence that some ACE inhibitors may be less efficacious in blacks<sup>[25-27]</sup>. In adult anti-hypertensive trials, side effects associated with use of ACE inhibitors include hyperkalemia, chronic cough and angioedema. In pediatric trials there have been no reports of angioedema and there are fewer reports of cough in pediatric compared to adult trials. However, many of the pediatric trials have been of shorter duration<sup>[28]</sup>. ACE inhibitors are teratogenic and should be discontinued as soon as pregnancy is detected. ACE inhibitors approved for treatment of pediatric hypertension by the FDA include enalapril, fosinopril, benazepril and lisinopril. Table 2 summarizes the FDA label dosing recommendations that resulted from review of the various pediatric clinical trials of these ACE inhibitors.

### Enalapril<sup>[29]</sup>

Enalapril was the first ACE inhibitor approved by the United States FDA for pediatric hypertension following completion of the required clinical trials in 2002 (Figure 1). Compared to placebo, children 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 four-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 young children with the only exception being neonates.

### Fosinopril<sup>[25,30]</sup>

Fosinopril was approved for treatment of pediatric hypertension by the United States FDA after the trials (including a 52-wk open label safety assessment) were completed in 2003 (Figure 1). In the clinical trials, all three

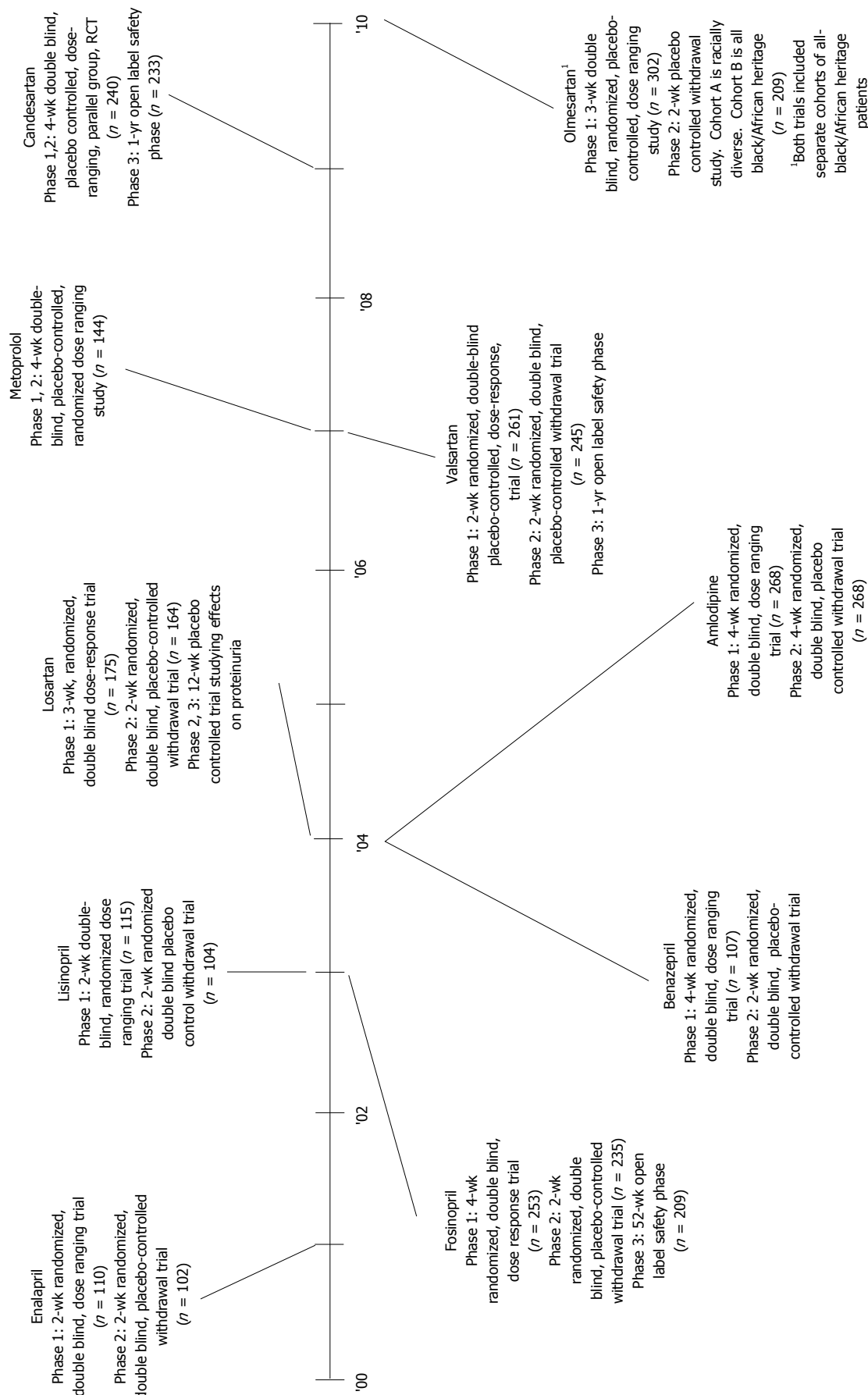


Figure 1 Timeline for completion of trials that have resulted in United States Food and Drug Administration labeling for treatment of hypertension in children and adolescents.

**Table 1 Anti-hypertensive class effects**

Drug class	Special indications	Precautions	Contraindications	Common adverse events
Angiotensin converting enzyme inhibitors	Proteinuria Chronic kidney disease	Less efficacious in blacks Risk of angioedema, increase risk of hyperkalemia Decreased glomerular filtration rate	Prior history of angioedema with use of ACE inhibitor Discontinue if pregnant: Pregnancy class C in 1 <sup>st</sup> trimester, pregnancy class D in 2 <sup>nd</sup> and 3 <sup>rd</sup> trimester	Headache Dizziness Abdominal pain Nausea Cough
Angiotensin receptor blockers	Proteinuria	Less efficacious in blacks Increase risk of hyperkalemia Decreased GFR	Discontinue if pregnant: Pregnancy class C in 1 <sup>st</sup> trimester, pregnancy class D in 2 <sup>nd</sup> and 3 <sup>rd</sup> trimester	Headache Dizziness Cough
Calcium channel blockers	None	Drug interactions with compounds that change cytochrome P450s metabolism ( <i>i.e.</i> : Azole antifungals, grapefruit juice, anti-seizure medications)	Pregnancy class C	Headache Peripheral edema Fatigue Dizziness Abdominal pain Epistaxis
Beta blockers	None	Increased risk of bronchoconstriction in asthma	Severe bradycardia Heart block greater than first degree Cardiogenic shock Decompensated cardiac failure	Headache Cough Nasopharyngitis Fatigue Diarrhea Dizziness

Pregnancy class C: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks; Pregnancy class D: There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks; ACE: Angiotensin converting enzyme.

**Table 2 Anti-hypertensive drugs that have been studied in pediatric clinical trials for United States Food and Drug Administration labeling**

Drug class	Drug	Starting dose	Max dose	Frequency	Suspension formulation	Pediatric indication
Angiotensin converting enzyme inhibitor	Enalapril	0.08 mg/kg (up to 5 mg)	0.58 mg/kg or 40 mg	Daily	Yes	All except neonates
	Fosinopril	0.1 mg/kg (5-10 mg)	0.6 mg/kg or 40 mg	Daily	No	Children > 50 kg
Angiotensin receptor blocker	Lisinopril	0.07 mg/kg (up to 5 mg)	0.6 mg/kg or 40 mg	Daily	Yes	> 6 yr
	Benazepril	0.2 mg/kg (up to 10 mg)	0.6 mg/kg or 40 mg	Daily	Yes	> 6 yr
	Losartan	0.7 mg/kg (up to 50 mg)	1.4 mg/kg or 100 mg	Daily	Yes	> 6 yr
	Valsartan	1.3 mg/kg (up to 40 mg)	2.7 mg/kg or 160 mg	Daily	Yes	> 6 yr
	Candesartan	1-6 yr: 0.2 mg/kg 6-17 yr, < 50 kg: 4 mg 6-17 yr, > 50 kg: 8 mg	1-6 yr: 0.4 mg/kg 6-17 yr, < 50 kg: 16 mg 6-17 yr, > 50 kg: 32 mg	Daily or divided dose	Yes	> 1 yr
	Olmesartan	20 to < 35 kg: 10 mg ≥ 35 kg: 20 mg	20 to < 35 kg: 20 mg ≥ 35 kg: 40 mg	Daily	Yes	> 6 yr
	Irbesartan	No FDA pediatric indication (efficacy not demonstrated)				
Beta blocker	Metoprolol XL	1.0 mg/kg (< 50 mg)	2 mg/kg up to 200 mg	Daily	No	> 6 yr
	Bisoprolol	No FDA pediatric indication (efficacy not demonstrated)				
Calcium channel blocker	Amlodipine	2.5 mg	0.3 mg/kg or 10 mg	Daily	No	> 6 yr
	Felodipine	No FDA pediatric indication (efficacy not demonstrated)				
Diuretic	Eplerenone	No FDA pediatric indication (efficacy not demonstrated)				

FDA: Food and Drug Administration.

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. It remains unclear whether the lack of dose response was attributable to: (1) the dose levels being too high; (2) an overly narrow dose range; or (3) true absence of a dose response. 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<sup>[25]</sup>. Fosinopril was well tolerated with no serious adverse events in the 52-mo 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 BP with headache (20.1%), nasopharyngitis (9.6%), cough (9.1%), pharyngitis (8.6%), and abdominal pain (6.2%) being the most common adverse events.

**Table 3** Other commonly used “off-label” antihypertensive drugs<sup>1</sup>

Drug class	Drug	Starting dose	Max dose	Frequency
Angiotensin converting enzyme inhibitor	Captopril	0.3-0.5 mg/kg per dose	6 mg/kg up to 450 mg/d	Two to three times daily
Beta blocker	Atenolol	0.5 mg/kg per day	2 mg/kg per day up to 100 mg	Once to twice daily
	Propranolol	1 mg/kg per day	16 mg/kg per day up to 640 mg	Two to four times daily
Calcium channel blocker	Extended release nifedipine	0.25 mg/kg per day	3 mg/kg per day up 120 mg/kg per day	Once to twice daily
Diuretic	Furosemide	0.5 mg/kg per dose	6 mg/kg per dose	Twice to three times daily
	Hydrochlorothiazide	0.5-1 mg/kg	3 mg/kg up to 50 mg	Daily

<sup>1</sup>These drugs have not been well studied in pediatric clinical trials and dosing/safety/efficacy are largely extrapolated from trials in adults.

### **Lisinopril<sup>[31]</sup>**

Lisinopril was approved for pediatric hypertension by the United States FDA in 2003. In the pivotal trial (Figure 1), 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 in the four-wk trial 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<sup>[32]</sup>**

Pediatric trials for benazepril have not been published in the literature, but the United States FDA approved it for pediatric hypertension in 2004 and the trials are summarized on the FDA label (Figure 1). Benazepril significantly lowered SBP but did not exhibit a dose response. Benazepril was well tolerated. The FDA label does not report if any patients discontinued the trial due to drug related adverse events.

### **Captopril**

Captopril is not approved for treatment of hypertension in children and adolescents, as it is an off-patent agent with no financial incentive for industry to sponsor clinical trials. Because captopril was one of the earliest ACE inhibitors approved for use in adults, there is a substantial body of clinical experience in children and adolescents and several trials have demonstrated clinical efficacy<sup>[33,34]</sup>. However, a major disadvantage of captopril is the need for frequent dosing (typically three times per day) (Table 3).

## **ANGIOTENSIN RECEPTOR BLOCKERS**

Angiotensin receptor blockers (ARBs) target the Angiotensin II type 1 receptors located on the heart, kidney, blood vessels, and adrenal glands. By blocking the final step of the RAAS, ARBs inhibit vasoconstriction and lower blood pressure<sup>[35]</sup>. Similar to ACE inhibitors, ARBs are particularly beneficial in reducing left ventricular hypertrophy in adults with heart failure. In adults and children, ARBs are effective at reducing proteinuria secondary to diabetes and may be particularly useful in patients with chronic kidney disease<sup>[36-38]</sup> (Table 1). However, ARBs are generally less efficacious in African Americans<sup>[26,39-42]</sup>. Adults who experience cough and can-

not tolerate ACE inhibitors often take ARBs as an alternative<sup>[43]</sup>. ARBs approved for the treatment of pediatric hypertension include losartan, valsartan, candesartan, and olmesartan. Table 2 summarizes the FDA label dosing recommendations that resulted from review of the various pediatric clinical trials of these ARBs. Children tolerated ARBs well, and the side effects most frequently experienced were headache and dizziness.

### **Losartan<sup>[38,44]</sup>**

Losartan was the first ARB approved for pediatric hypertension by the United States FDA in 2004 following completion of the required clinical trials (Figure 1). 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 BP between the low dose Losartan or placebo 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<sup>[38]</sup>. Losartan reduced proteinuria by 35.9% (95%CI: 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 authors postulated that a lack of change in BP 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<sup>[45]</sup>**

Valsartan was approved for pediatric use by the United States FDA in 2007. The Valsartan pediatric clinical trials are summarized in Figure 1. 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-wk 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**<sup>[46]</sup>

Candesartan was approved for pediatric use by the United States FDA in 2009. Pediatric clinical trials are summarized in Figure 1. In the dose ranging study, Candesartan demonstrated a significant decrease in SBP and DBP compared to placebo at all dose levels but not a dose response. The lack of dose response was attributed to a narrow dose range<sup>[46,47]</sup>. 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 to 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.

### **Olmesartan**<sup>[48]</sup>

Olmesartan was approved for pediatric hypertension by the United States FDA in 2010. In clinical trials (Figure 1) olmesartan demonstrated a dose response reduction in SBP and DBP, but the BP 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-wk period were headache (1.7%) and dizziness (1.3%).

### **Irbesartan**<sup>[49,50]</sup>

Irbesartan was not approved for pediatric hypertension due to lack of efficacy. The irbesartan pediatric trials (Figure 1) failed to demonstrate a dose response and although subjects demonstrated statistically significant increases in blood pressure following drug withdrawal, the effect size (+ 2.3 mg Hg increase in SBP) was small and was not felt to be clinically meaningful. Adverse events were more frequent than in other ARB trials and 2.5% discontinued study drug. There was also one case of erythema multiforme possibly related to irbesartan use.

## **CALCIUM CHANNEL BLOCKERS**

Calcium channel blockers (CCBs) encompass a diverse group of agents with different targets and functions. Second and third generation dihydropyridine CCBs, such as felodipine and amlodipine, are highly selective for vascular smooth muscle and are commonly prescribed for pediatric hypertension<sup>[20,21,51]</sup>. They target L type (long acting) voltage sensitive calcium channels and inhibit further influx of calcium into already depolarized smooth muscle cells, thereby inhibiting actin-myosin activation

and muscle contraction<sup>[51]</sup>. Unlike ACE inhibitors and ARBs, dihydropyridine CCBs do not demonstrate any anti-proteinuric effects in adults<sup>[52-54]</sup>; however, other studies have shown renoprotective effects in renal transplant patients<sup>[55]</sup>.

Side effects associated with CCBs include gingival hyperplasia and lower extremity edema. Other side effects such as flushing and headache are more commonly associated with immediate release preparations used for acute hypertension. Dihydropyridine CCBs are metabolized/excreted by the liver and dosing can be affected by drugs or compounds that alter CYP metabolism (*e.g.*, Azole antifungals, grapefruit juice)<sup>[51]</sup>. Pediatric trials have been performed for the CCBs amlodipine and felodipine and FDA dosing recommendations from these trials are summarized in Table 2. Only amlodipine is approved for treatment of pediatric hypertension as felodipine did not demonstrate efficacy.

### **Amlodipine**<sup>[56]</sup>

Amlodipine was approved for pediatric hypertension by the United States FDA in 2004. It is the most commonly prescribed CCB for pediatric hypertension<sup>[21]</sup>. In pediatric trials (Figure 1), amlodipine demonstrated a dose response reduction in SBP and DBP. SBP reduction was slightly greater in females compared to males; otherwise, SBP reduction across race, age, and etiology of HTN 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 ER**<sup>[57]</sup>

Felodipine is a long acting calcium channel blocker that has not been approved for pediatric HTN due to lack of efficacy. The felodipine pediatric trial included a three-wk dose response trial (*n* = 128) in children with primary hypertension and a 14-wk open label extension period to assess safety. Felodipine was well tolerated (0.8% discontinued due to adverse event) and there were no serious adverse events.

### **Nifedipine**

Nifedipine is a calcium channel blocking agent that was previously frequently prescribed to children and adolescents but was off patent and did not qualify for financial incentives and therefore has not been specifically studied for FDA labeling. Data are lacking on efficacy of short acting nifedipine and concerns have been raised about the dosing formulations which can lead to significant blood pressure fluctuations<sup>[34,58]</sup>. Sustained release nifedipine perhaps has more utility but also has not been formally studied in children and adolescents and therefore must be used "off-label"<sup>[34]</sup> (Table 3).

## BETA BLOCKERS

Beta blockers have been used for over 40 years and are recommended for hypertension treatment in adults with coronary artery disease, heart failure, post-myocardial infarction, and diabetes because of their beneficial cardiac effects<sup>[59]</sup>. Beta blockers lower blood pressure by antagonizing the beta 1 adrenergic receptor located on the myocardium to reduce heart rate and decrease contractility. However, beta blockers may also act on beta 2 adrenergic receptors on the smooth muscle of vasculature and the bronchi, increasing peripheral resistance and risk of bronchospasm<sup>[60]</sup>. Second generation beta blockers such as metoprolol, bisoprolol, and atenolol are relatively more selective for beta 1 receptors compared to first generation non-selective beta blockers, but at high doses, they may act on beta 2 receptors. Compared to other antihypertensives, first and second generation beta blockers are associated with a higher rate of insulin resistance and new onset diabetes<sup>[60-64]</sup>. The newest class of beta blockers including carvedilol and nebivolol are vasodilatory and do not appear to have negative effects on metabolic profile<sup>[60-63]</sup>.

Bisoprolol and extended release (XR) metoprolol have been studied in pediatric populations for the treatment of hypertension and their FDA dosing recommendations are summarized in Table 2. In both trials, children with asthma were excluded because of the drugs' potential broncho-constrictive effects. Bisoprolol did not demonstrate efficacy and, as a result, extended release metoprolol is the only FDA approved beta blocker for pediatric hypertension. Carvedilol has also been studied in pediatric populations but for the treatment of heart failure<sup>[65,66]</sup>. Efficacy was not demonstrated and, although indicated for treatment of hypertension in adults, carvedilol has never been studied for this indication in children or adolescents. Nonetheless there are data to support dosing of a pediatric formulation<sup>[65]</sup>. In all pediatric trials of beta blockers drug-related serious adverse events were rare.

### Metoprolol<sup>[67]</sup>

Metoprolol was approved for pediatric hypertension by the United States FDA in 2007. In clinical trials (Figure 1) metoprolol significantly reduced SBP compared to placebo, but with no dose-response effect. Only high doses of XR metoprolol (2 mg/kg) demonstrated significant reductions in DBP compared to 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 anti-hypertensive 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 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<sup>[68]</sup>

Bisoprolol fumarate/hydrochlorothiazide (HCT) (B/HT) is a combination hypertensive that failed to gain United States FDA approval for pediatric hypertension due to lack of efficacy. In a placebo controlled dose ranging pediatric trial ( $n = 94$ ), the percentage of patients in the B/HT group that achieved blood pressure control (SBP and DBP < 90<sup>th</sup>%) 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 to placebo.

### Propranolol and atenolol

As some of the oldest beta blockers, propranolol and atenolol fall into the category of off-patent drugs that have not qualified for financial incentives and no large pediatric trials have been performed. As a result, propranolol and atenolol are not labeled for treatment of hypertension in children and adolescents. Most pediatric studies of these beta blockers have been in small case series or for other non-hypertensive indications such as arrhythmias, syncope, hypertrophic cardiac cardiomyopathy, portal hypertension. In these studies, propranolol and atenolol have been effective with acceptable tolerability<sup>[34]</sup>. Due to the lack of pediatric data, dosing, safety, and efficacy have been extrapolated from adult trials (Table 3).

## DIURETICS

Most diuretics were off-patent before the implementation in Europe and the United States of financial incentives to conduct pediatric trials. Because off-patent drugs do not qualify for the financial incentives, diuretics represent the class of anti-hypertensive drugs with the least available pediatric clinical trial data. The only diuretic to be tested in a pediatric trial is eplerenone, but it was not approved due to lack of efficacy. Because other diuretics are often used as first line treatment in adults, they will be discussed briefly. Table 3 summarizes generally recognized (albeit not well studied) dosing recommendations for diuretics and select other commonly used antihypertensive drugs that are off-patent and thus have not been studied in clinical trials for FDA or EMA labeling.

Overall, diuretics are a diverse class of drugs that contain some of the oldest and most commonly prescribed agents for adult hypertension<sup>[59,69,70]</sup>. They can be broadly divided into three categories, thiazide diuretics, loop diuretics, and potassium sparing diuretics. All three classes target different parts of the nephron to decrease sodium

and water reabsorption, thereby creating a natriuretic effect that decreases extracellular volume and reduces blood pressure.

### Potassium sparing diuretics

Potassium sparing diuretics inhibit reabsorption of sodium in the collecting duct and can be further divided into two groups, pteridine analogs and aldosterone antagonists. Pteridine diuretics inhibit epithelial sodium channels (ENaC) and aldosterone antagonist down regulate the Na/K pump and (ENaC) on the collecting duct. Potassium sparing diuretics are often used in conjunction with other potassium losing diuretics to maintain serum potassium levels in a normal range<sup>[71,72]</sup>. Eplerenone is the only diuretic to be studied for FDA labeling but was not approved. In adults, eplerenone is sometimes preferred over spironolactone because it more selectively binds to aldosterone receptors and does not have unwanted progestational and anti-androgenic effects<sup>[72]</sup>.

### Eplerenone<sup>[73,74]</sup>

Eplerenone is a selective aldosterone antagonist that was not approved for pediatric hypertension by the United States FDA due to lack of efficacy. The pediatric trial consisted of a 6-wk dose ranging study ( $n = 304$ ) and a 4-wk 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 to 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 to the placebo group. Eplerenone was well tolerated with few serious adverse events (2.6%) or discontinuations in the ten-wk trial ( $< 1\%$ ).

### Thiazide diuretics

Thiazide diuretics, such as hydrochlorothiazide and chlorthalidone, are first line agents for uncomplicated adult hypertension and are commonly combined with beta blockers, loop diuretics, and ACE inhibitors in multi-drug regimens and in fixed-dose combination formulations<sup>[59,75,76]</sup>. They are preferred because of their efficacy and superiority in preventing cardiovascular disease compared to other classes of antihypertensives<sup>[77]</sup>. Thiazides block sodium-chloride co-transporters on the distal convoluted tubule to decrease sodium reabsorption; however, these effects are acute. The exact mechanism by which thiazides reduce peripheral resistance and chronically lower blood pressure is unknown<sup>[71,78]</sup>. Thiazides are contraindicated in patients with sulfa allergies. Side effects in adults include hypokalemia, hypercalcemia, orthostatic hypotension, worsening of gout (due hyperuricemia), and a worsened metabolic profile (increased rates of new onset diabetes, increase in low density lipoprotein (LDL) cholesterol triglycerides, and glucose)<sup>[64,71,78]</sup>.

### Loop diuretics

Loop diuretics (furosemide, bumetanide, torsemide, ethacrynic acid) are most commonly prescribed in combination with thiazide diuretics for reducing fluid volume in edematous disorders or patients with renal failure<sup>[71,79]</sup>. There is no data supporting the efficacy of loop diuretics alone to reduce blood pressure. When prescribed alone, loop diuretics lower blood pressure acutely, but not chronically because the activated RAAS will compensate for the lost fluid volume. Loop diuretics inhibit the sodium/potassium/chloride transporter (Na-K-2Cl transporter) on the thick ascending loop of Henle to decrease the osmotic gradient producing a potent natriuretic effect. All loop diuretics, other than ethacrynic acid are contraindicated in patients with sulfa allergies. Side effects in adults associated with loop diuretics include hyponatremia, hypokalemia, hypocalcemia, hypomagnesemia, and worsening of metabolic profile (increased cholesterol, LDL, and triglycerides)<sup>[71,80]</sup>.

## CONCLUSION

Regulatory initiatives in the United States and Europe over the last one and a half decades have stimulated numerous clinical trials of antihypertensive agents in children. The result has been an increase in the number of United States FDA approved drugs for treatment of pediatric hypertension from zero in 2000 to 11 at present (including esmolol approved for intravenous administration). This is very encouraging with the only caveat that most of the medications studied in pediatric trials belong to newer classes of drugs. There remains a relative dearth of clinical trial data regarding the safety and efficacy of older, commonly used antihypertensive drugs (*e.g.*, diuretics) in children. Nonetheless pediatric providers can now rely on clinical trial data to guide many treatment decisions in children and adolescents with hypertension. FDA labeled antihypertensive drugs have all been safe, efficacious and well tolerated. No deaths and only rare serious adverse events have been reported in clinical trials, albeit most have been of shorter duration. Furthermore, these clinical trials have highlighted the differences between drug safety and efficacy in children versus adults. Many of the approved drugs have demonstrated differences in dosing when compared to adult recommendations and several drugs approved for use in adult patient populations (irbesartan, bisoprolol fumarate/HCTZ, felodipine and eplerenone) have not demonstrated efficacy in pediatric hypertension trials. These data highlight that pediatric drug dosing, safety and efficacy cannot simply be extrapolated from adult clinical trials.

As the prevalence of childhood obesity and hypertension continue to rise, it is critical that providers familiarize themselves with these clinical trial data to guide appropriate treatment. Lifestyle changes should continue to form the mainstay of pediatric hypertension therapy; however the importance of medical therapy is increasingly recognized as a means to prevent end-organ damage and hope-

fully limit the long-term cardiovascular risk associated with hypertension.

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