# Safety Assessment and Pediatric-Specific Considerations

## in Antihypertensive Therapy

*What the Immature Kidney Tells Us About Evidence, Risk, and Extrapolation*

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*Disclosure: Speaker is employed by Eli Lilly and Company. Views expressed reflect the scientific evidence presented.*

# Three Questions for 15 Minutes

**01**

## Renal Growth & Development

How is the infant kidney structurally and functionally different from the adult — and when does it fully mature?

**02**

## Valsartan RCT Safety Evidence

What do the only three randomized controlled trials — and two additional non-randomized studies — in children under 6 years actually tell us about drug safety?

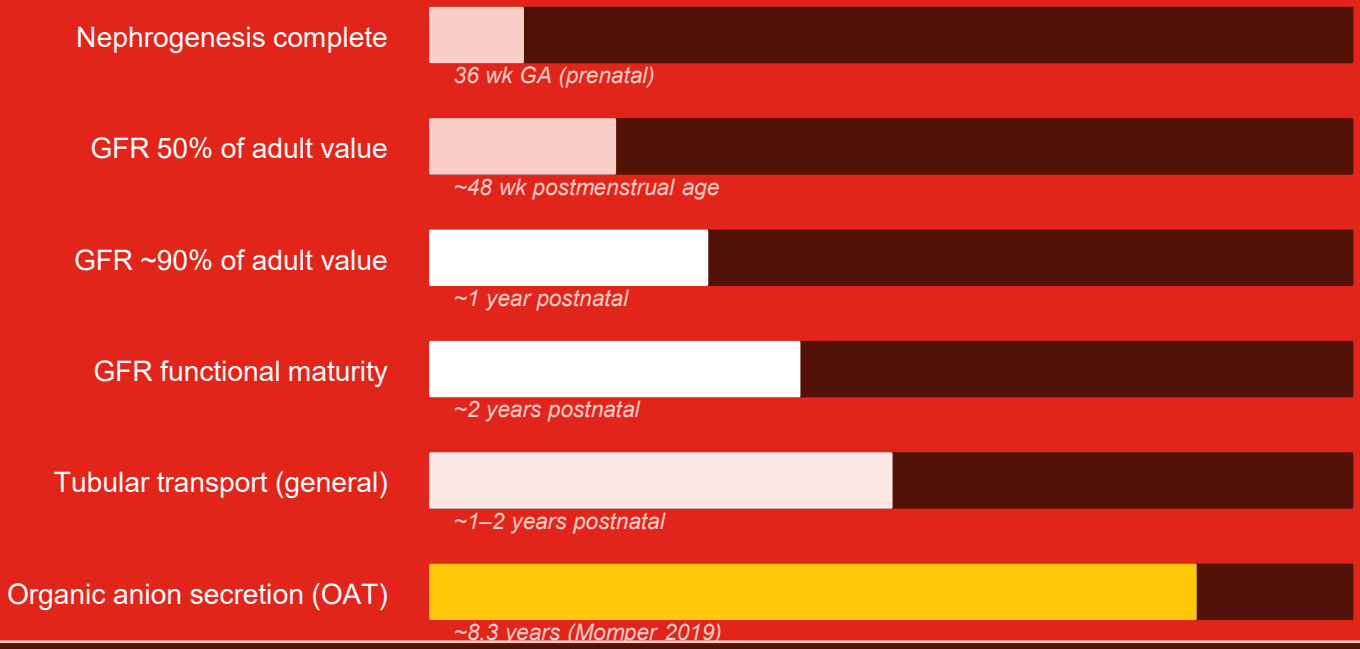
**03**

## Risks of Extrapolation

What are the mechanistic dangers of applying other antihypertensive drug classes to an immature kidney without controlled evidence?

PART I

# The Developing Kidney: A Protracted Postnatal Process




*Key insight: GFR approaches adult values by age 2 — but tubular secretion reaches 50% of adult capacity only at ~8 years (Momper et al., CJASN 2019)*

PART I

# Why Renal Immaturity Matters Pharmacologically

## Glomerular Filtration

- GFR approaches adult values by ~2 years
- Renally cleared drugs: clearance improves rapidly in infancy
- GFR still affected by underlying renal disease burden

*Rhodin et al., Pediatr Nephrol 2009*

## Tubular Transport

- Active secretion (OAT1/OAT3): <50% adult until ~8 years
- Drugs relying on tubular secretion may accumulate
- Electrolyte transport ($Na^+$, $K^+$, $H^+$) immature → dyselectrolytemia risk

*Momper et al., CJASN 2019*

## RAAS Dependency

- Neonatal GFR maintained by Angiotensin II–prostaglandin balance
- RAAS upregulated in infancy for renal perfusion
- RAAS blockade → unique hemodynamic and renal risk

*Drukker A, Paediatrics & Child Health 2002*

**The immature kidney is not just a filtration organ — it is a hormonally regulated, developmentally active system.**

PART II

# Three RCTs Exist in Children Under 6 Years — All With Valsartan

| | Flynn et al. 2008<br>Hypertension | Jankauskiene et al. 2021<br>Curr Med Res Opin | Schaefer et al. 2013<br>J Hypertens |
|---|---|---|---|
| **N (enrolled)** | 90 | 127 | 75 |
| **Age range** | 1–5 years (mean 3.2 yr) | 1–5 years | 6 mo–5 yr |
| **Design** | DB, placebo-ctrl, 3-dose<br>2 wk + 2 wk DB + 52 wk OL | DB, 2-dose (0.25 vs 4 mg/kg/d)<br>6 wk DB + 20 wk OL | DB, 3-dose (0.25/1/4 mg/kg/d)<br>6 wk + 2 wk DB + 18 wk OL |
| **CKD included** | Yes (Not formally stratified - ~80% had renal/urinary abnormality) | Yes — enriched (63/127; 50%) | Not reported / not stratified |
| **Primary endpoint** | SBP reduction vs placebo | Dose-response for mean SBP | Dose-response slope for mean SBP |
| **Regulatory context** | First ever RCT in <6 yr<br>(BPCA-driven) | Confirmatory; CKD-enriched cohort | Second RCT; replicates Flynn design |

***These remain the only placebo-controlled antihypertensive RCTs in children under 6 years of age as of 2025.***

PART II

# Flynn et al. 2008 — Safety Profile (Ages 1–5)

*Hypertension 2008;52:222–228 | DOI: 10.1161/HYPERTENSIONAHA.108.111054*

**2.2%**

**SAEs (double-blind phase)**

*Infrequent; not drug-related*

**5.6%**

**Drug-related AEs (double-blind phases)**

*Comparable across all dose groups*

**14.8%**

**SAEs (52-week open-label phase)**
**2 deaths not drug related**

*⚠ Higher — no concurrent placebo control*

**6.8%**

**Drug-related AEs (open-label phase)**

*Stable vs. double-blind rate*

## Key Safety Findings

- No dose-dependent increase in AEs across 3 dose groups
- Growth & development: no demonstrable negative effects observed
- Renal parameters: not flagged as primary safety signal (DB phase)
- Electrolytes: not primary concern in DB phase
- SBP <95th percentile achieved in 77.3% during OL phase

★ **Growth and development was a pre-specified safety endpoint — unique to the pediatric context and absent from adult trials.**

PART II

# Schaefer et al. 2013 — Second Valsartan RCT (Ages 6 mo–5 yr)

*J Hypertens 2013;31:993–1000 | DOI: 10.1097/HJH.0b013e32835f5721*

| 75 | 0 | 1 case | 6 wk DB |
|---|---|---|---|
| Children enrolled (ages 6 mo–5 yr) | Deaths reported | Marked liver transaminase elevation | + 2 wk placebo + 18 wk OL |

## Efficacy and Safety Highlights

| | |
|---|---|
| Dose–response trend for MSSBP | NS (P=0.099) |
| Suspension tolerability | Well tolerated |

PART II

# Jankauskiene et al. 2021 — CKD-Enriched Cohort (Ages 1–5)

*Curr Med Res Opin 2021;37:2113–2122 | DOI: 10.1080/03007995.2021.1982681*

| 127 | 94.5% | 50% | No deaths |
|---|---|---|---|
| Children enrolled (ages 1–5 yr) | Completion rate (120/127) | Had chronic kidney disease | No deaths reported |

## Adverse Event Incidence by Dose and CKD Status


⚠ **KEY SAFETY SIGNAL: Serum $K^+$ elevation >20% above baseline was more frequent in CKD patients — critical given immature tubular $K^+$ secretory capacity in this age group.**

PART II

# Beyond the Three RCTs: Candesartan (CINCH, 2010)

*J Hypertens 2010;28:1083–1090 | DOI: 10.1097/HJH.0b013e328336b86b | Randomized, double-blind, DOSE-RANGING design — not placebo-controlled; not counted among the three RCTs on Slide 5*

**93**
Children enrolled (ages 1–5 yr)

**80%**
Had underlying renal disorders (74/93)

**1 death**
Probable acute-on-chronic renal failure

**2 withdrew**
for AEs (abdominal pain; worsening renal insufficiency)

## Safety Signals by Dose Group (SAEs)


⚠ **KEY SAFETY ISSUE: One death occurred (probable acute-on-chronic renal failure) in a cohort where 80% had underlying renal disease — underscoring that the underlying disease, not the drug class alone, drives risk in this population.**

PART II

# Beyond the Three RCTs: Enalapril Pharmacokinetics (Wells 2001)

*J Clin Pharmacol 2001;41:1064–1074 | DOI: 10.1177/00912700122012661 | Non-randomized, open-label PK study — not RCT-level evidence*

| 40 | 4 | 2 SAEs | 0 |
|---|---|---|---|
| Children enrolled (ages 2 mo–15 yr) | Age strata sampled for PK | Neither attributed to enalapril | Discontinuations due to AEs |

## Design & Tolerability Highlights

| | | | |
|---|---|---|---|
| Formulation, ages <6 yr | Suspension | Dosing | 0.07–0.14 mg/kg/d |
| Suspension tolerability | Well tolerated | Study type | PK only — not RCT |

⚠ **DATA LIMITATION: This is a pharmacokinetic study only — no randomization, no control arm, and no RCT-level efficacy or safety data. PK was consistent across age groups; it cannot substitute for controlled ACE inhibitor safety evidence in this population.**

PART II

# Valsartan Safety Across Age Groups: Convergence Toward Adult Patterns

| Safety Parameter | Adults | Children 6–17 yr (Wells et al. 2011) | Children 1–5 yr (Flynn / Schaefer / Jankauskiene) |
|---|---|---|---|
| **Most common AE** | Headache, dizziness | Headache, nasopharyngitis | Respiratory infections, GI events |
| **Hyperkalemia** | Mild; manageable | Uncommon | ⚠ Elevated in CKD subset (tubular mechanism) |
| **Growth monitoring** | Not required | Monitored; no signal | Pre-specified endpoint; no short-term signal |
| **Renal function** | Well-characterized | Manageable | Under-characterized; CKD confounding present |
| **Long-term safety** | Known from CVOT data | Limited; max 52-wk OL | No data beyond 26–52 wk |
| **SAE rate (active)** | Low, well-defined | <5% typical | 2.2% DB; 14.8% OL (Flynn) |

***Absence of a safety signal ≠ confirmed safety — particularly when trials last weeks in a population with decades of physiological development ahead.***

PART III

# Mechanistic Risks of Extrapolating Other Drug Classes to the Immature Kidney

*No RCT data in <6 years — mechanism must guide risk characterization*

## ACE Inhibitors — HIGH

*Enalapril, Lisinopril, Fosinopril*

RAAS blockade removes afferent arteriole support in RAAS-dependent kidney → AKI risk

## Calcium Channel Blockers — LOWER

*Amlodipine (approved ≥6 yr)*

Reflex tachycardia; gingival hyperplasia; lower hemodynamic-developmental RAAS conflict

## Beta-Blockers — MODERATE

*Metoprolol (only FDA-approved BB in peds)*

Masks hypoglycemia in infants (critical); blunts compensatory tachycardia in volume depletion; no RCT <6 yr

## Thiazide Diuretics — MODERATE

*Hydrochlorothiazide, Chlorthalidone*

Electrolyte imbalance amplified by immature NCC expression and tubular $Na^+$ reserve

## MRAs / Aldosterone Antagonists — HIGH

*Spironolactone, Eplerenone, Finerenone*

Hyperkalemia risk critically amplified by immature $K^+$ secretory capacity; aldosterone has developmental role in tubular maturation

## Novel Agents (ARNi, SGLT2i, ET Antagonists) — UNKNOWN

*Sacubitril/Valsartan, Empagliflozin, Aprocitentan*

No pediatric data of any kind in <6 yr. SGLT2 expression itself is developmentally regulated in proximal tubule

PART III

# Why the Underlying Disease Makes Every Risk Worse

*In children under 6, hypertension is almost never isolated — the diseased kidney compounds every developmental safety vulnerability*

| ≥75% | Leading cause | Less common | Less common |
|---|---|---|---|
| Secondary etiology in children ≤5 yr | Renal parenchymal disease (dominant) | Aortic coarctation | Renovascular hypertension |

*Source: Jankauskiene et al., Curr Med Res Opin 2021*

## Renal Parenchymal Disease

*CKD · CAKUT · Glomerulonephritis · ARPKD*

- ⚠ RAAS is activated pathologically ON TOP of developmental dependency — RAAS-blocker-induced AKI risk may be synergistic, not additive
- ⚠ Reduced nephron mass further limits tubular electrolyte reserve — electrolyte adverse events amplified beyond what the Momper maturation curve predicts
- ⚠ Jankauskiene 2021: hyperkalemia signal in CKD children is the empirical demonstration of this double vulnerability — absent from adult safety data

## Renovascular Hypertension

*Renal Artery Stenosis · Mid-Aortic Syndrome · NF-1*

- 🚫 RAAS-blocking agents (ACEi/ARB/DRI) remove the sole compensatory mechanism maintaining GFR in the stenotic kidney — acute renal failure risk. Contraindication absent from adult RCT populations
- ⚠ Safety data from CKD pediatric populations (including the valsartan RCTs) cannot be extrapolated here — the pathophysiology is mechanistically opposite
- ⚠ An important, clinically meaningful cause in this age group — not rare enough to be ignored in a regulatory safety framework

## Coarctation of the Aorta

*Structural obstruction · reflex RAAS activation*

- ⚠ RAAS-acting agents carry partial renovascular contraindication risk if coarctation is residual or recurrent post-repair — a scenario with no adult analogue
- ⚠ Beta-blocker hypoglycemia masking in infants and toddlers is a developmentally specific adverse effect entirely absent from adult safety data
- ⚠ Paradoxical hypertension post-repair constitutes an acute crisis; IV antihypertensive safety data in this age group are extremely limited

***The safety question is not how a drug behaves in a developmentally immature kidney — it is how it behaves in an immature kidney simultaneously impaired by the disease causing the hypertension.***

SYNTHESIS

# What We Know vs What We Need

## ✓ Evidence Supports

- Valsartan: effective BP reduction in ages 1–5 (RCT evidence, three trials)
- Short-term ARB safety (weeks to 1 year) is acceptable in this age group
- Hyperkalemia is amplified in CKD children on ARBs — a developmentally specific signal
- Growth & development not negatively affected in short-term ARB trials

## ⚠ Gaps Requiring Evidence

- Long-term renal developmental consequences of RAAS blockade in a maturing kidney
- Safety of any drug class other than ARBs in <6 yr (RCT-level evidence absent)
- Effect of antihypertensives on nephrogenesis endpoints — nephron endowment, tubular maturation
- Electrolyte safety of diuretics and MRAs in the glomerulotubular imbalance window
- Drug-drug interaction profiles in polypharmacy-dependent CKD children

***The organ system being treated is still under construction. A negative short-term trial ≠ long-term developmental safety.***

# Key Messages for Safety Assessment in Pediatric Hypertension Under 6 Years

| | | |
|---|---|---|
| 1 | **The kidney is not mature:** | GFR approaches adult values by ~2 years; tubular secretion, electrolyte handling, and RAAS dependency continue maturing well into late childhood. |
| 2 | **Three RCTs exist — all valsartan:** | Flynn 2008, Schaefer 2013, and Jankauskiene 2021 are the totality of placebo-controlled evidence under 6 years. Short-term safety acceptable; hyperkalemia in CKD is a clinically meaningful signal. |
| 3 | **No other class has RCT evidence:** | Extrapolation from older children or adults carries mechanistically distinct risks across tubular transport, RAAS dependency, and electrolyte regulation. |
| 4 | **Mechanism must guide risk:** | RAAS-blocking agents: highest renal risk. Diuretics and MRAs: electrolyte risk amplified by tubular immaturity. CCBs and beta-blockers: primarily systemic risks. |
| 5 | **The underlying disease amplifies every risk:** | ≥75% of hypertension in this age group is secondary — predominantly renal. The diseased kidney may compound developmental vulnerability synergistically. Adult safety data are mechanistically inapplicable to renovascular and CKD-driven hypertension simultaneously. |
| 6 | **Short-term trials are necessary but not sufficient:** | Safety follow-up beyond 12 months incorporating renal functional endpoints and developmental markers is essential for regulatory approval in this age group. |

***Hypertension in children under 6 is real, consequential, and undertreated — but the solution cannot be extrapolation. It must be evidence.***

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