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Pharmacology of enalapril in children: a review

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Enalapril is an angiotensin-converting enzyme (ACE) inhibitor that is used for the treatment of (paediatric) hypertension, heart failure and chronic kidney diseases. Because its disposition, efficacy and safety differs across the paediatric continuum, data from adults cannot be automatically extrapolated to children. This review highlights paediatric enalapril pharmacokinetic data and demonstrates that these are inadequate to support with certainty an age-related effect on enalapril/enalaprilat pharmacokinetics. In addition, our review shows that evidence to support effective and safe prescribing of enalapril in children is limited, especially in young children and heart failure patients; studies in these groups are either absent or show conflicting results. We provide explanations for observed differences between age groups and indications, and describe areas for future research.

Introduction

Enalapril was the second angiotensin-converting enzyme (ACE) inhibitor to become widely available for therapeutic use after captopril, the first registered oral ACE inhibitor. Enalapril is an ethyl ester pro-drug, and its pharmacological effects are mediated by its active metabolite, enalaprilat (also known as MK422). The main effect of enalaprilat is the inhibition of ACE, a key component in the renin angiotensin aldosterone system (RAAS). This leads to a decrease in the formation of angiotensin II and thereby to peripheral vasodilation.

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This is followed by a diminished secretion of aldosterone, causing less sodium and fluid retention. These two mechanisms cause a decrease in blood pressure (BP), and a decreased preload and afterload of the heart [1]. In addition to its stimulatory effect on aldosterone secretion, angiotensin II is able to directly increase the activity of the epithelial sodium channel [2]. This leads to maximum sodium reabsorption, a process that is also reduced by ACE inhibitors. In adults, enalapril is used for the treatment of hypertension and heart failure, as well as for reducing proteinuria in chronic kidney disease (CKD). In addition to their BP lowering effect, ACE inhibitors have a role in the treatment of patients with heart failure, because they prevent (further) cardiac remodelling [3]. In CKD, the beneficial effect of enalapril is mostly the result of a decrease in glomerular pressure due to a relaxation of the efferent arterioles [4].

In children, enalapril is used for similar indications, but in the European Union it is only authorised for use in children with a body weight over 20 kg [5]. Although this label indicates a positive benefit/risk ratio of enalapril on the basis of an evaluation by the European Medicines Agency, data on the pharmacokinetics (PK) and pharmacodynamics (PD) of enalapril in this population appear scarce. In children below the weight of 20 kg, even less data are available. Current dose recommendations are based on empirical evidence combined with data extrapolated from adult studies, and as a consequence, a disparity in dosage criteria remains in paediatric patients [6].

The importance of pharmacological treatment in children with heart failure, especially dilated cardiomyopathies, is emphasised by the low availability of donor hearts. Owing to this scarcity, mortality within the first year of presentation remains extremely high, highlighting the need for optimal treatment in children to prevent or postpone transplantation [7].

This review aims to provide an overview of current knowledge on enalapril PK and PD characteristics in children and identify current knowledge gaps, as well as to suggest areas for further study. Adult PK data are included if and when relevant to paediatric PK data.

Pharmacokinetics

Disposition of enalapril

Because the active metabolite of enalapril, enalaprilat, is poorly absorbed from the gastrointestinal tract, enalapril is administered as a maleate salt to improve its absorption [8]. In adults, approximately 60–70% of enalapril is absorbed after oral administration [8]. Data on the intestinal uptake mechanism show inconsistent results. It has previously been hypothesised that enalapril is a substrate for the low-affinity H^+ peptide transporter 1 (PEPT1), because its structure resembles Ala-Pro dipeptide or Xaa-Ala-Pro tripeptide structures, which are intestinal PEPT1 substrates [9]. Because the reported affinity constants were significantly different between studies, experiments were repeated [10,11]. Morrison *et al.* studied the in vitro uptake of enalapril in both rat intestinal rings and Caco-2 cells (human cells that resemble the enterocytes lining the small intestine). Their results indicate that enalapril is absorbed through a passive diffusion process and its transport is non-saturable [10]. In three different cell experiments performed by Knutter *et al.*, an almost negligible affinity of enalapril for transport by PEPT1 and PEPT2 was found [11]. Therefore, they also concluded that transport in intestinal cells is not mediated via those transporters. They postulate, based on the lipophilic characteristics of enalapril, that uptake occurs via simple diffusion. On the basis of these two studies, the involvement of a human intestinal transporter in the uptake of enalapril is considered to be unlikely. Whether this transport is paracellular or transcellular remains to be undetermined.

In healthy volunteers, enalapril maximum serum concentrations (C_{max}) of around 45–49 ng/ml occur approximately 1 h after oral ingestion of a 10 mg tablet [12,13]. However, these values are measured using alkaline hydrolysis followed by ACE-inhibition assays. This means that all enalapril and enalaprilat levels were

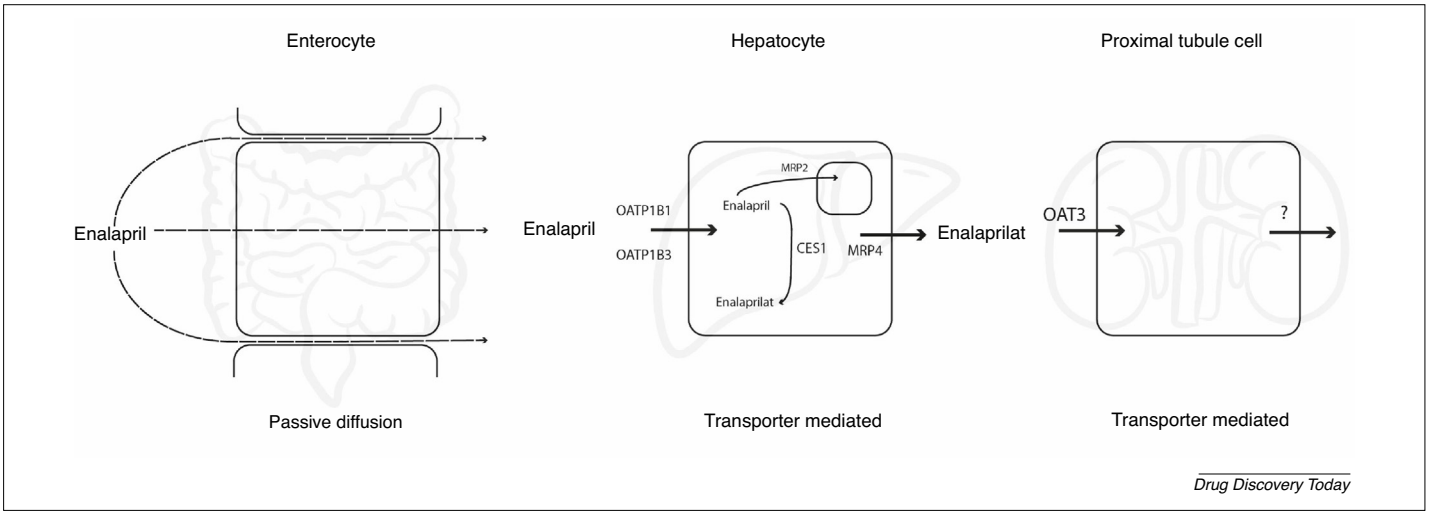

FIGURE 1

Transport of enalapril through various membranes. Abbreviations: CES1, carboxylesterase 1; MRP2, multidrug resistance-associated protein 2; MRP4, multidrug resistance-associated protein 4; OAT3, organic anion transporter 3; OATP1B1, organic anion transporting polypeptide 1B1; OATP1B3, organic anion transporting polypeptide 1B3.

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measured using a radioimmunoassay procedure in which enalaprilat was directly measured but enalapril levels were deduced on the basis of values obtained before and after hydrolysis. When measured using a more recently developed high-performance liquid chromatography method, enalapril C_{max} values were around ten times higher [14]. Also, a slight inaccuracy in determining enalaprilat concentrations using this method was demonstrated when compared with newer assays, such as enzyme-linked immunosorbent assays [15] or high-performance liquid chromatography–tandem mass spectrometry [16]. In our review, to compare adult and paediatric studies, we used the values derived by the radioimmunoassay. The oral bioavailability of enalapril was 61% on the basis of urinary excretion data when intravenous enalaprilat was used as a reference standard [17]. The elimination half-life ($T_{1/2}$) of enalapril is 1.6 (SD 1.5) h [14].

Conversion to enalaprilat

After absorption from the small intestine (Fig. 1), uptake of enalapril in hepatocytes is mediated by the organic anion transporting polypeptide 1B1 (OATP1B1) and OATP1B3 [18]. Approximately 60% of enalapril is metabolised in the hepatocyte to its active metabolite, enalaprilat, by one of the major hepatic hydrolases, carboxylesterase 1 (CES1) [13]. By removing the ethylester from enalapril to form enalaprilat, the molecule becomes negatively charged, and its potency to inhibit ACE increases. Following its formation, enalaprilat is transported into the systemic circulation by multidrug resistance-associated protein 4 (MRP4) [19]. But, because hepatic MRP4 expression is highly variable [20], the involvement of other basolateral transporters cannot be excluded. Although most enalapril will be eventually excreted renally as enalaprilat, untransformed enalapril is excreted in bile by MRP2 [18] or excreted back into the systemic circulation by an unknown transporter.

Peak concentrations of enalaprilat are observed between 3.5 and 4.5 h after ingestion in healthy adult volunteers and are between 54.8 and 57.2 ng/mL [14] after a dose of 10 mg. These values coincide with maximum inhibition of ACE [12], and over the usual therapeutic range, there is a direct linear correlation between the C_{max} of enalaprilat and given dose of enalapril [21]. The observed area under the curve ($AUC_{0–infinity}$) was 255.9–266.9 ng h/ml [14]. The protein binding of enalaprilat in the circulation is reported to be a little less than 50%, and it penetrates into most tissues, including the vascular endothelium of the lungs [21]. In the lung, ACE exists at the endothelial cell surface, where it is shed and hydrolyses circulating peptides [22].

Elimination

The excretion of enalaprilat is predominantly renal; 43% of the enalapril dose is recovered in urine as enalaprilat and 18% is recovered as enalapril [13]. This renal elimination of enalaprilat is biphasic. The initial phase seems to reflect glomerular filtration combined with tubular secretion, followed by a later phase that reflects the equilibrium of the drug from tissue distribution sites [23]. The entry of enalaprilat into the proximal tubular lumen is thought to be transporter-mediated, because the clearance of enalaprilat exceeds that of the glomerular filtration rate (GFR) marker inulin. This suggests that the elimination is based on glomerular filtration as well as on tubular secretion [24]. Because enalaprilat is an anion and the excretion of another ACE inhibitor (quinalaprilat) excretion is decreased in the presence of organic anions [25], it is likely that this secretion is mediated by an organic anion transporter. This was indeed confirmed by Ni *et al.*, who showed that the uptake of enalaprilat is mediated by the organic anion transporter 3 [26].

Reported clearances of enalaprilat range from 158 (SD 46) ml/min [13] to 173 (SD 13) ml/min [27], determined after administration of enalapril. After oral administration of enalapril or intravenous administration of enalaprilat itself in healthy adult volunteers, the effective half-life of enalaprilat after multiple doses range from 3.5 to 11 h [12–14,27,28]. The terminal half-life is much longer at 35–38 h, which is presumably caused by binding of enalaprilat to ACE [28], thus leading to slower elimination. To make steady-state predictions, the effective half-life should be used; the prolonged terminal phase contributes little to the accumulation of enalaprilat because this involves redistribution from the tissue distribution sites.

Estimates of the volume of distribution (Vd) of enalaprilat are not available in the literature but can be calculated using the formula $Vd = T_{1/2} \times$ clearance (CL)/0.693 [29], assuming 100% conversion of enalapril to enalaprilat. This yields values between 47 and 148 l (CL derived from [13], $T_{1/2}$ from [12–14,27,28].

Factors influencing PK

There are many factors that can influence enalapril PK, of which disease is a major one. The PK of both enalapril and enalaprilat is not altered in patients with hypertension [30]. In patients with congestive heart failure (CHF), this is less apparent. Two PK studies compared CHF patients to healthy volunteers and hypertensive patients, respectively. A slower absorption rate was suggested in CHF patients, but owing to the small sample size, no statistical significance could be shown [31,32].

The absorption of enalapril tablets is not influenced by food [33,34]. Interestingly, when studying the impact of food on an oral enalapril suspension, a significantly longer enalaprilat T_{max}, lower C_{max} and lower $AUC_{0–infinity}$ for enalaprilat were seen in 48 healthy volunteers after intake of a high-fat meal compared with fasting [35]. Because orally administered drug in tablet form is not absorbed until the tablet disintegrates and the drug particles are dissolved, it would be understandable if only the absorption of tablets was influenced by food compared with enalapril solution, not vice versa. But perhaps, when using an oral solution, more enalapril can bind to food particles, leading to a lower percentage available for absorption.

Hepatic impairment could theoretically alter the metabolism of enalapril to enalaprilat and the transport of enalaprilat out of the hepatocyte. The abundance of CES1 in cirrhotic livers is reduced to 25% in control livers [36]. A change in hepatic metabolism might also occur in CKD due to the interference of uremic toxins with transcriptional activation, causing inhibition of drug transporters and drug-metabolizing enzymes [37]. in vitro data suggest that disease status can also influence CES1 hydrolytic activity, because interleukin-6 (IL-6) decreased the expression of CES1 and CES2 by up to 60% [38]. Despite such a reduction, in vivo studies confirming the hypothetically lower enalaprilat levels are not available.

Because enalaprilat is renally excreted, renal impairment, defined as a GFR below 30 ml/min/1.73 m^2, will result in higher enalaprilat serum concentrations. Indeed, this was shown by Kelly

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et al. in 24 patients with different degrees of renal failure (GFR 5–88 ml/min/1.73 m^2) [39]. Furthermore, in addition to higher serum concentrations, reduced renal function led to longer times to reach C_{max}, because serum enalaprilat concentrations could further increase when excretion was delayed. T_{max} increased by up to 24 h, and the highest C_{max} observed was 214 ng/mL at a dose of 10 mg. This is four times higher than values observed in the absence of renal failure [14]. Because there is no reason to assume this will not be applicable to children, dose reduction of enalapril in paediatric patients might be necessary to prevent the accumulation of enalaprilat and further renal insufficiency. When taking the above-mentioned disease factors influencing PK into account, the effect of ACE inhibitor therapy still shows significant interindividual variability. We now focus on the impact of age on enalapril PK and PD variability.

Paediatric PK studies

We identified only three paediatric PK studies, including a total of 62 children with either hypertension [40] or HF [41,42]. This small number of patients, and interstudy variability limits conclusions on the PK of enalapril and enalaprilat in children and the potential impact of age and other co-variates.

All enalapril and enalaprilat levels were measured using a radioimmunoassay. Enalaprilat was directly measured, and enalapril levels were deduced on the basis of values obtained before and after hydrolysis [27]. This radioimmunoassay method was the same as in the referenced adult PK studies [12,13,27,28] and was at the time deemed to be accurate for enalaprilat concentrations over 2 ng/mL [43].

Enalapril PK

Two of the three studies described enalapril PK, in addition to enalaprilat (Table 1). In the 2001 study by Wells *et al.*, 40 hypertensive children (aged 2 months to 15 years) received 0.07–0.14 mg/kg enalapril once daily, administered as a dispersed suspension [40]. The enalapril T_{max} occurred approximately 1 h after administration, compared with 0.5–1.5 h as reported for adults [12,13]. Mean C_{max} values ranged between 24.6 and 45.4 ng/mL across the different age groups. C_{max} values in adults receiving average doses of 0.14 mg/kg were 45–49 ng/ml [12,13].

Nakamura *et al.* described the PK of enalapril after doses of 0.05 to 0.3 mg/kg in children with CHF ($n = 12$, age 10 days to 6.5 years) [41]. As described above for adults, one needs to take into account possible differences in PK in children with CHF versus other children. The results are presented normalised to an enalapril dose of 0.1 mg/kg. Enalapril $T_{1/2}$ was 2.7 (SD 1.4) h in children older than 20 days ($n = 10$, 11 observations), compared with 1.6 (SD 1.5) h as reported for adults [14,27]. Furthermore, the $AUC_{0-infinity}$ in children >20 days was 82.7 (SD 44.3) ng.h/mL, compared with 55.6 (SD 5.7) ng.h/mL in adults [27]. The $T_{1/2}$ and AUC in two neonates <20 days of age were 10.3 (SD 5.2) h and 268.7 (SD 138.9) ng.h/mL, respectively, based on three observations.

Enalaprilat PK

In the Wells study, enalaprilat AUC_{0-24h} and C_{max}, normalised per kg bodyweight, were significantly lower in nine children who were between 2 and 24 months of age compared with 12 children aged 12–16 years [AUC_{0-24h} 131.4 (95% CI 91.9–187.9) ng.h/mL versus 272.7 (95% CI 197.3–377.0) ng.h/mL per 0.1 mg/kg, C_{max} 13 (95% CI 9.2–18.4) ng/mL versus 31.8 (95% CI 23.5–43.0 ng/ml] [40]. No significant difference between the other age groups was observed. When corrected for body surface area, the AUC and C_{max} did not differ between age groups.

The percentage of enalapril dose excreted in the urine was calculated on the basis of measured urinary recovery of enalaprilat. This percentage might serve as surrogate marker of CES1 and hepatic transporter activity because it largely reflects conversion of enalapril to enalaprilat [40]. The mean percentage conversion of enalapril to enalaprilat showed great variability. This was largest within the age group of children from 1 to 24 months of age, with CI ranging from 42.6 to 89.1%. Across age groups, enalapril to enalaprilat conversion proportions were 64.7 to 74.6% and did not differ significantly between age groups. The observed difference in AUC between the youngest and oldest age groups might suggest increased CES1 and hepatic transporter activity in the youngest age group, but the conversion data cannot confirm this hypothesis. Because the patient numbers are small, an age-related change in either CES1 metabolism or hepatic transport can therefore not be excluded.

Nakamura *et al.* observed a normalised enalaprilat $AUC_{0-infinity}$ for children >20 days of 138.4 (SD 69.2) ng.h/mL per 0.1 mg/kg enalapril [41]. Because all but two of Nakamura *et al.*'s subjects were below the age of 24 months, this cohort might be comparable in age to the youngest age group of Wells *et al.* [40].

In children with CHF aged >20 days to 24 months, the average $T_{1/2}$ of enalaprilat was 11.1 (SD 4.3) h, whereas Wells reported, in the whole cohort, $T_{1/2}$ of enalaprilat up to 16.3 h, with large interindividual variability, as shown in Table 1 [40]. In healthy adults, $T_{1/2}$ ranges from 3.8 to 11 h, whereas in adults with CHF, a mean (SD) $T_{1/2}$ of 6.8 (SD 2.5) h was found [32].

The third PK article from 1989 describes a dose-finding study in ten paediatric patients (aged 6 weeks to 8 months) with CHF [42]. A dose escalation protocol was used, with dosages as low as 0.02 mg/kg in some children. These low doses resulted in a high proportion of the 24 h enalaprilat serum samples (four out of the ten children) being below the lower limit of quantification. Consequently, no useful PK parameters could be obtained from those children. In six children receiving the highest dose of 0.08 mg/kg, the serum $T_{1/2}$ of enalaprilat was 7.55 (SD 0.66) h and the C_{max} was 12.7 (SD 2.9) ng/mL per 0.1 mg/kg dose of enalapril.

Overall, the available PK data are too limited to support with certainty an age-related effect on enalapril and enalaprilat PK. Lower enalaprilat exposure after bodyweight-normalised dosing in young infants, as suggested by the Wells study, could be supported by the data from the two other PK studies, but all together, the small patient numbers across a wide age range and the difference in the underlying disease preclude definitive conclusions.

The unknown interplay of the different PK processes involved in the disposition of both enalapril and its active metabolite further hampers simple extrapolation of knowledge on the maturation of these processes to support the suggested age-related variation. CES1 protein abundance increases fivefold from neonates to adults [44]. At birth, the GFR is low, and at around two years of age, the GFR reaches its maximum value of around 3.2 ml/min/kg; hereafter, it decreases to reach adult values from the age of five onwards [45]. Although data on the ontogeny of hepatic MRP4 in humans are lacking, a juvenile rat study showed low expression at birth and

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TABLE 1

PK of enalapril and enalaprilat in children compared with adults

Age range and number of patients		**Wells et al. 2001 [40] 2 months–15 years: 40**	**Nakamura et al. 1994 [41] <20 days: 2 20 days to 6.5 years: 10 21–39 years : 7**	**Lloyd et al. 1989 [42] 6 weeks–8 months: 10**
Diagnosis		Hypertension	CHF[a]	CHF
Dose		0.07–0.14 mg/kg	Children: 0.05–0.3 mg/kg Adults: 10 mg	0.02–0.08 mg/kg
Pharmacokinetic parameters of enalapril				
C_{max}, mean		24.6–45.4 ng/ml	–	–
T_{max}, mean		±1 h	–	–
$AUC_{0-infinity}$ in ng.h/mL, mean (SD)		–	<20 days: 268.7 (139.9) >20 days: 82.7 (44.3)	–
$T_{1/2}$ in h, mean (SD)		–	<20 days: 10.3 (5.2) >20 days: 2.7 (1.4)	–
Pharmacokinetic parameters of enalaprilat[b]				
AUC per 0.1 mg/kg (ng.h/mL)	2–24 months	131.4 (91.9–187.9)	<20 days: 691.5 (225.6)	–
Wells: AUC_{0-24h}, geometric mean (95% CI)	2–6 years	140.7 (98.4–201.3)	>20 days: 138.4 (69.2)	–
Nakamura: $AUC_{0-\infty}$, mean (SD)	6–12 years	176.3 (125.6-247.5)	–	–
	12–16 years	272.7 (197.3–377.0)	–	–
	Adults	–	245.7 (61.8)	–
C_{max} per 0.1 mg/kg (ng/mL)	2–24 months	13 (9.2–18.4)	<20 days: 5.3 (3.0)	12.7 (2.9)
Wells: geometric mean (95% CI)			>20 days: 9.0 (4.7)	
Nakamura: mean (SD)	2–6 years	18.4 (13–26.1)		–
Lloyd: mean (SD)	6–12 years	22.7 (16.3–31.7)	–	–
	12–16 years	31.8 (23.5–43)		
	Adults	–	30.3 (14.0)	–
T_{max} (h)	2–24 months	6.0 (4.0–8.0)	<20 days:?	4
Wells: median (95% CI)	2–6 years	5.0 (3.1–6.9)	>20 days: 7.3 (2.4)	–
Nakamura: mean (SD)	6–12 years	5.0 (4.0–6.0)	–	–
	12–16 years	4.0 (3.0–5.0)	–	–
	Adults	–	3.7 (1.4)	–
$T_{1/2}$ (h)	2–24 months	–	<20 days:?	7.55 (0.66)
Wells: mean (95% CI)	2–6 years	15.37 (9.45–28.07)	>20 days: 11.1 (4.3)	–
Nakamura: mean (SD)	6–12 years	16.31 (10.98–20.44)		–
Lloyd: mean (SD)	12–16 years	14.61 (10.22–23.00)		–
	Adults	–	5.3 (1.6)	–

[a] Abbreviations: $AUC_{infinity}$, area under the curve; CHF, congestive heart failure; C_{max}, maximum serum concentration; $T_{1/2}$, elimination half-life; T_{max}, time to maximum concentration.
[b] Aggregated AUC and C_{max} values of enalaprilat reported by Wells and Lloyd *et al.* were normalised to a dose of 0.1 mg/kg per age group in order to facilitate comparison between studies. Used formulas: AUC, dose/CL; concentration, dose/CL and assuming linear kinetics for T_{max} as well as $T_{1/2}$.

an increase until day 60 of life [46]. Furthermore, the renal transporters involved in enalaprilat excretion are currently unknown.

Pharmacodynamics

Adults

Enalaprilat inhibits ACE, which leads to reduced formation of angiotensin II. Following an enalapril dose of 10 mg in healthy individuals, ACE inhibition (reflected by the reduced generation of angiotensin II) was almost complete between 4 and 10 h after administration. Accordingly, plasma renin levels increased with maximum levels after 4 h, and both angiotensin II and aldosterone levels decreased and remained low up to 10 h after administration [1]. The relationship between ACE activity and plasma enalaprilat levels, as well as BP and plasma enalaprilat levels, was inversely proportional, as was shown by de Leeuw *et al.* in hypertensive patients [47].

During decompensated cardiac failure, the RAAS is activated owing to a lower cardiac output, leading to a decrease in peripheral vascular resistance and a diminished volume of the extracellular fluid, but returns to normal when heart failure stabilises [48]. As would be expected, the formation of angiotensin II is decreased in patients using enalapril, leading to lower levels of angiotensin II, less activation of ACE and lower aldosterone levels [49].

Children

Data supporting the increased activity of the RAAS during infancy and childhood in healthy children (up to 4 years of age) have been previously published and are widely accepted [50]. Interestingly, and in a similar pattern to adults, after once-daily administration of 0.25 mg/kg enalapril, inhibition of ACE activity in eight infants with CHF (aged 3 weeks to 6 months) was 75.5% (SD 12.2%) at 4 h after intake compared with ten healthy children without ACE inhibitor treatment [51].

Angiotensin II concentrations decreased from 115 (SD 67) pg/mL to 60 (SD 30) pg/mL and plasma renin activity increased from 25 (SD 24) ng/mL/h to 45 (SD 37) ng/mL/h in 35 children with CHF (aged 1 month to 17 years) after an average of 17 days of treatment with enalapril at an average daily dose of 0.24 mg/kg twice daily [52]. To the best of our knowledge, no PD parameters have been measured during enalapril treatment in children with hypertension.

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TABLE 2

Paediatric enalapril trials

Indication (number of trials)	Reference	Number of patients	Age of population	Exact indication	Dosage and type of formulation (duration)	Type of trial	Level of evidence[a] [142]	Effect
Hypertension (9)	Burrello *et al.* 2018 [53]	2378	Median of 12 years	Hypertension	Mean 0.08 mg/kg/day of oral suspension once daily (2 weeks)	Meta-analysis	1a	Together with lisinopril, enalapril was superior to placebo in reducing SBP[b] and DBP compared to other antihypertensive agents
	Wells *et al.*2002 [54]	110	6–16 years	Hypertension	Mean 0.08 mg/kg/day of oral suspension once daily (2 weeks)	RCT (double blind)	1b	Administration of enalapril led to an effective lowering of BP; the dose–response relationship for enalapril had a negative slope and was linear over the chosen dosing range
	Di Salvo et al. 2016 [56]	51 (25 enalapril)	6–20 years	Aortic coarctation repair with hypertension	0.08–0.6 mg/kg/day, tablet, once daily (12 months)	RCT comparing enalapril with atenolol (open label)	1b	Reduction in 24 h SBP (135 (SD 6) mm Hg versus 127 (SD 7) mm Hg, $p = 0.001$) + significant reduction in left ventricular mass index
	Schaefer et al. 2011 [55]	300	6–17 years	Hypertension	Dependent on weight; tablet of 10, 20 or 40 mg/day, once daily (12 weeks)	Randomised, double-blind, parallel-group, active-controlled study with Valsartan	1b	Significant reduction in mean sitting SBP (−11.8 mm Hg) and DBP (−7.9 mm Hg) compared with baseline ($p < 0.0001$)
	Schilder et al. 1995 [57]	1	Preterm infant	Neonatal hypertension	0.1 mg/kg orally	Case study	4	Severe hypotension and renal failure
	Mason et al. 1992 [58]	2	Neonates	Neonatal hypertension	IV enalapril, 0.1 mg/kg/day divided every 6 h	Case study	4	Case 1: ventricular shortening fraction improved from 8% to 20%. Case 2: MAP decreased from 67 mm Hg to 40 mm Hg.
	Marcadis et al. 1991 [59]	1	3 days	Neonatal hypertension	IV enalaprilat, 0.01 mg/kg single dose	Case report	4	Mean BP decreased from 91 to 51 mm Hg
	Wells et al. 1990 [60]	10	26–36 weeks gestational age (post-conception age 29–44 weeks)	Neonatal hypertension	Enalaprilat IV, 5.2–28.8 μg/kg/24 h, median dosing interval 12 h (2–17days)	Case study	4	Significant reduction in mean arterial pressure (MAP) ($p < 0.05$)
	Miller et al. 1986 [61]	14	6 weeks–18.5 years	Various renal diseases and hypertension	2.5–30 mg/day orally (5–12 months)	Case study	4	Normal BP for age was achieved in all 14 children; however, eight children required the addition of a diuretic
Heart failure (14)	Hsu et al. 2010 [71]	230	20.1 (SD 8.9) days	Single ventricle physiology	0.1–0.4 mg/kg/day; exact formulation not described (14 months)	Double blind RCT with placebo	1b	No improvement in somatic growth, ventricular function or heart failure severity
	Kouatli et al. 1997 [81]	18	14.5 (SD 6.2) years	After Fontan procedure	0.2–0.3 mg/kg/day once daily (10 weeks)	Double blind placebo-controlled crossover trial	1b	Enalapril administration for 10 weeks did not alter abnormal systemic vascular resistance, resting cardiac index, diastolic function or exercise capacity
	Mori et al. 2000 [67]	24 (3 enalapril)	0.3–16 years	Aortic or mitral regurgitation	0.15–0.4 mg/kg/day [mean 3.4 (SD 2.0) years]	Prospective cohort (randomised)	2b	Mean change in Z-value for LV end diastolic dimensions −0.25 (SD 0.33) for ACEi group versus −0.42 (SD 0.48) for control group ($p = 0.0007$) Mean change in mass normalised to growth: −72 (SD 89)% of normal for the ACEi group vs. − 37 (SD 35)% of normal for control group ($p = 0.0007$)
	Leversha et al. 1994 [72]	63	4 years (SD 5.4 months)	Congenital and acquired heart disease	0.04–0.94 mg/kg/day, once, twice or three times daily (1 day–3 years)	Prospective cohort	2b	58% of all patients had improved signs of CHF. The dose received by those who improved was significantly greater ($p = 0.04$) than that received by those who showed no change.
	Webster et al. 1992 [73]	26	6 months–15 years	Intracardiac shunts	Enalaprilat IV 0.06 mg/kg (30 min)	Prospective cohort	2b	Mean pulmonary–systemic flow ratio decreased from 2.9 (SD 0.3) to 2.4 (SD 0.3) ($p < 0.05$) and the mean left-to-right shunt from 7.4 (SD 0.8) to 5.9 (SD 0.7) l/min/m^2 ($p < 0.02$) after enalapril treatment
	Sluysmans et al. 1992 [74]	8	<10 months	Isolated large ventricular septal defect	Enalaprilat IV 0.02 mg/kg (15 min) and enalapril 0.16 mg/kg orally once daily (7 days)	Prospective cohort	2b	IV administration: absolute left-to-right shunt decreased 27% [7.5 (SD 6.3) to 5 (SD 3.7) l/min/m^2, $p < 0.05$]. Systemic blood flow did not change. Pulmonary blood flow decreased 15.5% ($p < 0.1$). Mean decrease of aortic mean pressure was 9% (66 (SD 9) to 61 (SD 9) mm Hg, $p < 0.0001$). **Oral administration**: six patients had increased weight gain [82 (SD 59) to 166 (SD 94) g/week] and bottle feeding [milk, 139 (SD 16) to 158 (SD 13) ml/kg/day; $p < 0.05$]
	Seguchi et al. 1990 [52]	35	1 month–17 years	CHF	0.11–0.8 mg/kg/day orally, twice a day (7–44 days)	Prospective cohort	2b	Significant decrease in left ventricular end-diastolic dimension, hepatomegaly and cardiothoracic ratio ($p < 0.05$)
	Rheuban et al. 1990 [75]	11	1–13 months	CHF secondary to left-to-right shunt lesions	IV enalaprilat 0.01 mg/kg, single dose (20 min)	Prospective cohort	2b	Significant reduction in systemic vascular resistance [18.1 (SD 4.7) to 14.2 (SD 3.5) Wood units *m^2; $p < 0.001$]. Reduction in pulmonary/systemic blood flow ratio (p = non-significant).
	Lewis et al. 1993 [76]	81 (of which 27 ACE inhibitor and two enalapril)	3.6 (SD 0.6) years	Dilated cardiomyopathy	Dose not mentioned. (2 years)	Retrospective cohort	2b	Significantly better survival during the first year ($p < 0.05$) with continuation of this trend throughout the second year ($p = 0.06$). Beyond 2 years, this difference was no longer significant.
	Robinson et al. 2002 [77]	9	13.8 (SD 3) years	Transposition of the great arteries s/p intra-arterial switch after intra-arterial baffle	0.1–0.5 mg/kg/day, rounded to the nearest 2.5 mg (12 months)	Case study (prospective)	4	No improvement in exercise performance in patients with transposition of the great arteries in whom the intra-atrial baffle procedure had been performed
	Eronen et al. 1991 [78]	8	1.5–11.2 years	CHF and dilated cardiomyopathy	0.5 mg/kg/day, orally once daily (5 days)	Case study (prospective)	4	Diminished afterload, reflected by a decrease in mean SBP from 104 to 96 mm Hg ($p = 0.054$), and a decrease in heart size from 582 to 523 ml/m^2 ($p = 0.09$)
	Lipschultz et al. 2002 [79]	18	1–18.1 years	Ventricular dysfunction due to doxorubicin treatment	5–40 mg/day; exact formulation not described (10 years)	Case study (retrospective)	4	Progressive improvement towards normal values of LV dimension, afterload, fractional shortening and mass in the first 6 years of enalapril treatment
	Frenneaux et al. 1989 [80]	8	4 days–12 weeks	Severe heart failure	Suspension of crushed tablet, 0.12–0.43 mg/kg/day once daily (2 weeks)	Case study	4	Mean (SEM) liver size had decreased from 2.3 (0.36) cm to 1.2 (0.24) cm below the costal margin, mean respiratory rate had fallen from 63 (3.2) to 53 (2.8) breaths per minute. The mean heart rate increased from 136 (6.4) to 143 (4.2) beats per minute and the mean SBP fell from 88 (4.0) mm Hg to 82 (6.5) mm. No p-values were reported.
	Li et al. 2011 [143]	5		Mitral regurgitation after atrioventricular septal defect repair		Double-blind RCT		Seventeen months after the start, the study was terminated because of low patient accrual

TABLE 2 (*Continued*)

Indication (number of trials)	Reference	Number of patients	Age of population	Exact indication	Dosage and type of formulation (duration)	Type of trial	Level of evidence[a] [142]	Effect
Kidney disease (13)	Webb et al. 2012 [88]	268 (134 enalapril)	10.4 (SD 4.7) years	Children with proteinuria	Suspension or tablet, mean dose 0.26 mg/kg (12 weeks)	Double-blind RCT	1b	The LS percent mean reduction from baseline in the urinary protein–creatinine ratio was 40.45%. The LS mean change from baseline in eGFR was 7.0 ml/min per 1.73 m^2 (both after 3 years).
	Webb et al. 2013 [87]	27 (12 enalapril)	1–17 years	Alport disease	Suspension or tablet, 0.07–0.72 mg/kg/day (12 weeks)	Double-blind RCT	1b	The LS mean percent change from week 12 in urinary protein LS mean change from week 12 in eGFR was −9.1 ml/min/1.73 m^2 in the enalapril group
	Caletti et al. 2011 [89]	46 (14 enalapril)	2.08–13.89 years	Post-diarrhoea HUS	0.18–0.27 mg/kg/day single oral dose (7 months)	Double-blind RCT	1b	Decrease in proteinuria with enalapril was 66.3%. Significant decrease SBP of 12% ($p < 0.023$) after treatment with enalapril (no change after placebo or losartan).
	Bagga et al. 2004 [90]	25	1–16 years	Steroid-resistant nephrotic syndrome	0.2–0.6 mg/kg/day (2 × 8 weeks)	Randomised crossover trial (open label)	1b	High-dose enalapril (0.6 mg/kg/day) was associated with a significant reduction in urine albumin-to-creatinine ratio ($p < 0.01$)
	Hari et al. 2013 [91]	41 (20 enalapril)	2–18 years	CKD	0.4 mg/kg/day tablet once daily (1 year)	Open-label RCT	1b	The rate of decline in GFR was 3.0 (SD 4.2) in the enalapril and 4.2 (SD 5.1) ml/min/1.73 m^2 in the non-enalapril group ($p = 0.51$)
	Sasinka et al. 1999 [92]	48 (17 enalapril)	Unknown	Proteinuric children	Unknown (8 weeks)	Retrospective study	2b	Proteinuria decreased from 1.32 (SD 0.23) to 0.53 (SD 0.11) and 0.44 (SD 0.07) g/day on the 4th and 8th week of treatment
	Proesmans et al. 2000 [93]	7	5.15–13.75 years	Alport syndrome	Tablet, 0.13–0.29 mg/kg/day (24 months)	Case study (prospective)	4	Marked reduction in urinary protein excretion with a nadir of 23% (52 mg/kg to 12 mg/kg per 24 h) of the baseline at 18 months; no *p*-value reported
	Guez et al. 1998 [95]	1	22 months (born at 35 weeks gestation)	Finnish-type congenital nephrotic syndrome	0.8 mg/kg/day (1 month)	Case study (prospective)	4	Serum protein concentration was maintained without the need for albumin infusions (no *p*-value reported)
	Proesmans et al. 1996 [94]	5	7–17 years	Various renal diseases	0.5 mg/kg per day (24 months)	Case study (prospective)	4	Median decrease in proteinuria of 52% (no *p*-value reported)
	Trachtman et al. 1988 [96]	8 (1 enalapril)	5–22 years	Proteinuria unresponsive for standard therapy	2.5 mg/day (undefined)	Case study (prospective)	4	BP declined to the normal range in all cases and achieved a mean value of 112/73 mm Hg ($p < 0.005$)
	Caletti et al. 2013 [97]	17	0.25–5.33 years	Diarrheal HUS	0.20–0.56 mg/kg/day (5.92 years)	Case study (retrospective cohort)	4	Decrease in proteinuria with enalapril was 58% ($p = 0.023$)
	Fitzhugh et al. 2005 [98]	3	14–17 years	Sickle cell nephropathy	5–7.5 mg/day (3.0 ± 1.3 years)	Case study	4	Increase in serum albumin levels from 2.8 (SD 0.8) g/dl to 3.9 (SD 0.3) g/dl (no *p*-value reported)
	Lama et al. 2000 [99]	6	?	Steroid-resistant nephrotic syndrome	0.3 mg/kg/day (2 years)	Case study	4	In 71.4% enalapril therapy resulted in an important reduction of proteinuria

[a] Level of evidence according to Johansen et al.: systematic reviews and meta-analyses of RCTs (1a), RCT (1b), non-randomised controlled trials (2a), cohort studies (2b), case-control studies (3), case studies, expert opinion.
[b] Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; BP, blood pressure; CHF, congestive heart failure; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; HUS, haemolytic uraemic syndrome; IV, intravenous; LS, least squares; LV, left ventricle; MAP, mean arterial pressure; RCT, randomised controlled trial; SBP, systolic blood pressure; SEM, standard error of the mean.

Indications

In the paediatric population, enalapril is prescribed for patients with hypertension, CHF and CKD (Table 2). We identified 36 articles reporting the clinical effect of enalapril in children with (one of) these three different diagnoses. There was large heterogeneity both in the study methods and the outcome measures; therefore, the results are described below by underlying disease as well as level of evidence.

Hypertension

Children

Nine articles described the effect of enalapril in hypertensive patients, and one meta-analysis studied the pharmacological treatment of arterial hypertension in children and adolescents [53]. Together with lisinopril, enalapril seems to be superior in reducing systolic BP (SBP) and diastolic BP (DBP) compared with other antihypertensive agents. However, it is important to mention that the conclusion of this meta-analysis is solely based on one dose–response study investigating enalapril in 110 hypertensive children aged 6–16 years [54]. Enalapril was administered as a suspension, and patients were randomised to receive a low, middle or high dose. For children below 50 kg, this was 0.625, 2.5 or 10 mg of enalapril once daily, respectively. Above 50 kg, 1.25, 5 or 20 mg of enalapril was administered. A mean dose of 0.08 mg/kg seemed to be effective at lowering BP within 2 weeks in most patients. Higher doses were associated with a greater reduction in BP.

The other seven paediatric enalapril studies were excluded in this meta-analysis because they did not compare enalapril to placebo. One randomised controlled trial (RCT) compared the effectiveness of valsartan, an angiotensin II receptor blocking agent, to enalapril in 300 hypertensive children aged 6–17 years after a placebo run-in period [55]. Dosing was based on bodyweight, with doses up to 40 mg of enalapril and 320 mg of valsartan. The study found a reduction of 14.1 (SD 8.5) mm Hg in mean BP from baseline in the enalapril group. A similar reduction from baseline was seen in the valsartan group ($p < 0.0001$). In 51 children aged 6 to 20 years of age after aortic coarctation repair and hypertension, the superiority of enalapril to atenolol, a beta blocker, was shown. This was based on the reduction of the left ventricular mass index as well as 24 h SBP [56]. The remaining five studies were all case studies or series with one to 15 patients, and suggested a similar trend with a reported (statistically) significant decrease in BP after various lengths of treatment [57–61].

To further explore the dose–response relationship of enalapril, a PK/PD model was developed to predict its efficacy in children aged 0–6 years using BP as the PD end point [62]. A two-compartment model incorporating weight was built to predict a decrease in DBP using three datasets, two of which were from children [40,54]. On the basis of model predictions, researchers suggest that the dose–response of enalapril is similar in children between 1 month and 6 years of age compared with those older than 6 years of age when looking at the reduction of DBP after 2 weeks of treatment. However, these data need further validation because no PD data of children below the age of 6 years were used.

Next to age-related changes in PD, the effect of gender or sexual maturity (Tanner stage) was also investigated and did not explain variability in the antihypertensive effect of enalapril in 110 paediatric hypertensive patients, aged 6–16 years [54].

In African American adults, it is well established that ACE inhibitors are less effective in lowering BP, which is probably explained by lower renin levels in this population [63]. In a meta-analysis of six paediatric antihypertensive trials, BP decreased significantly from baseline in Caucasian (SBP $p = 0.003$, DBP $p < 0.0010$), but not in African American children (SBP $p = 0.139$, DBP $p = 0.397$) [64]. However, although it is not mentioned specifically for the paediatric population, the efficacy of ACE inhibitors is promising even in cases of enhanced renin secretion (hyper-reninaemic hypertension) [65,66].

In conclusion, moderate strong evidence supports the efficacy of enalapril in treating hypertension in Caucasian children older than 6 years of age. For younger children, data are scarce; for non-Caucasian children, the efficacy may be lower.

Heart failure

Adults

Enalapril has a positive effect on heart-failure parameters beyond its BP-lowering effect [67]. Because chronic volume overload will lead to ventricular dilatation and myocardial hypertrophy in certain forms of heart failure, irreversible structural and functional damage will occur. By reducing cardiac afterload, ACE inhibitors have been shown to reduce the extent of dilatation and development of redundant cardiac muscle mass, thereby reducing left ventricle (LV) volume overload and improving LV function [3]. As well as a reduction in afterload, this effect can be explained by the inhibition of hydrolysis of N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP), which is an important inhibitor of stem cell proliferation. By raising Ac-SDKP concentrations, ACE inhibition leads to reduced cardiac cell proliferation, inflammatory cell infiltration and collagen deposition [68]. This also explains why enalapril is beneficial in several types of heart failure.

Although the positive effect of ACE inhibitor therapy in adults with heart failure is well established and ACE inhibitor therapy has a major place in the therapy of adult heart failure in both Europe and the United States [69,70], this effect is less apparent in the paediatric population, in which studies show conflicting results.

Children

Fourteen studies addressed the efficacy of enalapril in children with heart failure; two of these studies were double-blind placebo-controlled randomised trials. These two RCTs comparing enalapril to placebo were conducted in paediatric heart failure patients with single ventricle physiology [71]. These children have a special haemodynamic situation, and the clinical effects of enalapril might not be comparable to other forms of heart failure. These studies are therefore discussed at the end of this section.

Six prospective cohort studies investigated the effect of enalapril, and they all showed a significant effect on several heart failure parameters (Table 2). In 24 patients aged 0.3–16 years with aortic or mitral regurgitation, treatment with enalapril (or another ACE inhibitor) led to a decrease in both posterior wall thickness and LV mass [67]. Similarly, among children [mean age 4 years (SD 5.4 months)] with CHF, 39 out of 67 treatment periods in 63 patients showed an improvement in clinical parameters after treatment with enalapril [72]. Although no clinical end points were assessed in 26 children aged 6 months to 15 years with a large ventricular septal defect in the study of Webster *et al.*, they found that after

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start of enalapril, aortic and pulmonary artery pressure decreased by 20% [73].

In eight children with an isolated large ventricular septal defect (aged <10 months), treatment with enalapril resulted in improved bottle feeding and increased body weight [74]. In 35 children (aged 1 month to 17 years) with mitral or aortic regurgitation following intracardiac repair or with dilated cardiomyopathy who received enalapril, hepatomegaly significantly decreased as well as cardiothoracic ratio, heart rate and BP. LV end-diastolic dimension also decreased [52]. Furthermore, in 11 children (aged 1–13 months) with CHF secondary to a left-to-right shunt, systemic vascular resistance was significantly decreased (18.1 (SD 4.7) to 14.2 (SD3.5) Wood units*m^2, $p < 0.001$) after treatment with enalapril. However, the reduction in pulmonary/systemic blood flow ratio was not significant [75].

In a retrospective study in 81 children (mean age 3.6 (SD 0.6) years) with a dilated cardiomyopathy, 27 children were treated with ACE inhibitor alone (enalapril $n = 2$, or captopril $n = 25$) versus conventionally with digoxin and diuretics ($n = 54$). Both captopril and enalapril treatment showed a statistically significant better survival rate during the first year compared to the other group ($p < 0.05$) [76].

Last, in three out of four reported case series, enalapril therapy showed positive outcomes. The results of these studies can be found in Table 2 [77–80].

The largest RCT on enalapril was performed in children with single ventricle physiology [71]. Enalapril at an oral dose of 0.4 mg/kg/day given in two divided doses did not improve somatic growth, ventricular function or heart failure severity in 230 infants (mean age 20 days) with a single ventricle that had stable systemic and pulmonary blood flow [71]. Based on the hypothesis that increased systemic vascular resistance and impaired diastolic function might contribute to decreased exercise capacity, a double-blind crossover trial was performed in 18 post-Fontan procedure patients (age 14.5 (SD 6.2) years, dose of 0.2–0.3 mg/kg/day for 10 weeks). Again, enalapril did not improve exercise capacity, systemic vascular resistance, resting cardiac index or diastolic function [81]. However, it is important to note that patients with CHF were excluded from this study.

As described above, the only two RCTs performed in children with heart failure in post-Fontan procedure patients or patients with single ventricle physiology failed to show an effect of enalapril on echocardiographic indices or clinical outcome. Yet these findings need to be interpreted with great caution. In patients with single ventricle physiology, the indication for ACE-inhibitor therapy is not clear because this is a circulation with a potentially underloaded systemic ventricle, especially after Fontan completion. But despite the absence of evidence, ACE inhibitors are still used in a large proportion of these patients, partly due to potential limitations of these studies [82]. In the Hsu *et al.* study, most patients (80%) had preserved ventricular function in the absence of neurohormonal activation at baseline, and systolic heart failure is only a late manifestation and thus unusual in this population [83,84]. In addition, there was a high rate of drug discontinuation, and target doses were not achieved in all patients. Furthermore, as the paediatric PK studies suggest, dosages of 0.07–0.3 mg/kg/day in children less than 2 years of age might not reach a similar level of enalaprilat exposure as in adults [40–42]. In the Hsu *et al.* study, the enalapril target dose was 0.4 mg/kg/day. Also, in the Kouatli *et al.* study, enalapril was dosed at 0.2–0.3 mg/kg/day in children with a single ventricle physiology [81].

Studies that showed a therapeutic effect of enalapril often also included patients above the age of 12 years [52,56,67,73,77,78] and/or directly administered enalaprilat [73–75]. Hence, in order to investigate the effect of enalapril in children with heart failure, new studies with higher dosages may be needed. Until then, low to moderate level of evidence supports the efficacy of enalapril for paediatric heart failure. For children with a single ventricle physiology specifically, the data are less supportive.

Chronic kidney disease

Although it was initially developed as an antihypertensive drug, enalapril is prescribed in patients with CKD with the aim of reducing proteinuria and thereby improving renal survival [85]. Its positive effect on kidney survival can be explained by two important factors [4]. ACE inhibitors in general decrease the pressure within the efferent arteriole and thereby the intraglomerular pressure. Furthermore, inhibition of cytokine production results in less glomerulosclerosis and less fibrosis. However, it is important to consider the differences in aetiologies of CKD, because the causes vary significantly between adults and children; in the latter, a non-glomerular origin of CKD is more common.

Children

ACE inhibitors are used in 80% of children with CKD of glomerular origin and only in 47% of those with non-glomerular CKD [86]. In total, 13 studies described the use of enalapril in children with various kidney diseases. Three double-blind RCTs were performed in 341 children in total, aged 1–17 years, and they all reported a significant decrease in proteinuria [87–89]. In two other open-label trials in 66 children with Alport disease or post-diarrhoea haemolytic uraemic syndrome (HUS) aged 1–18 years, enalapril significantly decreased proteinuria [90,91]. Furthermore, one retrospective cohort [92] as well as four prospective case studies [93–96] in patients aged 22 months to 22 years showed a similar result and supported the use of enalapril in this population. Last, three retrospective case studies also investigated the effect of enalapril, and all reported a positive effect on proteinuria in children aged 0.25–17 years [97–99].

Taken together, these studies provide a moderate level evidence to support the use of enalapril to reduce proteinuria in children with CKD. Whether enalapril is also beneficial for clinical end points such as dialysis-free survival or mortality remains unknown.

Adverse events

In adults, the most common adverse reactions seen with the use of enalapril are hypotension, renal failure, hyperkalaemia, cough and angioedema [100]. Whether ACE inhibitor-associated kidney failure is caused by direct nephrotoxicity, renal efferent arteriolar vasodilatation or hypotension and low renal perfusion remains unclear [101]. Cough is considered to be a frequent side effect of ACE inhibitor use, because it occurred in 13.5% of all patients on ACE inhibitor therapy, but only 37% of these cases can be attributed solely to the use of ACE inhibitors [102]. Also, patients suffering from allergic reactions to one ACE inhibitor have a relative contraindication to another ACE inhibitor as well as to

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angiotensin II receptor blockers. However, for angioedema, a low incidence of cross-reactivity is reported (<10%) [103].

In children, hypotension, impaired renal function and hyperkalaemia are the most commonly reported side effects of ACE inhibitors [104]. In a systematic review of 11 reports covering a total of 1050 paediatric heart failure patients taking enalapril, hypotension was reported in 0–19% of cases, renal failure in 0–29% and hyperkalaemia in 0–13% [104]. Articles that only included patients treated with captopril were excluded. Reported differences across studies can be (partly) explained by differences in adverse event definitions. There was no relation to dose, and neither angioedema nor cough was reported.

Furthermore, the use of ACE inhibitors is not recommended during the second or third trimester of pregnancy because of their potential foetotoxicity [105]. This can be explained by suppression of the foetal RAAS, which seems to disrupt foetal vascular perfusion and GFR. Little data are available regarding the use of ACE inhibitors during the first trimester. Animal data did not demonstrate a teratogenic effect, and human case reports ($n = 9$) did not record any embryo-foetal or postnatal outcome when enalapril exposure was limited to the first trimester [105,106].

We identified four more articles describing adverse events in children using enalapril. One case reported angioedema and hypertension in a 14-year-old patient with systemic lupus erythematosus who received enalapril at an unknown dose for three years [107]. One paediatric cohort study of 42 patients (median age 7.6 years) reported persistent isolated cough in 17% of patients using an ACE inhibitor, of which the majority used enalapril [108]. Cough resolved within days after discontinuing therapy. Furthermore, in the study of Seguchi *et al.* ($n = 35$), acute renal failure developed in a 3-month-old infant one day after administration of enalapril, and hyperkalaemia occurred in four children (12% of the study population) [52]. All five adverse events resolved after discontinuation of enalapril. Although adverse events were prospectively monitored in the study of Webster *et al.* [73], no adverse reaction occurred in the 26 children taking enalapril. Young children seem to be at an increased risk of adverse reactions related to acute kidney injury (AKI) induced by an ACE inhibitor because of their lower GFR and impaired autoregulation of renal blood flow [104]. More specifically, children of young age who are prone to dehydration, either owing to the concomitant use of diuretics or gastro-enteritis, seem to be at a higher risk of developing AKI-related adverse events.

In conclusion, enalapril seems to have a similar safety profile in children compared to adults, but the incidence of cough and angioedema seems to be much lower, although not completely absent. To define the proportion of placebo-adjusted cases of cough in children on ACE inhibitors, further studies are needed.

Drug–drug interactions

Adults

There are several compounds that can change efficacy and safety when taking enalapril, and dose adjustments might be necessary when taking enalapril together with other drugs. This includes the concomitant use of enalapril with diuretics or other medications working on the RAAS, such as angiotensin II receptor blockers or renin inhibitors (aliskiren). One in three adult patients with chronic heart failure developed AKI when ACE inhibitors were co-administered with diuretics, compared with only 2.4% of patients who were on ACE inhibitor alone [109]. Due to a possible decrease in GFR, caution is warranted when primarily renally cleared medication that has a narrow therapeutic index (i.e., digoxin) or that increases the risk of AKI (non-steroidal anti-inflammatory drugs) is co-administered. To decrease the risk of developing hyperkalaemia, no potassium supplements should be administered at the same time.

Children

Scant data are available about potential drug interactions and their severity in children. An interaction described for adults is usually also relevant for the paediatric population. However, the magnitude of these drug–drug interactions can differ greatly in children when compared to adult data, because the extent of any drug–drug interaction can be altered by physiological differences [110].

Only two articles described enalapril interactions in children, albeit in a very specific population. The therapeutic effect of allopurinol as well as hydroxyurea increased when enalapril was co-administered [98,111]. Emphasizing the importance of the possible development of hyperkalaemia when taking enalapril with potassium supplements, the interaction of enalapril with potassium chloride is within the top five drug–drug interactions that were most frequently overridden in a paediatric hospital [112]. For ACE inhibitor use in children, the co-administration of furosemide is an independent risk factor for developing AKI in patients [35,113]. This risk factor is also supported by data from pharmacovigilance databases [101].

Drug formulation

In the published studies, children received extemporaneous liquid formulations prepared from crushed tablets intended for adults. Several problems can arise when using such extemporaneously made medications. For example, inadequate mixing or settling of a suspension increases the risk of medication errors [114]. Therefore, several new formulations have been developed to ensure more precise dosing in children. First, an enalapril oral solution has been developed, thereby decreasing the risk of inappropriate preparation and reducing the risk of inadequate therapy in children because a solution requires no preparation by nurses or parents. Also, as an alternative, enalapril oral dispersible minitablets (ODMTs) have been developed in the context of the EU Framework Programme 7 labelling of enalapril from neonates up to adolescents (LENA) project. Compared to an oral liquid, such solid oral dosage forms have greater stability, easier transportation and storage, and allow accurate dosing without the need for a volumetric measuring device [115].

The solution is bioequivalent to original tablet formulations [35]. Enalapril ODMTs disperse in the mouth and have a slightly higher C_{max} but similar bioavailability to tablets [116]. These newer formulations thus offer practical possibilities for more accurate dosing in children [35,117]. In addition, ODMTs can be successfully administered through paediatric nasogastric tubes (Charrière 5) when dispersed in 1 ml tap water without causing obstruction [115]. The PK and safety of these enalapril ODMTs are currently being studied in children with heart failure [118].

When oral intake is undesirable, enalaprilat can be administered intravenously. This makes enalaprilat the only intravenous ACE inhibitor currently available, but availability of this intravenous (IV) formulation is limited from the global perspective, only

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including the United States, Canada, Germany, Poland, Czech Republic, Hungary and Ukraine. Moreover, its use is restricted to acute situations [119].

Discussion

In this review we have summarised the available PK and PD paediatric data. Although the efficacy of enalapril for the treatment of hypertension and proteinuria in CKD seems to be supported by several studies, the lack of a BP-lowering effect in African American children raises the limitation of these efficacy data of across ethnicities. Moreover, the evidence for its use in children with heart failure remains limited. It is important to realise that a positive effect of enalapril on heart failure parameters in children with different kinds of heart failure might exist, but the study designs used and the sample sizes of study populations were not sufficient to demonstrate these benefits. This problem was also addressed by Rossano *et al.*, who described differences between paediatric and adult heart failure populations [120]. Moreover, the potential impact of age-related variation on enalapril PK, as suggested by the limited PK data available, might further contribute to variation in observed efficacy of enalapril between young infants and adults. Only limited PK data are available, from 62 children in three studies, covering the paediatric age range from neonate to adolescent. These studies suggest that enalaprilat exposure might be lower in infants compared with older children and adults, but the data across the paediatric age range ($n = 60$), including neonates ($n = 2$), are too limited to draw any conclusions. If indeed young infants need higher mg/kg doses to reach similar exposure to adults, this might indicate that the lack of efficacy of enalapril observed in some studies, including these younger age ranges, might have been due to underdosing and not inefficacy of the drug.

Many years after approval of enalapril by the US Food and Drug Administration, large unexplained inter- and intraindividual variability in PK and PD exists, and the most prominent determinants of this variability remain to be established. Additionally, although some determinants of variations in enalapril PK were identified in the adult population, including the effect of hypertension [30], CHF [31,32], renal impairment [39], food [35] and race [63], these factors do definitely not account for all interindividual variability observed, let alone in the paediatric population.

Pharmacogenomics

Metabolomic and pharmacogenetic studies in children on ACE inhibitors might be promising for further understanding the observed variation. Pharmacogenomic analysis of patients on ACE inhibitor therapy has led to the discovery of new leads for explaining treatment responses. There are several genetic variants associated with ACE inhibitor effectiveness and safety, including mutations in *ACE* [121]. Also, because CES1 enzymatic activity has a key role in the conversion of enalapril to the active enalaprilat, the role of *CES1* gene variations was investigated. However, in healthy adults, variations of the *CES1* gene (the number of functional gene copies) did not have a clinically relevant impact on the metabolism of enalapril and could not explain the variability in effect [122]. This finding is not in accordance with previous published data, in which the AUC of another *CES1* substrate (methylphenidate) was markedly increased in individuals with four copies compared with carriers of only two copies of the gene, suggesting decreased metabolism [123]. The authors conclude that observed differences in the PK of enalapril must be explained by PK differences other than *CES1* genotype alone.

If, and to what extent, those genetic differences also contribute to the variability in outcomes observed in children needs further study. Pharmacogenomics in clinical paediatrics faces several challenges. For example, expression patterns of genes evolve during development and will therefore be different over time, which makes extrapolating adult data to paediatric clinical care challenging [124]. One study described the association of RAAS-upregulation genotypes with failure of reverse remodelling after superior cavopulmonary connection surgery, less improvement in renal function and impaired somatic growth [125]. This offers the possibility of defining a high-risk group of single ventricle patients who are at risk of therapy failure.

Metabolomics

Similar to pharmacogenetic profiling, metabolomics, the study of small organic molecules within biochemical pathways, has proven to be helpful to unravel part of the variability in observed disease and response to therapy in adult patients. For example, in adults with heart failure with preserved ejection fraction, a metabolomic approach has helped to reveal why the use of sildenafil was not beneficial in this group of patients [126]. Also, in patients with therapy-resistant hypertension, specific metabolite levels have been shown to predict future response to spironolactone [127]. Numerous metabolic alterations occur in the heart during adult heart failure, involving several metabolic pathways [128]. Some of these metabolites showed significant associations with BP in patients using ACE inhibitors and could therefore be of help in disentangling pathways that affect the response to ACE inhibitors [129].

The therapy of (paediatric) heart failure is still mostly based on targeting the downstream effects of heart failure instead of the underlying cause. Heart failure in children is predominantly based on genetic or inborn errors, contrary to adult heart failure, which is often acquired [130]. A small number of metabolomic studies has been conducted in the paediatric population, covering a variety of underlying (non-cardiac) diagnoses. In these studies, different metabolic profiles were identified in both healthy and diseased children, thereby offering the opportunity to identify biomarkers that have a diagnostic or therapeutic value [131–140].

To the best of our knowledge, no paediatric metabolomic studies have yet been conducted in patients on ACE inhibitor therapy. Unfortunately, adult findings cannot simply be extrapolated to children for multiple reasons. First, human serum metabolic profiles are age-dependent [141]. Second, paediatric heart failure differs from adult heart failure in many respects, including prevalence, aetiology, clinical manifestation and comorbidities. Third, maturation of the RAAS occurs in the first years of life, making the effect of ACE inhibitor therapy more complex and the extrapolation of data more prone to errors. Therefore, the metabolomic profile of children on ACE inhibitor therapy warrants further study.

Concluding remarks

In conclusion, a major information gap remains on the PK and PD of enalapril in children, especially in the youngest age groups, as well as for the indication heart failure. To offer children evidence-based enalapril therapy, further studies are needed to address these information gaps, including PK and PD studies such as the EU-funded LENA project [11,118].

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Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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