FACULTY OF PHARMACEUTICAL SCIENCES

REVIEW OF THE PHARMACOKINETICS AND ANTIHYPERTENSIVE EFFECTS OF ACE INHIBITORS IN CHILDREN WITH HYPERTENSION

A literature search from 1980 to 2018 investigating the study design, methodology and results of paediatric pharmacokinetic and pharmacodynamic studies of ACE inhibitors, including a comparison to study design and methodology of angiotensin-II receptor blockers.

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A Master dissertation for the study programme Master in Pharmaceutical Care

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INFLUENCE OF COVID-19

"*This master's thesis was executed in a period where corona measures have influenced research and education activities in various ways. These unusual circumstances may have had an impact on this thesis to a greater or lesser extent, despite all the efforts of the student, daily supervisor(s), and promoters. This generic preamble aims to frame this and was approved by the faculty.*"

SUMMARY

BACKGROUND: The prevalence of paediatric hypertension is high, estimated around 2 to 4%. In younger children (< 6 years), hypertension is most often secondary to underlying diseases, with the majority having renal pathology. The renin-angiotensin-aldosterone system is frequently activated in children having renal disease, being an ideal target for antihypertensive treatment. Therefore, angiotensin-converting enzyme (ACE) inhibitors and angiotensin-II receptor blockers (ARBs) are the most used antihypertensive drugs in children. In addition, both drugs have a nephroprotective effect. However, paediatric clinical studies are sparse due to the many challenges, such as difficult recruitment and limited number and volume of blood samples. Nevertheless, paediatric studies are necessary since children undergo constant developmental changes impacting both the pharmacokinetics (PK) and pharmacodynamics (PD) of a drug, making extrapolation from adult data difficult.

OBJECTIVES: The aim is to summarize what is known about studies focusing on PKPD of ACE inhibitors and ARBs in hypertensive children, informing future studies and thereby aiding drug approval in a vulnerable population. More paediatric labelling is necessary since currently more than 50% of the drugs in children are used off-label or unlicensed. In this master's thesis, the methodology, study design, and results of PKPD studies of ACE inhibitors in hypertensive children will be investigated, a comparison of study design and methodology between ACE inhibitors and ARBs will be examined and research gaps will be defined.

METHOD: Three different Boolean search strings were developed to thoroughly search PubMed for publications discussing the PKPD of ACE inhibitors and ARBs in the paediatric hypertensive population.

RESULTS: A total of 60 studies, of which 19 randomized controlled trials (RCTs), investigated the PK and/or PD of ACE inhibitors and ARBs in 3660 hypertensive children. The individual antihypertensive effects of ACE inhibitors could be verified in 8 of the 30 PD studies with a total of 77 patients. Of these 77 patients, 94.8% and 89.7% achieved a blood pressure (BP) decrease of ≥ 6 mmHg for systolic and diastolic BP, respectively. In addition, ACE inhibitors were generally well-tolerated and safe in the paediatric population concerning safety parameters and serious adverse events. Over the years, for both ACE inhibitors and ARBs, study design improved (more RCTs), especially with the introduction of multicentre studies.

CONCLUSION: The key for future research is standardisation of methodology and study results, for both PK and PD studies. For example, homogeneity in the reporting of BP decline must occur. In addition, investment in global, multicentre studies is needed in order to obtain more paediatric labelling. Lastly, several research gaps need to be covered by future studies.

SAMENVATTING

ACHTERGROND: De prevalentie van hypertensie bij kinderen is hoog en wordt geschat op 2 tot 4%. Bij jongere kinderen (< 6 jaar) is hypertensie meestal secundair aan onderliggende ziekten, waarbij de meerderheid een bepaalde nierpathologie heeft. Het renine-angiotensine-aldosteron systeem is vaak geactiveerd bij kinderen met nieraandoeningen, wat het een ideaal doelwit maakt voor antihypertensieve behandeling. Daarom zijn ACE inhibitoren en angiotensine-II-receptorblokkers (ARBs) de meest gebruikte antihypertensiva bij kinderen. Bovendien hebben beide geneesmiddelen een nefroprotectief effect. Echter, klinische pediatrische studies zijn schaars vanwege de vele uitdagingen, zoals moeilijke rekrutering en een beperkt aantal en volume van bloedstalen. Desondanks zijn pediatrische studies noodzakelijk omdat kinderen veranderingen ondergaan tijdens de ontwikkeling die zowel de farmacokinetiek (PK) als de farmacodynamiek (PD) van een geneesmiddel kunnen beïnvloeden, wat extrapolatie van gegevens vanuit volwassen studies moeilijk maakt.

DOELSTELLINGEN: Het doel is om samen te vatten wat er gekend is aangaande PKPD studies van ACE inhibitoren en ARBs bij kinderen met hypertensie, om zo toekomstige studies te informeren en de goedkeuring van geneesmiddelen in een kwetsbare populatie te bevorderen. Meer pediatrische indicaties zijn noodzakelijk aangezien momenteel meer dan 50% van de geneesmiddelen bij kinderen off-label of zonder vergunning worden gebruikt. In deze thesis zullen de methodologie, studieopzet en resultaten van PKPD studies van ACE inhibitoren bij hypertensieve kinderen worden onderzocht, zal een vergelijking van studieopzet en methodologie tussen ACE inhibitoren en ARBs worden uitgevoerd en zullen onderzoekshiaten worden gedefinieerd.

METHODE: Drie verschillende zoekreeksen werden ontwikkeld om PubMed grondig te doorzoeken op publicaties die de PKPD van ACE inhibitoren en ARBs in de pediatrische hypertensieve populatie bespreken.

RESULTATEN: Een totaal van 60 studies, waarvan 19 gerandomiseerde gecontroleerde trials (RCTs), onderzochten de PK en/of PD van ACE inhibitoren en ARBs bij 3660 hypertensieve kinderen. De individuele antihypertensieve effecten van ACE inhibitoren konden worden nagegaan in 8 van de 30 PD studies met een totaal van 77 patiënten. Van deze 77 patiënten bereikte 94.8% en 89.7% een bloeddruk (BD) daling van ≥ 6 mmHg voor de systolische en de diastolische BD, respectievelijk. Bovendien werden ACE inhibitoren in het algemeen goed verdragen en waren ze veilig in de pediatrische populatie wat betreft veiligheidsparameters en ernstige ongewenste bijwerkingen. In de loop der jaren is zowel van de ACE inhibitoren als de ARBs de studieopzet verbeterd (meer RCTs), vooral met de intrede van multicenter studies.

CONCLUSIE: Het belangrijkste voor toekomstig onderzoek is standaardisatie van methodologie en studie-resultaten, voor zowel PK als PD studies. Zo moet er bijvoorbeeld homogeniteit komen in de rapportering van BD-daling. Daarnaast moet worden geïnvesteerd in globale, multicenter studies om meer pediatrische indicaties te verkrijgen. Ten slotte moeten verschillende onderzoekshiaten door toekomstige studies worden opgevuld.

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TABLE OF CONTENTS

ABBREVIATIONS

ABPM	Ambulatory blood pressure monitoring
ACE	Angiotensin-converting enzyme
ADR	Adverse drug reaction
ARB	Angiotensin-II receptor blocker
AUC	Area under the concentration-time curve
BP	Blood pressure
BSA	Body surface area
CHMP	Committee for medicinal products for human use
CKD	Chronic kidney disease
CL	Clearance
C_{max}	Maximum plasma/serum/whole blood concentration
DBP	Diastolic blood pressure
eGFR	Estimated glomerular filtration rate
EMA	European medicines agency
FDA	Food and drug administration
GFR	Glomerular filtration rate
ICH	International council for harmonisation of technical requirements for pharmaceuticals for human use
KKS	Kallikrein-kinin system
LVH	Left ventricular hypertrophy
MA	Market authorisation
MeSH	Medical subject heading
PD	Pharmacodynamics
PIP	Paediatric investigation plan
PK	Pharmacokinetics
PKPD	Pharmacokinetics/pharmacodynamics
PPB	Plasma protein binding
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
RAAS	Renin-angiotensin-aldosterone system
RCT	Randomized controlled trial
RQ	Research question

SBP	Systolic blood pressure
SmPC	Summary of product characteristics
$t_{1/2}$	Elimination half-life
t_{max}	Time to reach C_{max}

1. INTRODUCTION

1.1. PAEDIATRIC DRUG RESEARCH

Drug research in the paediatric population is challenging, leading to fewer drug studies in children compared to adult ones. Only 16.7% of all clinical studies are conducted in children (1). Some of the challenges, making paediatric studies less attractive to sponsors, are the difficult recruitment of patients, ethical concerns (e.g. number and volume of blood samples), and the lack of age-appropriate formulations (2,3). However, paediatric drug studies are necessary due to inherent differences in these study populations (driven by anatomical and physiological developmental changes), affecting both the pharmacokinetics (PK) and pharmacodynamics (PD) of a drug (see 1.3.). Given the paucity of paediatric studies, a high-quality study design is critical to obtain dosing recommendations and to prove efficacy and safety of the studied drug, which is relevant with regards to paediatric labelling. More drugs with paediatric indications are needed since currently, more than 50% of the drugs in children are being used off-label or unlicensed (4–8).

In order to receive approval and licensing for a drug, the manufacturer must prove to authorities (e.g. the Food and Drug Administration (FDA) or European Medicines Agency (EMA)) that the drug is effective, safe and of good quality. Upon approval by the regulatory authorities, the drug receives Market Authorisation (MA), needed for manufacturing and marketing of the drug. Off-label drug use, meaning the drug is not used in accordance with the MA, includes among others use of a different dose, use of the drug for another indication, use of a different formulation or use when a contra-indication is present (9,10). Unlicensed drugs are drugs that are prescribed and taken in a country where it has not received approval by the national authorities (9). Consensus is that off-label and unlicensed drug use might be associated with therapeutic failure and safety issues, leading to adverse drug reactions (ADRs), due to possible inappropriate dosing and/or indication (4,9,11–14).

An incentive to encourage research in children was issued in 2007 when the EMA introduced the paediatric investigation plan (PIP). Since the appearance of the PIP, each drug that is under development in Europe must have an approved PIP, otherwise it can't receive MA (15). A PIP contains, among others, information about required paediatric clinical studies, the need and development of a child-friendly formulation, and the necessity of preclinical animal research (16). However, the EMA can give the company a waiver when the indication of the new drug is not applicable to the paediatric population, when the drug is likely to be ineffective or unsafe in children or when the new drug will not contribute to a significantly improved therapy compared to existing drugs (17). The PIP must be submitted to the Paediatric Committee, an expert panel at EMA, before completion of the phase I studies (adult PK). Once the PIP is approved by the Paediatric Committee, pharmaceutical

companies receive a 6-month patent extension as a reward for their extra efforts. When submitting to the EMA to obtain MA, the company must either include the results of the conducted paediatric studies in accordance with the PIP or the approval of the Paediatric Committee for a waiver or deferral. The latter makes it possible to postpone the paediatric studies until sufficient data are available from adult studies without having to withhold the drug from the market to be used by adults (16,18). For drugs approved before 2007 and aiming for paediatric indication, the 'paediatric use marketing authorisation', also requiring a PIP, was introduced (19). Despite the incentives to increase paediatric drug research, only 168 of the 1303 approved PIPs (12.9%) have been completed to date (July 22, 2021), which further emphasizes the difficulty of conducting paediatric clinical studies (20). Researchers realize that facilitating clinical studies in children will require a global, multicentre network, which led to the establishment of a few organisations such as 'conect 4 children' and 'I-ACT for children' (21,22).

1.2. PAEDIATRIC HYPERTENSION

1.2.1. Background

Hypertension in the paediatric population is a growing health problem. Different studies estimated the overall prevalence of hypertension in children and adolescents at 2-4%, which is therefore an important chronic disease when compared to other paediatric disorders (e.g. diabetes type 1 with a global prevalence of 0.2%) (23–27). In the last century, secondary hypertension (e.g. as a result of kidney problems or drug therapy) was the main type of hypertension, especially in the younger age categories (< 6 years old). However, in the past decade, a remarkable increase in essential or primary hypertension (no underlying disease) is notable. This substantial increase is mainly due to the increase of childhood obesity, which is a high-risk factor to develop primary hypertension. Not only lifestyle factors (e.g. unhealthy eating or lack of exercise), but also genetic elements may play an important role in the development of primary hypertension (28). Despite the increase in the rate of primary hypertension, the hypertensive paediatric population in Western-Europe remains dominated by secondary causes, with the vast majority having renal pathology (29). More important, paediatric hypertension often remains undiagnosed as most hypertensive patients are asymptomatic. A study conducted by *Hansen et al.* showed that 74% of the hypertensive children were undiagnosed and therefore not (adequately) treated (30). However, the consequences of untreated hypertension are not to be disregarded since it causes kidney damage and is correlated with a preordained development of hypertension and cardiovascular diseases in adulthood (31). To prevent missing the diagnosis of hypertension, new guidelines recommend measuring blood pressure (BP) annually in healthy children ≥ 3 years, but more frequently (at every clinical visit) in children having higher risk of developing hypertension (32). Moreover, children with confirmed hypertension are often inadequately treated due to a lack of appropriate paediatric drug studies (28,33).

1.2.2. Blood pressure classification and blood pressure measurement methods

Unlike adults, where a single BP value (140/90 mmHg) is used as a cut-off to diagnose hypertension, this is not an option for children since BP increases as a function of age, body size and gender (34). Therefore, paediatric hypertension is diagnosed using standardised BP reference tables of children without comorbidities and normally distributed for BP (31). An example can be found in **Figure 8.1, Appendix I**. Most recent guidelines recommend that a child's BP must be measured by auscultation on at least three separate visits before the diagnosis of hypertension can be made (32).

The American Academy of Paediatrics has made a classification of paediatric hypertension, as can be seen in **Table 1.1**. Hypertension for children aged < 13 years is defined as an average systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) equal to or greater than the 95th percentile for age, sex, and height whereas hypertension in children from 13 years on is defined as a BP of ≥ 130/80 mmHg (32).

Table 1.1: Classification of paediatric hypertension according to the American Academy of Paediatrics (32)

	Children aged 1 – < 13 years	**Children from 13 years on**
Normal BP	< 90th percentile	<120/<80 mmHg
Elevated BP	≥ 90th to < 95th percentile or between 120/80 mmHg and < 95th percentile (whichever is lower)	120-129/<80 mmHg
Stage 1 hypertension	≥ 95th but less than 95th percentile plus 12 mmHg or 130-139/80-89 mmHg (whichever is lower)	130-139/80-89 mmHg
Stage 2 hypertension	≥ 95th percentile plus 12 mmHg or ≥140/90 mmHg (whichever is lower)	≥140/90 mmHg

Although BP measured in the physician's practice should be used as a reference, the diagnosis of hypertension should be confirmed by an out-of-office method of BP measurement, such as ambulatory blood pressure monitoring (ABPM) or home BP measurement (34). Confirmation by these methods is necessary since children are more susceptible to white coat hypertension compared to adults, leading to a high number of false-positive results (35). Moreover, BP follows a circadian rhythm, so the measured BP depends on the time of the day. In all three BP measuring methods (auscultation, ABPM, or home BP measurement), use of the right cuff size is necessary, otherwise the result will be disrupted as stated by the European Society of Hypertension (34).

ABPM is considered the golden standard for children who can endure this form of BP measurement since it is a convenient way to measure phenomena that can't be measured in practice such as white coat hypertension,

or masked hypertension (normal BP in the office, high BP out-of-office). In addition, abnormal nocturnal dipping and isolated nocturnal hypertension, often seen in patients with secondary hypertension or type 1 diabetes, are also detected by means of ABPM (31,36–40). Recent data state that ABPM is more accurate than BP measured in the office (41). However, a few limitations should be taken into account considering the use of ABPM, e.g. inaccurate BP measurements during physical activity, inconvenience while sleeping, and its high cost (42).

1.2.3. Assessment of the aetiology of hypertension and evaluation of organ damage

Since hypertension can have multiple origins and can cause organ damage, these should be checked when hypertension is diagnosed in a child, as they will help to determine the appropriate treatment. Differentiating between primary and secondary hypertension requires a full clinical examination (including an ultrasound of the heart and kidneys), a blood test and a urine sample analysis (34). If no suspicious results emerge from the examination, primary hypertension, associated with risk factors such as obesity and high salt intake, is confirmed (31). Secondary hypertension is diagnosed when a particular cause can be derived from the investigations. The cause of secondary hypertension is for the vast majority due to renal parenchymal diseases (43). Moreover, about 50% of the children suffering from a chronic kidney disease (CKD) are hypertensive. The severity and progress of CKD can be predicted by (increased) proteinuria and the presence of hypertension (44). The evaluation of organ damage due to long-term elevated BP is performed by checking the heart, blood vessels, brain, eyes, and kidneys for abnormalities. Left ventricular hypertrophy (LVH), caused by elevated systemic BP, has a prevalence of 20-41% in hypertensive children and adolescents and is therefore a useful marker to assess organ damage. LVH is measured by means of an echocardiography and its presence often requires a faster and more intensive treatment of the hypertension (43,45,46).

1.2.4. Treatment of paediatric hypertension

1.2.4.1. General

In secondary hypertension, the focus primarily lays on treating the underlying disease, whereas in primary hypertension initial treatment consists of treating the risk factors resulting in the elevated BP. In general, a first consideration should be a non-pharmacological treatment (e.g. more physical activity, decreased intake of salt and weight management). Any pharmacological treatment is always associated with non-pharmacological advice, resulting in a more favourable cardiovascular risk profile. The different guidelines do not always agree on when to initiate a pharmacological treatment although in general, antihypertensive drugs are justified in case of symptomatic hypertension, secondary hypertension, organ damage, CKD, or diabetes mellitus (34).

1.2.4.2. Blood pressure target

The BP target after initiation of treatment (lifestyle changes and possibly antihypertensive drugs) varies depending on the presence or absence of kidney disease. According to the European Society of Hypertension, the BP target in the primary hypertensive population is set at a BP value < 95th percentile for age, sex, and height although they recommend that a value < 90th percentile would be wiser and safer. In the presence of underlying kidney disease, the BP target is lower: a BP value < 75th percentile in the absence of proteinuria and < 50th percentile in case of proteinuria (34). The ESCAPE trial group (2009) demonstrated the effect of an intensive BP control (BP < 50th percentile). To achieve the low BP target, additional antihypertensive drugs, not affecting the renin-angiotensin-aldosterone system (RAAS) (see 1.4.2.), were added to the angiotensin-converting enzyme (ACE) inhibitor ramipril. BP values < 50th percentile for 24 hours were associated with a better 5-year renal survival, even if proteinuria regained pre-treatment values. Regain of proteinuria is a very common phenomenon in children receiving ACE inhibitors for a long period of time. A possible explanation is 'aldosterone breakthrough', meaning chronic ACE inhibition causes other enzymes, such as chymase, to increase leading to production of angiotensin II which in turn provides aldosterone release. Elevated aldosterone levels may increase intravascular volume and glomerular filtration rate (GFR), resulting in a rise of proteinuria. Another possibility is the production of endothelin-1, which is a vasoactive compound leading to increased proteinuria. Lastly, progression of the underlying kidney disease may also cause an elevation in proteinuria (44).

1.2.4.3. Pharmacological treatment

The pharmacological options to lower the BP in children are the same as in adults, namely diuretics, calcium channel blockers, ß-blockers, ACE inhibitors and angiotensin-II receptor blockers (ARBs). *Meyers et al.* listed the antihypertensive drugs used in children for the treatment of chronic hypertension, including potential dose recommendations per age category, available formulations (with dosages) and availability for paediatric hypertensive indication (47). However, due to the lack of clinical data on the use of these antihypertensive drugs in children, physicians experience difficulties choosing the appropriate drug, dose (considering e.g. age and GFR) and dose regimen. The three drug classes mostly investigated for their use in paediatric patients are calcium channel blockers (in particular amlodipine), ACE inhibitors and ARBs (47). The meta-analysis of *Burrello et al.* included all available randomized, placebo-controlled studies using antihypertensive drugs in children and concluded that ACE inhibitors or ARBs should be the preferred treatment. Since data about other antihypertensive classes were sparse, this conclusion should be confirmed by other randomized controlled trials (RCTs), which are considered the best research method to evaluate a hypothesis (48).

Although the drug choice is difficult, some drugs are more appropriate in specific conditions than others. For example, ACE inhibitors and secondarily ARBs are the preferred treatment in children having renal disease, both in the presence and absence of proteinuria (34,47). Calcium channel blockers on the other hand are recommended if diabetes is an underlying disease since calcium channel blockers increase insulin sensitivity. ß-blockers, in contrast to antihypertensive prescribing in adults, are not often used in children because of the common side-effect 'bradycardia'. However, their use in children is appropriate in case of tachycardia and/or migraine. Also, diuretics are hardly used due to the lack of data in children and the presumption of a low effectiveness in monotherapy. ß-blockers and diuretics are therefore mostly used as an additional therapy and rarely in monotherapy for a hypertensive paediatric population. In general, physicians must take into account the patient's underlying disease(s), the safety/efficacy profile of the different drug options and any personal preferences to make a rational choice between the different antihypertensive classes and molecules. Besides appropriate drug selection, another problem is the lack of child-friendly formulations, often requiring manipulation of the drugs by pharmacists, leading to more medication errors due to inadequate drug preparation or unknown physical, chemical, and microbiological stability (46,47,49).

An initial drug is chosen considering the above and is administered to the child in the lowest dosage possible. Afterwards, the dose can be increased until the BP target is attained, or side effects occur. If the maximum dose is reached and the BP target is not yet attained, the physician can either add a second drug of a different class (combination therapy) or continue monotherapy but switch to a drug of another antihypertensive class (34,50).

1.2.4.4. Follow-up clinical visits

Once hypertension is diagnosed, long-term follow-up is required. During each visit, a clinical investigation is performed with special attention for organ damage and underlying diseases contributing to the development of secondary hypertension. If the child was placed on antihypertensive drugs, ADRs are closely monitored. The degree of proteinuria is another point of attention to monitor since it indicates the reno-protective effect of a drug (43). When the BP is under control, the physician should consider lowering the dose of the drug(s) stepwise and should evaluate the possibility to stop the pharmacological treatment (46).

1.3. PKPD IN CHILDREN

1.3.1. General

A well-known statement in paediatric pharmacology is: “children are not small adults”. Due to physiological and anatomical changes, which are consequences of the maturation and growth processes, both the PK profile and pharmacological effects of drugs in children may differ from adults (51,52). Therefore, an appropriately adjusted paediatric dose is necessary as extrapolation from an adult dose based on body weight, height, or body surface area (BSA) of the child can lead to therapeutic failure, ADRs or even death. However, since PK data of drugs in children are sparse, extrapolation from adult data is common practice (51–53).

1.3.2. Pharmacokinetics in children

The PK of drugs are influenced by several parameters which maturate as a function of the child's age: absorption, distribution, metabolism, and excretion. The major differences in PK are observed for children younger than 2 years of age with liver and kidney maturation having a great impact on the PK of drugs (see below), including ACE inhibitors and ARBs (51,52).

Multiple parameters influence drug **absorption**. Firstly, the gastric pH fluctuates until maturation at the age of 2 years, which has a consequence on the stability and the degree of drug ionization, influencing the drug's solubility (52). At birth, the gastric pH is neutral, then decreases until a pH of 3 to return to a neutral pH, and then eventually drops to mature levels (a pH of 1 to 2) (54–56). Secondly, children have a faster intestinal motility, implying that the amount of absorbed drug is lower (57). Thirdly, the processes of passive and active absorption only reach adult values after 4 months (58). Lastly, intestinal enzymes, breaking down medicines (e.g. CYP3A family), and transporters (e.g. P-glycoprotein), expulsing drugs out of the intestine wall, can negatively influence the absorption and bioavailability. However, data about their maturation are still insufficient so their influence on drug absorption is not completely known (59). In general, drug absorption is slower in neonates and infants compared to older children, extending the t_{max} (the time necessary to reach maximum plasma levels of the drug) (52).

The efficacy and the duration of effect of a drug are influenced by its **distribution** (51). Neonates and infants have a larger extracellular and total body water content in addition to a higher water/lipid ratio in their fat stores, resulting in a higher volume of distribution for hydrophilic drugs. Consequently, hydrophilic drugs must be given at a higher dosage (in mg/kg) to attain appropriate plasma and/or tissue concentrations (60,61). Contradictory, lipophilic drugs also have a greater volume of distribution, partially explained by the greater blood

flow to the liver and brain, which are fat-rich organs (52). The volume of distribution is also affected by the plasma protein binding (PPB), being the degree to which drugs attach to plasma proteins, but only if high PPB (> 95%) is present (51). In case of ACE inhibitors, the degree of PPB is highly dependent on the drug, ranging from negligible for lisinopril to 99% for fosinopril (62). For ARBs, the PPB varies between 90-99.9%, also depending on the type of molecule (63). Alterations in the amount of plasma proteins can therefore affect the distribution of the highly bound drugs. In very young children, less than 1 month of age, total plasma proteins are 86% of the adult value (51). Consequently, the free fraction of the drug and thus the volume of distribution will be higher, leading to a potentially greater PD-outcome since the free fraction is therapeutically active (51). The composition of the plasma proteins consists of albumin and α_1-acid glycoprotein (both present in a lower amount) and foetal albumin, having a lower affinity for weak acids. In addition, the presence of bilirubin and free fatty acids cause a drug to be displaced from albumin, providing a higher free fraction of the drug (52,64). Mature protein levels are reached at the age of 1 year (51).

The liver and kidneys play an important role in the elimination of drugs, characterized by drug **metabolism** and **excretion**. The liver enzymes, responsible for metabolizing drugs, must maturate after birth which may impact the rate of drug clearance (CL) (52). Higher plasma concentrations in younger children are therefore possible and could result in toxicity. Important to take into consideration is also that prodrugs (e.g. several ACE inhibitors and ARBs) will be converted more slowly into their active moiety, leading to an altered PK profile and delayed drug effects (52). The kidneys, mainly responsible for the excretion of unchanged drugs or metabolites, maturate quickly after birth. Renal function, expressed in terms of GFR, is about 2-4 mL/min/1.73m^2 in term neonates and increases rapidly to mature levels by the age of 1 year **(Figure 1.1)** (51,65). A commonly used formula to estimate GFR in children is the 'Schwartz formula' **(Equation 1.1)** (66). Since the kidneys in the newborn need maturation, an adjusted dose regimen is necessary for drugs that are primarily cleared renally (e.g. ACE inhibitors). This is of importance as a lower renal drug CL can lead to exposure to toxic drug levels (67).

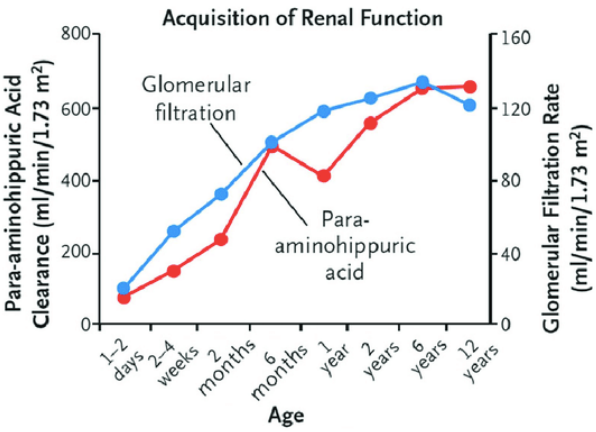

Figure 1.1: Maturation of renal function: GFR and para-aminohippuric acid clearance (reflecting renal blood flow) as a function of age (65)

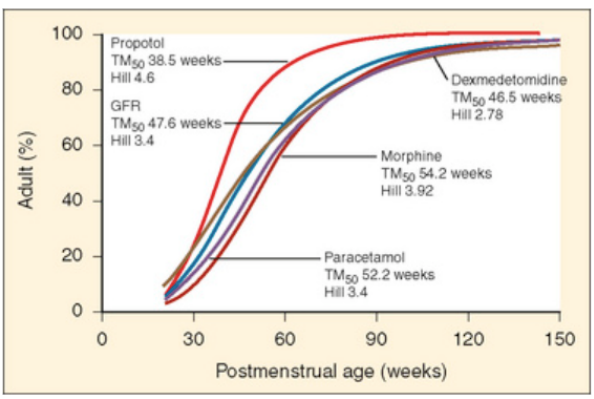

Figure 1.2: Maturation of drug clearance for several drugs, expressed as a percentage from adult value in function of postmenstrual age (68)

$$eGFR = kL/Scr \quad \text{(Equation 1.1)}$$

With: *eGFR* = estimated glomerular filtration rate (mL/min/1.73m^2)

k = 0.413

L = height (cm)

Scr = serum creatinine (mg/dL)

In general, drug CL, affected by the maturation of liver enzymes and the maturation of the kidneys, reaches adult values at the age of 2 years (150 weeks postmenstrual age) (Figure 1.2) (68).

1.3.3. Pharmacodynamics in children

PD is defined as "what the drug does to the body". The drug-receptor interaction can lead to the desired pharmacotherapeutic effects or ADRs. The response of a drug depends among others (e.g. receptor affinity, drug concentration at receptor site) on the relationship between concentration and effect. In a direct relationship, the response is directly linked to plasma concentration, whereas in an indirect relationship a time delay is present between plasma concentration and the response, called 'hysteresis'. A direct concentration-effect relationship can be easily detected, e.g. inhibition of ACE can be linked with plasma ACE inhibitor concentration. In contrast, an indirect relationship is sometimes difficult to investigate (e.g. pain relief as a function of plasma naproxen concentration) (69,70). Also, a difference between objective and subjective outcomes of drug response should be made. Objective outcomes (e.g. biomarker concentration in blood, BP measurement) are mostly easier to determine and are much more trustworthy compared to subjective outcomes (e.g. pain relief) which are difficult to monitor, especially in younger children (69).

1.4. ACE INHIBITORS AS AN ANTIHYPERTENSIVE TREATMENT

1.4.1. History

ACE inhibitors restore the balance between the RAAS and the kallikrein-kinin system (KKS), which play an important role in the development of hypertension (see 1.4.2.). The origin of these two systems can already be found in the late 19th century thanks to the work of several researchers, including Tigerstedt, Bergman and Bouchard (71,72). However, the enzyme 'ACE', playing a central role in both the RAAS and KKS, was not described until the 1950s. After the discovery of ACE, researchers were soon interested in developing inhibitors of the ACE enzyme due to the potential antihypertensive effects. In the 1960s, Sergio Ferreira extracted the first ACE

inhibitor from snake venom (72). *Laragh et al.* conducted the first clinical study in the United States, where 17 adult patients with primary hypertension received the first ACE inhibitor parenterally. Within the study, BP reduction was seen in 14 of the 17 patients, a remarkable result which led to the development of an oral formulation (73). Eventually, in the early 1980s, FDA approved the first orally active ACE inhibitor 'captopril' for the indication of primary hypertension in adults only (73).

1.4.2. Mechanism of action

The ACE enzyme can be found both in membrane-bound (e.g. in vascular endothelium) and soluble form (e.g. in blood) (71). Figure 1.3 explains the role of the ACE enzyme in the RAAS and KKS. The **RAAS** plays a central role in the regulation of BP. Renin is released from the juxtaglomerular unit of the kidney when the sympathetic nervous system is activated, when the perfusion pressure in the kidney is reduced, or when the kidneys detect a lower sodium concentration. Renin will in turn convert angiotensinogen (produced by the liver) to angiotensin I, which is inactive. Angiotensin I can be activated by cleavage using ACE, resulting in the production of angiotensin II. Through the interaction with AT_1-receptors, angiotensin II exerts 4 effects to increase BP, thereby preserving the filtering capacity of the kidneys (71):

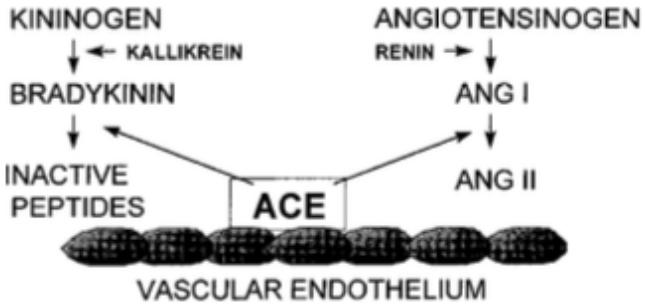

Figure 1.3: Kallikrein-kinin (left) and renin-angiotensin-aldosterone system (right); ANG I, angiotensin I; ANG II, angiotensin II (71)

1) A direct vasoconstrictive effect on the arteriolar smooth muscle tissue.
2) An increase of the sympathetic activity, resulting in a higher vascular muscle tone.
3) Augmentation of water and salt retention (with concurrent potassium excretion) via tubular salt reabsorption and through production of aldosterone by the adrenal glands.
4) Production of antidiuretic hormone by the pituitary gland, leading to an additional water retention.

In addition to the hypertensive effects, angiotensin II production also leads to hypertrophy of the kidneys (71).

Bradykinin, on the contrary, is generated from the **KKS** (Figure 1.3) and provides antihypertensive effects through increased natriuresis and through production of nitric oxide, having a vasodilatory effect. Bradykinin is inactivated by the action of ACE (71,74,75).

Figure 1.4 illustrates the site of action of ACE inhibitors (76). ACE inhibitors cause angiotensin II and bradykinin levels to return to balance. By blocking the ACE enzyme, less angiotensin II will be formed, causing a decrease in BP. In addition, bradykinin inactivation will be reduced, leading to an additional antihypertensive effect. Another consequence of the drop in angiotensin II level is the decrease in aldosterone secretion and the increase in plasma renin activity due to reduced negative feedback of angiotensin II on the renin secretion. Although ACE inhibitors and ARBs would be more effective in patients with high renin levels, efficacy has also been demonstrated in patients having low renin concentration (71,77,78).

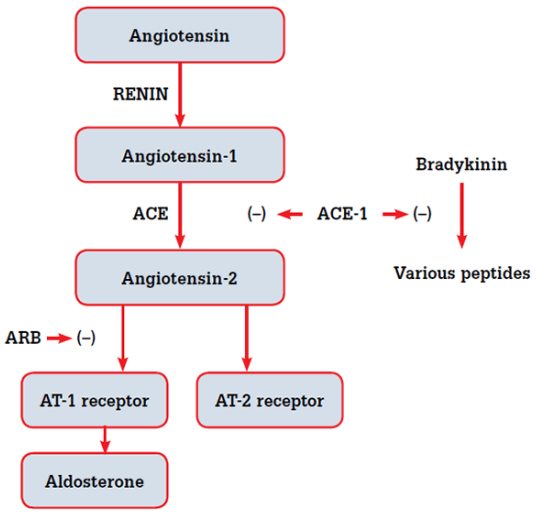

Figure 1.4: Site of action of ACE inhibitors (ACE-1) and ARBs on the RAAS (76)

1.4.3. Characteristics of ACE inhibitors

The first ACE inhibitors came on the market for the original indication of adult hypertension. Today, ACE inhibitors are prescribed for the treatment of hypertension, congestive heart failure, post-myocardial infarction and (non)diabetic nephropathy (71,79). In the paediatric population, ACE inhibitors are mostly used to treat primary or secondary (mostly due to CKD) hypertension, heart failure and nephropathies (80). CKD is classified into 5 stages according to eGFR (Table 1.2) (81):

Table 1.2: The 5 stages of CKD (81)

Stages of CKD	eGFR (mL/min/1.73m^2)
Stage 1	≥ 90
Stage 2	60 – 89
Stage 3	30 – 59
Stage 4	15 – 29
Stage 5	< 15 (end stage renal disease, dialysis need)

ACE inhibitors are divided into three different generations (Table 1.3) (82–85). With the exception of lisinopril and captopril, ACE inhibitors are prodrugs, implying that bioconversion by the liver into the active metabolite must occur first. In addition, dose reduction is required in case of decreased renal function since ACE inhibitors are mainly eliminated by the kidneys (71).

Table 1.3: **The different generations of ACE inhibitors**

	Characteristics	Examples
First generation	Presence of a sulfhydryl group	Captopril
Second generation	Non-sulfhydryl containing compounds	Enalapril, quinapril, lisinopril, ramipril
Third generation	Small lipophilic drugs with active carboxyl side group	Perindopril, zofenopril

The most frequent ADRs related to the use of ACE inhibitors are hypotension due to excessive drop in BP, dry cough, hyperkalaemia, and acute renal failure (71). However, long term use of an ACE inhibitor will provide a nephroprotective effect because of the reversal of glomerular hyperfiltration, thereby decreasing glomerular pressure, and eventually leading to a reduction in proteinuria. Since paediatric hypertension is often secondary to underlying renal pathology (usually associated with proteinuria), ACE inhibitors and secondarily ARBs are the most commonly prescribed drugs for hypertensive children (71,79,86). Due to the underlying renal pathology (varying eGFR), hyperkalaemia is the most feared ADR (87). A dry cough, hypothesized to be related to increased bradykinin levels, is a common side effect of ACE inhibitors. Although the prevalence in adults is estimated around 20%, the rate in children is substantially lower (3.2%) (71,86,88–90). Angioedema is another serious but rare side effect related to the use of ACE inhibitors with an estimated prevalence of 1 to 7 cases per 1000 patients (71,91). According to the review by *Snauwaert et al.*, the most reported ADRs of ACE inhibitors in the paediatric population are headache, dizziness, postural hypotension, and vertigo (86).

1.5. ANGIOTENSIN-II RECEPTOR BLOCKERS AS AN ANTIHYPERTENSIVE TREATMENT

1.5.1. History

Saralasin, a peptide angiotensin II analogue, was the first and most used compound tested in humans as a blocker of angiotensin II receptors. In a study conducted in 1979, saralasin lowered BP in adult hypertensive patients with high renin levels (92). Despite the promising results, the first angiotensin II antagonists had several shortcomings. The agents had to be administered intravenously since peptides are broken down in the gastrointestinal tract. Additionally, they only had a short hypotensive effect. Moreover, besides the antagonistic effect, an agonistic effect was also present, which caused BP to rise (93). In the next years, scientists searched for orally active compounds without these agonistic effects, which eventually succeeded in the late 1980s with the discovery of a new group of ARBs (nonpeptide imidazole derivates having a high affinity for AT_1-receptors). Losartan was the first orally active ARB clinically available for adults and was approved by the FDA in 1995, more than ten years after introduction of the first ACE inhibitor, captopril (78,93,94).

1.5.2. Mechanism of action

The ARBs have a unique mechanism of action since they attenuate the effects of angiotensin II by selectively blocking the AT_1-receptors (Figure 1.4). In addition to the formation of angiotensin II by ACE, other enzymes (e.g. chymase) can also convert angiotensin I to angiotensin II. By using ARBs, the effects of angiotensin II formed by these alternative pathways will also be inhibited, which is not the case with ACE inhibitor treatment. Since ARBs block the RAAS at its receptor level and thus block the effects of the produced angiotensin II, independent of the origin, ARBs exert a potentially greater BP lowering effect in comparison to ACE inhibitors (78).

1.5.3. Characteristics of ARBs

Despite the different mode of action, ARBs are used for the same indications as stated for ACE inhibitors, namely hypertension, heart failure, post-myocardial infarction, and (non)diabetic nephropathy (95). A major advantage of ARBs is the once-daily dosing for all the drugs within the class (96).

Since the ARBs consist of a variety of molecular structures, the binding affinity to the AT_1-receptors and the PK profiles of the different drugs within this class show a great diversity. ARBs are rapidly absorbed after oral administration, however, show a great difference in bioavailability between the drugs (13-80%) (63). ARBs have a high PPB (90-99.9%) and are mostly excreted in the faeces through bile (63). Only 2-33% is renally excreted, depending on the drug being used (63). Due to the lower extent of renal excretion in comparison to ACE inhibitors, dose adjustment in case of renal insufficiency is less of a concern (63).

ARBs and ACE inhibitors both act on the RAAS, so ADRs reported with ARBs are similar to those reported with ACE inhibitors, namely hypotension, hyperkalaemia, and increase of blood urea nitrogen and serum creatinine due to acute renal failure (78,96). The most common ADRs reported in paediatric studies investigating the effects of ARBs are headache, dizziness, and diarrhoea (78,96). Cough, rash, and angioedema however occur much less frequently with ARBs compared to ACE inhibitors. The lower reporting of these ADRs can be explained by the fact that ARBs do not interfere with the inactivation of bradykinin by ACE whose accumulation may be linked to the development of these specific ADRs (78,96).

Although ARBs have shown to be an effective and safe drug class, they are currently only used when ADRs such as cough or angioedema occur during treatment with an ACE inhibitor. Nevertheless, ARBs may result in fewer ADRs and would ensure a less pronounced regain of proteinuria (97). When using ARBs, aldosterone breakthrough, a potential cause for the reappearance of proteinuria (see 1.2.4.2.), will have fewer implications since the effects of the alternatively produced angiotensin II will be neutralized by blocking its receptors (44,97).

1.6. BIOANALYSIS METHOD

Blood samples are the most commonly collected samples in PK studies (98,99). A bioanalysis method is required to quantify the drug concentration and/or the concentration of their relevant metabolite(s). After the development and validation of the bioanalysis method, drug/metabolite concentration can be measured in different matrices, including blood. The collected (blood) samples must be stored correctly to assure stability of the analyte(s). The first step in the bioanalysis method is sample preparation, necessary to remove impurities that can interfere with the actual analysis and/or to concentrate the sample to enhance its detection. Extraction (e.g. liquid-liquid or solid phase), protein precipitation and ligand binding assays (e.g. antibodies) are some techniques used to purify samples (98,99).

Subsequently, analyte(s) quantification will be performed for which different techniques exist, e.g. radioimmunoassay and chromatography. In radioimmunoassay, a radiolabelled drug is bound to an antibody. Due to competitive binding, the drug present in the sample will displace the radiolabelled drug from the antibody, leading to a decreased radioactivity after the washing phase. The lower the radioactivity at the end, the higher the drug concentration in the sample (100). For chromatography, two different types are available for drug quantification, namely gas chromatography and (high performance) liquid chromatography. The principle is that the sample is separated into its various components by chromatography, which are then identified by a detector. Several detection methods are available, among others ultraviolet spectrophotometry, fluorescence, and mass spectrometry (100).

2. OBJECTIVES

Paediatric hypertension is a growing health problem that can cause kidney damage and is associated with the development of hypertension and cardiovascular diseases later in life (31). The prevalence of paediatric hypertension is estimated at 2-4% (23–26). Since lifestyle changes aren't always sufficient to control BP, clinicians must also rely on a pharmacological treatment. As renal pathologies are often involved in the development of paediatric hypertension, ACE inhibitors and ARBs are the most commonly prescribed antihypertensive drugs due to the activation of the RAAS in children having renal disease and the nephroprotective effect of ACE inhibitors and ARBs (28,29,47,79). However, information on dose and dose regimen is sparse due to the lack of paediatric studies as a result of the many challenges, such as difficult recruitment and limited number and limited volume of blood samples (2,3). Nevertheless, paediatric drug research is necessary because the constant developmental changes in anatomy and physiology of children impact the PKPD of drugs, making extrapolation from adult data difficult (see 1.3.) (51–53).

In this master's thesis, the aim is to summarize what is known about the paediatric studies focusing on PKPD of ACE inhibitors and ARBs in hypertensive children, hopefully informing future studies and consequently help increase drug approval in a vulnerable population. More paediatric labelling is necessary since currently more than 50% of the drugs in children are used off-label or unlicensed (4–7).

The main study objectives are:

1) What is known about the PK of ACE inhibitors in children?
2) What effect do ACE inhibitors have on lowering BP in children with hypertension? What are the characteristics of the studied populations?
3) What are the similarities and differences between ACE inhibitors and ARBs in hypertensive children in terms of study design and methodology?

To find an answer to these research questions (RQs), 3 different Boolean search strings will be developed, corresponding to the above study objectives, to thoroughly search PubMed for relevant literature.

3. METHODS

A descriptive review of the available PKPD studies regarding the use of ACE inhibitors and ARBs in hypertensive children was performed. Relevant articles, until June 16, 2021, have been collected by literature search in PubMed. To make it well-organized, three different search strings were developed, one for each RQ. The following medical subject headings (MeSH) were used in all three Booleans to cover the whole paediatric population: "infant, newborn" (first 28 days after birth), "infant" (1 to 23 months), "child, preschool" (2 to 5 years), "child" (6 to 12 years) and "adolescent" (12 to 18 years). Only the MeSH terms "infant", "child" and "adolescent" were included in the Booleans since the other MeSH terms are part of these three mentioned. The first selection of studies was based on their title/abstract, where irrelevant and/or non-English studies were excluded. The second selection was performed based on a full text analysis. Finally, the reference list of relevant articles was hand searched for other potentially relevant publications, referred to as 'hand picking'.

3.1. RQ 1: WHAT IS KNOWN ABOUT THE PK OF ACE INHIBITORS IN CHILDREN?

The following Boolean was used to search for relevant publications: (pharmacokinetics OR PK OR ADME OR "drug kinetics" OR popPK OR "population pharmacokinetics" OR PBPK) AND (ACE-inhibitors OR "ACE inhibitors" OR "kininase II inhibitors" OR "angiotensin converting enzyme inhibitors" OR lisinopril OR captopril OR enalapril OR quinapril OR fosinopril OR ramipril OR cilazapril OR perindopril OR zofenopril) AND (paediatric OR pediatric OR infant OR child OR children OR adolescent).

All ACE inhibitors currently available on the Belgian market were included. The search string (last reviewed on June 16th, 2021) resulted in **180 hits** ranging from 1978 to 2021. One additional publication was found by hand picking. After exclusion based on title/abstract, 27 articles were assessed for their eligibility by reading the full text. Adult trials and trials where PK parameters in children were lacking, were excluded. In the end, 9 articles were included for the qualitative analysis. The PRISMA flowchart can be found in **Appendix II, Figure 8.2**. To our knowledge, no publication has reviewed the available PK data of ACE inhibitors in the paediatric population.

3.2. RQ 2: WHAT EFFECT DO ACE INHIBITORS HAVE ON LOWERING BP IN CHILDREN WITH HYPERTENSION?

The Boolean for RQ 2 was the following: (pharmacodynamics OR "blood pressure" OR BP OR SBP OR DBP OR MAP OR SAP OR DAP) AND ("ACE inhibitors" OR lisinopril OR captopril OR ramipril OR enalapril OR fosinopril OR quinapril OR perindopril OR cilazapril OR zofenopril) AND (paediatric OR pediatric OR infant OR child OR children OR adolescent) AND (hypertension OR "high blood pressure").

As can be seen in **Figure 8.3 (Appendix III)**, the search string resulted in **904 hits** (June 16, 2021) with publications from 1979 to 2021. Next to irrelevant and/or non-English publications, case reports and case studies with less than 5 patients were excluded due to poor generalizability (they often describe serious, unique cases). 46 articles were assessed for their eligibility based on the full text. 14 publications were excluded, resulting in 32 included articles. The main reasons for excluding publications were no available BP data and wrong investigated population (no children or normotensive).

3.3. RQ 3: WHAT ARE THE SIMILARITIES AND DIFFERENCES BETWEEN ACE INHIBITORS AND ARBS IN HYPERTENSIVE CHILDREN IN TERMS OF STUDY DESIGN AND METHODOLOGY?

To form an answer to RQ 3, the following Boolean was used: (ARB OR "angiotensin receptor blocker" OR sartan OR sartans OR "angiotensin II type I receptor blocker" OR candesartan OR eprosartan OR irbesartan OR losartan OR olmesartan OR telmisartan OR valsartan) AND (paediatric OR pediatric OR infant OR child OR children OR adolescent) AND (hypertension OR "high blood pressure" OR SBP OR DBP OR MAP OR SAP OR DAP).

All ARBs currently available on the Belgian market were investigated. All PK and/or PD studies discussing the use of these ARBs in hypertensive children were included. The above Boolean yielded **673 hits** (June 16, 2021) with publications ranging from 1976 to 2021. Again, case reports and case studies discussing less than 5 patients were excluded due to poor generalizability. After exclusion of articles based on title/abstract, 45 publications were assessed based on their full text. Of the 45 articles, 20 were excluded, meaning 25 publications were eligible for the descriptive analysis. Main reasons for exclusion were no treatment with ARB, wrong population investigated and reviews of which the articles studied were already included in the review of this master's thesis. The PRISMA flowchart can be found in **Figure 8.4, Appendix IV**.

4. RESULTS

4.1. PK OF ACE INHIBITORS IN CHILDREN (RQ 1)

4.1.1. Methodology and study design

In the literature, 9 studies discussing the PK of ACE inhibitors were found with a cumulative total of 182 paediatric patients. Of those 9 studies, 44.4% (n=4) were sponsored by industry (101–104). The table summarizing the study setup can be found in **Appendix V, Table 8.1**. As can be seen in **Figure 4.1**, the publications range from 1983 to 2015 and are widely spread over time. PK data are available for captopril (3 studies), enalapril (3 studies), lisinopril (2 studies), and quinapril (1 study) (101–109). All patients were dosed in mg/kg and the used drug formulation was reported in 7 studies. In these 7 studies, the commercially available tablets were mostly reconstituted in an oral liquid form such as a suspension, solution, or syrup. Tablets were only administered to children from 6 years of age on.

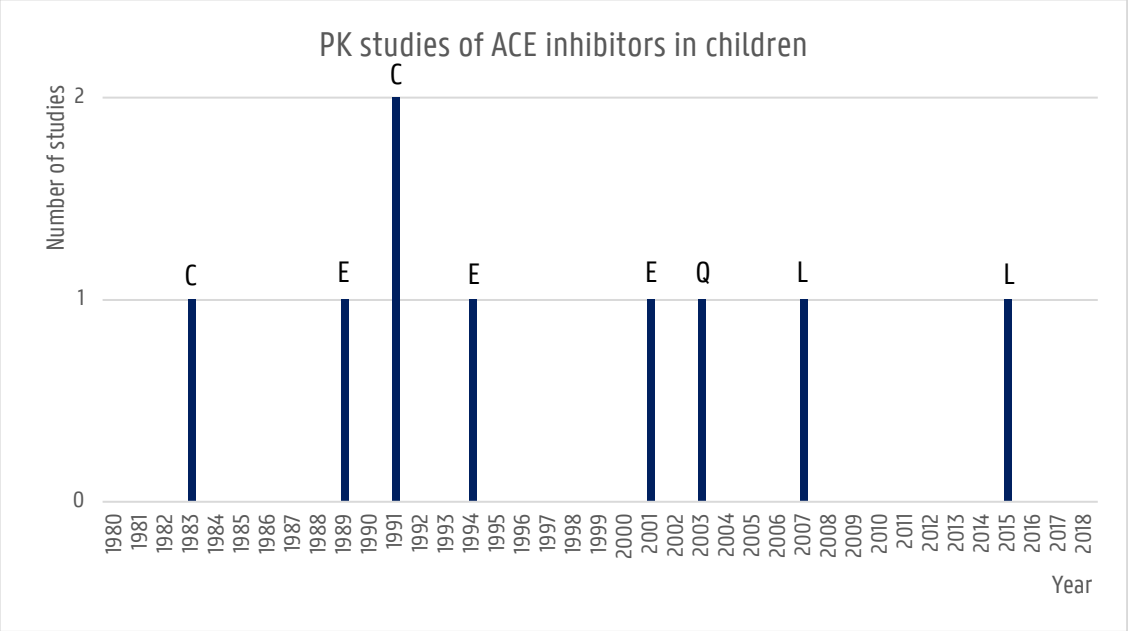

Figure 4.1: Distribution of the PK studies with ACE inhibitors in children; C = captopril, E = enalapril, Q = quinapril, L = lisinopril

First of all, the sample size was rather small, ranging from 8 to 46 patients with a mean of 20 patients per study. However, this is consistent with similar adult studies, so the low sample size of the included paediatric PK studies is probably due to the high cost rather than the difficult recruitment and limitations of blood sampling in children (110–113). The age of the participants ranged from 10 days to 20 years with all age groups well represented. Reporting of body weight lacked in one-third of the studies although this is important to determine as body weight has a consequence on the drug's PK. eGFR values were only available in 4 of the 9 studies, which

is regrettable to be excluded from the study results since ACE inhibitors are primarily cleared renally, requiring dose reduction in case of renal insufficiency (see 1.4.3). The eGFR reported ranged from 10 to 231 mL/min/1.73m^2 (mostly calculated by the Schwartz formula, **Equation 1.1**). Of the 182 patients, 15 patients (8.2%) had an eGFR < 60 mL/min/1.73m^2 of which 1 patient had stage 5, 3 patients had stage 4, and 11 patients had stage 3 CKD (104,105,108,109). In a total of 6 studies, patients having an eGFR < 30 mL/min/1.73m^2, having known renal impairment (not specified) or having a non-acceptable renal function (not specified) were excluded (102–104,107–109).

Secondly, 4 of the 9 studies were conducted in hypertensive children, accounting for 64.8% (n=118) of the total patients. In the studied hypertensive populations, at least 78.8% (n=93) had secondary hypertension and at least 14.4% (n=17) had primary hypertension, which is in line with the reported distribution of secondary and primary hypertension by *Raes et al.* (29,103,105,108,109). Of the 4 studies examining hypertensive patients, *Sinaiko et al.* and *Trachtman et al.* also included renal transplant recipients (105,109). In 3 of the 4 studies, severe (not defined) and/or symptomatic hypertension were excluded (103,108,109). Aside from the hypertension indication, 31.9% (n=58) of the total patients studied received an ACE inhibitor for the indication of congestive heart failure, congenital heart disease or renal scarring due to vesicoureteral reflux. Indication was unknown for the remaining 3.3% (n=6) of the patients (101,102,104,106,107). Concomitant drugs involved use of diuretics, antibiotics, digoxin, antimycotics, other antihypertensives, and immunosuppressants (in case of renal transplants). Only 1 study required patients not to take any comedication (101).

Thirdly, all studies were prospective and had an open-label design. Three of the 9 studies conducted PK analysis after a single dose of the ACE inhibitor (101,104,107). The single-dose PK study of *Nakamura et al.* was the only study incorporating a control group (7 healthy, normotensive males) (107). Two of the 9 studies made use of a titration protocol (102,105). The larger PK studies (4 studies with ≥ 22 patients per study) had a multicentre design (103,108,109), except the one by *Blumer et al.* (104). The latter has a unique study design since patients included in this study already took an ACE inhibitor as a chronic treatment. For one day, the normally administered ACE inhibitor was substituted for the study drug quinapril (104).

Last of all, study duration ranged from 1 day to a maximum of 12 months. Usually, the study duration was about 1 day to a few weeks.

4.1.2. Sampling regimen and bioanalysis method

The sampling regimen of the different paediatric studies can be found in **Table 8.2, Appendix V**. In all 9 studies, rich sampling (≥ 4 samples) was used, the number of samples ranging from 4 to 12 with a mean of 8 samples taken. Two studies had an adjusted sampling regimen if the children were aged < 4 years. Instead of 9 samples, only 5 or 6 were taken (103,108). Reasonably, a general trend of less sampling in younger children can be noted. The sampling regimen was taken on 1 (101,104–106,108,109), 2 (103), or 4 different occasions (102). Three of the 9 studies, accounting for 23.1% of the total population investigated, only performed sampling after the first dose of the ACE inhibitor (101,104,106). Three other studies (42.9% of the total population) just took samples at steady state (105,108,109). The 2 multi-occasion studies had sample collection after the first dose and at steady state (102,103). In the case of *Nakamura et al.*, the 12 patients had sampling after the initial dose, however, 2 of the 12 patients had additional samples taken after a minimum of 5 days taking enalapril (107).

The bioanalysis methods, used for measuring the ACE inhibitor concentration in the samples, are also listed in **Table 8.2, Appendix V**. The bioanalysis method used is related to the sample type collected from the patients. Serum, plasma, and whole blood samples were collected in case of radioimmunoassay, liquid chromatography, and gas chromatography, respectively.

4.1.3. Results of the PK analysis

The following PK parameters were incorporated: maximum plasma/serum/whole blood concentration (C_{max}), time to reach C_{max} (t_{max}), area under the concentration-time curve ($AUC_{0-\infty}$), elimination half-life ($t_{1/2}$), and drug CL. The values of the measured PK parameters in the paediatric studies can be found in **Table 8.3, Appendix V**. The results are described below per investigated ACE inhibitor.

4.1.3.1. Captopril

Three studies, published between 1983 and 1991 **(Figure 4.1)**, investigated the PK of captopril in a total of 24 patients. Patients' age ranged from 2 months to 20 years (101,105,106). Firstly, the t_{max} reported was similar across the 3 studies. Secondly, the study conducted by *Sinaiko et al.* proves that renal function does play a substantial role in the degree of drug exposure since $AUC_{0-\infty}$ doubled where drug CL lowered in patients having a lower creatinine CL (10-21 in comparison to 59 mL/min/1.73m^2). Thirdly, a higher drug CL and lower $AUC_{0-\infty}$ were noted in the patients of the study conducted by *Levy et al.* (renal scarring, however normotensive population, eGFR unknown) in comparison to those studied by *Sinaiko et al.*, despite equal age. The discrepancy in drug CL and $AUC_{0-\infty}$ may be due to the apparent renal disease present in the studied population of *Sinaiko et al.*, resulting

in low creatinine CLs of 10-21 mL/min/1.73m^2 and thus leading to lower drug CL and higher exposure (reflected by the higher $AUC_{0-\infty}$).

Lastly, looking at the study conducted by *Pereira et al.*, the reported C_{max}, $AUC_{0-\infty}$ and $t_{1/2}$ were higher and the drug CL was lower compared to those reported by *Levy et al.* An explanation for the anomalous results may be the age of the patients. *Pereira et al.* investigated the PK of captopril in infants and as mentioned in 1.3.2., the kidneys must maturate after birth before attaining their maximum filtering capacity. Therefore, renal function in infants is lower, resulting in a lower drug CL, leading to a higher $AUC_{0-\infty}$ and a longer $t_{1/2}$. The higher C_{max} may be explained by the higher dose used in the study conducted by *Pereira et al.* (1 mg/kg in comparison to 0.7 mg/kg used by *Levy et al.*).

4.1.3.2. Enalapril

The PK of enalapril was examined in a total of 62 patients across 3 studies, dated from 1989 to 2001 **(Figure 4.1)** (102,103,107). The age of the patients ranged from 10 days to 15 years. Firstly, C_{max} values of enalaprilat found in the study conducted by *Lloyd et al.* were substantially lower than those reported by *Wells et al.*, most likely due to the lower dosage used and the inclusion of a younger population in case of *Lloyd et al.* (6 weeks – 8 months). A younger population has immature metabolic enzymes (see 1.3.2.), resulting in a lower extent of bioconversion of enalapril to enalaprilat (reflected by the lower C_{max} values of enalaprilat). In addition, infants have a larger extracellular and total body water content (see 1.3.2.), leading to a higher volume of distribution for hydrophilic drugs such as enalaprilat, again resulting in lower serum concentrations (lower C_{max} values). Therefore, younger children may require a higher dose of prodrugs than older children to achieve a sufficiently high level of a drug's active moiety.

Secondly, statements about the patients aged < 20 days in the study by *Nakamura et al.* are difficult to interpret since the PK values were calculated based on 3 measurements in 2 patients. Comparing the adult values of enalaprilat to those of the patients > 20 days, a later t_{max}, a longer $t_{1/2}$ and a lower dose-adjusted C_{max} and $AUC_{0-\infty}$ can be observed in the paediatric patients. It may be possible that due to the presence of congestive heart failure in the paediatric patients, an inadequate absorption, distribution, and metabolism of the drug occurred, leading to a later t_{max}, and a lower dose-adjusted C_{max} and $AUC_{0-\infty}$ for enalaprilat. The observed longer $t_{1/2}$ may be explained by reduced blood flow to the kidneys due to the presence of heart failure, leading to a slower drug CL.

Finally, the youngest (1-24 months) and oldest (12-16 years) group in the study by *Wells et al.* showed divergent results for steady state enalaprilat compared to the two middle age groups. The youngest group had a lower dose-adjusted C_{max} and $AUC_{0-\infty}$, possibly due to immature metabolic enzymes and different body

composition (see above). The oldest group showed greater values for dose-adjusted C_{max} and $AUC_{0-\infty}$ because the mean dose administered was 0.07 mg/kg in comparison to 0.14, 0.13, and 0.11 mg/kg for the other age groups (young to old). Where the two youngest age groups received a suspension, the older children received tablets, making it difficult to dose in mg/kg.

4.1.3.3. Lisinopril

In total, 2 studies were found, published in 2007 and 2015 by *Hogg et al.* and *Trachtman et al.* **(Figure 4.1)**, examining the PK of lisinopril in a total of 68 patients (108,109). Firstly, the age of the children ranged from 6 months to 17 years and the t_{max} was similar across the 2 studies. Secondly, the two youngest (1 months – < 6 years) and the two oldest (6-16 years) groups of the study by *Hogg et al.* had similar C_{max} and $AUC_{0-\infty}$ values, however, C_{max} and $AUC_{0-\infty}$ values of the two oldest groups were twice those of the two youngest. The differences noted may be due to the way of drug administration, since administration of tablets (instead of a suspension) to the two older groups resulted in a higher mean dose, leading to higher C_{max} and $AUC_{0-\infty}$ values (108). Therefore, caution should be exercised when administering tablets to children, and introduction of child-friendly formulations to the market is desirable.

Thirdly, as mentioned before, a patient's eGFR plays a role in the degree of drug exposure. In the results obtained by *Trachtman et al.*, it can be noted that drug CL halved and $AUC_{0-\infty}$ doubled in the low eGFR group when compared to the high eGFR group. Fourthly, dose proportionality could be demonstrated in the study by *Trachtman et al.*, since doubling the dose (from 0.1 to 0.2 mg/kg) resulted in a doubling of both the $AUC_{0-\infty}$ and C_{max} while drug CL remained the same ($AUC_{0-\infty}$ = dose/CL). Therefore, drug CL is constant over the dose interval of 0.1-0.2 mg/kg and is not limited by e.g. transporter saturation in the kidneys (114).

Unfortunately, the two lisinopril studies are difficult to compare. However, it would be interesting for future research to examine whether the concomitant use of immunosuppressants (as in the *Trachtman et al.* study) would affect the absorption of lisinopril since ACE inhibitors are commonly administered to renal transplant recipients.

4.1.3.4. Quinapril

Only 1 study was performed with quinapril in 2003 **(Figure 4.1)** (104). Its PK was investigated in 24 patients, aging 2.5 months to 6.8 years. No other paediatric studies are available for comparison, although, the reported PK results were similar to those observed in adults (after a 10 mg dose of quinapril).

4.2. THE BP LOWERING EFFECTS OF ACE INHIBITORS IN HYPERTENSIVE CHILDREN (RQ 2)

4.2.1. Methodology and study design

A total of 30 studies (plus 2 continuations) discussed the antihypertensive effects of ACE inhibitors in hypertensive children. The table about the study setup can be found in **Appendix VI, Table 8.4**. As seen in **Figure 4.2** (page 25), publications range from 1980 to 2018 with no studies performed between 1992 and 2000. The studied ACE inhibitors were captopril (15 studies), enalapril or enalaprilat (7 studies), ramipril (4 studies), lisinopril (3 studies), and fosinopril (1 study) (29,33,44,105,109,115–141). Most studies (83.3%) used a weight-based dose regimen (dose in mg/kg or per weight category). In contrast, the 4 ramipril studies dosed according to BSA, and the dose used by *Miller et al.* was 2.5 – 30 mg (in accordance with adult doses) (44,129,136–139). Thirteen of the 30 studies reported their drug formulation, which included primarily (reconstituted) tablet use (84.6%). Intravenous administration was described in 2 studies (15.4%) (130,132).

The definition of hypertension was reported in 18 of the 30 studies (60.0%) and varied widely between studies. A total of 8 different definitions were used with 4 different percentiles as cut-off. The most reported definition was SBP and/or DBP higher than the 95th percentile (33.3%). Other definitions included the use of a lower or higher percentile as cut-off (ranging from the 75th to the 99th percentile) or the use of 24-hour SBP, DBP, or mean arterial pressure (27.8%).

A total of 1528 patients over the 30 studies, ranging from premature neonates to 20 years, received an ACE inhibitor treatment. At least 1156 patients (75.7%) had secondary hypertension, mostly having a renal cause (> 85%). Around two-thirds of the studies investigated ACE inhibitor use exclusively in children having secondary hypertension, which is in line with the vast majority of the indicated population in a clinical setting (29). In contrast, only 1 study (with 44 patients) examined the use of an ACE inhibitor (enalapril) in solely primary hypertensive children (134). The populations of the remaining 8 studies, accounting for 35.3% of the total population, consisted of both primary and secondary hypertensive children, with the proportions varying widely among the studies. To date, children having primary hypertension were included in 3 of the 9 available RCTs of ACE inhibitors (33,131,133).

The ACE inhibitors studied with their corresponding indications are listed in **Table 4.1**. Noticeably, the majority of the captopril studies (73.3%) consisted of a population with poor responsive, unresponsive, uncontrolled, severe, or refractory hypertension. In addition, captopril was the only ACE inhibitor studied for the treatment in these forms of hypertension (115–121,123–126).

Table 4.1: Indications of the ACE inhibitors studied in hypertensive children

ACE inhibitor studied	Number of studies	Publication year(s)	Total patients (age)	Indications	References
Captopril	15	1980-1992 + 1 additional study in 2018	284 (premature to 20 years)	Primary or secondary hypertension; secondary causes were renal pathology (mostly), umbilical artery catheterization, aortic coarctation repair, respiratory distress syndrome, bronchopulmonary dysplasia, and dexamethasone treatment	(105,115–128)
Enalapril	5	1987-2015	337 (6 weeks to 20 years)	Primary or secondary hypertension; secondary causes were renal pathology (mostly), umbilical artery catheterization, urologic disease, and aortic coarctation repair	(129,131,133–135)
Enalaprilat	2	1990-2003	16 (newborn to 13 years)	Newborns with primary or renal hypertension (n=10), hypertension after surgical repair of aorta coarctation (n=6)	(130,132)
Ramipril	4	2000-2009	451 (1.9 to 19.8 years)	Renal hypertension (n=447), primary hypertension (n=4)	(44,136–139)
Lisinopril	3	2003-2015	187 (0.2 to 17.6 years)	Primary or renal hypertension	(29,33,109)
Fosinopril	1	2004	253 (6 to 16 years)	Secondary hypertension or high-normal BP	(140,141)

eGFR and body weight were reported in less than 40% of the studies, in 7 (23.3%) and 11 (36.7%) studies, respectively. Due to > 60% missing values, eGFR and body weight were not included in the review of this master's thesis. However, some observations about the patient's renal function can be made. Firstly, despite more than 85% of the studied secondary hypertensive population having renal hypertension, only 61 patients (4.0%) had end stage renal disease (stage 5 CKD, requiring dialysis). All these 61 patients received captopril as ACE inhibitor treatment (105,115,117,120,121,123,124). Secondly, a total of 70 patients (4.6%) had a renal transplant, implicating a lower and/or varying renal function of these patients (105,109,115,117–122,129). Thirdly, in 5 studies (16.7%), patients with an eGFR < 30 mL/min/1.73m^2 were excluded, thereby excluding an important group of children who might benefit from an ACE inhibitor treatment since they are proven to have a nephroprotective effect (33,79,109,131,133,136). At last, in 10 of the 30 studies, nothing was reported about the patients' renal function (29,116,125–128,130,132,135,140,141).

As seen in Figure 4.2, 21 studies had an uncontrolled design being prospective or retrospective cohorts or case studies. The remaining 9 studies were RCTs with 4 of them having a prospective, open-label design (44,127,134,135,138). The studies conducted by *Morsi et al.*, *Assadi*, and *Di Salvo et al.* were active-controlled RCTs (type B design) (127,134,135,142). In the fourth study, the ESCAPE trial, patients were randomly assigned to either the conventional (50^{th}-95^{th} percentile) or the intensified (< 50^{th} percentile) BP control group. Introduction of the strict BP target led to a better 5-year renal survival (see 1.2.4.2.) (44,138). The other 5 RCTs had a prospective, double-blind design (33,131–133,140,141). Except the study by *Schaefer et al.* (type B design), all double-blind RCTs were placebo-controlled (142). In the study conducted by *Rouine-Rapp et al.*, patients were randomly assigned to either enalaprilat or placebo from the beginning of the study (type A design) (132,142). The other 3 double-blind RCTs had a type C design in which patients were initially randomized to a low, medium, or high dose of the drug. After 2 or 4 weeks of treatment, patients entered a 2-week placebo-controlled washout (33,131,140,141).

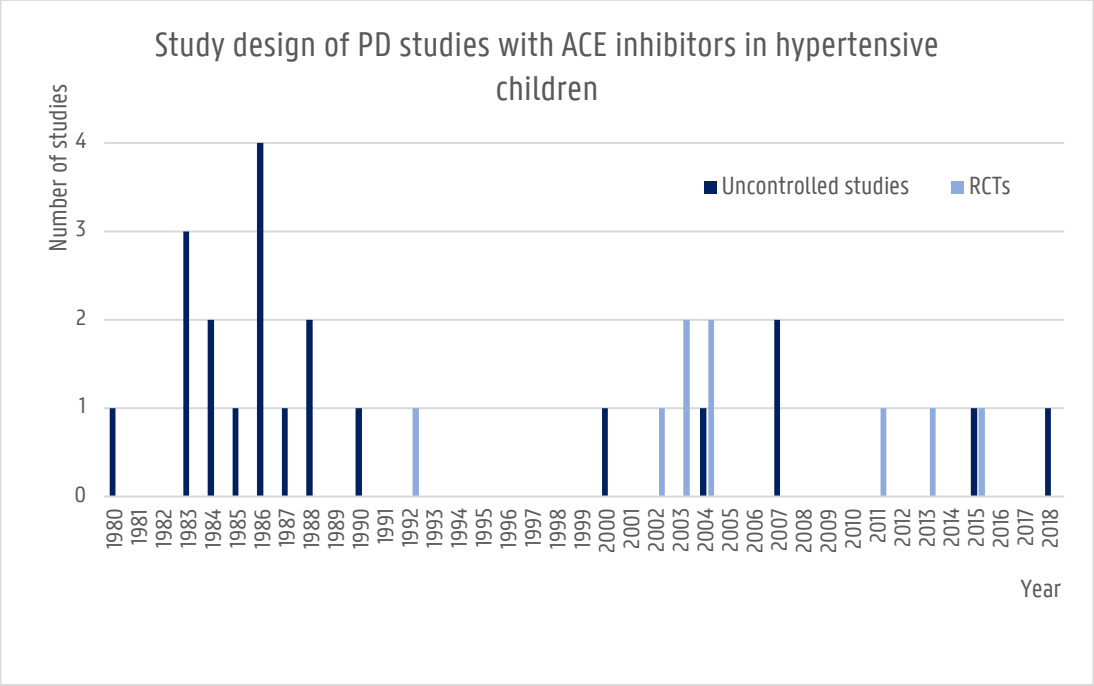

Figure 4.2: Distribution of uncontrolled studies and RCTs of PD studies with ACE inhibitors in hypertensive children

Sixteen of the 30 studies used a titration protocol, and 4 of the 30 studies were supported by industry (all being prospective, double-blind RCTs) (33,131,133,140,141). The studies all had an open-label design, except 5 who were double-blind, all RCTs (33,131–133,140,141). The study duration ranged from 36 hours to 6.1 years with most of the studies conducted over several months. Six studies had a study period of less than 1 month (109,126–128,130,132).

The BP measuring method was lacking in 12 studies (40.0%). The reported methods were mostly auscultatory or oscillometric by (automatic) monitors. 24h-ABPM was used in 6 studies with the first time in 2000 (44,133,135–139). All 4 ramipril studies used ABPM (44,136–139). As mentioned before (1.2.2.), recent data state that ABPM is more accurate than BP measured in the office (41).

4.2.2. Antihypertensive effects

The reported mean pre- and posttreatment BP values can be found in the same table **(Table 8.4, Appendix VI)**. Unfortunately, the studies all reported their BP decline differently, making it difficult to compare the results. To create uniformity, a clinical target was set in accordance with the study conducted by *Trachtman et al.* in 2015 (109). In adults, a decrease of 10 mmHg is considered clinically relevant since it is associated with a significant decrease in the risk of developing serious cardiovascular events (143). As children have lower values and smaller ranges of BP, a decrease of ≥ 6 mmHg was considered clinically relevant.

Individual BP values were reported in 8 of the 30 studies (26.7%) with a total of 77 patients. Of these 77 patients investigated, 94.8% and 89.7% achieved the clinical target (decrease of ≥ 6 mmHg) for SBP and DBP, respectively. For the remaining 22 studies, no individual BP data were available, and conversion of the results was out-of-scope for this master's thesis. However, in many studies, even in large ones like *Schaefer et al.* (133) and *Wühl et al.* (44,138), a decrease in mean BP of ≥ 6 mmHg was noted.

4.3. SAFETY PROFILE OF ACE INHIBITORS IN HYPERTENSIVE CHILDREN

The safety analysis **(Table 8.5, Appendix VII)** described results in line with the summary of product characteristics (SmPC) of the ACE inhibitors. Ten of the 37 studies reported a total of 14 serious adverse events. Hypotension with oliguria was the most frequent. In a few studies, the safety concern of serum potassium was reported, considering hyperkalaemia is a known side effect of ACE inhibitors. However, of the studies reporting the potassium change, the majority did not report a high count of hyperkalaemia. An exception was the study conducted by *Wühl et al.*, who included a high number of patients having a low eGFR (CKD stage 3 and 4) (44,138).

4.4. COMPARISON OF STUDY DESIGN AND METHODOLOGY OF PKPD STUDIES BETWEEN ACE INHIBITORS AND ARBS IN HYPERTENSIVE CHILDREN (RQ 3)

4.4.1. PKPD studies of ARBs in hypertensive children

In the literature, 6 studies discussed the PK of ARBs in hypertensive children. The study setup can be found in **Table 8.6, Appendix VIII**, and the used sampling regimen is summarized in **Table 8.7, Appendix VIII**. PK data is available for irbesartan, candesartan, valsartan, telmisartan, and olmesartan (144–149). A total of 22 PD studies (plus 1 continuation) investigated the antihypertensive effects of irbesartan, losartan, candesartan, valsartan, olmesartan, and telmisartan (133,144–146,148,150–167). Their study setup is listed in **Table 8.8, Appendix VIII**.

4.4.2. Comparison of study design and methodology between ACE inhibitors and ARBs

4.4.2.1. PK studies

Table 4.2 discusses the comparison of study design of paediatric PK studies between ACE inhibitors and ARBs. PK of ACE inhibitors was studied from 1983 to 2015, whereas for ARBs, studies were conducted in a more limited time range from 2001 to 2012. All PK studies, for both ACE inhibitors and ARBs, had a prospective, open-label design. However, some differences in study design can be noted. Firstly, PK substudies, where the PK analysis was performed in a subgroup of the population of a PD study, were more common with ARBs (4 of the 6 studies) compared to ACE inhibitors (2 of the 9 studies). Secondly, ARBs had more single-dose and less steady state PK studies in comparison to ACE inhibitors. Thirdly, inclusion of a control group or use of a titration protocol was no longer performed in the PK studies with ARBs. Fourthly, all ARB PK studies were supported by industry in contrast to the PK studies with ACE inhibitors, where 4 of the 9 studies were industry-driven. Finally, multicentre studies were standard practice with ARBs. However, the number of multicentre studies conducted with ACE inhibitors simultaneously increased, as all PK studies since 2001 had a multicentre design, except 1. In general, PK studies with ARBs had a more similar study design compared to ACE inhibitors.

Table 4.2: Comparison of study design of PK studies between ACE inhibitors and ARBs in children

Study design	ACE inhibitors (9 studies)	ARBs (6 studies)
PK substudy*	22.2%	66.7%
Single-dose PK	33.3%	66.7%
Steady state PK	55.5%	33.3%
Control group	11.1%	0.0%
Drug titration	22.2%	0.0%
Industry-driven	44.4%	100.0%
Multicentre	33.3%	100.0%

*PK analysis was performed in a subgroup of the population of a PD study

By comparing the methodology of PK studies between ACE inhibitors and ARBs, a few similarities and differences were found. The following similarities could be retrieved from the analysis:

- Most studies, for both ACE inhibitors and ARBs were initiated by the United States (66.7% and 83.3%, respectively).
- The exclusion criteria, concomitant drugs, and drug formulations used were comparable.
- The sampling regimen and the number of occasions it has been taken was similar, however, PK studies with ARBs were simpler since mostly PK samples were taken after a single dose of an ARB.

Despite the similarities, some remarkable differences in methodology between ACE inhibitors and ARBs should be noted:

- Sample size for ACE inhibitor studies ranged from 8 to 46 patients with a mean of 20 patients per study while for ARBs the sample size ranged from 10 to 48 patients with a mean of 26 patients per study. The larger mean sample size in ARB studies may be explained by their multicentre design (Table 4.2).
- The age range investigated with ACE inhibitors was 10 days to 20 years while with ARBs age ranged from 1 year to 17 years. PK data of ARBs in children < 1 year are completely lacking.
- The populations studied differed between ACE inhibitors and ARBs: the PK of ACE inhibitors was investigated in children with hypertension (mostly secondary, 78.8%), congestive heart failure, renal scarring due to vesicoureteral reflux, and congenital heart disease. In contrast, the PK of ACE inhibitors was only examined for their administration in children having primary or secondary hypertension.
- Four of the 9 studies with ACE inhibitors reported eGFR values (range or mean ± standard deviation). In contrast, no studies investigating the PK of ARBs reported eGFR.

4.4.2.2. PD studies

Table 4.3 compares the study design of the studies on the antihypertensive effects of ACE inhibitors and ARBs in children with hypertension. PD studies with ACE inhibitors were conducted between 1980 and 2018 while the antihypertensive effects of ARBs were studied from 2000 to 2018. Overall, for both ACE inhibitors and ARBs, a shift from uncontrolled studies (retrospective or prospective cohort and case studies) to RCTs was seen, especially noticeable for ACE inhibitors (Figure 4.2). As shown in Figure 4.3, the RCTs of ACE inhibitors and ARBs proceeded simultaneously but in proportion to uncontrolled studies, more RCTs were conducted with ARBs (Table 4.3). When comparing the design of RCTs, a higher rate of double-blind RCTs (more reliable) conducted with ARBs

is noted. In total, 19 RCTs were performed on the use of ACE inhibitors and ARBs in hypertensive children, mostly having a type B (8) or type C (8) design. The remaining 3 RCTs had a type A design.

The proportion of use of a titration protocol in PD studies was similar between ACE inhibitors and ARBs (about 50% of the studies). In contrast, PD studies with ARBs were substantially more likely to have a double-blind, industry-driven, and/or multicentre design. However, in the past 20 years, PD studies with ACE inhibitors also more frequently had a multicentre design with 4 of the 5 multicentre studies being double-blind RCTs. The industry was most likely to support multicentre, double-blind RCTs. But, unlike all industry-driven PD studies with ACE inhibitors being multicentre, double-blind RCTs, the industry also invested in ARB studies having a prospective and retrospective cohort design (5 studies) in addition to multicentre, double-blind RCTs (9 studies). In general, study design of the PD studies improved (more RCTs) with the introduction of multicentre studies since 13 of the 18 studies (72.2%) having a multicentre design were RCTs.

Table 4.3: Comparison of study design of PD studies between ACE inhibitors and ARBs in hypertensive children

Study design	ACE inhibitors (30 studies)	ARBs (22 studies)
Uncontrolled studies	70.0%	54.5%
RCTs	30.0%	45.5%
Open-label	44.4% (type B design)	10.0% (type B design)
Double-blind	55.6% (1 type A, 1 type B, and 3 type C design)	90.0% (2 type A, 2 type B, and 5 type C design)
Ratio uncontrolled studies:RCTs	7:3	6:5
Drug titration	53.5%	45.5%
Industry-driven	13.3%	63.6%
Blinding		
Open-label	83.3%	54.5%
Double-blind	16.7%	45.5%
Multicentre	16.7%	59.1%

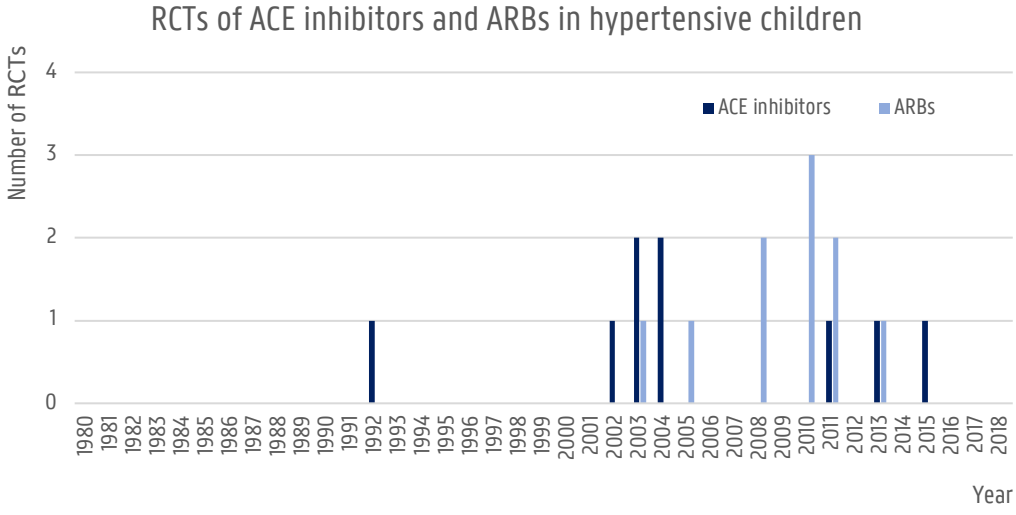

Figure 4.3: RCTs of ACE inhibitors and ARBs in hypertensive children

The comparison of methodology of PD studies between ACE inhibitors and ARBs in hypertensive children resulted in several similarities and differences. The following similarities were noted:

- Most of the studies, for both ACE inhibitors and ARBs, were initiated from the United States (53.3% and 45.5% respectively).
- Exclusion criteria and drug formulation used were similar between studies with ACE inhibitors and ARBs.

In addition to the similarities, many differences could also be retrieved from the analysis of methodology:

- Four of the 30 studies conducted with ACE inhibitors used a dose based on the BSA of the child while this type of dosing was no longer used in studies with ARBs.
- Definition of hypertension was reported in 18 of the 30 studies (60.0%) with ACE inhibitors with a total of 8 different definitions and 4 different percentiles as a cut-off. In contrast, the definition of hypertension in studies with ARBs was reported in 21 of the 22 studies (95.5%) with a total of 4 different definitions (no ABPM) but all using the 95th percentile as the cut-off.
- The total number of patients treated with ACE inhibitors was 1528 with a mean of 51 patients per study, while the total number of patients receiving ARBs was 1996 with a mean of 91 patients per study. The larger mean sample size for studies conducted with ARBs may be explained by the higher percentage of multicentre studies (Table 4.3).
- The age of the children in the studies with ACE inhibitors ranged from premature neonates to 20 years with 11 of the 30 studies (36.7%) including patients < 1 year while with ARBs, age ranged from 0.5 to 18 years with only 2 of the 22 studies (9.1%) including patients < 1 year.
- The focus of studies with ARBs remains mainly on secondary (specifically renal) hypertension, although, 50.0% of the studies were conducted in a mixed (primary and secondary) hypertensive population in contrast to 26.6% of the studies with ACE inhibitors. Two large studies with an ARB (accounting for 27.2% of the total population) were conducted within a mainly primary hypertensive population. Overall, ARBs have already been studied in more people having primary hypertension compared to ACE inhibitors.
- More studies with ARBs have been examined in a population consisting exclusively of children with CKD, however, fewer children had end stage renal disease compared to the CKD patients examined with ACE inhibitors.
- In contrast to the low reporting of eGFR in studies with ACE inhibitors (23.3%), half of the studies with ARBs reported a mean or range of eGFR of the patients.
- Among the studies with ACE inhibitors, 6 of the 30 studies (20.0%) used ABPM against 1 of the 22 studies (4.5%) using ABPM in the ARB studies.

5. DISCUSSION

5.1. PK OF ACE INHIBITORS IN CHILDREN (RQ 1)

Paediatric PK studies were available for captopril, enalapril, quinapril, and lisinopril. However, these studies were often conducted 20 or more years ago, except for the quinapril study and the lisinopril studies (most recent, see Figure 4.1). Of these drugs, lisinopril is currently often prescribed in a paediatric clinical setting.

The sample sizes were in line with similar PK studies performed in adults, with a mean of 20 paediatric patients per study. However, the paediatric PK studies sometimes divided their study population according to different age groups due to the differences in PK. This division resulted for some studies in age groups containing only 2 or 3 subjects making the obtained PK data from these small subgroups not reliable and generalizable for the defined age group (107,109). Even though challenging in practice, having sufficient inclusions per age group is highly recommended in order to have sufficient power of the study, to obtain a good precision of the estimates and to improve applicability of the results (168).

The number of samples, sampling volume, and inconveniences related to traditional blood sampling methods are often a concern to ethic committees, older children, and parents of the children. Therefore, microsampling may offer a solution to recruit more patients for paediatric and even adult PK studies. Microsampling is becoming increasingly popular because very small volumes of blood (< 100 µL) can be collected and analysed in a less invasive manner. In addition, these novel techniques are more cost-effective, less painful, less stressful, and the samples are easier to handle and store in comparison to traditional blood samples. Many techniques can be used for microsampling (e.g. dried blood spots, volumetric absorptive microsampling), however, each technique has its advantages and shortcomings, and their application in the paediatric setting needs to be investigated further by future research (169).

To date, only 1 of the 9 available paediatric PK studies with ACE inhibitors has required its patients not to take any concomitant drugs. However, some drugs used concomitantly may have caused drug-drug interactions with the ACE inhibitor being studied, potentially leading to an altered PK of the ACE inhibitor, making the results of the studies unreliable. For example, the concomitant use of diuretics in several studies may have provided an increase in the CL of the ACE inhibitor investigated. Therefore, researchers performing paediatric PK studies should consider investigating children who are not taking other drugs or must screen the children's drug list for the absence of drug-drug interactions.

The PK study by *Blumer et al.* had a unique study design since for one day, the normally administered ACE inhibitor was replaced by the ACE inhibitor quinapril (the study drug). This type of study design has 4 benefits. Firstly, since the study drug is administered to patients already taking ACE inhibitors as a chronic treatment, increased knowledge about ACE inhibitors in the population is valuable. Secondly, fewer safety risks are involved, as ACE inhibitors have already proven to be well-tolerated. Thirdly, generalizability to clinical practice is not a problem since the ACE inhibitor is administered to patients requiring one. The fourth benefit is the ease with which informed consent and recruitment are obtained since parents are already familiar with the use of ACE inhibitors (104). In conclusion, because of the many advantages (e.g. higher sample size) associated with this design, implementation of such a design may be interesting for future PK studies. However, application of this design in PD studies is not recommended as no washout period between the ACE inhibitors is present. Therefore, the obtained PD effects may originate from the intake of the chronic ACE inhibitor instead of from the administration of the study drug (e.g. quinapril). Consequently, inclusion of a washout period between antihypertensive drugs and inclusion of non-naive ACE inhibitor patients is advised for PD studies.

The sampling regimen **(Table 8.2, Appendix V)** varied widely among the different studies with the number of samples ranging from 4 to 12 with a mean of 8 samples over a period of maximum 24 hours. Therefore, the sampling is neither too rich nor too sparse. However, the application of microsampling may potentially provide a richer sampling, allowing a more detailed concentration-time curve to be generated, making the derived PK parameters more precise. Microsampling has already been often used in paediatric PK studies with antibiotics. However, the review by *Dorofaeff et al.* stated that the microsampling and the bioanalysis method first require validation in the paediatric population before microsampling can be widely applied in PK studies investigating antibiotics (170). Validation is also needed before applying microsampling in PK studies with ACE inhibitors, as to date no paediatric PK studies with ACE inhibitors assessed the use of microsampling.

Besides the varying sampling regimen, the reported PK parameters **(Table 8.3, Appendix V)** were often mean values of a population with a wide age range, resulting in the reported standard deviations being very high, possibly due to large inter-individual variability or outliers. Therefore, a standardised protocol per ACE inhibitor, including dose of the drug (adjusted to the patient's age and renal function), dose regimen, drug formulation, sampling regimen, bioanalysis method etc., would be interesting. In addition, the study population should be divided into different age categories (e.g. according to **Table 5.1**) since the PK differs among different age groups as seen by the reported PK values of the study by *Wells et al.* (103). Unfortunately, no paediatric PK study has investigated the use of a standardised protocol to date. However, the introduction of a standardised protocol

would allow the different PK studies of a drug to be more comparable, thereby facilitating the examination of the effects of different population characteristics (e.g. eGFR, pathology) on a drug's PK.

Table 5.1: **Age classification to be used in paediatric PK studies according to the ICH and CHMP guidelines** (171)

Age category	Age
Preterm and term newborn infants	0 – 27 days
Infants and toddlers	28 days – 23 months
Children	2 – 11 years
Adolescents	12 – 17 years

As the children's age or pathology (e.g. heart failure, liver pathology) may alter the absorption phase of a drug (see 1.3.2. and results obtained by *Nakamura et al.*), inclusion of an intravenous cohort on top of oral intake may be interesting (107). By including an additional intravenous cohort, a better view of the absorption phase and bioavailability of the investigated drug can be obtained.

The two studies administering tablets to children ≥ 6 years of age and a suspension to children < 6 years of age both reported varying PK parameters due to the way of drug administration (103,108). Logically, dosing in mg/kg with tablets is much more difficult compared to a suspension. Therefore, underdosing or overdosing may occur if tablets are administered to children due to the limited dosages available. However, unfortunately, no child-friendly formulations of ACE inhibitors are on the market in Belgium so far, leading to manipulation of the tablets by pharmacists to make the drugs accessible to young children, resulting in more medication errors (see 1.2.4.3.). Therefore, the development and commercialisation of child-friendly formulations are needed. Capsules may be an adequate drug formulation since they are accessible to both children who can swallow capsules and children who can't. For children having difficulties to swallow capsules, the content can be sprinkled on e.g. the child's tongue or food. Therefore, the powder in the capsules should be palatable to children. In a study by *Zgraggen et al.*, 20 healthy volunteers (paediatric medical officers and paediatricians) had to classify 7 different antihypertensive drugs, including 3 ACE inhibitors, according to palatability. The different drugs were administered by sprinkling the content of a capsule (crushed tablets) into the oral cavity of the volunteers. The study showed superior taste for lisinopril compared to enalapril and ramipril. Despite the impression that palatability preferences of crushed drugs would be similar for children and their caregivers, an investigation on the palatability of crushed antihypertensive drugs in a paediatric population is appropriate (172).

5.2. THE BP LOWERING EFFECTS OF ACE INHIBITORS IN HYPERTENSIVE CHILDREN (RQ 2)

Paediatric PD studies were available for captopril, enalapril, enalaprilat, ramipril, lisinopril, and fosinopril with the most recent studies investigating lisinopril and enalapril.

The 4 ramipril studies, as opposed to the other studies, based dosing on the BSA of the child (mg/m^2). In clinical practice, an adult dose is sometimes extrapolated to a paediatric dose based on the BSA because studies have shown that BSA is proportional to metabolic processes in the body. In addition, renal function can also be normalized using BSA. Therefore, extrapolating the dose based on BSA is thought to normalize drug concentrations (173–175). However, paediatric dosing based on BSA has some disadvantages. Firstly, the calculation of the child's BSA is difficult since the developed formulas are not so accurate, especially if the child is obese or very thin (174). Secondly, since a BSA-based dose assumes that PK parameters change in proportion to BSA, such a dose is not recommended for children under the age of approximately 2 years since in young children, several factors must be considered besides the size of the child when looking at PK (173,174). As mentioned in 1.3.2., maturation of metabolic enzymes and kidney function must occur in neonates and infants, causing overdosing if dosed based on BSA (173,174). Therefore, the formulas to calculate a child's BSA will require further improvement before the calculation of a paediatric dose based on BSA will become standard practice. In addition, for children < 2 years, a special formula for BSA calculation must be developed taking into account the renal and metabolic maturation. Dosing based on the child's body weight thus seems to be the most appropriate way to date.

A retrospective design was present in 4 of the 30 PD studies (29,121,125,130). However, a retrospective design has some limitations. Missing data may be present, resulting in a decrease of statistical power, a decrease in representativeness, and bias of the estimates. In addition, retrospective studies are susceptible to unknown confounders and various types of bias (e.g. recall bias) which cannot always be accounted for in the study analysis. Each of these disruptions may lead to invalid study conclusions (176,177). Due to the limitations of a retrospective design, future studies should preferably have prospective data collection.

As mentioned before, lisinopril is currently often prescribed in a paediatric clinical setting. However, to date, only one RCT (by *Soffer et al.*, 2003) has been conducted on lisinopril in a hypertensive population aged 6-16 years (33). In the study, a dose-response relationship could be demonstrated which is not always the case for studies having such a design (see 5.4.). Since a dose-response relationship was proven, a dose recommendation could be made, namely a starting dose of 2.5 mg for children < 50 kg and 5 mg for children ≥ 50 kg (with a mean of 0.07 mg/kg), which could be increased to a maximum of 40 mg (0.61 mg/kg) (33). Unfortunately, the number

of patients achieving the BP target (< 95th percentile) was not reported. Since lisinopril is commonly prescribed, RCTs examining the use of lisinopril in other populations (e.g. children < 6 years of age, children with CKD stage 4 and 5) are recommended.

Due to the heterogeneity of the studies in the reporting of BP decline, a direct comparison of the obtained results was not feasible. Therefore, an arbitrary clinical target (a decrease in BP of ≥ 6 mmHg), in accordance with the *Trachtman et al.* study, was set to make the results of the different studies more comparable (109). Verification whether the clinical target was achieved at an individual level was possible for 8 of the 30 studies (with a total of 77 patients). Of the 77 patients, 94.8% and 89.7% achieved the clinical target for SBP and DBP, respectively. For the remaining studies where individual BP values were unavailable, a decrease of ≥ 6 mmHg in mean BP was usually noted textually. However, a BP decrease of 6 mmHg may not be clinically relevant for all hypertensive children, e.g. severe hypertension. Therefore, investigators should use the standardised BP tables **(e.g. Table 8.1, Appendix I)** to determine whether the child's observed BP decrease is clinically relevant (achievement of BP target).

It was noted that BP reporting in the studies was often inappropriate. The studies where BP values were available all reported their BP as a mean value of the whole (sub)population, which usually included a wide age range. As mentioned before (see 1.2.2.), BP in children increases as a function of age, size, and gender. Therefore, percentiles rather than BP values are used for the classification of paediatric hypertension. However, the American Academy of Paediatrics recently (in 2017) updated their guidelines where, unlike the previous guidelines, BP values instead of percentiles are used for children 13 years and older **(Table 1.1)**. For further research, homogeneous reporting of BP decline for studies investigating the antihypertensive effects of drugs in children is necessary. Otherwise, determination of the preferable antihypertensive drug for a given population will not be possible. Ideally, studies should report how many of the patients reach their BP target (a percentile, see 1.2.4.2.). In addition, the primary endpoint of studies is preferably the decrease in DBP rather than SBP, since DBP exhibits less intra-patient variability (178).

The available studies on the antihypertensive effects of ACE inhibitors in children were previously reviewed by *Snauwaert et al.* (86). However, in this review only 16 studies, as opposed to 30 studies in this master's thesis, were included making the obtained results of *Snauwaert et al.* less complete. In this master's thesis, additional studies were found for captopril (8), enalapril (3), enalaprilat (2) and ramipril (1) of which 4 RCTs. Probably, the additional studies were missed by the rather limited search method used by *Snauwaert et al.* since only search

terms were used instead of a Boolean search string as in this master's thesis. Surprisingly, nothing was mentioned about the way BP was reported by the studies.

5.3. SAFETY PROFILE OF ACE INHIBITORS IN CHILDREN

Given the low number of reported serious adverse events and cases of hyperkalaemia, ACE inhibitors can be considered a well-tolerated and safe drug class in a hypertensive paediatric population (at least in the short term), which is in line with the review conducted by *Snauwaert et al.* (86). However, monitoring of serious adverse events and serum potassium remain necessary since ACE inhibitors are predominantly administered to children having renal pathology (varying eGFR).

5.4. COMPARISON OF STUDY DESIGN AND METHODOLOGY BETWEEN ACE INHIBITORS AND ARBS IN HYPERTENSIVE CHILDREN (RQ 3)

Of the 60 studies included in this review, 32 studies were initiated in the United States (53.3%). A possible explanation for the high degree of studies conducted in the United States, is the presence of more large pharmaceutical companies who can support paediatric research. However, in order to obtain more paediatric labelling from the EMA, an evolution from studies conducted solely in American children to studies having a global, multicentre design will be necessary since such a design is required by the EMA to eliminate the geographic differences. Therefore, several global, multicentre organisations (e.g. 'conect 4 children' and 'I-ACT for children') were established to facilitate paediatric studies in order to obtain more paediatric labelling (21,22).

Unfortunately, among the ARBs, no PK studies were conducted in children under 1 year of age in contrast to PK studies performed with ACE inhibitors. In addition, for the PD studies, only 2 studies included children with an age of 6 months to 1 year. The low inclusion of children < 1 year may be partly due to the fact that drugs acting on the RAAS are not recommended for children under 1 year of age since the RAAS plays a role in renal development. Blocking the RAAS by ACE inhibitors or ARBs could therefore have a negative impact on the development of the kidneys (179). Besides, clinical studies performed with neonates and infants also present some additional challenges compared to studies in older children, leading to 65% of the drugs used in neonates and infants being off-label or unlicensed (180). Due to the rapid physiological changes occurring in neonates and infants, appropriate dosing is difficult. In addition, an adapted drug formulation allowing low, flexible, and adjustable dosing is needed and potentially toxic excipients must be considered in the preparation of these formulations (180). Finally, ethical concerns also complicate research in neonates and infants (e.g. inability to give informed consent and limited blood collection) (181).

Multicentre studies were more common practice in the PKPD studies with ARBs, leading to a greater sample size. However, in the past 20 years, the number of multicentre studies conducted with ACE inhibitors also increased. In addition, study design of the PD studies, for both ARBs and ACE inhibitors, improved (more RCTs) with the introduction of a multicentre approach. Although multicentre studies can have many advantages compared to single-centre studies (e.g. more patients and faster recruitment), a critical mind remains necessary when interpreting the results in view of the methodological limitations (182). Normally, multicentre studies have a rigorous protocol, however, the rate of adherence to this protocol is lower compared to the protocol used in single-centre studies (182). In PK studies, protocol violation can lead to an altered sampling regimen which can cause variation in PK parameters. In addition, collected samples sometimes must be transferred for analysis (poor sample preservation can occur) or the analysis is performed in different labs and by different people, creating variability of the results. In this context, microsampling, more specifically dried blood spots, can provide a solution since the analyte remains stable once the blood spot has dried, making storage and transport less of a problem (183). Therefore, PK and PD samples from different centres can be collected in one laboratory for analysis, reducing the variability of the results. In studies where BP needs to be measured, a multicentre design can cause variability in BP values since BP will be measured by many different investigators who may be using different equipment than specified by the protocol. However, the above limitations can be avoided by training the investigators and ensuring a high adherence rate of the different centres to the high-quality protocol, which will be needed for the future global, multicentre studies.

Although the introduction of multicentre studies with ACE inhibitors and ARBs have led to more RCTs, the type of design of the RCTs should also be considered. Almost half of the RCTs conducted had a type C design (see Table 4.3). The FDA has promoted the type C design because such a design would be generally more acceptable to parents and the ethics committee since all children initially receive the study drug. However, some of the children are switched to placebo after a period of usually 2 to 4 weeks without a washout period. Therefore, a residual effect of the antihypertensive drug during the placebo phase is possible, leading to placebo data of low quality (184). In addition, the type C design was specifically developed to demonstrate dose-response relationships, thereby obtaining paediatric dose recommendations. However, many antihypertensive studies (including some studies of this review) fail to demonstrate a dose-response relationship. Usually, this is due to the poor dose selection, resulting in too narrow dose ranges thereby causing overlap between the different dose groups (low, middle, and high dose). Besides, dose-ranging studies not using a paediatric formulation (e.g. suspension, syrup) are also more likely to fail since dosing with tablets yields a wider range of drug exposure, resulting in more overlap between the dose groups, causing a non-significant dose-response relationship (178).

Therefore, future paediatric studies investigating antihypertensive drugs should use a wide dose range and an appropriate paediatric formulation in order to demonstrate a dose-response relationship, allowing to make dose recommendations. Even better would be to engage in individual dose titration to see what effect administering a higher dose has on lowering the BP. Another possibility, better for demonstrating drug efficacy, is to recommend the use of a type A RCT design in which a direct comparison of the BP lowering effects of a drug to a placebo group is possible. However, a lot of controversy surrounding the type A RCT design exists due to ethical issues (185).

5.5. PIPS OF ACE INHIBITORS AND ARBS

As described in 1.1., the EMA introduced the PIP in 2007 as an incentive to increase drug research in children. To date (July 22, 2021), 2199 PIPs were submitted to the EMA of which 1303 received approval (20). **Table 8.9, Appendix IX** demonstrates for which ACE inhibitors and ARBs a PIP was already submitted and what the decision of the Paediatric Committee was. In addition, the table also illustrates whether the PIPs have already been completed, leading to paediatric labelling for the drug. A total of 9 PIPs were presented to the EMA for captopril, enalapril (3), trandolapril, azilsartan, valsartan, candesartan, and losartan. Of these 9 PIPs, 7 received a positive decision and 2 got refusal. Valsartan and losartan are the only 2 drugs with completion of the PIP, leading to paediatric labelling for these drugs. According to the SmPC, valsartan and losartan are approved for the treatment of primary hypertension in children 6 years and older. Valsartan is the only one of all ACE inhibitors and ARBs on the Belgian market having a liquid oral formulation (a syrup).

According to the EMA, the following ACE inhibitors and ARBs require further development and/or investigation: captopril, ramipril, enalapril, irbesartan, candesartan, valsartan, and telmisartan (186). Noticeably, not much overlap exists between the ACE inhibitors and ARBs for which a PIP was submitted and those requiring further investigation. Due to the low completion of the PIPs, conducting future research as part of a PIP is important to obtain more paediatric labelling, also for children under the age of 6 years. Ideally, studies should first be performed with the drugs requiring further investigation. In addition, a PIP for lisinopril should be submitted since lisinopril is a commonly prescribed antihypertensive drug in a paediatric clinical setting.

5.6. LIMITATIONS OF THE LITERATURE FOR ACE INHIBITORS IN HYPERTENSIVE CHILDREN

The main **limitations** of the **literature** are:

1) The sparse description of the studied populations in terms of body weight and eGFR since only 16 of the 37 (43.2%) and 9 of the 37 (24.3%) PKPD studies with ACE inhibitors reported values for body weight and eGFR, respectively. However, reporting the children's weight is necessary in order to know what proportion of the studied population is obese (which has an influence on the drug's PK) and in order to compare different studies. More importantly, the eGFR should be reported considering ACE inhibitors are primarily renally cleared (see 1.4.3.). Therefore, administration of an ACE inhibitor to children having (unknown) low renal function may lead to an undesirable recommendation for lower doses.
2) The varying sampling regimen among PK studies and the reporting of the PK parameters as a mean of a population with often a broad age range (see 5.1.).
3) The between-study variability of the definition of hypertension (see 4.2.1.).
4) The sparse reporting of the desired BP target while the percentage of children reaching their BP target with the administered ACE inhibitor needs to be known.
5) The heterogeneity of reporting BP decline across studies and how BP was reported (see 5.2.).
6) The low reporting of serious adverse events (10 of the 37 PKPD studies) and change in serum potassium from baseline (18 of the 37 PKPD studies). However, these parameters are important for verifying whether the ACE inhibitor studied is safe for use in children.
7) The lack of reporting the method used to measure BP. The method was not reported in 12 of the 30 PD studies (40.0%). In addition, ABPM was only used in 6 of the 30 PD studies (20.0%).

5.7. LIMITATIONS OF THIS REVIEW

Although the best was done to provide a comprehensive summary of the methodology, study design, and results of the available PKPD studies of ACE inhibitors and ARBs in hypertensive children, some limitations must be recognized. Firstly, only the available literature in PubMed was considered for this review. Therefore, an incomplete collection of the literature regarding this topic may have occurred. Secondly, no bias control of the included studies was performed. Therefore, verification whether the obtained results from the studies were distorted was not possible. The review by *Snauwaert et al.* did control the risk of bias of the studies demonstrating that the non-randomized studies were often of low quality with a high risk of bias. However, to date, non-randomized studies are the only studies testing ACE inhibitors in higher-risk populations (e.g. infants, end stage renal disease, severe hypertension, etc.) as the RCT populations are highly selected and mildly

hypertensive (86). Lastly, only the BP lowering effects of ACE inhibitors were evaluated. However, for the complete assessment of the efficacy of ACE inhibitors, other PD parameters should also be taken into account. The blood renin/aldosterone ratio, for example, is often examined to assess the extent of ACE inhibition. As ACE inhibition should lead to lower angiotensin II levels and therefore lower aldosterone levels, the renin/aldosterone ratio should increase (29). In addition, fractional sodium excretion and urinary sodium and potassium should also be considered. The fractional sodium excretion helps in the evaluation of acute renal failure, which can occur after administration of an ACE inhibitor (187). The urinary sodium and potassium values give an idea about the mineralocorticoid effect of the ACE inhibitor since aldosterone (a mineralocorticoid) regulates urinary sodium and potassium concentrations.

5.8. RESEARCH GAPS AND RECOMMENDATIONS FOR FUTURE RESEARCH INVESTIGATING ACE INHIBITORS AND ARBS IN HYPERTENSIVE CHILDREN

The **research gaps** noted for ACE inhibitors and ARBs in the paediatric hypertensive population, which should be covered by future research, are summarized below:

1) To date, no studies on the long-term effects of ACE inhibitors and ARBs on cardiovascular mortality and morbidity have been conducted. Instead, all studies focused on the BP decline which is merely a surrogate endpoint. Therefore, prospective studies investigating the long-term effects and safety of ACE inhibitors and ARBs in hypertensive children are desirable.
2) Children having severe and/or symptomatic hypertension or having stage 4 or 5 CKD are often excluded from studies for safety reasons. However, in practice, ACE inhibitors and ARBs are also prescribed for these specific populations. Consequently, inclusion of these patients in future studies is desirable in order to safely administer ACE inhibitors and ARBs to these specific patients as well. Moreover, studies in all paediatric populations relevant for the administration of ACE inhibitors and ARBs are worthwhile, however, stratification of patients by subgroup is then required.
3) Comparative studies of different antihypertensive drug classes are lacking. However, such studies are the only way to determine which antihypertensive drug is superior for a given population.
4) A need for the development and commercialisation of child-friendly formulations exists. As mentioned before, capsules may be an appropriate solution (see 5.1.). In addition, e.g. orodispersible mini tablets or syrups (especially for the younger children) may also be adequate drug formulations (188).
5) To date, no PK and only 2 PD studies with ARBs are available for children < 1 year of age. In addition, the number of RCTs conducted in children < 6 years of age is limited, for both ACE inhibitors and ARBs.

6) Childhood obesity is a growing global health problem, increasing the prevalence of primary hypertension (28). According to the World Health Organisation, the prevalence of overweight and obesity in children aged 5-19 years increased from 4% in 1975 to 18% in 2016 (189). Therefore, more inclusion of children having primary hypertension in future well-conducted studies is important.
7) Studies examining combination therapy of antihypertensive drugs (including an ACE inhibitor or ARB) in children are lacking. However, combination therapy is often required in children having severe or therapy-resistant hypertension.
8) Access to individual PK and/or PD data of both paediatric and adult studies is necessary to perform population PK/PD meta-analyses (e.g. for covariate analysis). Publication and free access of these data should be encouraged as much as possible.

In general, standardisation of methodology and study results is the key for future research, for both PK and PD studies. An attempt at data standardisation has already been undertaken by the organisation 'CDISC' (Clinical Data Interchange Standards Consortium). For each disease area, a guide has been developed to support researchers from protocol to analysis and reporting of the results in order to introduce standardisation into clinical studies. Unfortunately, no guide is yet available for hypertension or any paediatric disease area at all, except for type 1 diabetes (190).

The main **recommendations** for **PK studies** with ACE inhibitors and ARBs in the paediatric hypertensive population include:

- A standardised protocol per drug + division of the study population into different age groups (see 5.1.)
- Prospective, global, multicentre studies with a high adherence rate to the protocol (see 5.4.)
- Use of microsampling, although validation must occur first (see 5.1. and 5.4.)
- Use of child-friendly formulations (see 5.1.)
- PK substudies (PK analysis is performed in a subgroup of the population of a PD study) to investigate PKPD in 1 study
- Use of a titration protocol to verify dose proportionality
- Reporting of eGFR and body weight of the children as a mean ± standard deviation but additionally, individual values in case of abnormal renal function or body weight
- Conducting studies of which patients are not taking concomitant drugs (see 5.1.)
- Inclusion of an adult control group to allow for direct comparison of differences in PK between adults and children

- Studies with intravenous drug administration on top of oral intake (see 5.1.)
- Reporting of serious adverse events and change in serum potassium from baseline as a function of the drug's safety

The following **recommendations** are made for **PD studies** investigating ACE inhibitors and ARBs in the paediatric hypertensive population:

- Prospective, global, multicentre studies with a high adherence rate to the protocol (see 5.4.)
- Standardisation of the definition of hypertension and BP target used
- Homogeneity in the reporting of BP decline; ideally, the percentage of children achieving their BP target is reported by using the standardised BP reference tables
- Well-designed, prospective, double-blind RCTs: use of a wide dose range and appropriate paediatric formulations in dose-ranging studies and increase of the use of type A and type B RCTs (see 5.4.)
- In addition to the BP lowering effects, other parameters such as renin/aldosterone ratio and mineralocorticoid effect should be measured (see 5.7.)
- Individual drug titration to find the optimal dose
- Perform PD and/or PK analysis of drugs using a model-based meta-analysis approach assessing the link between dose, drug exposure and response, and testing covariate effects in specific patient subpopulations
- Reporting of eGFR and body weight of the children as a mean ± standard deviation but additionally, individual values in case of abnormal renal function or body weight
- Use of microsampling, although validation must occur first (see 5.1. and 5.4.)
- Use of child-friendly formulations
- Reporting of the used BP method + increased use of ABPM
- Reporting of serious adverse events and change in serum potassium from baseline as a function of the drug's safety

6. CONCLUSION

This review examined the methodology, study design, and results of the available PKPD studies of ACE inhibitors in hypertensive children. In addition, a comparison in study design and methodology to similar ARB studies was performed. Thereby, recommendations for future studies were made in order to obtain more paediatric labelling for ACE inhibitors and ARBs as these are the most commonly prescribed antihypertensive drugs in a paediatric setting.

Firstly, of the 77 patients for which individual BP values were available after administration of an ACE inhibitor, 94.8% and 89.7% achieved the clinical target (a BP decrease of ≥ 6 mmHg) for SBP and DBP, respectively. However, a decrease of 6 mmHg may not be clinically relevant for all children and, therefore, standardised BP tables must be checked to determine whether the observed BP decrease is clinically relevant (achievement of BP target). In addition, as BP in children increases according to age, size and gender, the current reporting of BP as a mean value of the entire (sub)population with often a broad age range should change. Ideally, future studies should report the percentage of children reaching their BP target after treatment with the antihypertensive drug.

Secondly, study design improved over the years, for both ACE inhibitors and ARBs, with a shift from uncontrolled studies to more RCTs, especially with the introduction of multicentre studies, which also increased sample size. However, in order to obtain more paediatric labelling, future multicentre studies must have a global approach and a high adherence rate to the protocol by the different centres.

Thirdly, PK studies require a standardised protocol per drug in order to compare the studies, thereby assessing the effects of specific population characteristics (e.g. low eGFR, pathology) on the drug's PK. In addition, the population should be divided into several age groups since their PK differs. Moreover, individual PK and/or PD data should be published and freely available to conduct meta-analyses (e.g. covariate analysis) using a model-based meta-analysis approach.

Lastly, future studies should cover the existing research gaps. For example, few studies have been conducted in children having severe hypertension or having stage 4 or 5 CKD. However, ACE inhibitors and ARBs are also prescribed in these specific populations. In addition, more comparative and long-term studies are necessary.

In general, much research is still needed to administer evidence-based drugs to children, however, the ever-growing global, multicentre organisations such as 'conect 4 children' and 'I-ACT for children' are promising to obtain more paediatric labelling in the future.

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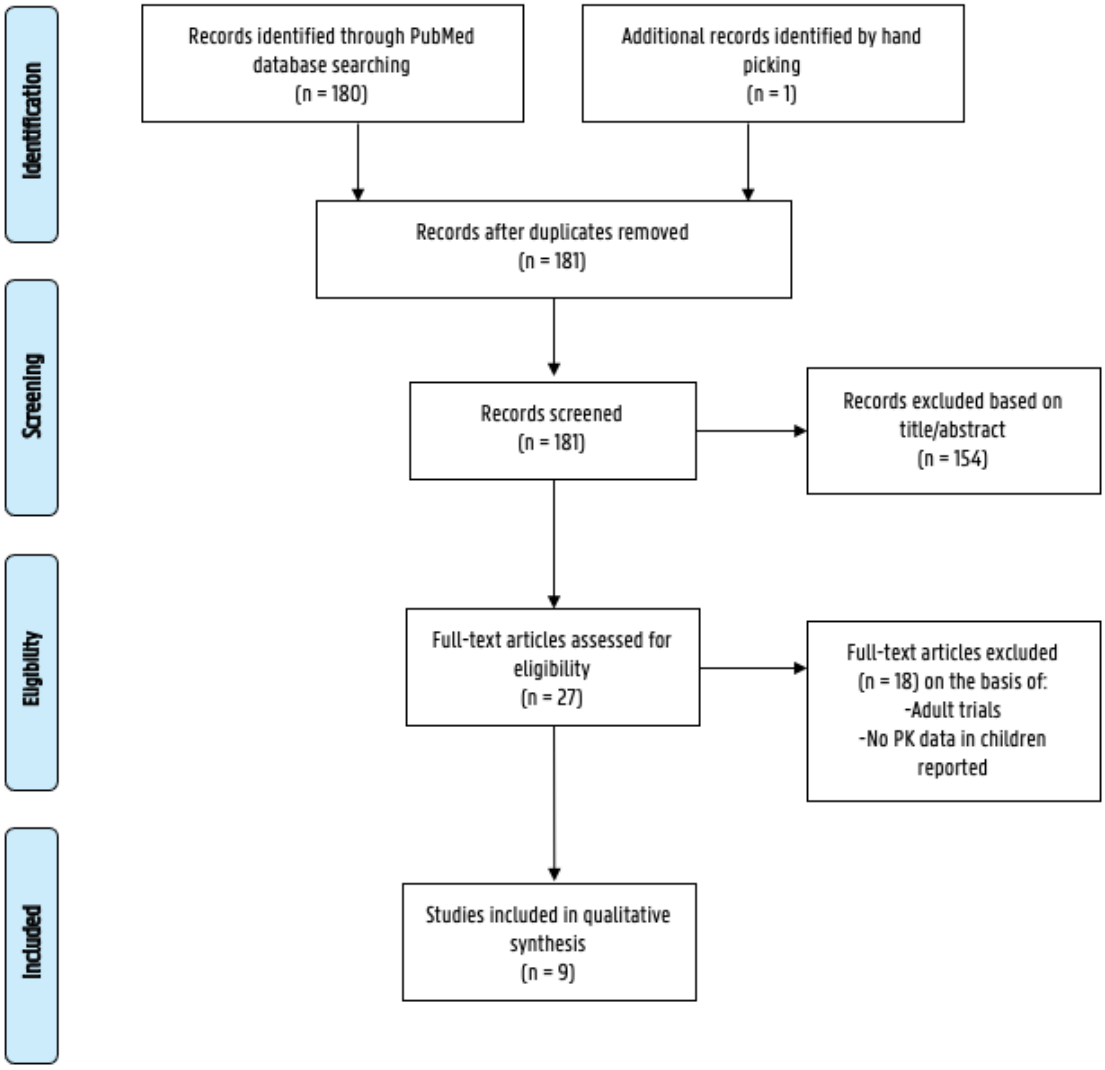
8. APPENDICES

8.1. APPENDIX I: EXAMPLE OF A STANDARDISED BP REFERENCE TABLE

Age, y	BP Percentile	SBP, mm Hg							DBP, mm Hg						
		Percentile of Height							Percentile of Height						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	80	81	83	85	87	88	89	34	35	36	37	38	39	39
	90th	94	95	97	99	100	102	103	49	50	51	52	53	53	54
	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
	99th	105	106	108	110	112	113	114	61	62	63	64	65	66	66
2	50th	84	85	87	88	90	92	92	39	40	41	42	43	44	44
	90th	97	99	100	102	104	105	106	54	55	56	57	58	58	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
	99th	109	110	111	113	115	117	117	66	67	68	69	70	71	71
3	50th	86	87	89	91	93	94	95	44	44	45	46	47	48	48
	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
	99th	111	112	114	116	118	119	120	71	71	72	73	74	75	75
4	50th	88	89	91	93	95	96	97	47	48	49	50	51	51	52
	90th	102	103	105	107	109	110	111	62	63	64	65	66	66	67
	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
	99th	113	114	116	118	120	121	122	74	75	76	77	78	78	79
5	50th	90	91	93	95	96	98	98	50	51	52	53	54	55	55
	90th	104	105	106	108	110	111	112	65	66	67	68	69	69	70
	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
	99th	115	116	118	120	121	123	123	77	78	79	80	81	81	82
6	50th	91	92	94	96	98	99	100	53	53	54	55	56	57	57
	90th	105	106	108	110	111	113	113	68	68	69	70	71	72	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
	99th	116	117	119	121	123	124	125	80	80	81	82	83	84	84
7	50th	92	94	95	97	99	100	101	55	55	56	57	58	59	59
	90th	106	107	109	111	113	114	115	70	70	71	72	73	74	74
	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
	99th	117	118	120	122	124	125	126	82	82	83	84	85	86	86
8	50th	94	95	97	99	100	102	102	56	57	58	59	60	60	61
	90th	107	109	110	112	114	115	116	71	72	72	73	74	75	76
	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
	99th	119	120	122	123	125	127	127	83	84	85	86	87	87	88
9	50th	95	96	98	100	102	103	104	57	58	59	60	61	61	62
	90th	109	110	112	114	115	117	118	72	73	74	75	76	76	77
	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
	99th	120	121	123	125	127	128	129	84	85	86	87	88	88	89
10	50th	97	98	100	102	103	105	106	58	59	60	61	61	62	63
	90th	111	112	114	115	117	119	119	73	73	74	75	76	77	78
	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
	99th	122	123	125	127	128	130	130	85	86	86	88	88	89	90
11	50th	99	100	102	104	105	107	107	59	59	60	61	62	63	63
	90th	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	99th	124	125	127	129	130	132	132	86	86	87	88	89	90	90
12	50th	101	102	104	106	108	109	110	59	60	61	62	63	63	64
	90th	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	99th	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	50th	104	105	106	108	110	111	112	60	60	61	62	63	64	64
	90th	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	99th	128	130	131	133	135	136	137	87	87	88	89	90	91	91
14	50th	106	107	109	111	113	114	115	60	61	62	63	64	65	65
	90th	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	99th	131	132	134	136	138	139	140	87	88	89	90	91	92	92
15	50th	109	110	112	113	115	117	117	61	62	63	64	65	66	66
	90th	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99th	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	50th	111	112	114	116	118	119	120	63	63	64	65	66	67	67
	90th	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99th	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	50th	114	115	116	118	120	121	122	65	66	66	67	68	69	70
	90th	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99th	139	140	141	143	145	146	147	92	93	93	94	95	96	97

Figure 8.1: BP values for boys by age and height percentile according to the fourth report on the diagnosis, evaluation and treatment of high BP in children and adolescents. SBP, systolic blood pressure; DBP, diastolic blood pressure (50).

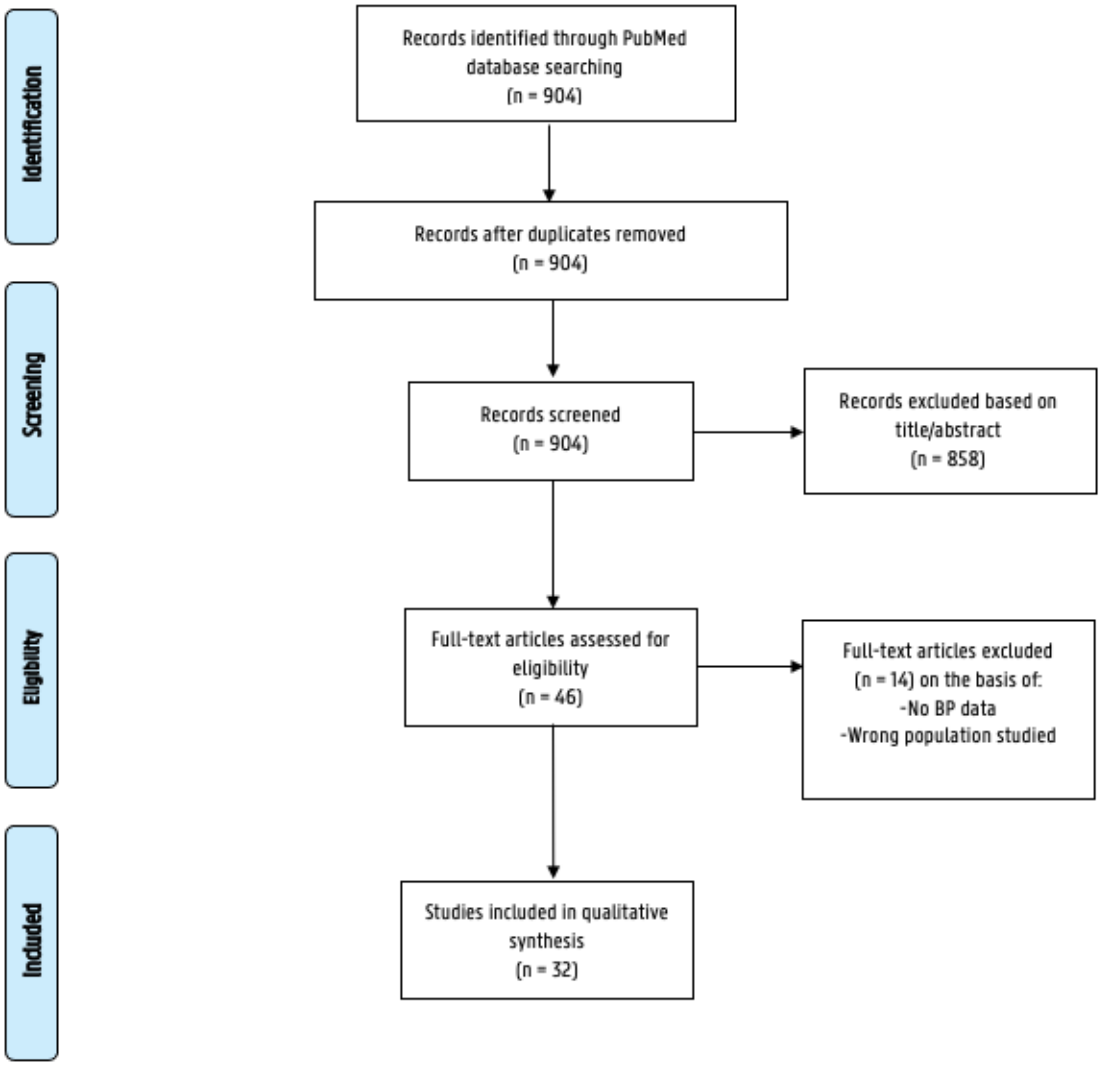
8.2. APPENDIX II: PRISMA FLOWCHART OF RQ 1



From: Moher D, Liberati A, Tetzlaff J, Atman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi: 10.1371/journal.pmed1000097

Figure 8.2: PRISMA flow diagram for the PK data of ACE inhibitors in children (RQ 1)

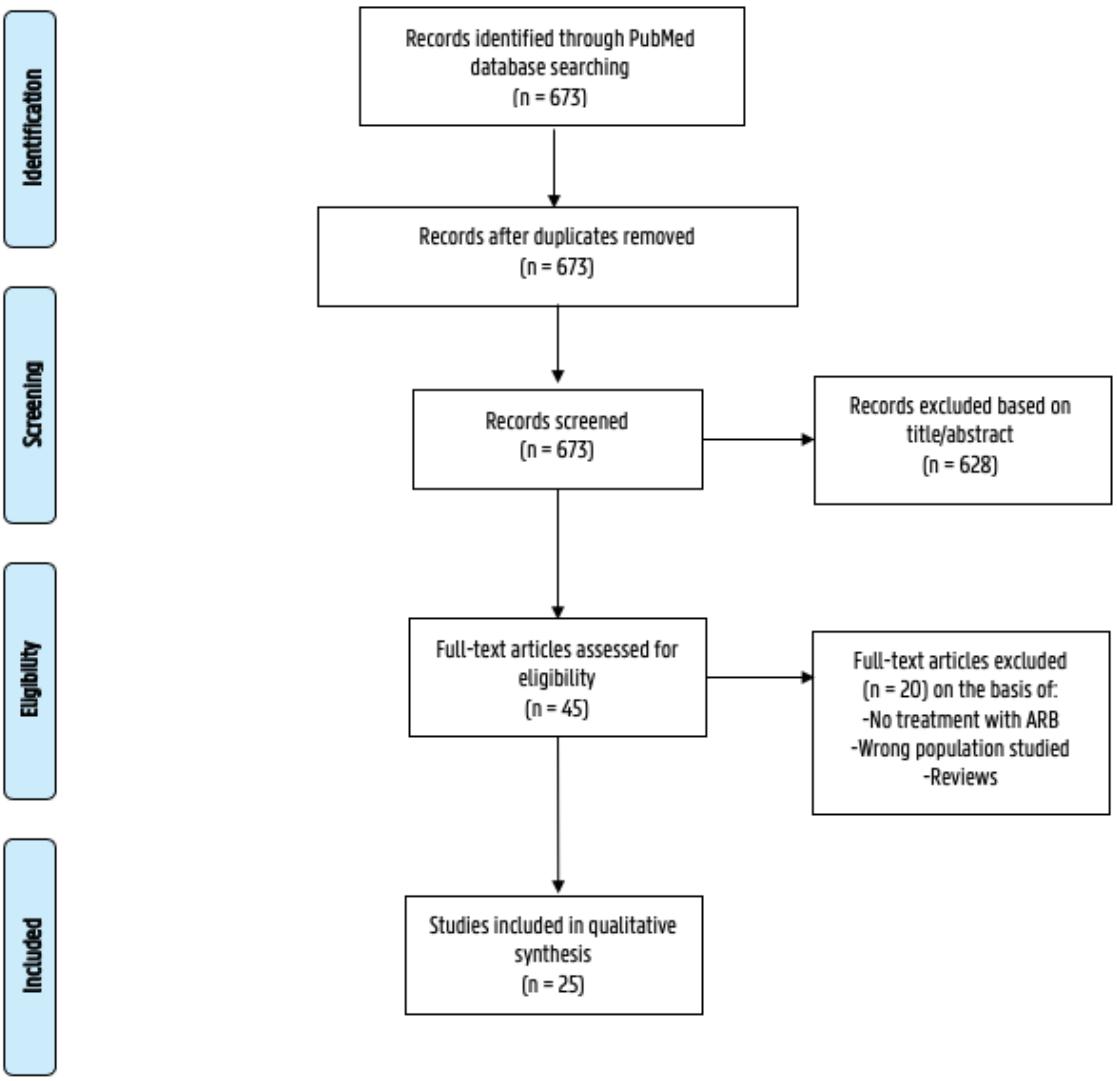
8.3. APPENDIX III: PRISMA FLOWCHART OF RQ 2



From: Moher D, Liberati A, Tetzlaff J, Atman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi: 10.1371/journal.pmed1000097

Figure 8.3: PRISMA flow diagram for the BP lowering effects of ACE inhibitors in hypertensive children (RQ 2)

8.4. APPENDIX IV: PRISMA FLOWCHART OF RQ 3



From: Moher D, Liberati A, Tetzlaff J, Atman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi: 10.1371/journal.pmed1000097

Figure 8.4: PRISMA flow diagram for the comparison in study design and methodology between ACE inhibitors and ARBs in hypertensive children (RQ 3)

8.5. APPENDIX V: TABLES OF RQ 1

Table 8.1: Study setup of PK studies with ACE inhibitors in children

Author (country, year)	Drug (active metabolite[a])	Dose and dose regimen (formulation)	n	Age range	Weight range (kg)	eGFR range (mL/min/1.73m^2)	Patient population	Concomitant drugs	Study design and duration
Sinaiko *et al.* (US, 1983) (105)	Captopril	0.5 – 2.0 mg/kg two- or three-daily, max 6 mg/kg/day (NA)	10	3.5 – 20 years	NA	10 – 118	Secondary HT due to RAS (n=2), renal parenchymal diseases (n=4), renal Tx rejection (n=4)	Furosemide (n=8), HCT (n=6)	Design: prospective cohort, open-label, drug titration[b] study Duration: 1 – 12 months
Levy *et al.* (Canada, 1991) (101)	Captopril	0.7 mg/kg, one dose (NA)	8	5 – 18 years	18 – 66	NA	Normotensive and normoreninemic with confirmed renal scarring due to grade III-V vesicoureteral reflux	No	Design: single-dose PK study, open-label, industry-driven Duration: 1 day
Pereira *et al.* (Canada, 1991) (106)	Captopril	1 mg/kg/8h (aqueous solution)	10	2 – 15 months	3.8 – 8.8	NA	CHF due to atrial or ventricular septal defects (n=7) or dilated cardiomyopathy (n=3); Down's syndrome (n=3), patent ductus arteriosus (n=2), bacterial endocarditis (n=1)	Digoxin (n=10), mycostatin (n=1), vancomycin (n=1), cloxacillin (n=1), gentamycin (n=1), furosemide (n=4), spironolactone + HCT (n=1)	Design: prospective cohort, open-label Duration: 1 week

Table 8.1: Study setup of PK studies with ACE inhibitors in children (continued)

Author (country, year)	Drug (active metabolite[a])	Dose and dose regimen (formulation)	n	Age range	Weight range (kg)	eGFR range (mL/min/1.73m^2)	Patient population	Concomitant drugs	Study design and duration
Lloyd *et al.* (US, 1989) (102)	Enalapril (enalaprilat)	0.02 – 0.08 mg/kg, once-daily (oral solution)	10	6 weeks – 8 months	NA	NA	Unresponsive CHF due to complete atrioventricular canal defects (n=2), ventricular septal defects (n=6), tetralogy of Fallot (n=1) or congestive cardiomyopathy (n=1); Down's syndrome (n=2) Excluded: renal, hematopoietic or hepatic impairment	Digoxin and furosemide (constant doses)	Design: prospective cohort, open-label, industry-driven, drug titration[c] study Duration: 9 days – 24 weeks[d]
Nakamura *et al.* (Japan, 1994) (107)	Enalapril (enalaprilat)	0.05 – 0.3 mg/kg, one dose (oral suspension)	12	10 days – 6.5 years	1.9 – 15.6	NA	CHF due to confirmed congenital heart anomalies; Down's syndrome (n=2), 18-trisomy (n=1) Excluded: renal, hematopoietic or hepatic impairment	Digoxin (n=10), furosemide (n=9), cefotaxime (n=1)	Design: open-label, single-dose PK study, adult control group (7 healthy, normotensive males, 21 – 29 years) Duration: 1 – > 5 days[e]
Wells *et al.* (US, 2001) (103)	Enalapril (enalaprilat)	0.07 – 0.14 mg/kg, once-daily (suspension or tablets[f])	40	2 months – 15 years	3.5 – 160.0	NA	Confirmed HT with normal renal function, 23 had secondary HT Excluded: eGFR < 30 mL/min/1.73m^2, symptomatic or severe HT, RAS, severe nephrotic syndrome, major Tx	NA	Design: multicentre, prospective cohort, open-label, industry-driven Duration: 4 – 19 days
Blumer *et al.* (US, 2003) (104)	Quinapril (quinaprilat)	0.2 mg/kg, one dose (syrup)	24	2.5 months – 6.8 years	3.7 – 31.4	41.4 – 231	Already under ACE inhibitor treatment, mostly for congenital heart diseases (n=18), acceptable renal function Excluded: previous adverse event(s) with ACE inhibitor	NA	Design: one-time substitution of chronic ACE inhibitor with quinapril, industry-driven, open-label Duration: 1 day

Table 8.1: Study setup of PK studies with ACE inhibitors in children (continued)

Author (country, year)	Drug (active metabolite[a])	Dose and dose regimen (formulation)	n	Age range	Weight range (kg)	eGFR range (mL/min/1.73m^2)	Patient population	Concomitant drugs	Study design and duration
Hogg *et al.* (US, 2007) (108)	Lisinopril	0.1 – 0.2 mg/kg, once-daily (suspension or tablets[g])	46	6 months – 15 years	NA	3 patients had an eGFR of 45.8, 46.5 or 26.8	HT; obesity (n=5), history of renal disease (n=38), HUS (n=10) or COB (n=3) Excluded: symptomatic HT, major Tx, comorbidities, angioedema, hypersensitivity to ACE inhibitors, eGFR < 30 mL/min/1.73m^2	Amlodipine (n=3), furosemide (n=3), captopril (n=1), propranolol (n=1)	Design: prospective cohort, open-label, multicentre, steady state PK study Duration: 6 – 12 days
Trachtman *et al.* (US, 2015) (109)	Lisinopril	0.1 – 0.4 mg/kg, once-daily (tablets)	22	7 – 17 years	51.3 ± 23.8*	30.3 – 140.2	HT with stable renal Tx[h] Excluded: eGFR < 30 mL/min/1.73m^2, allergy to ACE inhibitors, stage 2 HT, serum potassium > 6 mmol/L, history of angioedema	Yes[i]	Design: prospective cohort, open-label, multicentre study Duration: 10 – 16 days for the lisinopril-naïve group and 11 – 41 days for standard of care group

[a]Active metabolite is generated by de-esterification in the liver.
[b]Patients were hospitalized for min 3 days and received their first 3 doses: 0.5, 1.0 and 2.0 mg/kg (patients were randomly assigned to 1 of the 6 possible sequences); next dose was given if BP returned to baseline level; after dose titration phase, patients received individual dependent equal captopril doses two- or three-daily; dose was adjusted in clinical visits if necessary.
[c]During the dose escalation phase, patients received 0.02, 0.04 and 0.08 mg/kg of enalapril the first, second, and third day of the study, respectively.
[d]Inpatient study (9 days) followed by an optional outpatient treatment (up to 24 weeks); the inpatient study period was divided in 3 phases (each 3 days lasting): baseline phase (no enalapril intake), dose escalation phase[c] and treatment phase (0.08 mg/kg once-daily).
[e]In 2 patients, PK parameters were also determined at steady state (at least 5 days of once-daily dosing), in addition to determination after the initial dose.
[f]Children < 6 years received a suspension (0.15 mg/kg), older children received tablets.
[g]Children < 6 years and older children who weren't able to swallow tablets received a suspension (0.15 mg/kg), the other children took tablets.
[h]The children were divided into 2 populations: 1 lisinopril-naïve group (n=12) and 1 standard of care group (n=10, already took lisinopril as an antihypertensive drug); both populations were also divided into 2 groups according to eGFR: low (30 – 59 mL/min/1.73m^2) and high (≥ 60 mL/min/1.73m^2) eGFR group.

[i]Atenolol (n=2), carvedilol (n=1), clonidine (n=2), amlodipine (n=15), isradipine (n=2), mycophenolate (n=19), tacrolimus (n=16), prednisone (n=18), azathioprine (n=1), sirolimus (n=7), mycophenolate mofetil (n=1), odansetron (n=1), esomeprazole (n=1), vitamin D (n=1).

*Mean ± SD

ACE = angiotensin-converting enzyme, BP = blood pressure, CHF = congestive heart failure, COB = chronic obstructive bronchitis, eGFR = estimated glomerular filtration rate, HCT = hydrochlorothiazide, HT = hypertension, HUS = haemolytic uremic syndrome, max = maximum, min = minimum, n = number, NA = not available, PK = pharmacokinetics, RAS = renal artery stenosis, SD = standard deviation, Tx = transplantation, US = United States

Table 8.2: Sampling regimen and bioanalysis method of PK studies with ACE inhibitors in children

Author (country, year)	Drug (active metabolite[a])	n	Age range	Study duration	Sampling regimen	Bioanalysis method
Sinaiko *et al.* (US, 1983) (105)	Captopril	10	3.5 – 20 years	1 – 12 months	After a minimum of 3 months taking captopril (steady state), whole blood samples were taken predose and at 1, 2, 3, 4, 6 and 8h post-administration (blood samples were taken in 6 patients).	GC-MS
Levy *et al.* (Canada, 1991) (101)	Captopril	8	5 – 18 years	1 day	Plasma samples were taken predose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 5 and 6h post-administration.	HPLC-UV
Pereira *et al.* (Canada, 1991) (106)	Captopril	10	2 – 15 months	1 week	Plasma samples were taken predose and at 0.25, 0.5, 1, 1.5, 2, 4, 6 and 8h after first dose administration on day 1 and predose on days 3, 5 and 7.	HPLC
Lloyd *et al.* (US, 1989) (102)	Enalapril (enalaprilat)	10	6 weeks – 8 months	9 days – 24 weeks[b]	Serum samples were taken at 4, 6, 8 and 24h after each dose during the dose escalation phase and on the third day of the treatment phase.	RIA
Nakamura *et al.* (Japan, 1994) (107)	Enalapril (enalaprilat)	12[c]	10 days – 6.5 years	1 – > 5 days	Serum samples were taken at 2, 4, 8, 12 and 24h after the first dose in 12 cases; in 2 other cases, additional serum samples were taken in steady state condition and in that case, a predose sample was also taken.	RIA
Wells *et al.* (US, 2001) (103)	Enalapril (enalaprilat)	40	2 months – 15 years	4 – 19 days	Serum samples were taken predose on day 1 and at 1, 2, 4, 6, 8, 12, 16 and 24h post-administration on day 1 and once on day 4 – 19; in children < 4 years, serum samples were taken predose and at 1, 4, 8 and 24h post-administration.	RIA
Blumer *et al.* (US, 2003) (104)	Quinapril (quinaprilat)	24	2.5 months – 6.8 years	1 day	Plasma samples were taken predose and at 1, 2, 4, 8, 12 and 24h post-administration.	LC-MS/MS

Table 8.2: Sampling regimen and bioanalysis method of PK studies with ACE inhibitors in children (continued)

Author (country, year)	Drug (active metabolite[a])	n	Age range	Study duration	Sampling regimen	Bioanalysis method
Hogg *et al.* (US, 2007) (108)	Lisinopril	46	6 months – 15 years	6 – 12 days	Serum samples were taken predose and at 2, 4, 6, 8, 10, 12, 16 and 24h post-administration in children aged ≥ 4 years; in children aged < 4 years, serum samples were taken predose and at 4, 6, 8, 12 and 24h post-administration; sampling occurred 6, 7, 8 or 12 days after once-daily dosing.	RIA
Trachtman *et al.* (US, 2015) (109)	Lisinopril	22	7 – 17 years	10 – 16 days for the lisinopril-naïve group and 11 – 41 days for the standard of care group	On the PK visit (day 10 – 41), plasma samples were taken predose and at 1, 2, 4, 5, 8, 12 and 24h post-administration.	HPLC-MS/MS

[a]Active metabolite is generated by de-esterification in the liver.
[b]Inpatient study (9 days) followed by an optional outpatient treatment (up to 24 weeks); the inpatient study period was divided in 3 phases (each 3 days lasting): baseline phase (no enalapril intake), dose escalation phase and treatment phase (0.08 mg/kg once-daily).
[c]12 children were included in the study but 2 patients participated twice, leading to 14 cases.

ACE = angiotensin-converting enzyme, GC-MS = gas chromatography-mass spectrometry, HPLC = high performance liquid chromatography, HPLC-MS/MS = high performance liquid chromatography – tandem mass spectrometry, HPLC-UV = high performance liquid chromatography with ultraviolet detection, LC-MS/MS = liquid chromatography – tandem mass spectrometry, n = number, PK = pharmacokinetics, RIA = radioimmunoassay, US = United States

Table 8.3: PK parameters of PK studies with ACE inhibitors in children

Author (country, year)	n	Bioanalysis method	Drug	Age	t_{max} (h)	C_{max} (ng/mL) Mean (SD)	C_{max} (ng/mL per 0.1 mg/kg) Geomean (95% CI)	$AUC_{0-\infty}$ (ng/mL.h) Mean (SD)	$AUC_{0-\infty}$ (ng/mL.h per 0.1 mg/kg) Geomean (95% CI)	$t_{1/2}$ (h) Mean (SD)	CL (L/h/kg) Mean (SD)
Sinaiko *et al.* (US, 1983) (105)	6	GC-MS	Captopril	3.5 – 20 years	1 – 2	NA	NA	1766.4 (609.7)[a] 773.0[b]	NA	NA	0.8 – 1.1[a,*] 1.6[b]
Levy *et al.* (Canada, 1991) (101)	8	HPLC-UV	Captopril	5 – 18 years	0.5 – 2	267.6 (168.0)	NA	662.1 (495.9)	NA	1.5 (0.4)	1.7 (1.2)
Pereira *et al.* (Canada, 1991) (106)	10	HPLC	Captopril	2 – 15 months	1.6 (0.4)**	350 (184)	NA	1019 (331)	NA	3.3 (3.3)	1.1 (0.4)
Lloyd *et al.* (US, 1989) (102)	10	RIA	Enalaprilat	6 weeks – 8 months	4	12.7 (2.3)[c,***] 5.5 (1.6)[c,***] 2.1 (1.7)[c,***]	NA	NA	NA	7.6 (0.7)***	NA
Nakamura *et al.* (Japan, 1994) (107)	12[d]	RIA	Enalapril	< 20 days (n=3) > 20 days – 6.5 years (n=11) 21 – 29 years (n=7)	8 – 12 2 NA	NA	NA	NA	268.7 (138.9)** 82.7 (44.3)** 83.4 (8.6)**	10.3 (5.2) 2.7 (1.4) 1.4 (1.0)	NA
			Enalaprilat	< 20 days (n=3) > 20 days – 6.5 years (n=11) 21 – 29 years (n=7)	8 – 12 7.3 (2.4)** 3.7 (1.4)**	NA	NA 9.0 (4.7)** 30.3 (14.0)**	NA	691.5 (225.6)** 138.4 (69.2)** 245.7 (61.8)**	11.9 (5.3) 11.1 (4.3) 5.3 (1.6)	NA

Table 8.3: PK parameters of PK studies with ACE inhibitors in children (continued)

Author (country, year)	n	Bioanalysis method	Drug	Age	t_{max} (h)	C_{max} (ng/mL) Mean (SD)	C_{max} (ng/mL per 0.1 mg/kg) Geomean (95% CI)	$AUC_{0-\infty}$ (ng/mL.h) Mean (SD)	$AUC_{0-\infty}$ (ng/mL.h per 0.1 mg/kg) Geomean (95% CI)	$t_{1/2}$ (h) Mean (SD)	CL (L/h/kg) Mean (SD)
Wells *et al.* (US, 2001) (103)	40	RIA	Enalapril	First dose							
				2 months – 15 years	1	28.2 – 45.9*	NA	NA	NA	NA	NA
				Steady state							
				2 months – 15 years	1	24.6 – 45.4*	NA	NA	NA	NA	NA
			Enalaprilat	First dose							
				1 – 24 months (n=9)	6.0#	14.9 (10.1 – 21.9)##	11.2 (7.5 -16.8)	174.5 (124.2 – 245.3)##	131.4 (91.9 – 187.9)		
				2 – < 6 years (n=9)	5.0#	14.9 (10.1 – 21.9)##	10.9 (7.3 – 16.5)	191.0 (135.9 – 268.4)##	140.7 (98.4 – 201.3)		
				6 – < 12 years (n=10)	5.0#	18.3 (12.7 – 26.5)##	16.3 (11.1 – 23.9)	198.9 (144.0 – 274.8)##	176.3 (125.5 – 247.5)	NA	NA
				12 – < 16 years (n=12)	4.0#	17.4 (12.2 – 24.7)##	27.3 (18.9 – 39.4)	173.8 (127.8 – 236.5)##	272.7 (197.3 – 377.0)		
				Steady state							
				1 – 24 months (n=9)	4.2#	18.4 (13.3 – 25.4)##	13.0 (9.2 – 18.4)	222.0 (163.3 – 301.8)##	157.1 (112.7 – 218.9)	NA	
				2 – < 6 years (n=9)	4.0#	24.2 (17.5 – 33.4)##	18.4 (13.0 – 26.1)	277.6 (204.1 – 377.4)##	211.3 (151.6 – 294.5)	15.4#	NA
				6 – < 12 years (n=10)	3.0#	25.5 (18.8 – 34.7)##	22.7 (16.3 – 31.7)	263.3 (196.8 – 352.5)##	234.6 (171.3 – 321.6)	16.3#	
				12 – < 16 years (n=12)	3.0#	20.5 (15.5 – 27.1)##	31.8 (23.5 – 43.0)	199.9 (153.2 – 260.8)##	309.9 (232.4 – 413.2)	14.6#	

Table 8.3: PK parameters of PK studies with ACE inhibitors in children (continued)

Author (country, year)	n	Bioanalysis method	Drug	Age	t_{max} (h)	C_{max} (ng/mL) Mean (SD)	C_{max} (ng/mL per 0.1 mg/kg) Geomean (95% CI)	$AUC_{0-\infty}$ (ng/mL.h) Mean (SD)	$AUC_{0-\infty}$ (ng/mL.h per 0.1 mg/kg) Geomean (95% CI)	$t_{1/2}$ (h) Mean (SD)	CL (L/h/kg) Mean (SD)
Blumer *et al.* (US, 2003) (104)	24	LC-MS/MS	Quinaprilat	2.5 months – 6.8 years	1 – 2	260 (102)	NA	993 (257)	NA	2.3 (1.0)	0.2 (0.06)
Hogg *et al.* (US, 2007) (108)	46	RIA	Lisinopril	1 month – < 2 years (n=9)	5 – 6	22.1 (16.1 – 30.3)[##]	NA	311.0 (218.5 – 442.8)[##]	NA	NA	NA
				2 – < 6 years (n=8)	5 – 6	21.9 (15.6 – 30.5)[##]		301.1 (207.0 – 438.0)[##]			
				6 – < 12 years (n=12)	5 – 6	44.7 (34.0 – 58.7)[##]		570.3 (420.0 – 774.4)[##]			
				12 – < 16 years (n=17)	5 – 6	43.5 (34.6 – 54.7)[##]		549.8 (425.2 – 711.0)[##]			
Trachtman *et al.* (US, 2015) (109)	22	HPLC-MS/MS	Lisinopril	0.1 mg/kg (n=12)	5.0[#]	20.9 (41.2)[###]	26.9 (18.4 – 39.5)	298 (46.5)[###]	365 (243 – 549)	9.4 (30.1)[###]	0.3 (61.2)[###]
				0.2 mg/kg (n=8)	5.0[#]	47.7 (25.1)[###]	24.8 (20.9 – 29.5)	640 (28.6)[###]	333 (265 – 419)	9.0 (46.1)[###]	0.3 (34.4)[###]
				0.4 mg/kg (n=2)	4.5[#]	58.0 (41.2)[###]	NA	702 (66.4)[###]	NA	12.4 (131)[###]	0.5 (54.1)[###]
				Low eGFR group[e] (n=7)	NA	NA	NA	NA	553 (NA)	NA	0.17 (0.12 – 0.24)[##]
				High eGFR group[f] (n=15)					256 (NA)		0.34 (0.28 – 0.42)[##]

[a]Mean of patients with impaired renal function (n=5): CL_{cr} = 10 – 21 mL/min/1.73m^2.
[b]Patient with a CL_{cr} of 59 mL/min/1.73m^2.
[c]C_{max} is reported for 0.08, 0.04 and 0.02 mg/kg (top to bottom).

[d]12 children were included in the study but 2 patients participated twice, leading to 14 cases.
[e]eGFR = 30 – 59 mL/min/1.73m^2; mean eGFR ± SD: 44.4 ± 9.6 mL/min/1.73m^2.
[f]eGFR ≥ 60 mL/min/1.73m^2; mean eGFR ± SD: 84.8 ± 26.5 mL/min/1.73m^2.

*Range, **Mean (SD), ***Mean (SEM), [#]Median, [##]Geometric mean (95% CI), [###]Geometric mean (CV%)

The SD measures the amount of variability, or dispersion, from the individual data values to the mean, while the SEM measures how far the sample mean of the data is likely to be from the true population mean.

ACE = angiotensin-converting enzyme, AUC = area under the curve, CI = confidence interval, CL = clearance, CL_{cr} = creatinine clearance, C_{max} = maximum plasma/serum/whole blood concentration, CV = coefficient of variation, eGFR = estimated glomerular filtration rate, GC-MS = gas chromatography-mass spectrometry, Geomean = geometric mean, HPLC = high performance liquid chromatography, HPLC-MS/MS = high performance liquid chromatography – tandem mass spectrometry, HPLC-UV = high performance liquid chromatography with ultraviolet detection, , LC-MS/MS = liquid chromatography – tandem mass spectrometry, n = number, NA = not available, PK = pharmacokinetics, RIA = radioimmunoassay, SD = standard deviation, SEM = standard error mean, $t_{1/2}$ = elimination half-life, t_{max} = time to reach maximum plasma/serum/whole blood concentration (C_{max}), US = United States

8.6. APPENDIX VI: TABLE OF RQ 2

Table 8.4: Study setup and BP results of PD studies with ACE inhibitors in hypertensive children

Author (country, year)	Drug	Dose (formulation)	Definition HT	Patients	Study design and duration	Mean BP ± SD pretreat-ment (mmHg)	Mean BP ± SD post-treatment (mmHg)	Clinical target achieved (≥ 6 mmHg)*
Friedman *et al.* (US, 1980) (115)	Captopril	Max 2 mg/kg/dose (NA)	NA	n=6 Age: 6 – 18 years Population: poor responsive severe secondary HT, 3 on dialysis, 1 renal Tx, 2 renal failure	Design: prospective cohort, drug titration[a] study Duration: 3 – 16 months	199±26.0/ 137±22.5	128±10.9/ 77±8.3	SBP: 100% DBP: 100%
Hymes *et al.* (US, 1983) (116)	Captopril	1.5 – 5.4 mg/kg/ day (tablets or solution)	NA	n=5 Age: 5 weeks – 13 years Population: unresponsive, high-renin secondary HT due to UAC (n=1), chronic GNP (n=2), RAS (n=1), reflux nephropathy (n=1)	Design: prospective cohort, drug titration[b] study Duration: 6 – 26 months	154±21.0/ 91±8.1	117±10.7/ 76±6.7	SBP: 100% DBP: 100%
Sinaiko *et al.* (US, 1983) (105)	Captopril	0.5 – 2.0 mg/kg, max 6 mg/kg/day (NA)	NA	n=10 Age: 3.5 – 20 years Population: secondary HT due to RAS (n=2), renal Tx rejection (n=4), renal parenchymal diseases (n=4), 4 had an eGFR < 60 mL/min/1.73m^2	Design: prospective cohort, drug titration[c] study Duration: 1 – 12 months	146±14.1/ 106±13.5	119±17.0/ 74±14.2	SBP: 100% DBP: 90%
Friedman *et al.* (US, 1983) (117)	Captopril	Max 2 mg/kg/dose (NA)	NA	n=9 Age: 6 – 18 years Population: refractory HT due to ESRD with haemodialysis (n=3), renal Tx (n=2), SLE (n=1), HUS (n=1), RAS (n=1), primary HT (n=1)	Design: prospective cohort, drug titration[a] study Duration: NA	194±22.2/ 130±20.8	125±11.0/ 77±7.0	SBP: 100% DBP: 100%

Table 8.4: Study setup and BP results of PD studies with ACE inhibitors in hypertensive children (continued)

Author (country, year)	Drug	Dose (formulation)	Definition HT	Patients	Study design and duration	Mean BP ± SD pretreatment (mmHg)	Mean BP ± SD post-treatment (mmHg)	Clinical target achieved (≥ 6 mmHg)*
Chan *et al.* (England, 1984) (118)	Captopril	0.5 – 3 mg/kg/day (NA)	NA	n=5 Age: 9 – 20 years Population: HT after renal Tx, not adequately treated by triple therapy (ß-blocker, diuretic and vasodilator)	Design: case study with drug titration[d] Duration: 3 – 15 months	165/105	110/75	NA
Sigström *et al.* (Sweden, 1984) (119)	Captopril	0.5 – 11 mg/kg/day (NA)	NA	n=30 Age: 8 months – 16 years Population: unresponsive renal HT[e], 14 patients had reduced eGFR	Design: prospective cohort, drug titration[f] study Duration: 1 – 47 months	158/109	120/76	NA
Mirkin *et al.* (US, 1985) (120)	Captopril	0.3 – 2 mg/kg/8h (tablets or suspension)	SBP and/or DBP > 95th percentile	n=73 Age: 11 days – 15 years Population: severe and refractory HT[g] intolerant or unresponsive to other acceptable antihypertensive agents, also renal impairment and dialysis	Design: prospective cohort, multicentre, drug titration[h] study Duration: < 3 months – > 1 year	165/110	After 1 month: 130/84	NA
Bouissou *et al.* (France, 1986) (121)	Captopril	Initial: 1.3 mg/kg/day Sustained: 2.2 mg/kg/day (NA)	BP > 97.5th percentile; mild HT: BP > 10 mmHg > 97.5th percentile; severe HT: BP > 30 mmHg > 97.5th percentile	n=25 Age: 1.5 – 18 years Population: severe renal HT due to GNP (n=15), vascular problems (n=2), interstitial nephritis (n=8), 10 renal Tx, 10 on dialysis, 4 CRF, only 5 patients had normal renal function	Design: retrospective cohort Duration: 2 – 40 months	NA	NA	NA

Table 8.4: Study setup and BP results of PD studies with ACE inhibitors in hypertensive children (continued)

Author (country, year)	Drug	Dose (formulation)	Definition HT	Patients	Study design and duration	Mean BP ± SD pretreat-ment (mmHg)	Mean BP ± SD post-treatment (mmHg)	Clinical target achieved (≥ 6 mmHg)*
Sinaiko *et al.* (US, 1986) (122)	Captopril	0.01 – 2 mg/kg/day, infants 0.01 – 0.5 mg/kg/day (NA)	NA	n=34 Age: premature neonates to adolescents Population: HT due to renal disease (n=10), UAC (n=7), RAS and CHF (n=1), renal Tx (n=16)	Design: prospective cohort, drug titration[i] study Duration: NA	0.5 mg/kg: 144±4/107±4 1.0 mg/kg: 143±4/101±3 2.0 mg/kg: 144±5/104±4 UAC: 127±4/ 81±5 RAS: 127/93 Tx: MAP= 103±2	0.5 mg/kg: 120±5/78±6 1.0 mg/kg: 120±4/72±7 2.0 mg/kg: 116±6/70±6 UAC: 98±10 /57±7 RAS: 80/45 Tx: MAP= 88±2	NA
Callis *et al.* (Spain, 1986) (123)	Captopril	0.3 – 3 mg/kg/day (NA)	NA	n=42 Age: 1 – 17 years Population: uncontrolled secondary HT (ESRD), on haemodialysis	Design: prospective cohort, drug titration[i] study Duration: 1.5 – 6.1 years	162±10.0/ 106±4.0	114±8.6/ 86±1.6	NA
Sagát *et al.* (Slovakia, 1986) (124)	Captopril	1 – 5 mg/kg/day (NA)	NA	n=9 Age: 2 months – 13 years Population: uncontrolled renal HT due to renal hypoplasia (n=1), RAS (n=2), chronic GNP (n=3), reflux nephropathy (n=1), polycystic kidneys (n=2), 5 had renal insufficiency of which 2 had ESRD	Design: prospective cohort Duration: 1 – 14 months	NA	NA	NA

Table 8.4: Study setup and BP results of PD studies with ACE inhibitors in hypertensive children (continued)

Author (country, year)	Drug	Dose (formulation)	Definition HT	Patients	Study design and duration	Mean BP ± SD pretreat-ment (mmHg)	Mean BP ± SD post-treatment (mmHg)	Clinical target achieved (≥ 6 mmHg)*
Tack *et al.* (US, 1988) (125)	Captopril	Initial: 0.3 mg/kg Sustained: 0.2 ± 0.02 mg/kg (NA)	SBP > 95th percentile (> 113 mmHg)	n=9 Age: 10 – 269 days (gestational age was 25 – 41 weeks) Population: CLD + secondary HT unresponsive to hydralazine, mostly renal (n=5) due to unilateral RAT (n=4), renal parenchymal disease (n=1); LVH (n=2), RVH (n=5)	Design: retrospective cohort Duration: 9 days – > 24 months	SBP: 154±22.1	After initial dose, SBP: 94±18.7	SBP: 100%
O'Dea *et al.* (US, 1988) (126)	Captopril	Initial: 0.01 – 0.5 mg/kg/day Sustained: 0.85 ± 0.3 on day 4 and 0.48 ± 0.19 mg/kg/day on day 21 (oral solution)	NA	n=11 Age at diagnosis: 2 – 84 days (gestational age was 27 – 43 weeks) Population: severe secondary HT[k]	Design: prospective cohort, drug titration[l] study Duration: 3 – 21 days	124±4/84±4	After 1 day: 95±6/59±4	SBP: 100% DBP: 91%
Morsi *et al.* (Egypt, 1992) (127)	Captopril (C) or reserpine + furosemide (R+F)	C: initial 0.2 mg/kg, sustained 1.5 mg/kg/day R: initial 0.02 mg/kg, sustained 0.01 mg/kg/day + 2 mg/kg/day F (NA)	BP > 95th percentile	n=20 (10 C, 10 R+F) Age: 4 – 10 years Population: secondary HT due to acute post-streptococcal glomerulo-nephritis	Design: prospective, randomized comparative study Duration: 3 days	C: 156±14/ 133±11 R+F: 155±14/ 108±6	C: 122±7/ 81±8 R+F: 131±8/ 90±9	NA

Table 8.4: Study setup and BP results of PD studies with ACE inhibitors in hypertensive children (continued)

Author (country, year)	Drug	Dose (formulation)	Definition HT	Patients	Study design and duration	Mean BP ± SD pretreatment (mmHg)	Mean BP ± SD post-treatment (mmHg)	Clinical target achieved (≥ 6 mmHg)*
Sehgal *et al.* (Australia, 2018) (128)	Captopril	Initial: 0.01 mg/kg Sustained: max 0.5 mg/kg/dose (NA)	SBP > 99th percentile	n=6 Age: 39 – 54 weeks gestational age Population: severe BPD with HT	Design: case series with drug titration[m] Duration: 3 – 5 weeks	NA	NA	NA
Miller *et al.* (US, 1987) (129)	Enalapril	2.5 – 30 mg/day (NA)	NA	n=15 Age: 6 weeks – 18.5 years Population: secondary HT due to UAC (n=2), renal Tx (n=5), hydronephrosis (n=3), polycystic kidneys (n=2), RAS (n=1), reflux nephropathy (n=1), vasculitis (n=1)	Design: case study Duration: 5 – > 12 months	NA	NA	NA
Wells *et al.* (US, 1990) (130)	Enalaprilat	5.2 – 28.8 µg/kg/day (IV)	NA	n=10 Gestational age was 26 – 36 weeks Population: HT, mostly secondary (renal or renovascular lesions (n=6), unknown aetiology (n=4))	Design: case study (retrospective) Duration: 2 – 17 days	MAP: 88	After 7 days, MAP: 46	NA
Wells *et al.* (US, 2002) (131)	Enalapril	(<50/≥50 kg): Low: 0.02 mg/kg (0.625/1.25 mg) Middle: 0.08 mg/kg (2.5/5 mg) High: 0.58 mg/kg (20/40 mg) (suspension or tablets)	DBP > 95th percentile	n=110 Age: 6 – 16 years Population: HT, mostly secondary (> 50% urogenital or glomerular disease) Excluded: < 20 kg, eGFR < 30 mL/min/1.73m^2, RAS, major Tx, severe or symptomatic HT, hypersensitivity to ACE inhibitors, comorbidities	Design: multicentre, prospective, industry-driven, randomized, double-blind, placebo-controlled, dose-response study Duration: a 2-week double-blind, dose-ranging phase + a 2-week placebo-controlled washout	Low: 128±13.6/ 88±8.4 Middle: 130± 15.5/ 89±8.0 High: 129±13.4/ 91±9.5	Low: 121±9.3/ 82±7.8 Middle: 123±10.1/ 80±8.7 High: 116±11.7/ 76±8.7	NA

Table 8.4: Study setup and BP results of PD studies with ACE inhibitors in hypertensive children (continued)

Author (country, year)	Drug	Dose (formulation)	Definition HT	Patients	Study design and duration	Mean BP ± SD pretreatment (mmHg)	Mean BP ± SD post-treatment (mmHg)	Clinical target achieved (≥ 6 mmHg)*
Rouine-Rapp *et al.* (US, 2003) (132)	Enalaprilat (E) or placebo (P)	31 – 40 µg/kg (IV)	BP > 95th percentile	n=12 (6 E, 6 P) Age: 1.3 – 13 years Population: HT after surgical repair of aorta coarctation, bicuspid aortic valve (n=3) Excluded: heart malformations, RAS, renal abnormalities, CHF, asthma, hypersensitivity to ACE inhibitors	Design: prospective, randomized, double-blind, placebo-controlled study Duration: 36h	E: 127/76 P: 118/68	At 6h: E: 117/59 P: 111/56	NA
Schaefer *et al.* (Germany, 2011) (133)	Enalapril (E) or valsartan (V)	18-34 kg: 10 mg E, 80 mg V 35-79 kg: 20 mg E, 160 mg V 80-160 kg: 40 mg E, 320 mg V (tablets)	SBP ≥ 95th percentile	n=281 (143 E, 138 V) Age: 6 – 17 years Population: primary or secondary HT, 17% CKD, 32% renal or urological diseases Excluded: eGFR < 30 mL/min/1.73m^2, severe HT, hypersensitivity to ACE inhibitors or ARBs	Design: prospective, multicentre, industry-driven, randomized, double-blind, parallel-group, active-controlled study Duration: 12 weeks	E: 135±9.3/ 80±9.1 V: 134±9.9/ 78±9.0	E: 123/72 V: 121/70	NA
Assadi (US, 2013) (134)	Enalapril (E) or enalapril + allopurinol (E+A)	E: 0.15 mg/kg/day, max 20 mg/day A: 5 mg/kg/day, max 300 mg/day (NA)	Stage 1 HT: SBP or DBP between 95th – 99th percentile + 5 mmHg	n=44 (20 E, 24 E+A) Age: 12 – 19 years Population: stage 1 primary HT with hyperuricemia (≥ 5.5 mg/dL), some obesity Excluded: other than primary HT, CL_{cr} < 100 mL/min/1.73m^2, renal/ urological abnormalities	Design: prospective, randomized, comparative, open-label study Duration: 8 weeks	E: 133/85 E+A: 134/86	E: 129/83 E+A:126/80	NA

Table 8.4: Study setup and BP results of PD studies with ACE inhibitors in hypertensive children (continued)

Author (country, year)	Drug	Dose (formulation)	Definition HT	Patients	Study design and duration	Mean BP ± SD pretreatment (mmHg)	Mean BP ± SD post-treatment (mmHg)	Clinical target achieved (≥ 6 mmHg)*
Di Salvo *et al.* (Italy, 2015) (135)	Enalapril (E) or atenolol (A)	E: 0.08 – 0.6 mg/kg/day A: 0.5 – 2 mg/kg/day (tablets)	Mean 24h-SBP or 24h-DBP > 95th percentile	n=51 (25 E, 26 A) Age: 6 – 20 years Population: HT after successful aortic coarctation repair, BMI < 90th percentile Excluded: comorbidities, intolerance to the drugs, liver/renal insufficiency	Design: prospective, randomized, comparative, open-label, drug titration^{n} study Duration: 12 months	E: 135±6/ 73±8 (24-h ABP) A: 133±11/ 71±10 (24h-ABP)	E: 127±7/ 71±7 (24h-ABP) A: 124±16/ 69±6 (24h-ABP)	NA
Soergel *et al.* (Germany, 2000) (136)	Ramipril	1.5 – 3 mg/m^2/day (NA)	Mean 24h-SBP or 24h-DBP > 95th percentile	n=14 Age: 5 – 18 years Population: moderate HT due to HUS (n=2), uropathy (n=3), chronic glomerular disease (n=9), CKD patients (4 eGFR < 60 mL/min/1.73m^2) Excluded: renal Tx, poor adherence, eGFR < 30 mL/min/1.73m^2	Design: prospective cohort, drug titration^{o} study Duration: 6 months	128±8.0/ 80±5.5 (24h-ABP)	119±7.3/ 71±4.0 (24h-ABP)	SBP: 86% DBP: 86%
Seeman *et al.* (Czech Republic, 2004) (137)	Ramipril	1.5 – 6 mg/m^2/day (NA)	Mean 24h-SBP and/or 24h-DBP ≥ 95th percentile	n=31 Age: 1.9 – 19.8 years Population: proteinuria and/or secondary HT due to polycystic kidneys (n=18), chronic glomerular disease (n=2), reflux nephropathy (n=6), HUS (n=3), chronic tubulointerstitial nephritis (n=2), 10 eGFR < 60 but > 30 mL/min/1.73m^2	Design: prospective cohort, drug titration^{p} study Duration: 6 months	NA	-11±6/-10±5 (daytime ABP)	NA

Table 8.4: Study setup and BP results of PD studies with ACE inhibitors in hypertensive children (continued)

Author (country, year)	Drug	Dose (formulation)	Definition HT	Patients	Study design and duration	Mean BP ± SD pretreatment (mmHg)	Mean BP ± SD post-treatment (mmHg)	Clinical target achieved (≥ 6 mmHg)*
Wühl *et al.* (Germany, 2004) (138) + continuation by Wühl *et al.* (Germany, 2009) (44)	Ramipril	6 mg/m^2/day (tablets)	24h-MAP > 95th percentile	n=352 (2004), n=385 (2009) Age: 3 – 18 years Population: secondary HT due to acquired glomerulopathy (13%), inherited or other renal disease (17%), renal hypo- or dysplasia (70%), all patients had an eGFR ≤ 80 mL/min/1.73m^2 Excluded: RAS, renal Tx, unstable condition	Design: international, prospective, randomized study Duration: 6 months (2004) with extension to 5 years (2009)	119±11.4/ 73±9.3 (24h-ABP)	After 6 months: 110±14.4/ 65±12.3 for total population	NA
Seeman *et al.* (Czech Republic, 2007) (139)	Ramipril	1.5 – 6 mg/m^2/day (NA)	Mean 24h-SBP or 24h-DBP ≥ 95th percentile	n=21 Age: 3.3 – 17.8 years Population: primary HT (n=4) or secondary HT due to renal dysplasia (n=2), reflux nephropathy (n=5), HUS (n=1), polycystic kidneys (n=8), IgA nephropathy (n=1), 1 eGFR < 60 but > 30 mL/min.1.73m^2	Design: prospective cohort, drug titration^p study Duration: 6 months	126/75 (24h-ABP)	116/67 (24h-ABP)	NA

Table 8.4: Study setup and BP results of PD studies with ACE inhibitors in hypertensive children (continued)

Author (country, year)	Drug	Dose (formulation)	Definition HT	Patients	Study design and duration	Mean BP ± SD pretreatment (mmHg)	Mean BP ± SD post-treatment (mmHg)	Clinical target achieved (≥ 6 mmHg)*
Soffer *et al.* (US, 2003) (33)	Lisinopril	(<50/≥50 kg): Low: 0.02 mg/kg (0.625/1.25 mg) Middle: 0.07 mg/kg (2.5/5 mg) High: 0.61 mg/kg (20/40 mg) (suspension or tablets)	DBP > 95th percentile	n=115 Age: 6 – 16 years Population: HT, mostly secondary (renal disease) Excluded: eGFR < 30 mL/min/1.73m^2, 20 kg	Design: prospective, double-blind, randomized, industry-driven, multicentre, placebo-controlled, dose-response study Duration: 2 weeks of double-blind lisinopril treatment followed by 2 weeks of double-blind withdrawal (lisinopril or placebo)	Low: 126± 12.7/88±8.7 Middle: 134± 15.1/91±9.4 High: 129± 11.6/90±7.7	Low: 120± 9.9/80±9.3 Middle: 122 ±9.1/82±8.7 High: 113± 12.1/74±11.7	NA
Raes *et al.* (Belgium, 2007) (29)	Lisinopril	0.1 – 0.5 mg/kg/day, mean of 0.105 mg/kg/day (tablets, capsules or powder papers)	BP > 95th percentile	n=59 Age: 0.2 – 17.6 years Population: renal HT (n=58), primary HT (n=1)	Design: retrospective chart review with drug titration[q] Duration: 18 days – 5.9 years	136±13.7/ 90±11.3	After 6 months: 116±13.5/ 72±11.3	NA
Trachtman *et al.* (US, 2015) (109)	Lisinopril	0.1 – 0.4 mg/kg/day (tablets)	SBP ≥ 75th percentile	n=13 Age: 7 – 17 years Population: HT with stable renal Tx[r], 7 patients had an eGFR < 60 mL/min/1.73m^2 Excluded: eGFR < 30 mL/min/1.73m^2, allergy to ACE inhibitors, stage 2 HT, serum potassium > 6 mmol/L, history of angioedema	Design: prospective cohort, open-label, multicentre study Duration: 10 – 16 days for the lisinopril-naïve group and 11 – 41 days for standard of care group	NA	-9.0±6.9/- 6.2±9.9	SBP: 85% DBP: 77%

Table 8.4: Study setup and BP results of PD studies with ACE inhibitors in hypertensive children (continued)

Author (country, year)	Drug	Dose (formulation)	Definition HT	Patients	Study design and duration	Mean BP ± SD pretreatment (mmHg)	Mean BP ± SD post-treatment (mmHg)	Clinical target achieved (≥ 6 mmHg)*
Li *et al.* (US, 2004) (140) + extrapolation by Menon *et al.* (US, 2006) (141)	Fosinopril	Low: 0.1 mg/kg (10 mg > 60 kg) Middle: 0.3 mg/kg (20 mg > 60 kg) High: 0.6 mg/kg (40 mg > 60 kg) (tablets)	SBP or DBP > 95th percentile	n=253 Age: 6 – 16 years Population: HT or high-normal BP with associated condition (renal disease (20.9%), diabetes mellitus)	Design: multicentre, prospective, double-blind, randomized, industry-driven, placebo-controlled study Duration: 58 weeks (4 weeks of dose-ranging, 2 weeks of placebo-controlled withdrawal and 52 weeks of open-label safety study[s])	Low: 134± 11.1/71±11.3 Middle: 133± 12.0/71±9.4 High: 134± 10.6/73±9.2	Low: 123/67 Middle: 122/67 High: 122/68 (after 4 weeks)	NA

[a]The initial dose was 1 mg, which increased to 2.5 and 5 mg after 2 and 4h, respectively. Every 8-24h, the dosage increased by 12.5 mg until DBP < 105 mmHg. Titration continued every 24h until DBP was below 105 mmHg for at least 8h after single-dosing; max dose was 2 mg/kg/dose.
[b]Starting dose was 0.3 mg/kg; every 8-24h, the dose was increased by 0.3 mg/kg until satisfactory BP control; max dose was 2 mg/kg/8h.
[c]Patients were hospitalized for min 3 days and received their first 3 doses: 0.5, 1.0 and 2.0 mg/kg (patients were randomly assigned to 1 of the 6 possible sequences); next dose was given if BP returned to baseline level; after dose titration phase, patients received individual dependent equal captopril doses two- or three-daily; dose was adjusted in clinical visits if necessary.
[d]Starting dose was 25 mg; dose increased every week or every month according to BP control with a max dose of 250 mg/day.
[e]Due to symptomatic uraemia (n=8), chronic glomerulopathy (n=3), SLE (n=3), renovascular disease (n=3), postinfectious renal scarring (n=2), undefined nephropathy (n=5), poststreptococcal glomerulonephritis (n=1), HUS (n=1), polycystic kidneys (n=1), Wilms' tumour (n=1), posttraumatic renal damage (n=1), after renal Tx (n=1).
[f]Initial dose was 6.25 mg; dose was adjusted according to BP effect the next days until normalization or decrease in DBP ≥ 20 mmHg.
[g]Due to HUS (n=13), renal parenchymal disease (n=19), renal Tx (n=13), renal vascular disease (n=16), primary/malignant/renin-induced HT (n=5), vasculitis (n=6), HT after aortic coarctation repair and ventricular septal defect (n=1).
[h]Initial dose was 0.3 mg/kg/8h; according to response, the dose was increased every 8-24h (first to 0.6, then to 1.2 and lastly to 2.0 mg/kg/dose with a max of 6 mg/kg/day); when max dosage was insufficient, hydrochlorothiazide or furosemide was added; if this was still ineffective, a ß-blocker was added to the regimen.
[i]The 10 patients with HT due to renal disease underwent a dose titration protocol; the doses were 0.5, 1.0 and 2.0 mg/kg (patients were randomly assigned to 1 of the 6 possible sequences); the next dose was administered when BP returned to baseline level; after this 3-dose protocol, captopril was taken daily at the dose that gave the desired response during the titration protocol.
[j]Starting dose was 0.3 mg/kg/day; dose was increased up to a max of 8 mg/kg/day (mostly 3 mg/kg/day) according to BP response.
[k]Aetiology is uncertain; possible causes are respiratory distress syndrome, BPD, RAS, polycystic kidney disease, UAC or dexamethasone treatment; each of these possible causes are already documented as having a relationship with the development of hypertension.
[l]After dramatic BP decrease in one infant with an initial dose of 0.5 mg/kg, the other patients received 0.01 mg/kg as initial dose; this starting dose was increased according to BP response.

[m]Starting dose was 0.01 mg/kg; this dose increased to 0.1 mg/kg within 7 days; this dose was further increased to max 0.5 mg/kg according to SBP at a 5-to-7-day interval.
[n]In the first month, patients returned weekly to the clinic to adjust dosage according to heart rate and BP response.
[o]If HT persisted, the starting dose of 1.5 mg/m^2/day was increased to 3 mg/m^2/day after 2 weeks.
[p]After 1 month, starting dose of 1.5 mg/m^2/day was doubled if mean BP values were not < 95th percentile; max dose was 6 mg/m^2/day.
[q]The starting dose was 0.1 mg/kg/day; during clinical visits, dose was adjusted according to BP response; if 0.5 mg/kg/day was insufficient, another antihypertensive drug was added, mostly a calcium channel blocker.
[r]The children were divided into 2 populations: 1 lisinopril-naïve group and 1 standard of care group (already took lisinopril as an antihypertensive drug); both populations were also divided into 2 groups according to eGFR: low (30 – 59 mL/min/1.73m^2) and high (≥ 60 mL/min/1.73m^2) eGFR group.
[s]During the last phase of 52 weeks, dose was titrated (0.1 – 0.6 mg/kg with a maximum of 40 mg) until BP target (< 90th percentile) was achieved; additional antihypertensive agents were allowed.

ABP = ambulatory blood pressure, ACE = angiotensin-converting enzyme, ARB = angiotensin-II receptor blocker, BMI = body mass index, BP = blood pressure, BPD = bronchopulmonary dysplasia, CHF = congestive heart failure, CKD = chronic kidney disease, CL_{cr} = creatinine clearance, CLD = chronic lung disease, CRF = chronic renal failure, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, ESRD = end stage renal disease, GNP = glomerulonephritis, HT = hypertension, HUS = haemolytic uremic syndrome, IgA = immunoglobulin A, LVH = left ventricular hypertrophy, MAP = mean arterial pressure (MAP = DBP + 1/3 (SBP – DBP)), max = maximum, min = minimum, n = number, NA = not available, PD = pharmacodynamics, RAS = renal artery stenosis, RAT = renal artery thrombosis, RVH = right ventricular hypertrophy, SBP = systolic blood pressure, SD = standard deviation, SLE = systemic lupus erythematosus, Tx = transplantation, UAC = umbilical artery catheterization, US = Unites States

The following parameters were not included due to unavailability in literature (> 60% missing values): eGFR and body weight

*Individual BP values were available in 8 of the 30 studies (26.7%) with a total of 77 patients. For these 77 patients, it was possible to check if the clinical target was achieved, and the percentage of achievement is noted in the table for SBP and/or DBP. For the remaining 22 studies, no individual BP data were available, and conversion of the results was out-of-scope for this master's thesis.

8.7. APPENDIX VII: SAFETY PROFILE OF ACE INHIBITORS IN HYPERTENSIVE CHILDREN

Table 8.5: Safety profile of ACE inhibitors in hypertensive children

Author (country, year)	n	Drug	Simplified patient population*	Age range	PK/PD study	Study duration	Serum creatinine/urea/BUN	Serum potassium	SAE**
Levy *et al.* (Canada, 1991) (101)	8	Captopril	Normotensive and normoreninemic with confirmed renal scarring	5 – 18 years	PK	1 day	Elevated serum creatinine values (n=1)	/	/
Pereira *et al.* (Canada, 1991) (106)	10	Captopril	CHF	2 – 15 months	PK	1 week	/	/	/
Lloyd *et al.* (US, 1989) (102)	10	Enalapril	Unresponsive CHF, no renal impairment	6 weeks – 8 months	PK	9 days – 24 weeks	Serum creatinine and urea did not change significantly	Increased from 4.7 ± 0.7 to 5.1 ± 0.6 mmol/L ($p<0.05$)	/
Nakamura *et al.* (Japan, 1994) (107)	12	Enalapril	CHF, no renal impairment	10 days – 6.5 years	PK	1 – > 5 days	/	/	/
Wells *et al.* (US, 2001) (103)	40	Enalapril	HT with normal renal function, 23 had secondary HT	2 months – 15 years	PK	4 – 19 days	No clinically relevant changes in serum creatinine	No clinically relevant changes in serum potassium	No SAE related to the drug
Blumer *et al.* (US, 2003) (104)	24	Quinapril	Already under ACE inhibitor treatment, mostly for congenital heart diseases, acceptable renal function	2.5 months – 6.8 years	PK	1 day	/	/	/
Hogg *et al.* (US, 2007) (108)	46	Lisinopril	HT, history of renal disease (n=38), eGFR > 30 mL/min/1.73m^2	6 months – 15 years	PK	6 – 12 days	No clinically relevant changes in serum creatinine	No clinically relevant changes in serum potassium	No SAE related to the drug

Table 8.5: Safety profile of ACE inhibitors in hypertensive children (continued)

Author (country, year)	n	Drug	Simplified patient population*	Age range	PK/PD study	Study duration	Serum creatinine/urea/BUN	Serum potassium	SAE**
Friedman *et al.* (US, 1980) (115)	6	Captopril	Poor responsive severe secondary HT	6 – 18 years	PD	3 – 16 months	Increased serum creatinine (n=1)	Hyperkalaemia (n=1), the other patients had no significant change in serum potassium	/
Hymes *et al.* (US, 1983) (116)	5	Captopril	Unresponsive, high-renin secondary HT	5 weeks – 13 years	PD	6 – 26 months	Reversible renal insufficiency (n=1). Rise in serum creatinine (n=1). Rise in BUN (n=1).	/	/
Sinaiko *et al.* (US, 1983) (105)	10	Captopril	Renal HT	3.5 – 20 years	PK/PD	1 – 12 months	/	/	/
Friedman *et al.* (US, 1983) (117)	9	Captopril	Refractory HT	6 – 18 years	PD	NA	/	/	/
Chan *et al.* (England, 1984) (118)	5	Captopril	HT after renal Tx	9 – 20 years	PD	3 – 15 months	/	/	Transient anuria (n=1)
Sigström *et al.* (Sweden, 1984) (119)	30	Captopril	Unresponsive renal HT	8 months – 16 years	PD	1 – 47 months	Decrease in eGFR (n=2)	/	/
Mirkin *et al.* (US, 1985) (120)	73	Captopril	Severe and refractory HT intolerant or unresponsive to other acceptable antihypertensive agents, also renal impairment and dialysis	11 days – 15 years	PD	< 3 months – > 1 years	Rise in serum creatine with ≥ 50% (n=19). Statistically significant but not clinically relevant changes of BUN and serum creatinine.	Statistically significant increase in serum potassium but < 5 mmol/L	/

Table 8.5: Safety profile of ACE inhibitors in hypertensive children (continued)

Author (country, year)	n	Drug	Simplified patient population*	Age range	PK/PD study	Study duration	Serum creatinine/urea/BUN	Serum potassium	SAE**
Bouissou *et al.* (France, 1986) (121)	25	Captopril	Severe renal HT, 10 renal Tx, 10 on dialysis, only 5 had normal renal function	1.5 – 18 years	PD	2 – 40 months	Reversible acute renal failure (n=1)	Mean increase of 1.6 mmol/L but no severe hyperkalaemia	/
Sinaiko *et al.* (US, 1986) (122)	34	Captopril	Mostly renal HT	Premature neonates to adolescents	PD	NA	Increase of serum creatinine in 62% of the patients. Increase in serum creatinine from 1.1 ± 0.1 to 1.7 ± 0.2 mg/dL in renal Tx group (p<0.05).	/	/
Callis *et al.* (Spain, 1986) (123)	42	Captopril	Uncontrolled secondary HT (ESRD), on haemodialysis	1 – 17 years	PD	1.5 – 6.1 years	/	Concentration of 5.3 ± 0.7 mmol/L	/
Sagát *et al.* (Slovakia, 1986) (124)	9	Captopril	Uncontrolled renal HT, 5 had renal insufficiency	2 months – 13 years	PD	1 – 14 months	Increase in serum creatinine (n=1)	/	/
Tack *et al.* (US, 1988) (125)	9	Captopril	CLD + secondary HT unresponsive to hydralazine	10 – 269 days	PD	9 days – > 24 months	Serum creatinine increased from 0.3 ± 0.2 to 1.6 ± 0.6 mg/dL (p<0.001). BUN increased from 9.5 ± 4.0 to 34 ± 14 mg/dL (p<0.001).	/	Hemorrhagic infarction (n=1), severe hypotension with oliguria (n=4)
O'Dea *et al.* (US, 1988) (126)	11	Captopril	Severe secondary HT	2 – 84 days	PD	3 – 21 days	/	/	Hypotension with oliguria (n=1)
Morsi *et al.* (Egypt, 1992) (127)	20	Captopril	Secondary HT due to acute post-streptococcal glomerulonephritis	4 – 10 years	PD	3 days	BUN and serum creatinine did not change significantly	/	/

Table 8.5: Safety profile of ACE inhibitors in hypertensive children (continued)

Author (country, year)	n	Drug	Simplified patient population*	Age range	PK/PD study	Study duration	Serum creatinine/urea/BUN	Serum potassium	SAE**
Sehgal *et al.* (Australia, 2018) (128)	6	Captopril	Severe BPD with HT	39 – 54 weeks gestational age	PD	3 – 5 weeks	/	/	/
Miller *et al.* (US, 1987) (129)	15	Enalapril	Secondary HT	6 weeks – 18.5 years	PD	5 – > 12 months	BUN decreased from 24.0 ± 17.6 to 22.3 ± 8.1 mg/dL. Serum creatinine increased from 0.8 ± 0.3 to 0.9 ± 0.4 mg/dL.	Serum potassium increased from 4.56 ± 0.8 to 4.62 ± 0.6 mmol/L	/
Wells *et al.* (US, 1990) (130)	10	Enalaprilat	HT, mostly secondary	26 – 36 weeks gestational age	PD	2 – 17 days	Mild renal failure (n=1)	Serum potassium increased from 4.5 ± 1.0 to 4.8 ± 1.0 mmol/L (not SN). Hyperkalaemia (n=2)	Oliguria (n=2)
Wells *et al.* (US, 2002) (131)	110	Enalapril	HT, mostly secondary, eGFR > 30 mL/min/1.73m^2	6 – 16 years	PD	4 weeks	Small increase in creatinine and/or BUN. No change in mean serum creatinine.	No change in mean serum potassium.	/
Rouine-Rapp *et al.* (US, 2003) (132)	6	Enalaprilat	HT after surgical repair of aorta coarctation, no renal abnormalities	1.3 – 13 years	PD	36h	/	/	/
Schaefer *et al.* (Germany, 2011) (133)	143	Enalapril	Primary or secondary HT, eGFR > 30 mL/min/1.73m^2	6 – 17 years	PD	12 weeks	Slight mean increases in BUN and creatinine	> 5.5 mmol/L (n=4) > 6 mmol/L (n=2)	Avulsion fracture (n=1), renal injury (n=1)

Table 8.5: Safety profile of ACE inhibitors in hypertensive children (continued)

Author (country, year)	n	Drug	Simplified patient population*	Age range	PK/PD study	Study duration	Serum creatinine/urea/BUN	Serum potassium	SAE**
Assadi (US, 2013) (134)	44	Enalapril	Stage 1 primary HT with hyperuricemia (≥ 5.5 mg/dL), CL_{cr} > 100 mL/min/1.73m^2, no renal abnormalities	12 – 19 years	PD	8 weeks	/	/	/
Di Salvo *et al.* (Italy, 2015) (135)	25	Enalapril	HT after successful aortic coarctation repair, no renal insufficiency	6 – 20 years	PD	12 months	/	/	/
Soergel *et al.* (Germany, 2000) (136)	14	Ramipril	Moderate secondary HT, 4 eGFR < 60 but > 30 mL/min/1.73m^2	5 – 18 years	PD	6 months	Transient drop in eGFR (n=1)	/	/
Seeman *et al.* (Czech Republic, 2004) (137)	31	Ramipril	Proteinuria and/or secondary HT, 10 eGFR < 60 but > 30 mL/min/1.73m^2	1.9 – 19.8 years	PD	6 months	No significant decrease in eGFR	No significant change in mean serum potassium. Mild hyperkalaemia (5.6 and 5.7 mmol/L).	/
Wühl *et al.* (Germany, 2004) (138) + continuation by Wühl *et al.* (Germany, 2009) (44)	385	Ramipril	Renal HT, eGFR 15 – 80 mL/min/1.73m^2	3 – 18 years	PD	6 months with extension to 5 years	Decreased eGFR (n=50)	Serum potassium increased from 4.3 ± 0.5 to 4.5 ± 0.8 after 6 months ($p<0.05$). Hyperkalaemia (n=18), severe hyperkalaemia (n=7)	Death (n=1)

Table 8.5: Safety profile of ACE inhibitors in hypertensive children (continued)

Author (country, year)	n	Drug	Simplified patient population*	Age range	PK/PD study	Study duration	Serum creatinine/urea/BUN	Serum potassium	SAE**
Seeman *et al.* (Czech Republic, 2007) (139)	21	Ramipril	Primary HT (n=4) or secondary HT (n=17), 1 eGFR < 60 but > 30 mL/min/ 1.73m^2	3.3 – 17.8 years	PD	6 months	/	No significant change in mean serum potassium. Mild hyperkalaemia (5.3 and 5.6 mmol/L).	/
Soffer *et al.* (US, 2003) (33)	115	Lisinopril	HT, mostly secondary (renal disease), eGFR > 30 mL/min/1.73m^2	6 – 16 years	PD	4 weeks	Increased BUN and creatinine (n=2)	Hyperkalaemia (n=1)	/
Raes *et al.* (Belgium, 2007) (29)	59	Lisinopril	Renal HT (n=58), primary HT (n=1)	0.2 – 17.6 years	PD	18 days – 5.9 years	Serum creatinine did not change	Serum potassium did not change	Tachycardia (n=1)
Trachtman *et al.* (US, 2015) (109)	22	Lisinopril	HT with stable renal Tx, eGFR > 30 mL/min/1.73m^2	7 – 17 years	PK/PD	10 – 41 days	22% decrease in eGFR (n=1)	Change from 0.1 (-1.3 – 0.7) mmol/L	Gastro-enteritis with hospitalization but drug-unrelated (n=1)
Li *et al.* (US, 2004) (140) + extrapolation by Menon *et al.* (US, 2006) (141)	253	Fosinopril	Secondary HT or high-normal BP	6 – 16 years	PD	58 weeks	Serum creatinine levels were normal	Hyperkalaemia (n=1, 6.6 mmol/L)	/

*For detailed information about the patient population see Table 8.1 for PK studies and Table 8.4 for PD studies.
**A SAE is any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization or results in persistent or significant disability/incapacity of the child.

ACE = angiotensin-converting enzyme, BPD = bronchopulmonary dysplasia, BUN = blood urea nitrogen, CHF = congestive heart failure, CLD = chronic lung disease, eGFR = estimated glomerular filtration rate, ESRD = end stage renal disease, HT = hypertension, n = number, PD = pharmacodynamics, PK = pharmacokinetics, SAE = serious adverse event, SN = statistically significant, Tx = transplantation, US = United States

8.8. APPENDIX VIII: TABLES OF RQ 3

Table 8.6: Study setup of PK studies with ARBs in hypertensive children

Author (country, year)	Drug	Dose and dose regimen (formulation)	n	Age range	Weight range (kg)	eGFR range (mL/min/1.73m^2)	Patient population	Concomitant drugs	Study design and duration
Sakarcan *et al.* (US, 2001) (144)	Irbesartan	2 mg/kg, max 150 mg, once daily (capsules or powder)	23	1 – 16 years	10.4 – 113.4	NA	Confirmed HT (SBP and/or DBP ≥ 95th percentile) Excluded: severe HT, comorbidities, dialysis, renovascular problems, renal Tx, CL_{cr} < 25 mL/min/1.73m^2, hypersensitivity to ARBs	Nifedipine and/or HCT (n=11)	Design: open-label, industry-driven, multicentre study Duration: 2 – 4 weeks
Trachtman *et al.* (US, 2008) (145)	Candesartan	16 mg, one dose (tablets)	22	6 – 17 years	Mostly ≥ 50 kg	NA	HT (SBP or DBP > 95th percentile), mostly primary; obesity Excluded: < 25 kg, severe HT, secondary HT due to aorta coarctation or endocrinological disorders, DM, RAS, nephrotic syndrome, eGFR < 50 mL/min/1.73m^2	NA	Design: open-label, industry-driven, multicentre, single-dose PK study Duration: 1 day
Schaefer *et al.* (Germany, 2010) (146)	Candesartan	0.2 mg/kg, one dose (suspension)	10	1 – 5 years	11 – 22	NA	HT (SBP or DBP > 95th percentile), mostly secondary; obesity Excluded: severe HT, secondary HT due to aorta coarctation or endocrinological disorders, DM, RAS, nephrotic syndrome, eGFR < 30 mL/min/1.73m^2	NA	Design: open-label, industry-driven, multicentre, single-dose PK study Duration: 28h

Table 8.6: Study setup of PK studies with ARBs in hypertensive children (continued)

Author (country, year)	Drug	Dose and dose regimen (formulation)	n	Age range	Weight range (kg)	eGFR range (mL/min/1.73m^2)	Patient population	Concomitant drugs	Study design and duration
Blumer *et al.* (US, 2009) (147)	Valsartan	2 mg/kg, max 80 mg, one dose (suspension)	26	1 – 16 years	NA	NA	HT (SBP or DBP ≥ 95th percentile) Excluded: chronic disorder or unstable clinical condition	Yes[a]	Design: open-label, industry-driven, multicentre, single-dose PK study Duration: 1 day
Wells *et al.* (US, 2010) (148)	Telmisartan	Low: 1 mg/kg, once daily High: 2 mg/kg, once daily (tablets)	48	7 – 17 years	20 – 120	NA	HT (SBP ≥ 95th percentile) Excluded: severe HT, symptomatic HT, heart problems, RAS, CKD, hepatic impairment, organ or bone marrow Tx	NA	Design: open-label, industry-driven, multicentre, steady state PK study Duration: 4 weeks
Wells *et al.* (US, 2012) (149)	Olmesartan	< 6 years: 0.3 mg/kg, max 20 mg ≥ 6 years, < 35 kg: 20 mg ≥ 6 years, ≥ 35 kg: 40 mg One dose (suspension or tablets[b])	24	4 – 16 years	18 – 136	NA	HT (SBP or DBP ≥ 95th percentile or ≥ 90th percentile in case of DM or family history of HT), primary HT (n=21); obesity (n=16), asthma Excluded: eGFR < 30 mL/min/1.73m^2, unstable clinical condition	Amlodipine (n=6), atenolol (n=1), HCT (n=1), enalapril (n=3), valsartan (n=3), metoprolol (n=1), nifedipine (n=1), ß-agonists, cortico-steroids	Design: open-label, industry-driven, multicentre, single-dose PK study Duration: 48h

[a]Amoxicillin (n=1), amlodipine (n=2), hydrocortisone (n=1), budesonide (n=1), fludrocortisone acetate (n=1), salbutamol (n=2), ibuprofen (n=1), loratadine (n=1), oxybutynin (n=1), levothyroxine (n=1), sodium bicarbonate (n=1), sodium citrate (n=1), calcium carbonate (n=1)
[b]Children < 6 years and children ≥ 6 years who couldn't swallow tablets, received a suspension.

ARB = angiotensin-II receptor blocker, CKD = chronic kidney disease, CL_{cr} = creatinine clearance, DBP = diastolic blood pressure, DM = diabetes mellitus, eGFR = estimated glomerular filtration rate, HCT = hydrochlorothiazide, HT = hypertension, max = maximum, n = number, NA = not available, PK = pharmacokinetics, RAS = renal artery stenosis, SBP = systolic blood pressure, Tx = transplantation, US = United States

Table 8.7: Sampling regimen and bioanalysis method of PK studies with ARBs in hypertensive children

Author (country, year)	Drug	n	Age range	Study duration	Sampling regimen	Bioanalysis method
Sakarcan *et al.* (US, 2001) (144)	Irbesartan	23	1 – 16 years	2 – 4 weeks	Plasma samples were taken predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24h after the first and the last dose (steady state).	HPLC-FL
Trachtman *et al.* (US, 2008) (145)	Candesartan	22	6 – 17 years	1 day	Plasma samples were taken predose and at several timepoints post-administration for 24h.	LC-FL
Schaefer *et al.* (Germany, 2010) (146)	Candesartan	10	1 – 5 years	28h	Plasma samples were taken at several timepoints post-administration for 28h.	LC-FL
Blumer *et al.* (US, 2009) (147)	Valsartan	26	1 – 16 years	1 day	Plasma samples were taken predose and at 0.5, 1, 2, 3, 4, 6, 8, 12 and 24h post-administration in children aged 6 – 12 years; in children aged 1 – 5 years, plasma samples were taken predose and at 0.5, 1, 2, 4, 12 and 24h post-administration.	HPLC-MS/MS
Wells *et al.* (US, 2010) (148)	Telmisartan	48	7 – 17 years	4 weeks	On day 28 (steady state), plasma samples were taken predose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6 and 10h post-administration.	NA
Wells *et al.* (US, 2012) (149)	Olmesartan	24	4 – 16 years	48h	Plasma samples were taken predose and at 1, 2, 4, 8, 12, 24 and 48h post-administration.	HPLC-MS/MS

ARB = angiotensin-II receptor blocker, (HP)LC-FL = (high performance) liquid chromatography - fluorescence, HPLC-MS/MS = high performance liquid chromatography – tandem mass spectrometry, n = number, NA = not available, PK = pharmacokinetics, US = United States

Table 8.8: Study setup of PD studies with ARBs in hypertensive children

Author (country, year)	Drug	Dose (formulation)	Definition HT	Patients	Study design and duration
Von Vigier *et al.* (Switzerland, 2000) (150)	Irbesartan	Initial: 2.7 mg/kg Sustained: 3.3 mg/kg (NA)	SBP or DBP > 95th percentile	n=20 Age: 4 – 17 years Population: CKD with HT (n=11), proteinuria (n=3) or both (n=6); normal (n=8), mildly reduced (n=8) or moderately reduced (n=4) renal function; glomerulopathies (n=11), RAS (n=1), urological abnormalities (n=3), renal Tx (n=1)	Design: prospective cohort, drug titration[a] study Duration: 2 – 17 months
Sakarcan *et al.* (US, 2001) (144)	Irbesartan	2 mg/kg, max 150 mg (capsules or powder)	SBP and/or DBP ≥ 95th percentile	n=23 Age: 1 – 16 years Population: confirmed HT Excluded: severe HT, comorbidities, dialysis, renal Tx, renovascular problems, CL_{cr} < 25 mL/min/1.73m^2, hypersensitivity to ARBs	Design: prospective cohort, open-label, industry-driven, multicentre study Duration: 2 – 4 weeks
Franscini *et al.* (Switzerland, 2002) (151)	Irbesartan	HT initial: 2.6 mg/kg HT sustained: 4.1 mg/kg P: 2.9 mg/kg (tablets)	BP > 95th percentile	n=44 Age: 3.7 – 18 years Population: CKD with secondary HT (n=23), proteinuria (P, n=8) or both (n=13); HT due to glomerulopathies (n=13), urological abnormalities (n=12), renal Tx (n=6), polycystic kidneys (n=3), RAS (n=1), NPH (n=1); normal (n=19), mildly reduced (n=13) or moderately reduced (n=7) renal function, 5 on dialysis	Design: prospective cohort, drug titration[b] study Duration: 18 weeks
Gartenmann *et al.* (Switzerland, 2003) (152)	Irbesartan (I) or amlodipine (A)	I initial: 2.9 mg/kg I sustained: 4.8 mg/kg A initial: 0.19 mg/kg A sustained: 0.33 mg/kg (tablets)	SBP 5-30 mmHg and DBP 1-15 mmHg > 95th percentile	n=26 (13 I, 13 A) Age: 6.1 – 17 years Population: CKD with proteinuria and HT due to reflux nephropathy (n=3), HUS (n=5), polycystic kidneys (n=3), IgA nephropathy (n=3), glomerular sclerosis (n=2), NPH (n=2), GNP (n=3), Alport syndrome (n=1), SLE (n=1), renal hypoplasia (n=2), Wegener's granulomatosis (n=1)	Design: open-label, randomized, active-controlled, drug titration[c] study Duration: 16 weeks

Table 8.8: Study setup of PD studies with ARBs in hypertensive children (continued)

Author (country, year)	Drug	Dose (formulation)	Definition HT	Patients	Study design and duration
Ellis *et al.* (US, 2003) (153)	Losartan	Initial: 0.8 mg/kg Sustained: 1 mg/kg (NA)	BP > 95th percentile	n=52 Age: 3.73 – 17.99 years Population: CKD with proteinuria (n=30) or proteinuria and HT (n=22) due to IgA nephropathy (n=21), glomerular sclerosis (n=7), GNP (n=16), other (n=8); eGFR 25 – 90 mL/min/1.73m^2 (n=25) Excluded: dialysis, CL_{cr} < 25 mL/min/1.73m^2	Design: retrospective cohort, industry-driven, drug titration[d] study Duration: 1.0 – 6.3 years
Ellis *et al.* (US, 2004) (154)	Losartan	Initial: 0.8 mg/kg Sustained: 1 mg/kg (NA)	BP > 95th percentile	n=45 Age: 3.7 – 17.9 years Population: CKD with HT (n=21) or HT and proteinuria (n=24) due to renal (n=34) or urological diseases (n=11); eGFR 25 – 49 mL/min/1.73m^2 (n=6), eGFR 50 – 89 mL/min/1.73m^2 (n=12) Excluded: CL_{cr} < 25 mL/min/1.73m^2	Design: retrospective cohort, drug titration[d] study Duration: max 6.24 years
Shahinfar *et al.* (US, 2005) (155)	Losartan	(<50/≥50 kg): Low: 0.07 mg/kg (2.5/5 mg) Middle: 0.75 mg/kg (25/50 mg) High: 1.44 mg/kg (50/100 mg) (suspension or tablets)	DBP > 95th percentile	n=175 Age: 5 – 16 years Population: HT, > 50% renal HT Excluded: < 20 kg, eGFR < 30 mL/min/1.73m^2	Design: prospective, double-blind, randomized, placebo-controlled, industry-driven, multicentre study Duration: 3 weeks of treatment followed by 2 weeks of placebo-controlled washout

Table 8.8: Study setup of PD studies with ARBs in hypertensive children (continued)

Author (country, year)	Drug	Dose (formulation)	Definition HT	Patients	Study design and duration
Litwin *et al.* (Poland, 2006) (156)	Losartan (add-on therapy on ACE-I)	0.5 - 2 mg/kg (NA)	NA	n=11 Age: 0.5 – 18 years Population: CKD with HT and/or proteinuria due to HUS (n=4), nephrotic syndrome (n=3), acute cortical necrosis (n=1), reflux nephropathy (n=2), prune-belly syndrome (n=1); eGFR 14 – 156, 5 ≤ 30 mL/min/1.73m^2	Design: prospective cohort Duration: 24 months
Webb *et al.* (UK, 2010) (157)	Losartan (L) or amlodipine (A)	L: 0.7 – 1.4 mg/kg A: 0.05 – 0.2 mg/kg, max 5 mg/day (suspension or tablets)	SBP or DBP > 95th percentile	n=60 (30 L, 30 A) Age: 6 – 17 years Population: CKD with HT and proteinuria due to glomerular diseases (n=35), HUS (n=6), hypoplasia/ dysplasia/aplasia (n=2), reflux nephropathy (n=2), Alport syndrome (n=6), other (n=1), unknown (n=8) Excluded: severe HT, renal Tx, eGFR < 30 mL/min/1.73m^2	Design: prospective, double-blind, randomized, active-controlled, industry-driven, multicentre, drug titration[e] study Duration: 12 weeks of double-blind treatment followed by open-label, randomized follow up for 3 years (losartan or enalapril)
Sakalli *et al.* (Turkey, 2014) (158)	Losartan (add-on therapy on enalapril)	50 mg (NA)	SBP and DBP ≥ 95th percentile	n=31 Age: 4 – 18 Population: renal Tx with mild HT and proteinuria; GNP (n=13), urological disorders (n=11), polycystic kidneys (n=1), nephrosclerosis (n=2), unknown (n=4); 5 eGFR < 60 mL/min/1.73m^2 Excluded: RAS	Design: retrospective cohort Duration: 1 – 6 months
Webb *et al.* (UK, 2014) (159)	Losartan	Low: 0.1 mg/kg Middle: 0.3 mg/kg High: 0.7 mg/kg (suspension)	SBP and/or DBP ≥ 95th percentile or ≥ 90th percentile in case of end organ damage or comorbidities	n=99 Age: 0.5 – 6 years Population: HT, renal HT (n=66); stage 1 (n=45), 2 (n=12), 3 (n=5), 4 (n=1) CKD; obesity Excluded: eGFR < 30 mL/min/1.73m^2	Design: prospective, open-label, randomized, industry-driven, multicentre, drug titration study[f] Duration: 12 weeks of treatment followed by 2 years extension

Table 8.8: Study setup of PD studies with ARBs in hypertensive children (continued)

Author (country, year)	Drug	Dose (formulation)	Definition HT	Patients	Study design and duration
Simonetti *et al.* (Switzerland, 2006) (160)	Candesartan	Initial: 0.23 mg/kg Sustained: 0.35 mg/kg (suspension or tablets)	SBP or DBP > 95th percentile	n=17 Age: 0.5 – 16 years Population: HT (n=6), proteinuria (n=2) or both (n=9); glomerular disease (n=11), renal Tx (n=2), polycystic kidneys (n=3), primary HT (n=1); normal (n=9), moderately reduced (n=5) or strongly reduced (n=3) renal function	Design: prospective cohort, drug titration[g] study Duration: 4 months
Franks *et al.* (US, 2008) (161)	Candesartan	Initial: 0.05 – 0.1 mg/kg Sustained: 0.13 mg/kg (NA)	SBP and/or DBP > 95th percentile	n=11 Age: 6 – 18 years Population: HT, ≥ 20 kg Excluded: symptomatic HT, hypersensitivity to ARBs, RAS, aorta coarctation, hepatic impairment, renal Tx, eGFR < 30 mL/min/1.73m^2	Design: prospective cohort, drug titration[h] study Duration: 2 or 4 weeks
Trachtman *et al.* (US, 2008) (145)	Candesartan	<50/≥50 kg: Low: 2/4 mg Middle: 8/16 mg High: 16/32 mg (tablets)	SBP or DBP > 95th percentile	n=240 Age: 6 – 17 years Population: HT, mostly primary; renal or urological history (n=22), CKD (n=2), obesity Excluded: severe HT, secondary HT due to aorta coarctation or endocrinological disorders, DM, RAS, nephrotic syndrome, eGFR < 50 mL/min/1.73m^2	Design: prospective, double-blind, randomized, placebo-controlled, industry-driven, multicentre study Duration: 4 weeks of placebo-controlled dose ranging followed by 52 weeks of open-label clinical experience[i]
Schaefer *et al.* (Germany, 2010) (146)	Candesartan	Low: 0.05 mg/kg Middle: 0.2 mg/kg High: 0.4 mg/kg (suspension)	SBP or DBP > 95th percentile	n=93 Age: 1 – 5 years Population: renal (n=71) or primary HT (n=22); 10 eGFR < 60 but > 30 mL/min/1.73m^2, CKD (n=47), obesity (n=21) Excluded: severe HT, secondary HT due to aorta coarctation or endocrinological disorders, DM, RAS, nephrotic syndrome, eGFR < 30 mL/min/1.73m^2	Design: prospective, double-blind, randomized, industry-driven, multicentre study Duration: 4 weeks of dose ranging followed by 52 weeks of open-label clinical experience[j]

Table 8.8: Study setup of PD studies with ARBs in hypertensive children (continued)

Author (country, year)	Drug	Dose (formulation)	Definition HT	Patients	Study design and duration
Flynn *et al.* (US, 2008) (162)	Valsartan	<18/≥18 kg: Low: 5/10 mg Middle: 20/40 mg High: 40/80 mg (suspension)	SBP ≥ 95th percentile	n=90 Age: 1 – 5 years Population: HT, mostly secondary; renal or urological disorders (n=57), infection (n=42), obesity (n=6) Excluded: < 8 kg, severe HT, CL_{cr} < 30 mL/min/1.73m^2, abnormal lab values, RAS, hypersensitivity to ARBs, aorta coarctation, unstable clinical condition	Design: prospective, double-blind, randomized, placebo-controlled, industry-driven, multicentre study Duration: 2 weeks of treatment + 2 weeks of placebo-controlled washout + 52 weeks of open label dose finding phase[k]
Wells *et al.* (US, 2011) (163) + continuation by Meyers *et al.* (US, 2011) (164)	Valsartan	(<35/≥35 kg): Low: 0.4 mg/kg (10/20 mg) Middle: 1.3 mg/kg (40/80 mg) High: 2.7 mg/kg (80/160 mg) (NA)	SBP ≥ 95th percentile	n=261 Age: 6 – 16 years Population: HT; renal or urological disorders (n=99), obesity (n=142), renal Tx (n=21), DM (n=8) Excluded: < 20 kg, severe HT, CL_{cr} < 40 mL/min/1.73m^2, heart diseases, RAS, hepatic impairment, abnormal electrolytes, hypersensitivity to ARBs	Design: prospective, double-blind, randomized, placebo-controlled, industry-driven, multicentre study Duration: 2 weeks of treatment + 2 weeks of placebo-controlled washout + 52 weeks of open-label dose finding phase[l]
Schaefer *et al.* (Germany, 2011) (133)	Valsartan (V) or enalapril (E)	18-34 kg: 80 mg V, 10 mg E 35-79 kg: 160 mg V, 20 mg E 80-160 kg: 320 mg V, 40 mg E (tablets)	SBP ≥ 95th percentile	n=281 (138 V, 143 E) Age: 6 – 17 years Population: primary or secondary HT; 17% CKD, 32% renal or urological diseases Excluded: eGFR < 30 mL/min/1.73m^2, severe HT, hypersensitivity to ACE inhibitors or ARBs	Design: prospective, double-blind, randomized, active-controlled, industry-driven, multicentre study Duration: 12 weeks

Table 8.8: Study setup of PD studies with ARBs in hypertensive children (continued)

Author (country, year)	Drug	Dose (formulation)	Definition HT	Patients	Study design and duration
Schaefer *et al.* (Germany, 2013) (165)	Valsartan	Low: 0.25 mg/kg Middle: 1 mg/kg High: 4 mg/kg (suspension)	SBP ≥ 95th percentile	n=75 Age: 0.5 – 5 years Population: HT, mostly secondary; renal or urological history (n=46), infection (n=40), thoracic disorders (n=20) Excluded: severe HT, aorta coarctation, hypersensitivity to ARBs, clinical abnormalities, eGFR < 30 mL/min/1.73m^2	Design: prospective, double-blind, randomized, placebo-controlled, industry-driven, multicentre study Duration: 6 weeks of dose-ranging + 2 weeks of placebo-controlled washout + 18 weeks of open-label extension[m]
Lou-Meda *et al.* (Guatemala, 2018) (166)	Valsartan	18-34/35-79/80-160 kg: Initial: 40/80/160 mg Sustained: 80/160/320 mg (NA)	SBP ≥ 95th percentile	n=150 Age: 6 – 17 years Population: HT with (n=75) or without CKD (n=75); reflux nephropathy (n=9), hypoplasia/dysplasia/aplasia (n=10), glomerular diseases (n=29), systemic (n=9), NA (n=16); stage 2 or 3 CKD (n=44) Excluded: severe HT, clinical abnormalities, DM, serum potassium > 5.3 mmol/L, eGFR < 30 mL/min/1.73m^2, RAS, aorta coarctation, heart failure, hepatic impairment	Design: prospective cohort, open-label, industry-driven, multicentre, drug titration[n] safety study Duration: 18 months
Hazan *et al.* (US, 2010) (167)	Olmesartan	>20-34/≥35 kg: Low: 2.5/5 mg High: 20/40 mg (suspension)	SBP ≥ 95th percentile	n=302 Age: 6 – 17 years Population: primary (n=225) or secondary HT (n=77) Excluded: < 20 kg, CL_{cr} ≤ 25 mL/min/1.73m^2, severe HT, chronic disorder or unstable clinical condition, hypersensitivity to ARBs	Design: prospective, double-blind, randomized, placebo-controlled, industry-driven, multicentre study Duration: 3 weeks of dose-ranging phase followed by 2 weeks of placebo-controlled washout
Wells *et al.* (US, 2010) (148)	Telmisartan	Low: 1 mg/kg High: 2 mg/kg (tablets)	SBP ≥ 95th percentile	n=76 Age: 7 – 17 years Population: HT, 20 – 120 kg Excluded: severe HT, symptomatic HT, heart problems, RAS, CKD, hepatic impairment, organ or bone marrow Tx	Design: prospective, double-blind, randomized, placebo-controlled, industry-driven, multicentre study Duration: 4 weeks

[a]Starting dose of 75 (≤35 kg) or 150 mg (>35 kg) was doubled in the hypertensive children (n=17) if SBP didn't decrease ≥ 5 mmHg after 3 to 4 weeks or if SBP remained > 95th percentile after 6 to 8 weeks of treatment.
[b]Starting dose of 37.5 (10-20 kg), 75 (21-40 kg) or 150 mg (>40 kg) was doubled in the hypertensive children (n=36) if SBP didn't decrease ≥ 10 mmHg after 3 to 5 weeks or if SBP remained > 95th percentile after 8 to 12 weeks of treatment.
[c]Starting dose of irbesartan (75 mg for 20-40 kg and 150 for >40 kg) or amlodipine (5 mg for 20-40 kg and 10 mg for >40 kg) was doubled if SBP didn't decrease ≥ 10 mmHg after 3 to 5 weeks or if SBP or DBP remained > 95th percentile after 8 to 12 weeks of treatment.
[d]Starting dose of 0.8 mg/kg was increased if BP remained > 90th percentile for 1 week or if the value of proteinuria didn't half at clinical visit according to baseline.
[e]Starting dose of losartan was 0.7 mg/kg; after 2 weeks, dose was increased to max 1.4 mg/kg. Starting dose of amlodipine was 0.05 mg/kg or 0.1 mg/kg; after 2 weeks, dose was increased to 0.2 mg/kg (max 5 mg) if necessary to attain BP < 90th percentile.
[f]Starting dose of 0.1, 0.3 or 0.7 mg/kg could be up titrated to max 1.4 mg/kg (max 100 mg) after 3, 6 and 9 weeks if BP target (< 95th or < 90th percentile) wasn't achieved; additional antihypertensives could be added to the max dose of 1.4 mg/kg if BP didn't achieve target value.
[g]Starting dose of 2 (<10 kg), 4 (10-19 kg) or 8 mg (≥20 kg) was doubled if SBP didn't decrease ≥ 10 mmHg or if SBP or DBP remained > 90th percentile after 4 to 8 weeks of treatment.
[h]Starting dose of 2 (<40 kg), 4 (40-79 kg) or 8 mg (≥80 kg) was doubled if BP remained > 95th percentile after 2 weeks of treatment; the doubled dose was given for another 2 weeks.
[i]Starting dose of 4 or 8 mg (based on body weight) could be adjusted to 2-32 mg according to BP control; additional antihypertensives (no ARBs) were allowed as add-on to 32 mg of candesartan if BP wasn't controlled.
[j]Starting dose of 0.2 mg/kg could be adjusted to a max of 0.4 mg/kg; additional antihypertensives were allowed if necessary.
[k]Starting dose of 20 mg was increased to 40 mg and further to 80 mg until BP target (SBP < 95th percentile) was achieved; if BP target wasn't achieved by monotherapy with valsartan, 12.5 mg of HCT was added.
[l]Starting dose of 40 mg could be up titrated to 80 mg and further to 160 mg, each after 2 weeks of treatment, if SBP remained ≥ 95th percentile; if SBP remained ≥ 95th percentile after 2 weeks of treatment with max dose (160 mg), additionally antihypertensive treatment (HCT, 12.5 mg) was added.
[m]Starting dose of 1 mg/kg could be up titrated to 2 mg/kg and further to 4 mg/kg, each after 2 weeks of treatment, if SBP remained ≥ 95th percentile; if SBP remained ≥ 95th percentile after 2 weeks of treatment with max dose (4 mg/kg), additionally antihypertensive treatment (HCT or amlodipine) was added.
[n]Starting dose of 40, 80 or 160 mg was doubled after 1 week of treatment; if necessary, dose could be down titrated again; up titration after down titration was allowed; if SBP and/or DBP remained ≥ 95th percentile after 8 weeks of taking the sustained dose, either amlodipine and/or HCT could be added, or dose of background antihypertensive drugs could be adjusted appropriately.

ACE = angiotensin-converting enzyme, ARB = angiotensin-II receptor blocker, BP = blood pressure, CKD = chronic kidney disease, CL_{cr} = creatinine clearance, DBP = diastolic blood pressure, DM = diabetes mellitus, eGFR = estimated glomerular filtration rate, GNP = glomerulonephritis, HCT = hydrochlorothiazide, HT = hypertension, HUS = haemolytic uremic syndrome, IgA = immunoglobulin A, max = maximum, n = number, NA = not available, NPH = nephronophthisis, PD = pharmacodynamics, RAS = renal artery stenosis, SBP = systolic blood pressure, SLE = systemic lupus erythematosus, Tx = transplantation, UK = United Kingdom, US = United States

8.9. APPENDIX IX: PIPS OF ACE INHIBITORS AND ARBS

Table 8.9: Submitted PIPs of ACE inhibitors and ARBs with their decision and compliance check (20)

Drug	Indication	Formulation	Decision date	Decision type	Compliance check
Azilsartan	Treatment of hypertension	Tablets, granules for oral suspension	29/01/2019	Approved	No
Enalapril	Treatment of heart failure	Age-appropriate oral solid dosage form	07/12/2018	Approved	No
Trandolapril	Treatment of hypertension	Hard capsules	17/07/2018	Refusal on a request for waiver	No
Enalapril	Treatment of heart failure	Oral solution	03/09/2014	Approved	No
Captopril	Treatment of heart failure	Age-appropriate oral liquid dosage form	08/08/2014	Approved	No
Enalapril	Treatment of hypertension	Tablet for oral suspension, orodispersible film	05/05/2014	Approved	No
Valsartan	Heart failure following recent myocardial infarction, treatment of heart failure, treatment of hypertension	Film-coated tablet, age-appropriate liquid dosage form	26/06/2009	Approved	Yes
Candesartan	Diabetic retinopathy, heart failure, essential hypertension	Tablets, suspension for oral use	20/02/2009	Refusal on a proposed PIP	No
Losartan	Proteinuria, treatment of heart failure, treatment of hypertension	Film-coated tablet, age-appropriate oral liquid dosage form	29/02/2008	Approved	Yes

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