Received: 13 September 2022 | Revised: 29 March 2023 | Accepted: 13 April 2023

DOI: 10.1111/bcp.15781

ORIGINAL ARTICLE

Guiding future paediatric drug studies based on existing pharmacokinetic and efficacy data: Cardiovascular drugs as a proof of concept

Nori J. L. Smeets[1,2] | Lieke P. M. Raaijmakers[1] | Tjitske M. van der Zanden[1,2,3] | Christoph Male[4] | Saskia N. de Wildt[1,2,3]

[1]Department of Pharmacology and Toxicology, Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, The Netherlands

[2]Intensive Care and Department of Paediatric Surgery, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands

[3]Dutch Knowledge Center Pharmacotherapy for Children, The Hague, The Netherlands

[4]Department of Paediatrics and Adolescent Medicine, Medical University of Vienna, Vienna, Austria

Correspondence
Saskia de Wildt, MD, PhD, Department of Pharmacology and Toxicology (137), Radboudumc, Postbus 9101, 6500 HB. Nijmegen, The Netherlands.
Email: saskia.dewildt@radboudumc.nl

Funding information
The Dutch Paediatric Formulary has been developed by Dutch Knowledge Center Pharmacotherapy for Children, which is funded by a government grant by the Dutch Ministry of Health. This work was performed in close collaboration with the Dutch Knowledge Center Pharmacotherapy for Children.

Introduction: Off-label drug use in the paediatric population is common, and the lack of high-quality efficacy studies poses patients at risk for failing pharmacotherapy. Next to efficacy studies, pharmacokinetic (PK) studies are increasingly used to inform paediatric dose selection. As resources for paediatric trials are limited, we aimed to summarize existing PK and efficacy studies to identify knowledge gaps in available evidence supporting paediatric dosing recommendations, thereby taking paediatric cardiovascular drugs as proof of concept.

Methods: For each cardiovascular drug, paediatric indication and prespecified age group, together comprising one record, the authorized state was assessed. Next, for off-label records, the highest level of evidence was scored. High-quality efficacy studies were defined as meta-analysis or randomized controlled trials. Other comparative research, noncomparative research or consensus-based expert opinions were considered low quality. The level of evidence for PK studies was scored per drug and per age group, but regardless of indication.

Results: A total of 58 drugs included 417 records, of which 279 (67%) were off-label. Of all off-label records, the majority (81%) were not supported by high-quality efficacy studies, but for 140 of these records (62%) high-quality PK studies were available.

Conclusion: We demonstrated that for the majority of off-label cardiovascular drugs, only low-quality efficacy studies were available. However, high-quality PK studies were frequently available. Combining these PK data with extrapolation of efficacy data from adults may help to close the current information gap and prioritize the drugs for which clinical studies and safety data are urgently needed.

KEYWORDS
neonatology, paediatric pharmacology, paediatrics, pharmacokinetics

1 | INTRODUCTION

Despite joint efforts to increase scientific evidence and drug approvals for children, off-label drug use in the paediatric population remains common.[1] Off-label drug use is defined as the prescription of drugs for indications, age groups, dosages, formulations or routes of administration different from those that are listed in the product label.[2] Even in recent years, off-label drugs have continued to be prescribed to children at high rates in the ambulatory and in-hospital setting.[1,3] This raises concerns as off-label drug use is associated with lower safety.[4,5] In general, there is a higher risk of adverse drug reactions (ADRs) for off-label versus authorized drug use.[5] Furthermore, in adults, more ADRs occurred when off-label drug use was not substantiated by strong scientific evidence (defined as at least one randomized controlled trial [RCT]).[5] Hence, patients are at increased risk of toxicity when off-label drugs lack strong scientific evidence.

Recently, we investigated the level of evidence for each drug used in the paediatric population, per indication and per pre-specified age group, together comprising one record each. We confirmed that a substantial number of records (42%) are still off-label in paediatrics and the majority (87%) of these off-label records were not supported by efficacy studies with a high level of evidence (either meta-analysis or RCTs of high quality).[6]

There is thus a lack of high-quality studies, which puts children at a possible risk for failing pharmacotherapy. Conducting multiple RCTs for the many age-specific indications where high-quality evidence is lacking faces major challenges for obvious financial, ethical and practical reasons. Thus, innovative approaches are needed to close this information gap. Recent regulatory guidelines for paediatric drug development encourage such approaches, for instance with the extrapolation of efficacy data from adults to the paediatric population in cases where disease progression and response to intervention are assumed reasonably similar.[7,8] Using this approach, pharmacokinetic (PK) data in children can be considered as a biomarker for effect and used to extrapolate adult efficacy data as they are important for validating predicted doses because unexpected age-related variation in drug disposition might occur.[9] Even though paediatric clinical studies are still needed, PK studies may require a smaller sample compared to traditional efficacy studies and are in general easier to perform, especially when modelling and simulation can support their design.[10,11] The feasibility of developing model-informed dosing guidelines for clinical implementation using existing PK data has been demonstrated and frameworks are available.[12,13] For instance, the efficacy of esomeprazole was extrapolated using adult efficacy and paediatric PK data.[14] Also, PK data have an important role in guiding decisions on paediatric off-label drug use as they provide important information on treatment risks and benefits. This includes decisions on different treatment options by patients, parents and physicians, but also on selecting which drugs to include in treatment protocols or formularies.[15]

Consequently, to evaluate the need for paediatric data and future research to close the off-label information gap, the availability of paediatric efficacy and PK studies is equally important. Of all the drug classes we evaluated, the evidence underlying off-label use was especially low for cardiovascular drugs: 69% of all records were off-label and only 12% of these records were supported by high-quality efficacy studies.[6] Although several reviews have focused on the available evidence for individual drugs[16] or gave an overview of available efficacy studies for a selected group of drugs or patient population,[17–19] a summary of both efficacy and PK evidence has not been presented for an entire drug class. Furthermore, although the value of PK studies is well recognized by paediatric drug development programmes, existing paediatric decision tools do not prioritize certain drugs for further study based on existing evidence.[7] We therefore aimed to summarize existing PK and efficacy studies to identify knowledge gaps in available evidence supporting paediatric dosing recommendations by taking paediatric cardiovascular drugs as an example.

What is already known about this subject

- Off-label drug use in the paediatric population is common and the lack of high-quality efficacy studies poses patients at risk for failing pharmacotherapy.
- Pharmacokinetic (PK) studies are increasingly used to inform paediatric dose selection.
- In what extent PK studies are available to do so was unknown.

What this study adds

- For the majority of off-label cardiovascular drugs only low-quality efficacy studies are available.
- High-quality PK studies were frequently available in case efficacy studies were lacking.
- Combining these PK data with extrapolation of efficacy data from adults may help to close the current information gap.

2 | METHODS

This study builds on the previous published review on the level of evidence for paediatric pharmacotherapy.[6] We used the data repository that was generated to collect data on the level of evidence for paediatric pharmacology (https://doi.org/10.17026/dans-27e-s6yf). This study evaluated the level of evidence underlying the dosing recommendations of the Dutch Paediatric Formulary (DPF; www.kinderformularium.nl).

2.1 | Data source

The DPF was launched in 2008 to provide dosing guidelines for all drugs, both authorized and off-label, relevant to the paediatric population in the Netherlands. Drugs are included in the formulary when the drug is licensed for a paediatric age group or, in case of off-label use, when a medical need is identified by paediatric professionals. For every drug, a monograph is developed and maintained following a structured decision framework. As part of this process, for every drug the authorization status is evaluated. A drug is considered to be authorized for paediatric use when the posology section Summary of Product Characteristics (SmPC) (paragraphs 4.1 and 4.2), issued by the Dutch Medicines Evaluation Board, contains an explicit and unambiguous dose recommendation for paediatric age groups. For these authorized drug-indication combinations, we did not assess the underlying evidence. Our project focuses on off-label drug indications.

For off-label use, a standardized PubMed search was performed by a senior pharmacist to retrieve available scientific information on efficacy, safety and dose in the paediatric population. The exact search query is shown in Supporting Information Table S1. The available scientific evidence supporting a dose recommendation and related safety issues are documented in benefit-risk analysis documents and reviewed by a multidisciplinary editorial board. The assessments are repeated every 5 years or more frequent if warranted by emerging evidence. In the past 12 years, paediatric dose recommendations for more than 750 drugs were established (either based on SmPC or based on assessment of original literature) and the repository continues to expand as it is constantly updated. Recently, we licensed the information and database use to Germany, Austria and Norway for country-specific versions.

2.2 | Data collection

Using the results of the literature reviews we performed to support the dosing recommendations, we evaluated the highest level of evidence for efficacy for all drugs described in the DPF. For each drug the highest level of evidence per indication and age group (together constituting one record) was scored using the documented studies in the benefit-risk analysis documents. Thus, each drug might have multiple records when it is prescribed for multiple indications and/or age groups.

2.3 | ATC classification of drugs

Drugs were classified according to the Anatomical Therapeutic Chemical (ATC) system to allow analysis on several levels of drug classes. This international classification system assigns drugs to a group based on the organ or system on which they act and their therapeutic, pharmacological and chemical properties. At ATC level 1, 14 major drug groups are defined (A to V). For this substudy, we only included ATC level 1 Cardiovascular system drugs (code C) and present our results specified for each ATC level 2 class to provide more detail. The total DPF dataset by Van der Zanden[6] was used to define the highest level of evidence for each indication and each age group as listed in the DPF for cardiovascular drugs (ATC C). Only creatine monohydrate (C01EB06) was excluded as it did not contain a cardiovascular indication in the DPF.

2.4 | Definition of age groups

Age categories were defined according to the European Medicines Agency (EMA) classification system. Groups were defined as preterm neonates (<37 weeks gestational age and <28 days postnatal age), term neonates (≥37 weeks gestational age and <28 days postnatal age), infants (1 month-2 years), young children (2-6 years), children (6-12 years) and adolescents (12-18 years). Corresponding weight-based categories were defined using Dutch Growth chart data to enable appropriate scoring when only weight categories were listed in the SmPC or DPF 19. Records for preterm and term neonates were only included when explicitly specified in the DPF. When the dose recommendation applied to only a part of the EMA classified age range (eg, 4-6 years), the evidence level was scored for the entire EMA category (eg, 2-6 years).

2.5 | Scoring of the level of evidence

All records were scored using a predefined scoring system. First, the authorization status per record was evaluated. Next, if a record was off-label, the listed literature from the benefit-risk analysis document was scored for the level of evidence, defined by the evidence-based medicine methodology. The quality of RCTs was evaluated using the Jadad classification. When no published scientific evidence was available, the dose recommendation of the DPF was established based on clinical practice and the expert opinion of the editorial board. These records were scored as consensus (D). For off-label records, levels A1 and A2 were considered high-level evidence, whereas levels B, C and D were considered low-level evidence.

To ensure that no high-quality evidence was missed due to a lag time between the latest update (<5 years ago) and the current study, the initial PubMed DPF search was repeated for all drugs with a level B, C or D classification. In addition, the European Public Assessment Reports as part of Articles 45 and 46 of the Paediatric Regulation were checked on additional clinical studies.

2.6 | Data verification

To verify our scoring system, a senior pharmacist verified the scored level of evidence for a sample of 10% of all drugs listed in the DPF. All drugs were sorted based on the ATC code to ensure every ATC group and thus each assessor was reflected in the sample. Every 10th drug based on the ATC5 code was incorporated in the verification sample.

The Intraclass Correlation Coefficient (ICC), a two-way mixed model, was selected to assess conformity between two assessors. As suggested by Koo et al, a score above 0.75 indicates good/excellent agreement and therefore a score of higher than 0.75 was considered acceptable for further analysis.

Data validation took place for 77 drugs, including 168 indications, with a total of 1008 records. The interrater reliability for these cases had an ICC of 0.869 (95% confidence interval [CI] 0.853-0.883). For 80.8% (n = 814) of records the level of evidence scored by the first observer was exactly similar to the level scored by the senior pharmacist. For 89.2% (n = 899) the level of evidence was exactly similar or deviated only by one level. Underestimation of the level of evidence (n = 106) occurred approximately as frequently as overestimation (n = 88).[6]

Based on these results, we believe our results are reproducible and the criteria used for scoring were adequate. Furthermore, we are confident that the dose recommendations of the DPF are complete, up-to-date and based on the best available evidence.

3 | DEFINITIONS

3.1 | Age groups

Age categories were defined according to the EMA classification system.[20] Groups were defined as preterm neonates (<37 weeks gestational age and <28 days postnatal age), term neonates (≥37 weeks gestational age and <28 days postnatal age), infants (1 month-<2 years), young children (2-<6 years), children (6-<12 years) and adolescents (12-<18 years). Corresponding weight-based categories were defined using Dutch Growth chart data to enable appropriate scoring when only weight categories were listed in the SmPC or DPF.[21] Records for preterm and term neonates were only included when explicitly specified in the DPF. When the dose recommendation applied to only a part of the EMA classified age range (eg, 4-6 years), the evidence level was scored for the entire EMA category (eg, 2-6 years).

3.2 | Efficacy and PK studies

The highest level of evidence for efficacy studies available for each drug, indication and pre-specified age group, together comprising one record each, was scored. Thus, each drug may have multiple records when it is prescribed for multiple indications and/or age groups. For instance, metoprolol is included in the DPF and dosing recommendations are listed for two indications: hypertension from term neonates up to adolescents (five age groups) and dilated cardiomyopathy with heart failure from young children up to adolescents (three age groups). Metoprolol therefore comprises a total of eight records (Figure 1).

Literature was assessed in March 2021 using a standardized scoring system using seven categories for efficacy studies and six categories for PK studies (Figure 2). For each record, the highest level of evidence was assessed for efficacy studies. If the drug was licensed for that record, this was considered and referred to as the highest level of available evidence (A0). For off-label records, the level of evidence was defined by the evidence-based medicine methodology (Figure 2). Single RCTs were evaluated using the Jadad scoring system.[22] When no scientific evidence was available at all, the level of evidence was scored as consensus (D). Levels A1 and A2 were considered as high levels of evidence whereas levels B, C and D were considered low levels of evidence.[5]

For PK studies, the highest level of evidence was assessed per drug and age group, regardless of indication. If the drug was licensed for that record, this was considered and referred to as the highest level of available evidence. As no universal classification system for PK studies exists, we combined the definitions presented by Barker et al[23] and Gastine et al[24] Accordingly, population PK models (A1, A2

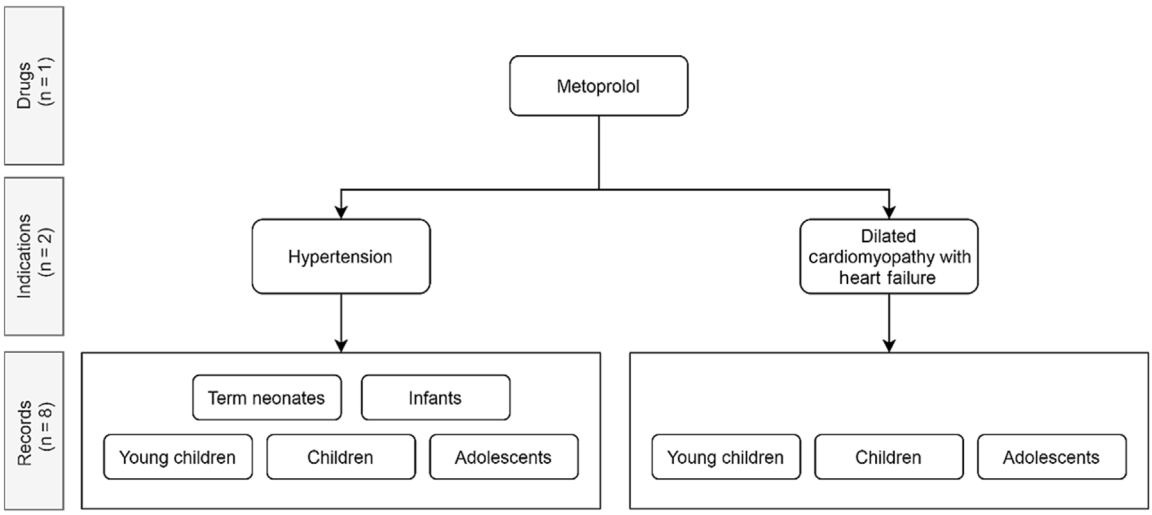

FIGURE 1 Structured approach to scoring evidence for drugs, indications and records, taking metoprolol as an example. Metoprolol comprises two indications and eight records.

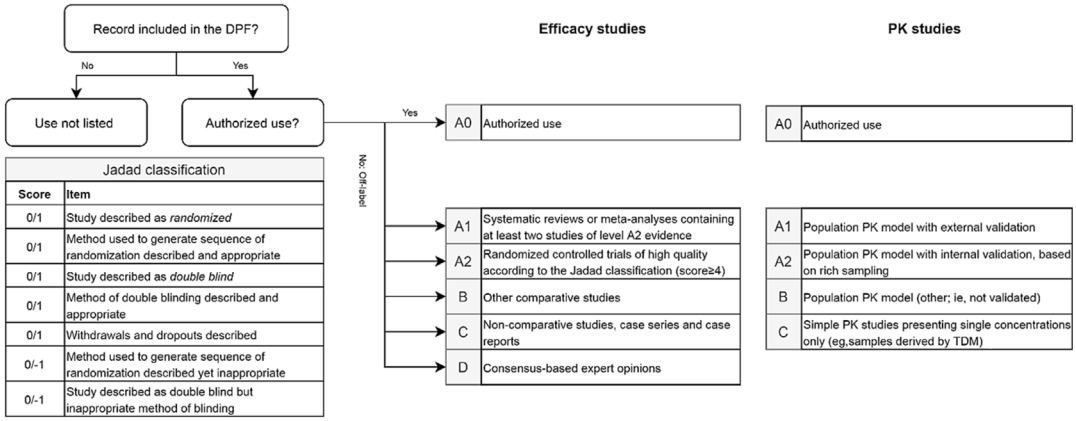

FIGURE 2 Scoring system of the level of evidence of efficacy and PK studies. Jadad classification adapted from Jadad et al.[22] DPF, Dutch Paediatric Formulary; PK, pharmacokinetic; TDM, therapeutic drug monitoring.

and B) were considered as high levels of evidence whereas traditional PK studies (C) reporting single concentrations only were considered a low level of evidence. The standardized PubMed search for efficacy and PK studies is listed in Supporting Information Table S1. We deliberately chose not to differentiate between PK and PK/pharmacodynamic (PD) studies, although the latter might provide more information than PK studies alone. To what magnitude PK/PD studies can yield insights on PD determinants of drug action would require an additional scoring system for the amount and quality of PDs that is included in a particular study. This is beyond the scope of the current manuscript and was therefore not investigated.

4 | DATA ANALYSIS

Data were first analysed on a drug level to indicate the percentage of off-label drugs. Next, the highest level of evidence per record was analysed. The latter is more informative for the clinical situation as this takes the varying levels of evidence per indication into account. For instance, enalapril is used on-label for the treatment of hypertension and symptomatic heart failure in children weighing more than 20 kg.[25] Yet its use is off-label for children below 20 kg for hypertension and symptomatic heart failure and for children of all weights for the treatment of proteinuria. The latter would not be taken into account when only analysing our data on a drug level. Following, the analysis was performed on a ATC level 2 (ATC2) to enable comparison between the different ATC2 classes. ATC2 distinguishes drugs used for cardiac therapy (C01), antihypertensives (C02), diuretics (C03), peripheral vasodilators (C04), vasoprotectives (C05), beta blocking agents (C07), calcium channel blockers (C08), agents acting on the renin-angiotensin system (C09) and lipid-modifying agents (C10). For each class, the percentage of off-label records was assessed.

With the aim of guiding the future research agenda, we combined the level of evidence of PK studies as well as efficacy studies to identify drugs for which critical evidence is lacking (Figure 3). To do this we extended the paediatric study decision tree by Dunne et al[7] by adding steps at the top of the algorithm focussed on the availability of both PK and efficacy studies. We proceeded on the basis that the design of the efficacy studies performed was appropriate. Thus, for records supported by high-quality efficacy studies, we assumed that the study used an appropriate paediatric dose and study design. We therefore considered records for which high-quality efficacy studies are available as having no priority. For records lacking high-quality efficacy studies, the level of evidence of available PK studies was assessed. If high-quality PK studies were available, records were categorized as intermediate priority and when both high-quality PK and efficacy studies were lacking, records were classed as high priority. The validity of extrapolation of efficacy to the paediatric population from adult data and paediatric PK data depends on two important assumptions.[26] First, there should be similar disease progression and response to intervention. Next, adults and children should have a similar exposure-response relationship. Because determining similarity is a complex process involving the review of pathophysiological characteristics and discussion with experts, this did not fit the scope of the current manuscript. We rherefore focused on the first two steps of the extended decision tool by assessing the availability of efficacy as well as PK studies because we believe these are the first steps for selecting drugs for further study. For each ATC level 2 subgroup, the percentage of records lacking high-quality efficacy studies was calculated as well as the percentage of records for which PK studies are available.

Data were collected using Castor EDC version 2020.2.32. Analysis took place using descriptive statistics in IBM SPSS Statistics version 25.0.0.1. Microsoft Excel was used to create tables and figures.

5 | RESULTS

A total of 58 drugs (Supporting Information Table S2) were analysed with a total of 108 indications, together representing a total of 417 records across six age groups (Supporting Information Table S3).

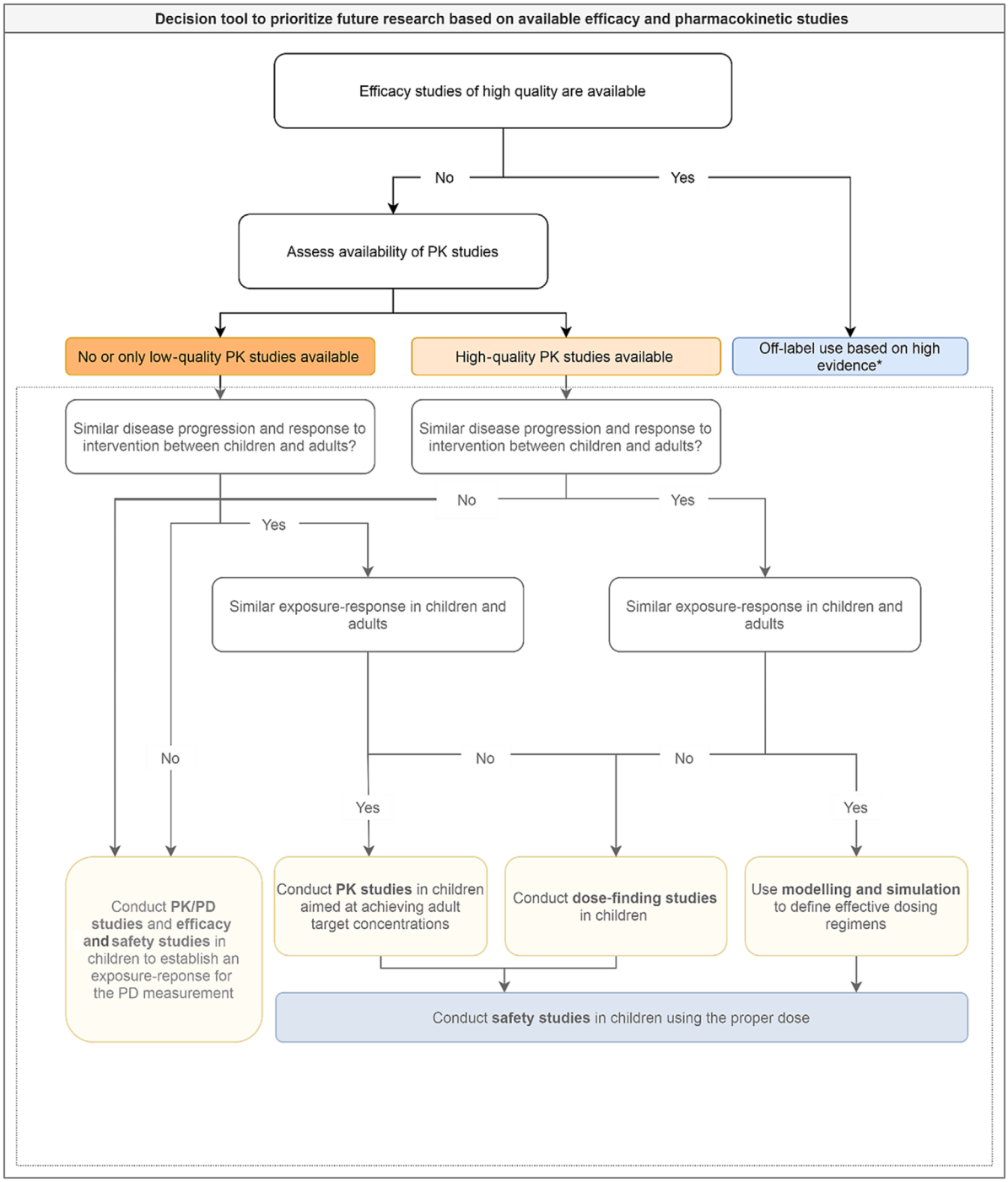

FIGURE 3 Decisiontool to select drugs for future research based on efficacy and pharmacokinetic studies, embedded in the paediatric decision tree from Dunne et al. The opacified area reflects the Dunne paediatric decision tree. Systematic reviews or meta-analyses with at least two studies of level or randomized controlled trials with at least four points on the Jadad scale were considered to be high-quality efficacy studies. Population PK models were considered a high level of evidence whereas individual PK studies were considered a low level of evidence for PK studies. PK, pharmacokinetics; PD, pharmacodynamics. *Assuming efficacy studies applied the appropriate dose and study design.

The available records in the DPF increased with age. Of the 108 listed indications, 12% had at least one dosing recommendation for preterm neonates, 37% for term neonates, 78% for infants, 79% for young children, 90% for children and 91% for adolescents. When data were categorized based on ATC level 2, cardiac therapy (C01) was the largest subgroup, with 18 drugs and 106 records. Peripheral vasodilators (C04) and vasoprotectives (C05) were the smallest groups, with only one drug and four records in each group (Table 1).

TABLE 1 Number of drugs and records included in the cardiovascular drug class (C), sorted by ATC level 2 class.

ATC level 2	Number of drugs	Number of indications	Number of records (number of indications × number of age groups)
C01: Cardiac therapy	18	26	106
C02: Antihypertensives	5	12	46
C03: Diuretics	6	12	64
C04: Peripheral vasodilators	1	1	4
C05: Vasoprotectives	1	1	4
C07: Beta blocking agents	7	22	80
C08: Calcium channel blockers	4	9	31
C09: Agents acting on the RAAS	9	14	54
C10: Lipid modifying agents	7	11	28
Total	58	108	417

Abbreviations: ATC, anatomical therapeutic chemical; RAAS, renin-angiotensin-aldosterone system.

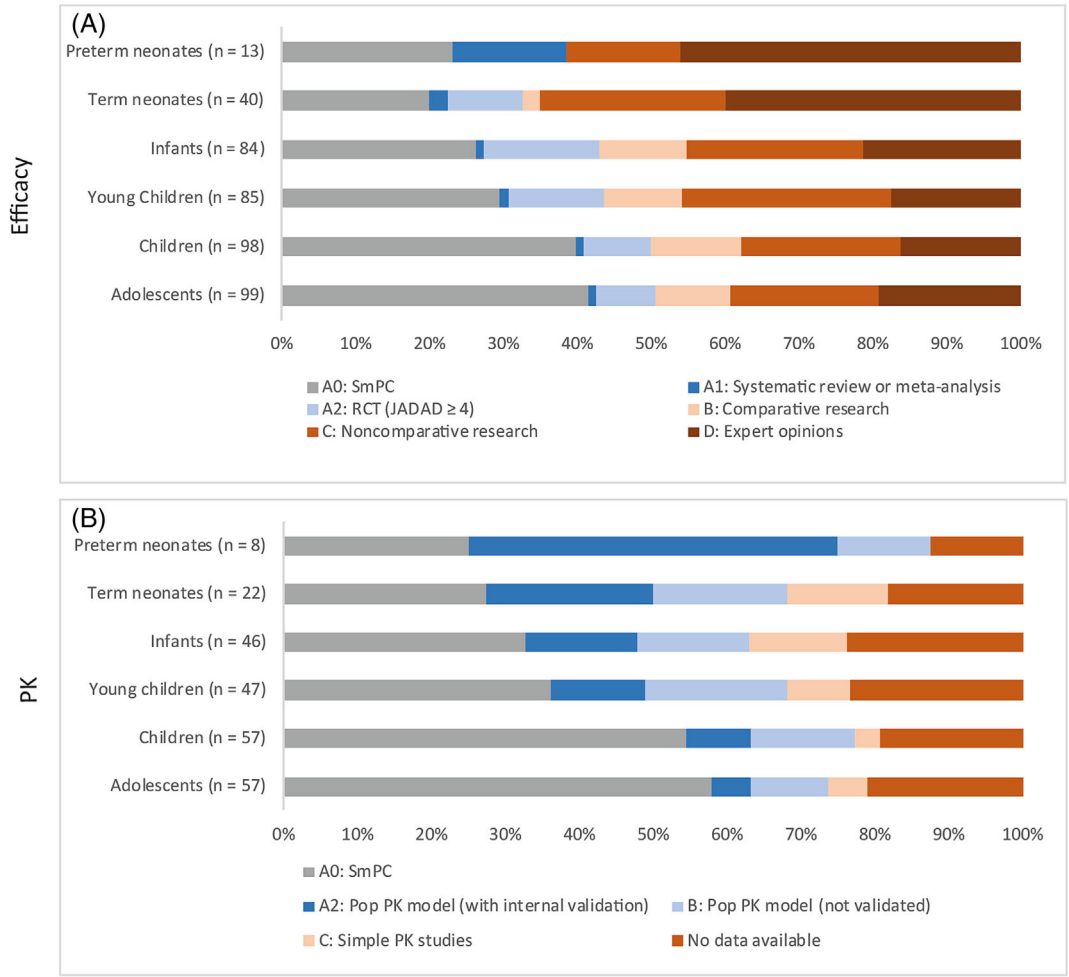

FIGURE 4 (A) The level of evidence of efficacy studies per age group (per record). The highest level of evidence available per record (drug-indication age). A0, licensed for use; A1, systematic review or meta-analysis with at least two studies of level A2; A2, randomized controlled trial with at least four points on the Jadad scale; B, comparative research with a maximum of three on the Jadad scale; C, noncomparative research; D, consensus or expert opinion; JADAD, ; n, number of records; SmPC. (B) The level of evidence for pharmacokinetic studies per age group (per drug). A0, ; A1, population PK models with external validation; A2, population PK models with internal validation; B, other population PK models; C, studies mentioning single samples or single PK parameters; n, the number of drugs listed in the Dutch Paediatric Formulary for each age group; PK, pharmacokinetic; SmPC.

5.1 | Efficacy studies

The percentage of off-label records was 67% (n = 279). Across age groups, the percentage of off-label records decreased from 80% in term neonates to 58% in adolescents (Figure 4A). The proportion of off-label records across age groups with a high level of evidence (A1 and A2) was 19% (range 16-23%). To gain more insight in the distribution of level of evidence between the different drug classes, data were organized into ATC level 2 subgroups and the percentage of off-label records for each subgroup was assessed. Excluding subgroups with only one drug (C04 and C05), this varied between 32% (lipid-modifying agents, C10) up to 91% (beta-blocking agents, C07), regardless of age. Beta-blocking agents and calcium-channel blockers had the highest proportion of off-label records (91% and 84%) and of these off-label records, only 16% and 0% were supported by a high level of evidence, respectively (Figure 5 and Supporting Information Table S1).

5.2 | PK studies

Externally validated population PK models (level A1 evidence) were not available for any of the drugs. The number of authorized drugs ranged from 25% in preterm neonates up to 58% in adolescents. PK studies of high quality (A2 or B) were frequently available, with more PK studies being available in the younger age groups (63% of all drugs) compared to the older age groups (16% of all drugs). The proportion of drugs with only low (level C) or no supporting PK evidence varied between 13% and37% (Figure 4B).

5.2.1 | Records without high-level efficacy studies

In total, 227 records were neither authorized nor supported by high-quality efficacy studies. For 140 of these records (62%), high-quality PK studies were available. This was especially the case in preterm (88%) and term (63%) neonates. Between the different ATC2 subgroups, C04 and C05 excluded, the percentage of records for which PK studies were available varied between 0% (lipid-modifying agents, C10) and 58% (beta-blocking agents, C07) (Figure 5). The full research priority list including drugs that lack efficacy studies of high quality, specified per drug, indication and age group, is summarized in Table 2.

6 | DISCUSSION

We have summarized existing paediatric cardiovascular PK and efficacy studies, thereby presenting a clear information gap and suggesting priorities for future research. To the best of our knowledge, we are the first to report the level of evidence for both PK and efficacy studies for any drug class used in the paediatric population and offer a clinically relevant list of drugs lacking high-quality evidence. We have demonstrated that for cardiovascular off-label records, the majority (81%) are only supported by a low level of evidence and there is a significant deficit in knowledge on efficacy data, especially in the younger age groups. Furthermore, beta-blocking agents and calcium-channel blockers are the two subgroups with the highest percentage of off-label records. For these records, high-quality efficacy studies are scarce. Not only efficacy studies can inform paediatric drug

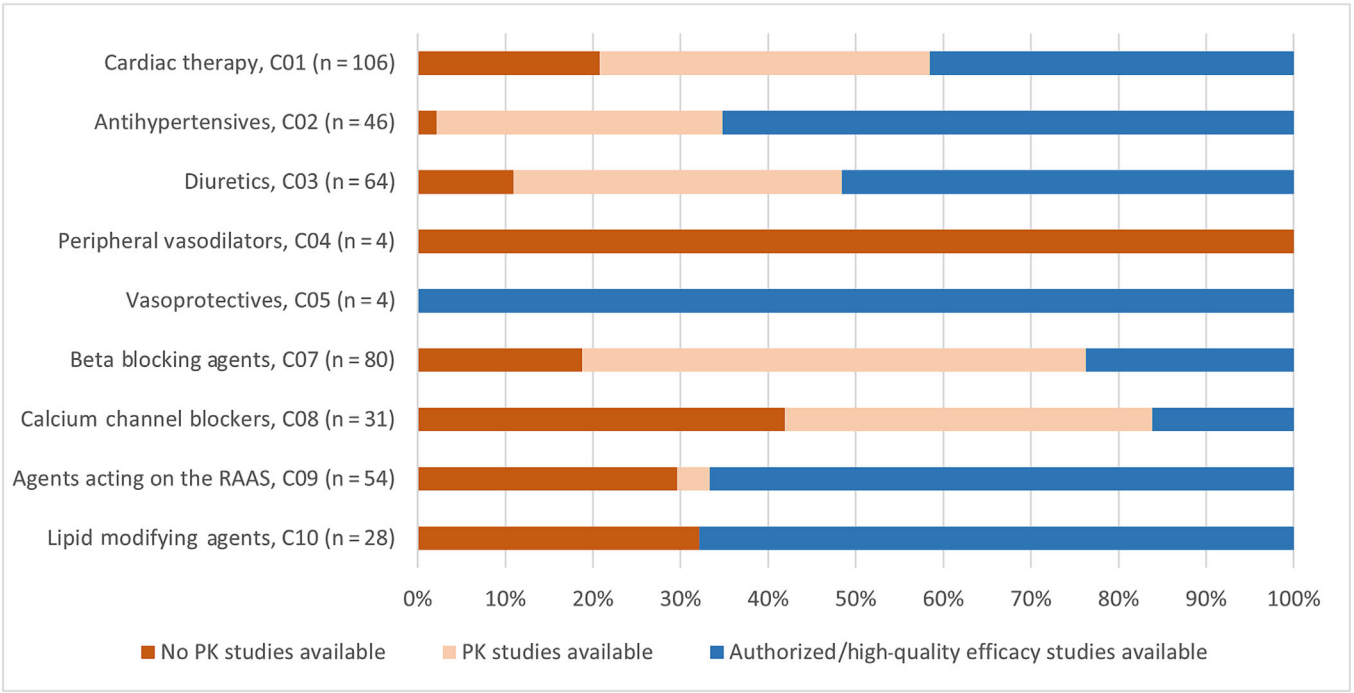

FIGURE 5 Proportion of available efficacy and PK studies in the Anatomical Therapeutic Chemical 2 group. PK, pharmacokinetic; RAAS, renin-angiotensin-aldosterone system.

TABLE 2 Records for which high-quality efficacy studies are lacking

Drug name	Indication	Age group	Level of evidence: efficacy studies	Level of evidence: PK studies
Adrenalin (epinephrine)	Positive inotropic and chronotropic effect	Term neonates	D	A2
	Reanimation	Term neonates	D	A2
	Subglottic laryngitis	Infants to adolescents	D	SmPC
	Vasoconstriction, hypotension	Term neonates	D	A2
Amiodarone	Severe treatment resistant cardiac arrhythmias	Infants	B	A2
		Young children to adolescents	B	C
Amlodipine	Hypertension	Infants	D	A2
		Young children	C	A2
Atenolol	Hypertension	Infants	D	No data available
	Supraventricular arrhythmias	Young children	D	B
		Children to adolescents	B	B
		Infants	B	No data available
		Young children to adolescents	B	B
Bumetanide	Diuretic (for oedema)	Infants to children	C	B
		Adolescents	C	No data available
Captopril	Heart failure	Term neonates	D	No data available
		Infants to adolescents	B	C
	Hypertension	Term neonates	C	No data available
		Infants, adolescents	C	C
		Young children to children	B	C
Carvedilol	Heart failure in Duchenne Muscular Dystrophy	Infants to children	D	A2
		Adolescents	B	A2
Clonidine	ADHD	Infants	D	A2
	Adjuvant to other analgesics	Young children	C	A2
	Growth hormone secretion test	Adolescents	B	A2
	Hypertension	Infants to adolescents	C	A2
	Sleeping disorders in ADHD	Infants to adolescents	D	A2
		Young children to adolescents	C	A2
Cholestyramine	Cholestatic pruritus	Infants	D	No data available
	Diarrhoea caused by bile salts	Infants	B	No data available
	Hypercholesterolaemia	Infants	D	No data available
Dopamine	Circulatory insufficiency, hypotension	Infants to adolescents	D	B
	Increasing kidney perfusion	Term neonates to adolescents	D	B
Ephedrine	Hypotension in regional anaesthesia and resuscitation	Infants to children	C	No data available
Enalapril	Heart failure	Term neonates	C	C
	Hypertension	Term neonates	D	C
	Proteinuria	Term neonates	D	C
Esmolol	Arrhythmias	Infants to adolescents	C	B
	Perioperative hypertension	Children to adolescents	C	B
	Supraventricular tachycardia	Infants - Adolescents	C	B
Ezetimibe	Homozygous familiar hypercholesterolaemia	Children	B	No data available
		Adolescents	D	No data available
	Homozygous sitosterolaemia (phytosterolaemia)	Children	B	No data available
		Adolescents	D	No data available
	Primary hypercholesterolaemia	Children	B	No data available

(Continues)

TABLE 2 (Continued)

Drug name	Indication	Age group	Level of evidence: efficacy studies	Level of evidence: PK studies
		Adolescents	D	No data available
Flecainide acetate	Supraventricular arrhythmias, life-threatening ventricular arrhythmias	Term neonates to adolescents	C	B
Hydrochlorothiazide	Bronchopulmonary dysplasia	Preterm neonates	D	A2
	Diuresis	Young children to adolescents	D	SmPC
	Hypercalciuria		D	A2
	Hypertension	(Pre)term neonates	C	A2
	Nephrogenic diabetes insipidus	(Pre)term neonates	C	SmPC
		Infants to adolescents	D	A2
		(Pre)term neonates	D	A2
		Preterm neonates	C	A2
		Term neonates	C	SmPC
		Infants		
Isoprenaline	Increasing cardiac output	Infants to young children	D	C
		Children to adolescents	D	B
Labetalol	Hypertension	Infants	D	C
	Hypertensive crisis	Young children to adolescents	D	No data available
			B	C
		Infants	C	No data available
		Young children to adolescents		
Levosimendan	Acute heart failure (second line)	Term neonates, young children	B	B
			C	B
		Children		
		Adolescents	C	No data available
Lisinopril	Hypertension	Infants to young children	B	B
Metoprolol	Dilated cardiomyopathy and heart failure	Infants	B	No data available
		Young children	B	C
		Children to adolescents	B	SmPC
	Hypertension	Term neonates	D	C
		Infants	D	No data available
		Young children	C	C
Midodrine	(Orthostatic) hypotension	Infants to adolescents	B	No data available
Milrinone	Circulatory insufficiency, treatment of a low-output state following cardiac surgery	Preterm neonates	D	A2
		Term neonates	D	SmPC
	Thromboembolic-threatened limbs			
Nicardipine	Acute hypertension	Term neonates	C	No data available
	Hypertensive crisis	Infants	B	No data available
		Young children to adolescents	C	No data available
Nifedipine	Hypertension	Infants	C	B
		Young children to children	C	No data available
		Adolescents	C	C
	Raynaud's phenomenon	Infants	C	B
		Young children to children	C	No data available
		Adolescents	C	C
Nitroglycerin	Hypertensive crisis	Infants	D	C
		Young children to adolescents	D	No data available
Nitroprusside	Hypertensive crisis	Term neonates	C	No data available
Noradrenalin (norepinephrine)	Circulatory insufficiency	Preterm neonates to adolescents	C	A2

TABLE 2 (Continued)

Drug name	Indication	Age group	Level of evidence: efficacy studies	Level of evidence: PK studies
Phentolamine mesylate	Prophylaxis of dermal necrosis in norepinephrine extravasation	Infants to adolescents	D	No data available
Phenylephrine hydrochloride	Cyanotic spell	Infants to young children	C	A2
		Children	D	A2
		Adolescents	D	No data available
	During bypass	Adolescents	D	No data available
Propafenone	Severe therapy-resistant (supra)ventricular arrhythmias	Term neonates to infants	C	C
Propranolol	Hypertension	Term neonates	D	B
	Prevention of cyanotic spell in tetralogy of Fallot	Infants	D	SmPC
		Young children	B	B
	Long-QT syndrome	Children to adolescents	B	SmPC
		Term neonates	D	B
		Infants	C	SmPC
		Young children	C	B
		Children to adolescents	D	SmPC
		Term neonates, young children	D	B
		Infants, children, adolescents	D	SmPC
Quinidine sulphate	Brugada syndrome	Infants	C	No data available
		Young children to adolescents	C	B
Ramipril	Hypertension	Young children to adolescents	C	No data available
Sotalol	Conversion of arrhythmias	Infants to children	C	A2
	(Supra)ventricular arrhythmias	Adolescents	C	B
		Term neonates to children	C	A2
		Adolescents	C	B
Spironolactone	Ascites	Infants to adolescents	C	SmPC
	Fluid accumulation and oedema	(Pre)term neonates	D	No data available
Triamterene	Hypertension	Infants to adolescents	D	No data available
Verapamil	Hypertension	Young children to adolescents	D	SmPC
	Myoclonic epilepsy (Dravet syndrome)	Infants	C	C
	Prophylaxis of supraventricular tachycardia	Young children to adolescents	C	SmPC
		Young children to adolescents	D	SmPC
	Severe therapy-resistant supraventricular tachycardia	Infants	B	C

Note: The final column indicates whether no or only low-quality PK studies were available (dark orange) or if high-quality PK studies were available (light orange).

Abbreviations: ADHD, attention deficit hyperactivity disorder; PK, pharmacokinetic. For efficacy studies: B, comparative studies of poor quality (Jadad<4); C, noncomparative studies, case reports and case series; D, consensus and expert opinion. For PK studies: SmPC, summary of product characteristics; A2, population PK models with internal validation; B, other population PK models and studies where a PK curve was made; C, studies mentioning single samples or single PK parameters.

dosing, we also investigated the availability and quality of PK studies. We found that for many drugs lacking high-quality efficacy studies, high-quality PK studies were available (62%). Especially in preterm and term neonates, high-quality PK studies were frequently available (88% and 63%) in situations where high-quality efficacy studies were lacking.

Related to our decision tree, the highest priority for further research are records with low quality efficacy and PK studies

(eg, atenolol to treat hypertension in infants). There is some need for future studies for records with no high-quality efficacy data but high-quality PK data (eg, hydrochlorothiazide to treat bronchopulmonary dysplasia in preterm neonates) and little need for records that are authorized or for which high-quality efficacy studies are available (eg, spironolactone to enhance diuresis in children/adolescents).

Up to now similar studies providing an overview of the level of evidence supporting off-label drug use in the paediatric population including PK studies have not been published. Only for specific subclasses, the level of evidence of efficacy studies was summarized or an overview of safety data was given. The level of evidence supporting the use of beta-blockers in various paediatric and vascular conditions by efficacy studies was investigated qualitatively by Kaley et al.[17] In line with our results, they demonstrated that the level of evidence was only moderate or low for most indications. However, they did not take PK studies into account, although these studies might be of great value in the absence of high-quality efficacy studies when disease progression, response to drug intervention and dose-response relationship are sufficiently similar in both groups.[7] Similarly, a meta-analysis regarding the pharmacological treatment of arterial hypertension in children and adolescents exclusively included RCTs and did not look into studies with a lower level of evidence.[18] Lastly, the safety of statins in the paediatric population was investigated, but again only RCTs were included in the analysis.[27] Thus, although studies are available that summarize existing efficacy or safety data, the available evidence has not been combined with PK data.

The added value of PK studies was recently highlighted by a published framework for conducting benefit-risk assessments of off-label drugs in children.[15] Using paediatric PK studies, extrapolation approaches are increasingly used in drug development programmes in both the United States and European Union.[28] However, even though anecdotal examples are available for individual drugs in which PK and efficacy studies are both reviewed,[16,29] neither an overview of existing PK data nor a practical framework exists for prioritizing drugs for further study. This is surprising because PK studies have already supported paediatric dose selection, also in the DPF. For instance, for clonidine, high-quality PK data are available across the paediatric age span.[30–32] These data provide information on age-related PK changes, also in age groups and indications for which high-quality efficacy studies were absent. Therefore, by summarizing available PK and efficacy studies and by using the extended decision tree, information gaps in paediatric prescribing might be identified, as we demonstrated for cardiovascular drugs.

Our study has some limitations. First, we only addressed the availability and quality of PK studies, but could not assess the similarity of disease between adults and children or the similarity in the dose-response relationship This is due to the complex nature of defining similarity across populations, which needs to be performed on a drug and indication basis by experts. Also, when creating a research priority list, other aspects, such as epidemiological data on the frequency and severity of disease, should be taken into account, next to the availability of appropriate therapeutic alternatives and drug costs. However, defining suitable alternatives faces multiple difficulties as indications for use might be similar but the proposed alternative differs significantly in mechanism of action, side effects, PK or available formulations. This prevents the interchangeable use of similar drugs with a low level of evidence and drugs with a high level of evidence. We did not assess the feasibility of extrapolating efficacy data to younger age groups based on published PK data. Also, even when high-quality paediatric PK data are available, several points need to be addressed before the paediatric dose and dosage regimen can be estimated from adult and paediatric PK data.[7] Second, we assumed similar PK properties of one drug across indications. Differences in PKs between different conditions might very well exist due to variations in the target paediatric population, eg, obese or critically ill children, but these are not taken into account in the first steps of the decision tool. Also, we did not investigate the availability of safety studies. Even though PK studies are able to provide valuable dosing information, they are not able to replace the need for clinical safety studies. For drugs where PD markers are more relevant for dose selection than PK data, eg, anticoagulants, antihyperglycaemic drugs or lipid lowering drugs, PK and safety studies only may not be enough and PK-PD studies across the age range may be needed. Finally, we did not address the quality of PK studies next to type of studies, even though this can also affect the robustness of the evidence.

As records were based on dosing recommendations in the DPF, some limitations were encountered in our analysis. First, on-label drug use does not necessarily mean that the drug is well investigated in the paediatric population, which is especially true for old drugs. Second, a lack of dosing recommendations for certain age groups could be due to a complete lack of evidence or nonrelevance. For instance, for amiodarone only dosing recommendations for infants up to adolescents are included in the DPF, but neonates may also need amiodarone treatment. On the other hand, clonidine to treat sleeping disorders in the context of attention deficit hyperactivity is not relevant in neonates. This distinction between a lack of evidence and nonrelevance is not taken into account in our analysis. In general, the selection of drugs represents prescribing patterns in the four European countries where the DPF dosing guidelines are available. This may differ across other parts of the world, but since the number of drugs is so large and will overlap considerably, we do not expect a significant different overall trend for other countries. For cardiovascular drugs specifically, the same applies and we consider the selected drugs to be the most relevant within the paediatric population. Furthermore, our search string could have been insufficient to cover all available literature, but we consider this limitation as minor as this string was checked by a librarian.

Finally, our assumption that the design of the performed efficacy studies was appropriate unfortunately does not always hold true. For instance, in infants with single ventricle physiology, the administration of enalapril was not beneficial in a large double-blind RCT conducted by Hsu et al.[33] Enalapril PK studies indicate that young children require higher mg/kg dosages than the dosages used in the Hsu study to reach adequate target concentrations.[34,35] Furthermore, there were several concerns about the generalisability of the study findings by Hsu et al,[36,37] therefore the lack of efficacy of enalapril observed

in this trial might have been due to underdosing and the characteristics of the patient population, not inefficacy of the drug itself.[16] Again, we would like to stress that our analysis is concentrated on the first steps of the decision tool only. Later steps merit further consideration by experts to select drugs for further study and to design appropriate paediatric studies. With our research priority list, we aim to give an overview of drugs that lack scientific evidence, which can be regarded as a starting point for further study.

In conclusion, by extending the paediatric decision tree we are the first to report the level of scientific evidence of both efficacy and PK studies in the paediatric population for multiple drugs. For cardiovascular drugs, high-quality efficacy studies were often not available, but for some of these drugs PK studies have been conducted and could therefore be of value in paediatric dose selection. This is especially promising for cardiovascular drugs as traditional clinical trials in paediatric cardiology face unique challenges.[38] We therefore emphasize the importance of using paediatric PK data in closing current information gaps as the feasibility and added value of developing model-informed dosing guidelines for clinical implementation based on existing PK data have already been demonstrated.[12] PK data are thus able to fill important knowledge gaps, especially when external validation is available. This approach can solidify the benefit-risk assessment for paediatric pharmacotherapy. This may be of help for guideline or dosing handbook committees. The identified knowledge gaps may be valuable to regulators, policymakers or researchers worldwide to drive the research agenda.

AUTHOR CONTRIBUTIONS

Nori J. L. Smeets: Conceptualization, methodology, validation, investigation, data curation, visualization, writing—original draft. **Lieke P. M. Raaijmakers**: Investigation, data curation. **Tjitske M. van der Zanden**: Conceptualization, methodology, validation, writing—original draft. **Christoph Male**: Writing—review and editing, supervision. **Saskia N. de Wildt**: Writing—review and editing, supervision.

CONFLICT OF INTEREST STATEMENT

Tjitske van der Zanden is managing director of the Dutch Knowledge Center Pharmacotherapy for Children. Saskia de Wildt is medical director of the Dutch Knowledge Center Pharmacotherapy for Children.

DATA AVAILABILITY STATEMENT

The entire dataset used for the analysis is available upon reasonable request.

ORCID

Nori J. L. Smeets https://orcid.org/0000-0002-4927-2459
Saskia N. de Wildt https://orcid.org/0000-0002-0502-0647

REFERENCES

1. Weda M, Hoebert J, Vervloet M, et al. Study on the off-label use of medicinal products in the European Union.: www.ec.europa.com; 2017 [updated March, 14, 2017].
2. Frattarelli DA, Galinkin JL, Green TP, et al. Off-label use of drugs in children. *Pediatrics*. 2014;133(3):563-567. doi:10.1542/peds.2013-4060
3. Hoon D, Taylor MT, Kapadia P, Gerhard T, Strom BL, Horton DB. Trends in off-label drug use in ambulatory settings: 2006-2015. *Pediatrics*. 2019;144(4). doi:10.1542/peds.2019-0896
4. Turner S, Nunn AJ, Fielding K, Choonara I. Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: a prospective study. *Acta Paediatr*. 1999;88(9):965-968. doi:10.1111/j.1651-2227.1999.tb00191.x
5. Eguale T, Buckeridge DL, Verma A, et al. Association of off-label drug use and adverse drug events in an adult population. *JAMA Intern Med*. 2016;176(1):55-63. doi:10.1001/jamainternmed.2015.6058
6. van der Zanden TM, Smeets NJL, de Hoop-Sommen M, et al. Off-label, but on-evidence? A review of the level of evidence for pediatric pharmacotherapy. *Clin Pharmacol Ther*. 2022;112(6):1243-1253. doi:10.1002/cpt.2736
7. Dunne J, Rodriguez WJ, Murphy MD, et al. Extrapolation of adult data and other data in pediatric drug-development programs. *Pediatrics*. 2011;128(5):e1242-e1249. doi:10.1542/peds.2010-3487
8. Agency EM. *Reflection paper on the use of extrapolation in the development of medicines for paediatrics*. EMA; 2018.
9. Cella M, Knibbe C, Danhof M, Della PO. What is the right dose for children? *Br J Clin Pharmacol*. 2010;70(4):597-603. doi:10.1111/j.1365-2125.2009.03591.x
10. van den Anker J, Reed MD, Allegaert K, Kearns GL. Developmental changes in pharmacokinetics and pharmacodynamics. *J Clin Pharmacol*. 2018;58(Suppl 10):S10-S25. doi:10.1002/jcph.1284
11. European Medicines Agency. *Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population*; 2006.
12. Hartman SJF, Swaving JGE, van Beek SW, et al. A new framework to implement model-informed dosing in clinical guidelines: piperacillin and amikacin as proof of concept. *Front Pharmacol*. 2020;11:592204. doi:10.3389/fphar.2020.592204
13. Vinks AA, Emoto C, Fukuda T. Modeling and simulation in pediatric drug therapy: application of pharmacometrics to define the right dose for children. *Clin Pharmacol Ther*. 2015;98(3):298-308. doi:10.1002/cpt.169
14. Earp JC, Mehrotra N, Peters KE, et al. Esomeprazole FDA approval in children with GERD: exposure-matching and exposure-response. *J Pediatr Gastroenterol Nutr*. 2017;65(3):272-277. doi:10.1097/MPG.0000000000001467
15. van der Zanden TM, Mooij MG, Vet NJ, et al. Benefit-risk assessment of off-label drug use in children: the bravo framework. *Clin Pharmacol Ther*. 2021;110(4):952-965. doi:10.1002/cpt.2336
16. Smeets NJL, Schreuder MF, Dalinghaus M, et al. Pharmacology of enalapril in children: a review. *Drug Discov Today*. 2020;25(11):1957-1970. doi:10.1016/j.drudis.2020.08.005
17. Kaley VR, Aregullin EO, Samuel BP, Vettukattil JJ. Trends in the off-label use of β-blockers in pediatric patients. *Pediatr Int*. 2019;61(11):1071-1080. doi:10.1111/ped.14015
18. Burrello J, Erhardt EM, Saint-Hilary G, et al. Pharmacological treatment of arterial hypertension in children and adolescents: a network meta-analysis. *Hypertension*. 2018;72(2):306-313. doi:10.1161/HYPERTENSIONAHA.118.10862
19. Back J, Wåhlander H, Hanseus K, Bergman G, Naumburg E. Evidence of support used for drug treatments in pediatric cardiology. *Health Sci Rep*. 2021;4(2):e288. doi:10.1002/hsr2.288
20. European Medicines Agency. ICH Topic E 11 R1 Clinical Investigation of Medicinal Products in the Paediatric Population 2017(Revision 1).
21. Netherlands Organisation for Applied Scientific Research. Growth charts in PDF format: TNO; 2010 [Available from: https://www.tno.nl/nl/aandachtsgebieden/gezond-leven/roadmaps/youth/groeidiagrammen-in-pdf-formaat/].

22. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17(1):1-12. doi:10.1016/0197-2456(95)00134-4
23. Barker CI, Standing JF, Turner MA, McElnay JC, Sharland M. Antibiotic dosing in children in Europe: can we grade the evidence from pharmacokinetic/pharmacodynamic studies – and when is enough data enough? *Curr Opin Infect Dis*. 2012;25(3):235-242. doi:10.1097/QCO.0b013e328353105c
24. Gastine S, Rashed AN, Hsia Y, et al. GAPPS (grading and assessment of pharmacokinetic-pharmacodynamic studies) a critical appraisal system for antimicrobial PKPD studies - development and application in pediatric antibiotic studies. *Expert Rev Clin Pharmacol*. 2019;12(12):1091-1098. doi:10.1080/17512433.2019.1695600
25. EMA. Summary of product characteristics Enalapril maleate 20 mg tablets; 2020.
26. US Department of Health and Human Services FaDA. Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling—Guidance for Industry. 2019.
27. Lamaida N, Capuano E, Pinto L, Capuano E, Capuano R, Capuano V. The safety of statins in children. *Acta Paediatr*. 2013;102(9):857-862. doi:10.1111/apa.12280
28. Johnson TN, Small BG, Berglund EG, Rowland YK. A best practice framework for applying physiologically-based pharmacokinetic modeling to pediatric drug development. *CPT Pharmacometrics Syst Pharmacol*. 2021;10(9):967-972. doi:10.1002/psp4.12678
29. Mahoney L, Shah G, Crook D, Rojas-Anaya H, Rabe H. A literature review of the pharmacokinetics and pharmacodynamics of Dobutamine in neonates. *Pediatr Cardiol*. 2016;37(1):14-23. doi:10.1007/s00246-015-1263-9
30. Potts AL, Larsson P, Eksborg S, Warman G, Lönnqvist PA, Anderson BJ. Clonidine disposition in children; a population analysis. *Paediatr Anaesth*. 2007;17(10):924-933. doi:10.1111/j.1460-9592.2007.02251.x
31. Xie HG, Cao YJ, Gauda EB, Agthe AG, Hendrix CW, Lee H. Clonidine clearance matures rapidly during the early postnatal period: a population pharmacokinetic analysis in newborns with neonatal abstinence syndrome. *J Clin Pharmacol*. 2011;51(4):502-511. doi:10.1177/0091270010370587
32. Klein RH, Alvarez-Jimenez R, Sukhai RN, et al. Pharmacokinetics and pharmacodynamics of orally administered clonidine: a model-based approach. *Horm Res Paediatr*. 2013;79(5):300-309. doi:10.1159/000350819
33. Hsu DT, Zak V, Mahony L, et al. Enalapril in infants with single ventricle: results of a multicenter randomized trial. *Circulation*. 2010;122(4):333-340. doi:10.1161/CIRCULATIONAHA.109.927988
34. Wells T, Rippley R, Hogg R, et al. The pharmacokinetics of enalapril in children and infants with hypertension. *J Clin Pharmacol*. 2001;41(10):1064-1074. doi:10.1177/00912700122012661
35. Nakamura H, Ishii M, Sugimura T, Chiba K, Kato H, Ishizaki T. The kinetic profiles of enalapril and enalaprilat and their possible developmental changes in pediatric patients with congestive heart failure. *Clin Pharmacol Ther*. 1994;56(2):160-168. doi:10.1038/clpt.1994.119
36. Singh TP. Letter by Singh regarding article, "Enalapril in infants with single ventricle: results of a multicenter randomized trial". *Circulation*. 2011;123(10):e374. doi:10.1161/CIRCULATIONAHA.110.989897
37. Burchill LJ, Ross HJ, Wald RM. Letter by Burchill et al regarding article, "Enalapril in infants with single ventricle: results of a multicenter randomized trial". *Circulation*. 2011;123(10):e373. doi:10.1161/CIRCULATIONAHA.110.986315
38. Harris KC, Mackie AS, Dallaire F, et al. Unique challenges of randomised controlled trials in pediatric cardiology. *Can J Cardiol*. 2021;37(9):1394-1403. doi:10.1016/j.cjca.2021.06.013

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Smeets NJL, Raaijmakers LPM, van der Zanden TM, Male C, de Wildt SN. Guiding future paediatric drug studies based on existing pharmacokinetic and efficacy data: Cardiovascular drugs as a proof of concept. *Br J Clin Pharmacol*. 2023;1-14. doi:10.1111/bcp.15781