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Review Article

Direct oral anticoagulants: What will be their role in children?

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ABSTRACT

Thrombotic events in children differ from those in adults in epidemiology, pathophysiology, and anatomical location. However, anticoagulation in children is mostly based on evidence from adults while scarce evidence exists from children. The classical anticoagulants currently used in children have several limitations, resulting in the need for regular monitoring.

Several direct oral anticoagulants (DOACs) are now authorized for adults in whom they have established efficacy and safety without the need for monitoring. Given their pharmacological properties and the special characteristics of children requiring anticoagulation, the DOACs have the potential to be particularly suitable for children.

All currently approved DOACs have paediatric development plans, targeting various indications for prevention and treatment of thrombosis. Paediatric formulations are being developed and systematic age-specific dosing information will be generated. Whether therapeutic drug monitoring will be necessary in certain situations in children remains to be elucidated. The results of ongoing clinical studies still need to demonstrate whether there is a positive benefit-risk balance in all targeted paediatric indications and age-groups, particularly in indications that have not been explored in adults, such as catheter-related thrombosis or congenital heart disease.

If the advantages of DOACs bear out in the results of the current paediatric studies, they will likely be used widely in children. As of now, the DOACs should not be used routinely in children as there is still insufficient information on appropriate dosing, safety and efficacy. The paediatric community is encouraged to promote participation of children and adolescents into the multiple ongoing studies of DOACs.

1. Thrombosis in children

Thrombotic events (TE) in children are less common than in adults but are a recognized entity. Most TE in children are secondary complications of severe underlying diseases or their treatment, the most common risk factor being central venous or arterial lines [1–3]. The incidence of TE in children has increased over the last decades [4]. This increase is probably due to improved medical care of life-threatening conditions in children, causing at the same time more secondary morbidity such as thrombosis. Moreover, better clinical awareness and improved radiographic detection methods may contribute to the increased frequency of TE reported in children. Consequently, anticoagulation, both for prophylaxis and treatment of TE, is used with increasing frequency in children [4].

Indications for anticoagulant prophylaxis or treatment overlap to some extent between children and adults, e.g. treatment of acute VTE, but even here, the different types and location of TE in children potentially affect the response to anticoagulation. On the other hand, there are several indications specific to children, such as some congenital heart defects, Kawasaki syndrome, and others [5, 6]. Moreover, relatively more children requiring anticoagulation have serious comorbidity, some of which is unique for children, e.g. prematurity. These underlying conditions may affect the choice of anticoagulant drug, dose-requirements, efficacy or risk of bleeding, and the risk of interactions with concomitant drugs.

There are published guidelines for anticoagulation in children [7]. However, these are mostly based on evidence from adults while scarce evidence exists from children, particularly for specific paediatric disease populations. Table 1 lists relevant indications for which anticoagulant prophylaxis or treatment is (variably) used in children, although in most instances not based on clear evidence.

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Table 1
Indications for anticoagulant prophylaxis and treatment in children

Prevention		Treatment
Venous TE	Cardiac, arterial TE	
- Central venous lines - Peri-operative prophylaxis	- Central arterial lines - Mechanical heart valves - Shunts (e.g. Fontan); stents - Dilated cardiomyopathy - Kawasaki syndrome - Ventricular assisted devices	- Venous thrombosis, pulmonary embolism - Cerebral sino-venous thrombosis - Arterial ischemic stroke - Cardiac, arterial thrombosis
- Peri-procedural prophylaxis (e.g. cardiac catheterization) - Extracorporal circulation (haemodialysis, extracorporal membrane oxygenation, cardiac bypass surgery)		

2. Challenges with current anticoagulants in children

The anticoagulants currently used predominantly in children are unfractionated heparin (UFH), low molecular heparin (LMWH), and the vitamin K antagonists (VKA) [7, 8]. These anticoagulants pose several challenges in children.

The heparins exert their anticoagulant effect via endogenous antithrombin which has plasma levels that are physiologically low in neonates or may be decreased in sick children [9]. The pharmacokinetic (PK) and pharmacodynamics (PD) properties of UFH are influenced by age and various other factors [10]. Particularly in clinically unstable children, UFH has highly unpredictable PK/PD properties, as reflected by poor correlation between UFH dose and anticoagulant effect [11]. Nevertheless, UFH is frequently used for short-term prophylaxis (procedures, intensive care, surgery) and treatment of acutely ill children at risk of bleeding because of its short half-life and availability of an antidote. Low molecular heparins have more stable, though age-dependent, PK/PD properties, and require less frequent monitoring than UFH. Their longer half-life makes them useful for longer-term use, including the outpatient setting [12]. Both heparins may cause heparin-induced thrombocytopenia (HIT) although this has rarely been reported in children [13]. Danaparoid is an alternative heparinoid, occasionally used in children with HIT and for thrombosis prevention in hepatic veno-occlusive disease [14, 15].

Some newer parenteral anticoagulants have the advantage of a more targeted and, in part, direct (no co-factor) anticoagulant effect on factor Xa or thrombin (fondaparinux, argatroban, bivalirudin), resulting in more predictable PK/PD properties compared to heparins. Although some data in children have been generated on these anticoagulants, there is not much paediatric experience and they are currently not widely used in children [16]. Parenteral administration is useful in sick patients but is impractical for longer-term anticoagulation, particularly in children.

The VKA are currently the only oral anticoagulants available for children. However, VKA have a slow onset and slow offset, are strongly influenced by dietary intake, and show multiple drug interactions. These problems are aggravated in children who frequently have serious underlying diseases, may have feeding problems, and often receive concomitant drugs potentially interacting with VKA. Dose requirements of VKA for children have been shown to be dependent on age and comorbidity [17]. The use of VKA is particularly difficult in infants due to variable vitamin K intake through breast milk or infant formulas. The need for frequent venipuncture to monitor VKA levels is also challenging in the paediatric/adolescent population, especially in areas of the world in which point of care monitoring is not readily available or typically covered by medical insurance.

All current anticoagulants require regular monitoring and dose-adjustments in children. Access to age-appropriate administration forms and dose strengths covering the wide range of doses required for children is also a challenge. VKA are not commercially available in a liquid formulation. For parenteral anticoagulants, dose vials are only available in strengths sized for adults, requiring families to “waste” anticoagulant before injecting, or even having to dilute the medication at home, both of which can lead to medication errors. Lastly, none of the classical anticoagulants has been systematically developed and authorized for children.

3. Pharmacological properties of direct oral anticoagulants

The direct oral anticoagulants (DOACs) are small molecules, designed to selectively inhibit specific coagulation factors in the coagulation pathway. They exert their effect directly without the need for endogenous co-factors. Table 2 summarizes the relevant pharmacological properties in adults of the currently approved DOACs. Rivaroxaban, apixaban, edoxaban, and betrixaban inhibit factor Xa, while dabigatran inhibits thrombin. They all achieve their pharmacologic effect relatively quickly (peak concentration within 0.5 to 4 h), but show some differences in their plasma half-lives, which are shortest for rivaroxaban (5–9 h) and longest for betrixaban (19–27 h). Oral bioavailability ranges from 7% for dabigatran to 80% for rivaroxaban. There are also substantial differences in the ratio of renal versus extra-renal excretion, ranging from 80:20% for dabigatran to 15:85% for betrixaban [18]. In spite of these differences in renal elimination, all DOACs may accumulate in patients with renal impairment and, therefore, all have dose reductions recommended for moderate to severe renal impairment (creatinine clearance 15–49 ml/min) and should not be used with a creatinine clearance < 15 mL/min. All DOACs are contraindicated in patients with hepatic disease associated with coagulopathy

Table 2
Pharmacological properties of direct oral anticoagulants in adults[a].

	Target	Oral bioavailability (%)	T max (h)	Half-life (h)	Excretion renal (%)	Excretion extrarenal (%)
Dabigatran	Thrombin	7	0.5–2	11–14	80	20
Rivaroxaban	Factor Xa	80–100	2–4	5–9	66	34
Apixaban	Factor Xa	50	3–4	9–14	25	75
Edoxaban	Factor Xa	62	1–2	10–14	50	50
Betrixaban	Factor Xa	34	3–4	19–27	15	85

Abbreviations: T max, time to peak plasma concentration; h, hours.
[a] For authorized DOACs, based on label information [21–25].

Table 3
Indications and doses for direct oral anticoagulants currently approved for adults[a].

	Prevention of VTE	Prevention of cardiac, arterial TE	Treatment of VTE
Dabigatran (Pradaxa®)	Hip/knee replacement 110 mg (1st dose), 220 mg daily[c]	Atrial fibrillation 150 mg BID[c]	VTE treatment LMWH for 1 week, 150 mg BID[c]
Rivaroxaban (Xarelto®)	Hip/knee replacement 10 mg daily	Atrial fibrillation 20 mg daily[c] Acute coronary syndrome 2.5 mg BID & antiplatelet therapy	VTE treatment 15 mg BID for 3 weeks, 20 mg daily
Apixaban (Equilis®)	Hip/knee replacement 2.5 mg BID	Atrial fibrillation 5 mg BID[c]	VTE treatment 10 mg BID for 2 weeks, 5 mg BID
Edoxaban (Lixiana®, Roteas®)	–	Atrial fibrillation 60 mg daily[c]	VTE treatment LMWH for 1 week, 60 mg daily[c]
Betrixaban[b] (Bevyxxa®)	Medical illness at risk for VTE 160 mg (1st dose), 80 mg daily[c]	–	–

Abbreviations: VTE, venous thromboembolism; BID, twice daily.
[a] Based on EU marketing authorizations [21–24].
[b] Currently approved only in the USA (2017) [25].
[c] Dose reductions are recommended for patients with renal impairment and/or some other risk factors (for details refer to label information).

Table 4
Indications targeted by current Paediatric Investigation Plans for Direct Oral Anticoagulants [1]

	Prevention of VTE	Prevention of cardiac, arterial TE	Treatment of VTE
Dabigatran	-	-	1. Acute VTE (dabigatratran vs SOC) 2. Extended secondary prevention (dabigatran single arm)
Rivaroxaban	-	Post Fontan surgery [2] (rivaroxaban versus aspirin)	Acute VTE (rivaroxaban vs SOC)
Apixaban	Acute leukemia/lymphoma, asparaginase treatment, with central venous catheter (apixaban versus placebo)	Various cardiac diseases (apixaban versus SOC)	Acute VTE (apixaban versus SOC)
Edoxaban	-	Various cardiac diseases (edoxaban versus SOC)	Acute VTE (edoxaban versus SOC)
Betrixaban	1. Medical illness or surgery (betrixaban single arm) 2. Neonates/preterms with umbilical catheter (betrixaban single arm)	-	-

and clinically relevant bleeding risk (for details refer to label information).

4. Direct oral anticoagulants in adults

Several DOACs have been developed for adults and are now authorized for various indications for prophylaxis and treatment of thrombosis [19, 20]. The authorized indications and recommended doses for adults are listed in Table 3 [21–25].

For VTE prevention, dabigatran, rivaroxaban, and apixaban are authorized for use in patients undergoing hip or knee replacement surgery. Betrixaban, with its longer half-life compared to the other DOACs, is indicated for prevention of VTE in patients with medical illness at risk for TE. So far, betrixaban has only been approved in the USA [20].

Dabigatran, rivaroxaban, apixaban, and edoxaban are all licenced for prevention of stroke and peripheral arterial embolism in patients with non-valvular atrial fibrillation. Rivaroxaban is additionally licenced for prevention of atherothrombotic events in adult patients after acute coronary syndrome, co-administered with single or dual antiplatelet therapy.

For treatment, dabigatran, rivaroxaban, apixaban, and edoxaban are authorized for treatment of acute DVT and PE and (extended) prevention of recurrent DVT and PE.

In adults, solid evidence has been generated with these DOACs in all authorized indications, demonstrating efficacy and safety at least non-inferior to the classical anticoagulants without the need for monitoring anticoagulant levels [26, 27]. In a “real-world” study utilizing community-based healthcare data for over 59,000 adult VTE patients in Canada and the United States, the risk of major bleeding was similar for DOACs as compared to warfarin (pooled hazard ratio 0.92, 95% confidence interval 0.82 to 1.03) [28].

5. Direct oral anticoagulants for children

The pharmacological properties of DOACs and clinical results from adult trials suggest that this group of drugs may have advantages particularly suitable for children: oral administration, predictable pharmacokinetics, no anti-thrombin dependence, no food interaction, few drug interactions, wider therapeutic window, and possibly no monitoring requirements.

New paediatric legislations in the United States and European Union now require pharmaceutical companies to perform paediatric medicine development for all medicines intended for new, or extensions of,

Table 5
Current Paediatric Investigation Plans for direct oral anticoagulants[a].

Study	Age range	Phase	N of patients	Status	Reference; expected completion
Dabigatran PIP					
Development of age-appropriate formulation				C	
Bioequivalence studies in adult patients					
Population PK model				P	Liesenfeld et al. [71]
In-vitro concentration response studies					Dietrich et al. [44]
Treatment of VTE					2018-Q4
Multiple dose*/single dose PK/PD, safety, tolerability	12 ≤ 18 y*	2a	9	P	Halton et al. [48]
	1 ≤ 12 y		18		Halton et al. [49]
	< 1 y		8		Halton et al. [49]
RCT, SOC-controlled, efficacy, safety; 3 mo VTE treatment	0–18 y	2b/3	180	R	2018-Q2
Single arm, safety, long-term treatment/secondary prevention	0–18 y	3	100	R	2018-Q4
Rivaroxaban PIP					
Development of age-appropriate formulation				C	
Bioequivalence studies in adult patients					
Juvenile animal studies				C	
Physiologically-based PK model				P	Willmann et al. [40]
In-vitro concentration response studies					Attard et al. [45, 46]
Treatment of VTE					2019-Q4
Single dose PK/PD, safety	6 mo ≤ 18 y	1	63	C	2017-Q4
Single dose PK/PD, safety (granules for oral suspension)	2 mo ≤ 12 y	1	58	R	2018-Q1
RCT, SOC-controlled, PK/PD, safety; 4 weeks VTE treatment	6 ≤ 18 y	2	63	C	2017-Q2
Single arm, PK/PD, safety; 4 weeks VTE treatment	6 mo ≤ 6 y		47		
Single arm, PK/PD, safety, efficacy; 7 days treatment	0 ≤ 6 mo	1/2	10	C	2018-Q1
RCT, SOC-controlled, efficacy, safety; 3 mo VTE treatment	0 ≤ 18 y	3	270	R	2019-Q3
Prevention of cardiac/arterial TE					
RCT, versus aspirin, safety, efficacy; after Fontan surgery	2–8 y	3	100	R	2022-Q1
Apixaban PIP					
Development of age-appropriate formulation				O	
Bioequivalence studies in adult patients					
Juvenile animal studies					
PK Modelling and simulation					
In-vitro concentration response studies				P	Yetman et al. [47]
Single dose PK/PD, safety, tolerability	0 ≤ 18 y	1	44	R	2019-Q4
Prevention of VTE					2021-Q1
RCT, placebo-controlled, efficacy, safety; children with acute lymphoblastic leukemia/lymphoma, asparaginase, central venous catheter	1 ≤ 18 y	3	500	R	2020-Q2
Prevention of cardiac/arterial TE					
RCT, SOC-controlled, safety, PK; children with cardiac disease	0 ≤ 18 y	2	150	R	2020-Q3
Treatment of VTE					
RCT, SOC-controlled, efficacy, safety; 3 mo VTE treatment	0 ≤ 18 y	3	150	R	2020-Q4
Edoxaban PIP					2020-Q4
Development of age-appropriate formulation					
Bioequivalence studies in adult patients					
Juvenile animal studies					
Physiologically-based PK model					
In-vitro concentration response studies					
Single dose PK/PD, safety, tolerability	0 ≤ 18 y	1	60	R	2019-Q4
Treatment of VTE					
RCT, SOC-controlled, PK/PD, efficacy, safety; 3 mo VTE treatment	0 ≤ 18 y	3	274	R	2020-Q4
Prevention of cardiac/arterial TE					
RCT, SOC-controlled, efficacy, safety; children with cardiac disease	0 ≤ 18 y	3	150	NR	2021-Q1
Betrixaban PIP					2024-Q4
Development of age-appropriate formulation					
Bioequivalence studies in adult patients					
Juvenile animal studies					
Prevention of VTE					
PK/PD modelling and simulation					
Single dose PK/PD, safety, tolerability	1 mo ≤ 18 y	1	60	NR	2022-Q2
Single arm; safety, PK/PD; children with acute medical or surgical illness requiring thromboprophylaxis	1 mo ≤ 18 y	3		NR	
Single arm; safety, PK/PD; neonates/preterms with umbilical vein/artery catheter	< 28 days	3		NR	

Abbreviations: PIP, Paediatric Investigation Plan; VTE, venous thromboembolism; PK, pharmacokinetics; PD, pharmacodynamics; SOC, standard-of-care; mo, month; y, year; C, studies completed; P, results published; O, ongoing; R, recruiting; NR, not yet recruiting; Q1/2/3/4, quarter of that year; empty fields = no public information available.

[a] Information based on published Paediatric Investigation Plans [33–38], and study details and study status reported on www.clinicaltrials.gov [32].

marketing authorization [29, 30]. As a consequence, all DOACs have 'Paediatric Investigation Plans' (PIPs) that must be approved by these regulatory agencies [31]. The majority of these paediatric developments are ongoing and some have already progressed quite far [32]. Thus, we may expect most DOACs eventually to be authorized for children, providing paediatric formulations, and data from clinical trials regarding age-specific dosing, efficacy and safety.

6. Paediatric Investigation Plans for direct oral anticoagulants

Table 4 lists the indications targeted by current PIPs for rivaroxaban, dabigatran, apixaban, edoxaban, betrixaban, comprising prophylaxis of venous thromboembolism (VTE), prophylaxis of arterial/cardiac thrombosis, and treatment of VTE. These indications reflect the wide spectrum of anticoagulation in children although several paediatric indications are not covered (Table 1). Table 5 lists the details of all current PIPs on DOACs including preclinical and clinical studies, their timelines and current status [32–38].

Relevant elements for paediatric development of anticoagulants have been outlined by a recommendation by the Paediatric Scientific and Standardization Committee (SSC) of the International Society of Thrombosis and Haemostasis (ISTH) [39]. A fundamental element is the development of age-appropriate paediatric formulation(s) to ensure reliable and accurate administration of the medicine to children of different ages. This includes studies to establish bioequivalence with the adult formulations.

Almost all paediatric developments are built upon existing data from adult studies. By systematically incorporating information from adults and other sources, using in-silico tools such as physiologically-based PK/PD models and/or population PK/PD modelling and simulations, PK/PD studies in children can be optimized and the number of blood samples required from children minimized. A paediatric physiologically-based PK (PBPK) model for rivaroxaban has been published, using PK data from adults and physiological information from children [40]. The model predicted that for children weighing < 40 kg, relatively higher weight-related doses would be required due to differences in medicine uptake, metabolization and clearance compared to children with higher weights. These predictions were subsequently confirmed by real PK data from children from the rivaroxaban paediatric clinical studies [41–43].

In-vitro concentration-response studies spiking the anticoagulant at increasing concentrations into plasma from healthy children of different age groups are a means to explore whether age-dependent differences in the coagulation system affect the drug concentration–anticoagulant effect (PD) relationship. In-vitro spiking studies have been reported for dabigatran [44], rivaroxaban [45, 46], and apixaban [47]. The studies found no relevant differences in concentration-response relationships between adults and children, including infants, but observed some small differences in neonatal plasma [46, 47].

For clinical studies, most PIPs on DOACs perform single-dose PK/PD studies in children of all age groups for initial dose-finding and safety assessment. Only the dabigatran programme involved a multiple-dose PK/PD study over three days in adolescents and a few children [48, 49] but proceeded with single-dose assessments in younger children [49, 50]. Phase 1 studies on anticoagulants cannot be performed on healthy children but usually target children with previous thrombosis shortly after the end of a course of anticoagulation. Such studies are ethically challenging as short-term exposure to the drug offers no therapeutic benefit and repeated venipunctures for PK/PD samples are a significant burden for the child. The PIP for rivaroxaban performed an intermediate step of a phase 2, dose-confirmation and safety study over the last four weeks of anticoagulation therapy for acute VTE [33]. Initially, the study randomized children to rivaroxaban versus standard-of-care (SOC) anticoagulants (LMWH or VKA). Subsequently, it was amended for younger children to a rivaroxaban single arm study, to increase feasibility and collect more information on rivaroxaban treatment. All other paediatric programmes continue from their single-dose PK/PD studies immediately to phase 3 safety & efficacy studies.

For investigations targeting treatment of VTE, all paediatric phase 3 studies comprise open-label randomized controlled trials (RCTs) comparing the respective DOAC versus SOC anticoagulants. Following diagnosis of VTE, children are initially treated by UFH or LMWH as per SOC allowing a time window for randomization to study treatment which then continues for the duration of anticoagulant treatment after acute VTE, usually 12 weeks, or longer if clinically indicated. The dabigatran PIP additionally runs a long-term study targeting the indication of extended secondary prevention for up to 12 months. The studies on VTE treatment are based on rather limited patient numbers between 150 and 274, not powered to independently demonstrate efficacy or safety in children. On one hand, these relatively small sample sizes are explained by the feasibility challenges of such trials. On the other hand, the paediatric developments are supported by the principle of extrapolation from evidence in adults, based on the concept that VTE treatment is reasonably similar between children and adults. The paediatric studies aim to confirm the proof of efficacy from adults, accounting for potential differences in outcome frequencies such as recurrent VTE [51]. The results of the ongoing trials will show whether this extrapolation concept holds true and the combined data from adult and paediatric trials will provide sufficient evidence to conclude on efficacy and safety of DOACs in children.

A number of PIPs also target the various indications of primary prevention of TE. The apixaban PIP has an ongoing study in children with acute lymphoblastic leukemia or lymphoma, asparaginase treatment, and presence of a central venous catheter [35]. In studies of anticoagulant prophylaxis to prevent catheter-related VTE, a positive benefit-risk balance has never been unequivocally demonstrated, neither in adults nor children. Thus, this apixaban paediatric trial is a proof-of-concept study comparing apixaban versus placebo in a fully powered RCT (n = 500). The PIP for apixaban is the most comprehensive, as it also includes a study targeting primary and secondary prevention of cardiac and arterial TE. In this RCT of children with various congenital and acquired cardiac diseases, apixaban is compared versus SOC anticoagulants for long-term anticoagulation up to one year. The study sample is limited to 150 patients, mainly for feasibility reasons. There is little room for extrapolation from adults to children in this setting, as the adult indication of atrial fibrillation differs largely from those of children with cardiac disease. Prevention of cardiac TE, specifically in children after Fontan surgery, is also targeted by an ongoing study on rivaroxaban versus aspirin [32]. A study for prevention of cardiac TE has also been agreed for the PIP on edoxaban which is not yet recruiting [37]. For betrixaban, a PIP has been agreed targeting children with medical illness or surgery at risk of VTE, and neonates/preterms with umbilical vein/artery catheters [38]. This PIP has not started yet [32].

7. Challenges of paediatric studies with direct oral anticoagulants

Several PIPs of DOACs target similar indications, particularly for VTE treatment, even though the availability of several similar drugs is likely not needed in children. These parallel PIPs are competing for study patients worldwide, which aggravates the feasibility challenges typically faced by paediatric drug studies. There are ongoing efforts to streamline paediatric developments of medicines with similar mode of action to make sure they target diverse indications and address the whole spectrum of paediatric indications for anticoagulation [52]. There are many challenges of performing clinical trials on anticoagulants in children beyond the limited numbers of available patients [53]. Given the diverse and severe underlying diseases in children suffering from thrombosis, it is difficult to define eligibility criteria for clinical trials that reflect the real-life population of children requiring anticoagulation. Recruitment is further limited by difficulties in obtaining parental consent and also physicians' reluctance to randomize. Moreover, adherence to study assessments, particularly if they involve frequent blood sampling for PK studies, or radiographic investigations, can be challenging in small and sick children. It is important to find the right balance between stringent study protocols to optimize scientific validity and study burdens acceptable to children and their families.

8. Available paediatric clinical data on direct oral anticoagulants

For dabigatran, the results of the phase 2b, PK/PD, safety, and tolerability studies in adolescents (aged 12 to < 18 years), children (aged 1 to < 12 years), and infants (aged < 1 years) have already been published [48–50]. Dabigatran etexilate was generally well tolerated and the dabigatran PK/PD relationship was reported largely similar between paediatric age groups and adult patients. Modelling results comparing paediatric PK/PD data from these studies between age groups and with adult data have been reported in abstract form, showing that the effects of dabigatran plasma concentrations on certain coagulation assays were comparable between children and adults, except for some deviations in young infants [54].

For rivaroxaban, PK/PD results have been reported only as conference abstracts so far. In the phase 1 study in children 0.5 to 18 years of age, a single dose of rivaroxaban was administered as either tablet or oral suspension [43]. Age-specific weight-adjusted doses were based on PBPK modelling to target the adult exposure of 10 mg once-daily. There were no bleeding events. PK results were consistent with the PBPK model, and PD results showed linear correlation between change from baseline and rivaroxaban plasma concentrations in line with adult data.

In the phase 2 study, children 6 to 18 years, and 0.5 to < 6 years of age with VTE who had completed ≥2 months of anticoagulation received 30 days of rivaroxaban treatment [41, 42]. Children 6 to 18 years who received rivaroxaban tablets were dosed once daily at a weight-adjusted 20 mg equivalent dose. Children 0.5 to 12 years of age who received rivaroxaban suspension were dosed twice daily with a 10 mg equivalent dose, based on the PBPK model predictions and the phase 1 data. In a total of 80 children reported, no major bleeding or symptomatic recurrent VTE occurred, and repeat imaging of the TE was improved in 94%. Rivaroxaban plasma concentrations were in the range of PBPK model predictions and levels of adult VTE patients. Children < 30 kg tended to have lower trough plasma levels, suggesting they require a twice-daily rivaroxaban regimen. PD values were within the adult ranges and a linear correlation between rivaroxaban plasma concentrations was confirmed.

The phase 3 studies for dabigatran and rivaroxaban are ongoing and no data have been reported to date. No clinical paediatric data have been published for apixaban or edoxaban so far, while no clinical studies have commenced yet for betrixaban.

A number of case-reports of DOACs use in children have already appeared in the literature. Martinelli et al. reported on a 6 year old girl with severe protein S deficiency treated with rivaroxaban after failure of all conventional anticoagulants [55]. The PK profile in this child demonstrated rapid clearance of rivaroxaban with a mean half-life 3.5 h. The child required more frequent and higher weight-relative (and absolute) doses of rivaroxaban (4 × 10 mg/day) compared to adult doses to suppress recurrent episodes of skin necrosis. Rivaroxaban was also used in a 12-year-old girl with homozygous antithrombin mutation and severe VTE who was not responsive to LMWH [56]. Beyer-Westendorf reported PK data from a 15 year old girl treated off-label with rivaroxaban 20 mg once daily for acute VTE [57]. Plasma concentrations of rivaroxaban at peak and trough were substantially lower than those known from adults. Thus, the authors discouraged rivaroxaban use in non-adult patients until data are available from paediatric trials.

Among series of patients with dabigatran and rivaroxaban overexposure reported to poison control centers, several children have been reported with accidental exposure who generally experienced few moderate effects, no major effects and no deaths [58–61].

9. Development of reversal agents for DOACs for children

Given the potent anticoagulant effects of DOACs, there is a need for reversal agents to prevent bleeding in case of emergency surgical procedures and to treat major hemorrhages. Idarucizumab, a reversal agent specific for dabigatran, has been developed [62] and is (conditionally) approved for adults. A PIP for idarucizumab is ongoing, consisting of a single dose study of idarucizumab used as rescue medication in children, and a registry of paediatric patients treated in practice with idarucizumab [63].

Shapiro et al. reported on a case of massive dabigatran overdose in a 15 year old girl after suicidal ingestion of 30–50 tablets dabigatran 150 mg [64]. The patient had only minor gum bleeding and was haemodynamically stable. After administration of 5 g idarucizumab (adult dose), dabigatran plasma levels dropped from around 2000 ng/ml (> 10-fold therapeutic levels) to zero within 30 min, with only a small rebound. Idarucizumab was well tolerated by this girl.

Andexanet alpha, an agent specific for factor Xa inhibitors, is under development for adults [65] and currently under review by FDA. A PIP has been agreed upon for andexanet alpha, comprising single dose studies to evaluate the PK/PD of andexanet alfa, administered at the end of anticoagulant treatment with either enoxaparin, apixaban, betrixaban, edoxaban, and rivaroxaban, to children of different age groups [66]. These studies have not yet started.

Another agent, ciraparantag, designed to reverse the effect of a wide range of anticoagulants (UFH, LMWH, other parenteral and oral factor Xa inhibitors, dabigatran, argatroban) is in early clinical development and no PIP has yet been agreed upon [67].

10. Discussion

What will be the role of DOACs in children? Given the pharmacological properties of the DOACs and the special characteristics of children requiring anticoagulation, the DOACs have the potential to be of particular benefit for children. If these advantages bear out in the results of the current studies, the DOACs will likely be used widely in children. Even if shown to be equal to conventional anticoagulants with regards to safety and efficacy, the increased convenience of DOACs will likely favor their use. Moreover, in real-life practice increased convenience may translate into improved compliance with the potential for increasing safety and efficacy.

As oral drugs, the DOACs will be most useful for long-term anticoagulation. Whether they will also be suitable for prophylaxis or initial treatment in acutely ill children will have to be studied. Use in acutely ill children, particularly infants and neonates, will require that administration via gastric feeding tubes is demonstrated possible, and that enteral absorption is reasonably reliable. Given the differences between DOACs in oral bioavailability, not all drugs may be equally applicable for acutely ill or very young children. Differences between DOACS in the ratio of renal versus hepatic clearance may also render certain drugs more or less applicable for children with renal insufficiency or hepatobiliary disease. More information from adults will still be needed regarding differential use of DOACs but paediatric data will as well be required.

All of the currently approved DOACs have paediatric developments ongoing or planned, some of which are substantially progressed into phase 3 studies. Paediatric formulations have been developed and are being tested in the ongoing studies. The key for use in children is to generate explicit age-appropriate dosing information for all age-groups. Unfortunately, the PK/PD studies of current PIPs have very small numbers of infants and neonates, and premature infants are mostly not included. Conversely, pharmacological and haemostatic differences are most pronounced in the youngest age groups, with a potential for differences in PK and/or PD. Similarly, the phase 3 studies are struggling to recruit younger children.

Whether and in which situations there will be the need for therapeutic drug monitoring in children will have to be elucidated. It is possible that in very young children (infants, neonates, prematures), acutely sick children, and children with relevant comorbidities, monitoring drug levels or activity may be required to establish the initial dose, or for dose adjustments during rapid weight gain or changing clinical situations. In addition, monitoring may be necessary for acute

surgery, bleeding or thrombotic complications, and possibly, to assess compliance.

The results of ongoing clinical studies in children still have to demonstrate whether there is a positive benefit risk balance for DOACs in all targeted paediatric indications and age-groups. This accounts particularly for indications that have not been explored in adults such as prevention of catheter-related VTE, or anticoagulation for congenital heart disease such as Fontan surgery. In adults with mechanical heart valves, dabigatran was found to have a negative benefit-risk profile compared to warfarin [68], apparently due to insufficient suppression of thrombin generation [69]. Based on these findings, the efficacy of DOACs could potentially be different in children with various intravascular artificial surfaces (CVC, shunts, stents, etc.). Likewise, the risk and type of bleeding may be different in the paediatric population. For example, epistaxis is a more common bleeding complaint in preschool and school-age children, as compared to older patients. Menstruating females will also make up a substantial percentage of paediatric trials and special attention will need to be paid to reproductive bleeding in this sub-population. In adult populations, evidence suggests that rivaroxaban in particular may have a higher rate of heavy menstrual bleeding as compared to traditional therapies [70]. It will not be possible to clarify all these questions from pre-authorization studies in children. Thus post-authorization studies will be required to generate more data on long-term safety and efficacy, neonates/prematures, and other paediatric special disease populations, e.g. renal, gastrointestinal, hepatic, intensive care patients, and use of DOACS in extracorporal circulation or cardiac devices.

The authors believe that DOACs should currently not be used off-label in children and adolescents. First, because this preliminary use puts children at risk as there is still insufficient information available on dosing, safety and efficacy; second, because off-label use jeopardizes recruitment of children into the ongoing PK/PD and comparative studies through loss of equipoise. The regulatory requirements for paediatric drug development provide unique chances to obtain systematic data for DOACs in children. On the other hand, there are significant challenges to performing valid and informative drug studies in children. Therefore, all efforts should currently go into treating children with DOACs within the ongoing studies. Subsequently, the systematic evaluation of DOACs in post-authorization studies targeting special population subgroups and sub-indications will be a major responsibility of the academic community. Moreover, systematic documentation of real-life DOAC use in children through registries will be necessary to complement the paediatric evidence.

In conclusion, the DOACs are not yet ready for use in children in clinical practice due to lack of evidence on appropriate dosing, safety and efficacy. Based on the public time plans of current PIPs and their actual status, we may expect the first publications of phase 3 study results in the next 1–2 years and paediatric market authorizations for some of the DOACs by the early 2020ies. The paediatric community is encouraged to promote participation of children and adolescents into the multiple ongoing studies of DOACs, allowing for a much stronger evidence base underlying our management strategies in paediatric anticoagulation.

Author contributions

C.M. has conceptualized and drafted the manuscript, K.T. and S.O.B have contributed to drafting and critically revising the manuscript, and all authors have approved the final version to be submitted.

Declaration of potential conflicts of interest

C. M. has received consulting and speaker honoraria, travel support, and study patient fees from Bayer, speaker honoraria and study patient fees from Boehringer Ingelheim, and consulting honoraria and study patient fees from Bristol-Myers-Squibb. K.T. has received study patient fees from Bayer, Boehringer Ingelheim, and Bristol-Myers-Squibb. S.O.B. has received consulting honoraria and travel support from Pfizer, institutional salary support and travel support from Bristol Myers Squibb, advisory board honoraria and travel support from Shire, and advisory board honoraria and travel support from CSL Behring.

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