Anticoagulation in Pediatric Patients

Christoph Male¹

¹ Department of Paediatrics, Medical University of Vienna, Vienna, Austria

Hamostaseologie 2022;42:46–53.

Address for correspondence Christoph Male, MD, MSc, Department of Paediatrics, Medical University of Vienna, Waehringer Guertel 18-20, Vienna, A-1090, Austria
(e-mail: christoph.male@meduniwien.ac.at).

Abstract

Special aspects of anticoagulation in children include the different epidemiology of thrombosis, developmental changes in the coagulation system, age-dependent pharmacokinetics of anticoagulants, risk of bleeding, and practical hurdles to anticoagulation. The classical anticoagulants so far used in children have several limitations, resulting in the need for regular monitoring. The pharmacological properties of direct oral anticoagulants (DOACs) and the special challenges of anticoagulation in children make the DOACs particularly attractive for children. All DOACs have pediatric development programs, targeting various indications for prevention and treatment of thrombosis. Child-appropriate formulations have been developed, age-specific dosing information generated, and safety and efficacy evaluated in ongoing phase 3 trials. Rivaroxaban and dabigatran have already been authorized for children for treatment of acute venous thrombosis and for extended secondary prevention. Their safety and efficacy have been demonstrated comparable to that of standard-of-care anticoagulants, without need for monitoring. Further studies are ongoing, which are expected to lead to pediatric authorizations of DOACs for primary venous thromboembolic event prevention in some high-risk settings. More real-life data will be necessary from postmarketing studies and registries to complement the evidence base for DOAC use in children, particularly in the youngest age groups and special disease populations.

Keywords

- ▶ children
- ▶ anticoagulation
- ▶ thromboprophylaxis
- ▶ direct oral anticoagulants

Zusammenfassung

Spezielle Aspekte der Antikoagulation bei Kindern umfassen die unterschiedliche Epidemiologie von Thrombosen, entwicklungsbedingte Veränderungen im Gerinnungssystem, altersabhängige Pharmakokinetik von Antikoagulantien, Blutungsrisiko und praktische Hürden für die Antikoagulation. Die bislang bei Kindern eingesetzten klassischen Antikoagulantien haben zahlreiche Limitationen, weswegen sie regelmäßiges Monitoring erfordern.

Die pharmakologischen Eigenschaften der direkten oralen Antikoagulantien (DOAKs) und die speziellen Herausforderungen von Antikoagulation bei Kindern machen die DOAKs für Kinder besonders attraktiv. Alle DOAKs haben pädiatrische Entwicklungsprogramme, die auf verschiedene Indikationen von Prävention und Behandlung von Thrombosen abzielen. Kindergerechte pharmazeutische Formulierungen wurden entwickelt, altersspezifische Dosisinformation generiert, und Sicherheit und Wirksamkeit werden in laufenden Phase 3 Studien evaluiert.

Rivaroxaban und Dabigatran erhielten bereits Zulassungen für Kinder für die Behandlung der akuten Venenthrombose und längerfristige sekundäre Prophylaxe. Ihre

Schlüsselwörter

- ▶ Kinder
- ▶ Antikoagulation
- ▶ Thromboprophylaxe
- ▶ direkte orale Antikoagulantien

received
October 20, 2021
accepted after revision
November 21, 2021

© 2022. Thieme. All rights reserved.
Georg Thieme Verlag KG,
Rüdigerstraße 14,
70469 Stuttgart, Germany

DOI <https://doi.org/10.1055/a-1703-0821>.
ISSN 0720-9355.

Sicherheit und Wirksamkeit zeigten sich jener von Standardantikoagulantien vergleichbar, ohne die Notwendigkeit für Monitoring. Weitere Studien sind noch am Laufen, welche voraussichtlich zu pädiatrischen Zulassungen von DOAKs für primäre Thromboprophylaxe in verschiedenen Hochrisikosituationen führen werden. Im Weiteren werden noch mehr Daten aus der Anwendung in der Praxis aus Postmarketing-Studien und Registern erforderlich sein, um die Evidenzbasis für die Anwendung von DOAKs bei Kindern zu erweitern, besonders für die jüngsten Altersgruppen und Kinder mit speziellen Erkrankungen.

Introduction

Thromboembolic events (TEs) in children differ from those in adults in epidemiology, anatomical location, and clinical presentation. TEs in children are much less frequent compared with those in adults and mostly occur in hospitalized children as secondary complications of severe acute or chronic diseases and their treatment.^{1–4} The reported incidence of TEs in hospitalized children has increased over the last decades,⁵ attributed to improved medical care of life-threatening conditions in children but causing more secondary morbidity such as thrombosis. Additionally, more TEs are identified in children due to increased clinical awareness and improved radiographic detection methods.

The risk for venous thromboembolic events (VTEs) in children is associated with age, with peaks in early infancy and in postpubertal age. As VTEs are rare in healthy neonates, the increased incidence in early life reflects clinical risk factors in sick term and preterm neonates or infants with severe congenital diseases, e.g., heart defects. In postpubertal age, the risk of VTEs increases towards the risk in young adults mainly due to the changes in hormonal status.

The most important risk factors for TEs in children are central venous catheter (CVC) and central arterial catheter, commonly used for treatment of underlying diseases. Other risk factors include intensive care treatment, mechanical ventilation, and prolonged hospital admission.⁶ Children frequently have several risk factors in combination, including cardiac disease, cancer, inflammation, trauma, surgery, and medications. Immobilization is a common underlying factor in older sick children, causing decreased venous flow. A relatively small proportion of children, predominantly adolescents, develop unprovoked VTEs. Such events may or may not be associated with an endogenous thrombophilic predisposition.

Special Aspects of Anticoagulation in Children

Several special aspects of TEs affect anticoagulation in children.⁷ First, the different epidemiology of TEs occurring in children limits the possibility to rely on adult evidence for efficacy and safety of anticoagulants for their use in children. Second, the coagulation system undergoes developmental changes during childhood, with the largest changes occurring in fetal life and early infancy. Preterm or term neonates have much lower levels of several procoagulant and anticoagulant

proteins compared with adults,⁸ which may result in altered responsiveness of the coagulation system to the effect of anticoagulant drugs. Third, age-dependent differences in drug uptake, absorption, metabolism, and elimination affect the pharmacokinetics of anticoagulants. These differences in both pharmacokinetic (PK) and pharmacodynamic (PD) properties result in age-dependent dose requirements for anticoagulants for children of various ages. Since dose requirements are not weight-proportional to those of adults, dedicated dose-finding studies in all pediatric age groups are necessary. Fourth, the risk of bleeding may be different in children during anticoagulation as a result of underlying diseases, e.g., thrombocytopenia or hepatopathy, and due to the risk of trauma in active children. Finally, there are several practical hurdles to anticoagulant therapy, as discussed in the following sections.

Indications for Anticoagulation in Children

► **Table 1** lists indications where anticoagulant prevention or treatment is used in children. Guidelines on anticoagulation in children are mostly based on evidence from adults, while scarce evidence exists from children. For many instances, the benefit–risk balance has not been established in children, particularly for young children and specific pediatric disease populations.^{9,10}

Some indications for anticoagulation show some similarity between children and adults, e.g., treatment of acute VTEs, but even in this instance, different types and location of TEs in children potentially affect the response to anticoagulation. Conversely, there are several indications specific to children, such as congenital heart defects, Kawasaki's syndrome with coronary aneurysms, and others.^{11,12} Furthermore, relatively more children requiring anticoagulation have serious comorbidity, some of which are unique for children, e.g., prematurity. These underlying conditions affect the choice of anticoagulant drug, dose requirements, efficacy or risk of bleeding, and the risk of interactions with concomitant drugs.

Acute symptomatic VTE in children is usually treated with therapeutic anticoagulation, based mostly on evidence from adults. Whether asymptomatic VTE, found incidentally or by radiographic screening, requires anticoagulant treatment is a matter of ongoing debate.^{13–15} In practice, this decision is usually individualized dependent on the location and

Table 1 Indications for anticoagulant prevention or treatment in children^a

Thrombosis	Prevention	Treatment
Venous	<ul style="list-style-type: none"> • Central venous catheter • Critically ill • Trauma • Perioperative prophylaxis 	<ul style="list-style-type: none"> • Deep vein thrombosis and pulmonary embolism • Cerebral sinovenous thrombosis
Both	<ul style="list-style-type: none"> • Cardiac catheterization • Shunts (e.g., Fontan); stents • Hemodialysis • Extracorporeal membrane oxygenation • Cardiopulmonary bypass surgery • Ventricular assist devices 	<ul style="list-style-type: none"> • Cardiac thrombosis
Arterial	<ul style="list-style-type: none"> • Central arterial catheter • Mechanical heart valves • Dilated cardiomyopathy • Kawasaki's syndrome 	<ul style="list-style-type: none"> • Arterial thrombosis • Arterial ischemic stroke

^aIndications where anticoagulation is used in children but in many instances not based on robust evidence.^{9,10}

extension of TE, and the anticipated risk of complications, for example, a central thrombus with risk of obstruction or embolization. Another pertinent question is the optimal duration of anticoagulation for children, specifically after provoked VTE once the triggering risk factor has resolved, e.g., a CVC that has been removed. The recently completed Kids-DOTT trial that compared 6 versus 12 weeks of anticoagulation in children after provoked VTE found that shorter anticoagulation was noninferior to longer anticoagulation.¹⁶

The evidence when to use anticoagulant thromboprophylaxis in children is scarce and heterogenous and adult indications for thromboprophylaxis are not directly informative for the various pediatric indications.⁹ Whether thromboprophylaxis is beneficial in preventing CVC-related VTEs, the most frequent risk-setting in children, has long been unresolved.¹³ A recent landmark trial of 954 children with leukemia and asparaginase treatment, the majority of whom had CVC, was the first to provide definite evidence of a benefit of low-molecular-weight heparin (LMWH) for thromboprophylaxis in such a high-risk setting. A strength of the study was that it assessed symptomatic VTEs as clinically relevant outcome.¹⁷ Children with cardiac disease are another group at high risk of TE where, in spite of very scarce evidence, thromboprophylaxis is usually given in several subindications (→Table 1).¹⁸

Challenges with the Classical Anticoagulants in Children

The anticoagulants predominantly used so far in children are unfractionated heparin (UFH), LMWH, and the vitamin K antagonists (VKAs).^{7,9} These anticoagulants pose several challenges in children.

For heparins, the anticoagulant effect is dependent on endogenous antithrombin, which is physiologically low in neonates and frequently decreased in sick children. Moreover, UFH has highly unpredictable PK and PD properties, influenced by age and various other factors.¹⁹ Consequently, there is poor correlation between UFH dose and anticoagu-

lant effect, particularly in clinically unstable children.²⁰ Nevertheless, UFH is currently still the drug of choice for short-term anticoagulation because of its short half-life and the availability of an antidote (protamine sulfate). LMWH have more stable, though age-dependent PK/PD properties, and require less frequent monitoring than UFH, and their longer half-life makes them useful for longer-term use, including the outpatient setting.²¹

Until recently, VKAs were the only oral anticoagulants available for children, but they have a slow onset and a slow offset, are strongly influenced by dietary intake, and show multiple drug interactions. These challenges are aggravated in children with serious underlying diseases, feeding problems, or receiving concomitant drugs. Dose requirements for VKAs in children have been shown to be dependent on age and comorbidity.²² Particularly in infants, VKA use is difficult due to variable vitamin K intake through breast milk or infant formulas.

All the classical anticoagulants require regular monitoring and dose adjustments. Lastly, none of the classical anticoagulants has been authorized for children, except for the recent license of dalteparin in the United States, which was however based on very limited pediatric data.²³ Therefore, no commercial age-appropriate administration forms and dose strengths are available covering the wide range of doses.

Direct Oral Anticoagulants for Children

Direct oral anticoagulants (DOACs) selectively inhibit specific coagulation factors without the need for a cofactor. They include the factor Xa inhibitors rivaroxaban, apixaban, and edoxaban, and the direct thrombin inhibitor dabigatran. They are all approved in adults for the prevention and treatment of VTEs where they have established efficacy and safety without the need for monitoring.

The pharmacological properties of DOACs make them particularly interesting for children: oral administration, predictable pharmacokinetics, no antithrombin dependence, little food interaction, few drug interactions, a wider therapeutic window, and possibly no monitoring requirements. As a result

Table 2 Indications targeted by pediatric programs for direct oral anticoagulants

	Prevention of VTEs	Prevention of cardiac/arterial TEs	Treatment of VTEs
Rivaroxaban	–	Post Fontan surgery ^a (rivaroxaban vs. aspirin)	Acute VTEs ^b (rivaroxaban vs. SOC)
Dabigatran	–	–	<ul style="list-style-type: none"> • Acute VTEs^b (dabigatran vs. SOC) • Extended secondary prevention^b (dabigatran single arm)
Apixaban	Acute leukemia/lymphoma, asparaginase treatment, with central venous catheter (apixaban vs. placebo)	Various cardiac diseases (apixaban vs. SOC)	Acute VTEs (apixaban vs. SOC)
Edoxaban	–	Various cardiac diseases (edoxaban vs. SOC)	Acute VTEs (edoxaban vs. SOC)

Abbreviations: SOC, standard of care; TEs, thromboembolic events; VTEs, venous thromboembolic events.

^aStudy completed and pediatric authorization for the indication granted in the US.

^bPrograms completed and pediatric authorizations for the indication granted.

of pediatric legislations in the United States and European Union (EU) to stimulate pediatric drug development, all DOACs have pediatric study programs ongoing or already completed.²⁴ The indications targeted by the individual programs are listed in **Table 2**. The individual studies of these programs have previously been described in detail.^{24–26}

Principles of anticoagulant development for children have been outlined by a recommendation by the Pediatric Scientific and Standardization Committee (SSC) of the International Society of Thrombosis and Hemostasis (ISTH).²⁷ A fundamental element is development of age-appropriate pediatric formulation(s) to ensure accurate and reliable administration of the medicine to children of different ages.

Pediatric dose finding usually builds 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 (PBPK) models and/or population PK/PD modelling and simulations, dose finding studies in children can be optimized and the number of blood samples required from children minimized.

Most pediatric DOACs programs perform single-dose PK/PD studies in children of all age groups for initial dose-finding and safety assessment, except for a multiple-dose study on dabigatran in adolescents.²⁸ The rivaroxaban program performed an intermediate step of a phase 2, dose-confirmation and safety study over the last 4 weeks of anticoagulation therapy for acute VTEs.²⁹ All other pediatric programs continue from their single-dose PK/PD studies immediately to phase 3, safety and efficacy studies.

All current DOAC pediatric programs target the indication of treatment of VTEs, comprising open-label randomized controlled trials (RCTs) comparing the respective DOAC versus standard-of-care (SOC) anticoagulants for a main treatment phase of 3 months, and allowing for extended treatment if necessary. Several programs also target various indications of primary prevention of TEs, mostly in small-scale RCT comparing the DOAC to SOC for a defined period of risk (**Table 2**).

The pediatric phase 3 studies have rather limited patient numbers between 100 and 500, mostly not powered to

independently demonstrate efficacy or safety in children. The relatively small sample sizes are explained by the feasibility challenges of such trials. Moreover, pediatric developments can build on extrapolation from the evidence in adults, if there is reasonable similarity between children and adults. Pediatric studies aim to confirm the proof of efficacy from adults, accounting for potential differences in frequencies of outcomes.³⁰ Reasonable similarity between adults and children may be assumed for VTE treatment but is uncertain for most clinical settings of VTE prevention, e.g., pediatric cardiac diseases.

DOACs Approved for Children

The pediatric programs for rivaroxaban and dabigatran, targeting anticoagulant treatment of children with acute VTE, have already been completed and led to pediatric authorizations.

Rivaroxaban

A pediatric rivaroxaban oral solution has been developed in addition to the adult tablets and is now commercially available. A PBPK model for rivaroxaban was developed, using PK data from adults and physiological information from children,³¹ to predict rivaroxaban dosing regimens targeting adult exposures to be tested in the pediatric clinical studies. These dosing regimens were validated in phase 1 and 2 studies with some modifications for the phase 3 study.

EINSTEIN-Jr Studies

A phase 1 study assessed a single body weight-adjusted dose of rivaroxaban (equivalent to 10 mg or 20 mg) in 59 children aged 6 months to 18 years.³² The study reported predictable PK/PD profiles across all age groups and no bleeding episodes.

EINSTEIN-Jr phase 2 comprised several studies across different age groups evaluating the safety, efficacy, and PK/PD of body weight-adjusted rivaroxaban in 93 children with VTE. No major bleeding events or symptomatic recurrent VTEs occurred.²⁹

The EINSTEIN-Jr pivotal phase 3 study was an open-label RCT comparing rivaroxaban versus SOC anticoagulation (UFH, LMWH, fondaparinux, VKAs) in a 2:1 ratio in 500 children aged between birth and less than 18 years with confirmed acute VTE.³³ The main treatment period was 3 months (1 month for children aged <2 years with CVC-related VTE), whereafter the main outcomes were assessed. Patients requiring longer-term anticoagulation could receive study treatment for up to 12 months. Approximately 25% of index VTE events were catheter-related, 23% were cerebral vein or sinus thromboses, and 51% had other, non-catheter-related VTEs. VTE recurred in 4/335 (1.2%) patients receiving rivaroxaban and in 5/165 (3%) patients on SOC (hazard ratio [HR], 0.4; 95% confidence interval [CI], 0.1–1.4). On repeat imaging, complete resolution of the index thrombosis was significantly more frequent in the rivaroxaban group (38%) than in the SOC group (26%; odds ratio, 1.70; 95% CI, 1.1–2.6). Clinically relevant bleeding occurred in 3% of patients on rivaroxaban (all nonmajor) and in 1.9% on SOC (two major; one nonmajor; HR, 1.6; 95% CI, 0.5–6.3). Outcome rates and relative efficacy and safety of rivaroxaban versus SOC in children were consistent with those observed in adult patients from previous rivaroxaban studies. Assessment of PK parameters from the phase 3 study confirmed that plasma levels of rivaroxaban were equivalent to those seen with the 20-mg once-daily dose in adults. There was no association between levels of PK parameters and recurrent VTE, bleeding, or adverse events.³⁴ The now authorized weight-adjusted pediatric dose regimes require once-daily dosing in children weighing more than 30 kg, twice-daily dosing in children weighing between 12 and 30 kg, and three-times daily dosing in children weighing 12 kg or less.³⁵

Another rivaroxaban trial (UNIVERSE) targeted prevention of thrombosis in children (aged 2–8 years) with single ventricle physiology after the Fontan procedure comparing rivaroxaban versus aspirin for up to 12 months.³⁶ The study results have just been published showing that children receiving rivaroxaban had a similar safety profile and a trend to less frequent thrombotic events compared with children receiving aspirin. However, with a sample size of $n = 112$, the study was not powered to formally demonstrate superior efficacy.³⁷

Dabigatran

The pediatric dabigatran formulations include coated granules for children aged less than 12 years and an oral suspension for infants less than 12 months, in addition to the adult capsules. For the approved age- and weight-based pediatric dose regimens, readers are referred to the product information.³⁸

Pediatric dabigatran doses were estimated from an adult-population PK model using renal function as the main covariate. The predicted dose regimens were evaluated in a series of phase 2a studies assessing PK/PD in all age groups.^{28,39,40} No deaths, bleeding events, or drug-related serious adverse events were reported and the PK/PD relationships for dabigatran were consistent with those seen in adult patients with VTE.

The pivotal 2b/3 trial (DIVERSITY) was an open-label RCT of the safety and efficacy comparing dabigatran versus SOC (LMWH or VKA) in 2:1 ratio in 267 children aged 0 to less than 18 years with acute VTE.⁴¹ The composite primary outcome (complete thrombus resolution, freedom from recurrent VTE or VTE-related death) was reached in 81 (46%) patients receiving dabigatran and 38 (42%) patients receiving SOC (risk difference, 0.04; 95% CI, –0.14 to 0.07), demonstrating noninferiority. Also, the frequency of any bleeding (22 vs. 24%) and major bleeding events (2 vs. 2%) were similar. Moreover, the PK/PD relationship for dabigatran was reported to be similar to that of adults.

The dabigatran program included a further single-arm phase 3 study assessing dabigatran for extended secondary VTE prevention in 199 children after anticoagulant treatment for 3 months who had an unresolved clinical risk factor requiring extended anticoagulation, e.g., inherited or acquired thrombophilia.⁴² The median duration of extended dabigatran treatment was 36 weeks. Only 1% of children experienced recurrent VTE, and 1.5 and 1% experienced major and clinically relevant nonmajor bleeding events, respectively.

A PD modeling and simulation analysis for dabigatran was based on the data from the four single-arm and the randomized, comparative pediatric VTE studies ($n = 358$ children aged birth to <18 years) and a healthy adult study.⁴³ The PK simulation indicated that, using the final updated dosing algorithms for administering dabigatran to pediatric patients as oral solution, pellets, or capsules, no dose adjustment or routine monitoring is needed. However, in DIVERSITY and the secondary prevention study, dabigatran treatment had to be discontinued prematurely in 9.7 and 12.3% of children, respectively, because they failed to reach target dabigatran concentrations.^{41,42} This raises concern whether dabigatran can be given unmonitored in all children.

Ongoing DOAC Pediatric Programs

Apixaban

Pediatric apixaban formulations under study are a dissolvable minitab and an oral solution, in addition to the adult tablets. The apixaban pediatric program has the widest spectrum of indications targeting both prevention and treatment of TE in children.

A single-dose phase 1 study has evaluated PK/PD parameters of prophylactic apixaban doses in children of all ages at risk for a venous or arterial thrombosis.⁴⁴ Study results have not yet been published.

The pivotal pediatric apixaban study is an ongoing trial in children with acute lymphoblastic leukemia or lymphoma, asparaginase treatment, and presence of a central venous catheter (PREVAPIX-ALL).⁴⁵ This is a proof-of-concept study comparing apixaban versus placebo in a fully powered RCT ($n = 500$), since the benefit of anticoagulant prophylaxis of catheter-related VTE has never been unequivocally demonstrated.

The apixaban program also includes an RCT in children with various congenital and acquired cardiac diseases,

comparing apixaban versus SOC anticoagulants for up to 1 year for long-term primary and secondary prevention of venous, arterial, and cardiac TE (SAXOPHONE).⁴⁶ The study sample is limited to 200 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.

Finally, a phase 4 trial assesses the safety and efficacy of apixaban for treatment of acute VTEs in pediatric patients (CANINES).⁴⁷

Edoxaban

A pediatric edoxaban oral suspension is evaluated for children, in addition to the available tablets. A single-dose phase 1 study evaluates the PK/PD of edoxaban in pediatric patients of all age groups.⁴⁸

A phase 3 open-label RCT evaluates the safety and efficacy of edoxaban for thromboprophylaxis in children with cardiac disease at risk for TEs for a duration of up to 9 months (ENNOBLE-ATE).⁴⁹

Finally, a phase 3, open-label RCT evaluates the safety, efficacy, and PK/PD of edoxaban compared with SOC for anticoagulant treatment in pediatric patients with acute VTE.⁵⁰

Expected Role of DOACs for Children and Further Needs

Two of the DOACs, rivaroxaban and dabigatran, are already authorized for children in the EU, rivaroxaban in Canada, and dabigatran in the United States, and the pediatric pharmaceutical formulations are now commercially available. Both rivaroxaban and dabigatran are indicated for treatment of acute VTEs and extended secondary prevention.^{35,38} As their efficacy and safety has been demonstrated comparable to that of SOC anticoagulants, oral administration and no need for monitoring will likely favor their use.

As per pediatric license, both DOACs can only be initiated after at least 5 days of parenteral anticoagulation, which for rivaroxaban is different from the adult regimen. The pediatric studies included this initial phase of SOC anticoagulation to allow for time for consent and randomization of children. Therefore, parenteral anticoagulation, mainly LMWH, will always be required initially, and longer in children who are not on enteral feeding. Thus, the DOACs will be most suitable for children who are clinically stable and for long-term anticoagulation.

To date, none of the DOACs is licensed for primary prevention of TEs in children. However, some of the ongoing studies targeting prevention are close to completion and will hopefully lead to pediatric authorization of some DOACs for thromboprophylaxis in children with cancer and CVC and children with cardiac disorders. Obviously, the pediatric studies do not cover all indications where thromboprophylaxis is used in children, e.g., perioperative prophylaxis, trauma, or critically ill children, but the evolving evidence may allow some extension beyond the studied settings.

Importantly, the preauthorization pediatric studies have generated only limited evidence, as patient numbers overall are still small, but particularly young age groups were underrepresented, and prematures were not studied at all. Moreover, children with severe comorbidities were excluded. Therefore, following the pediatric authorizations of DOACs, systematic evaluation of their use in children from postmarketing studies and real-life data from registries will be essential, to validate dosing regimens and their benefit-risk in neonates/prematures and other special disease populations, e.g., renal, gastrointestinal, hepatic, and intensive care patients, and their long-term safety and efficacy. Moreover, other pediatric indications will possibly be explored off-label, e.g., the use of DOACs in extracorporeal circulation or cardiac devices.

Based on the results of clinical studies, therapeutic monitoring is not routinely required for children receiving rivaroxaban and dabigatran. Whether monitoring may be necessary in the very young, acutely sick children, or children with relevant comorbidities, to establish the initial dose, for dose adjustments during changing clinical situations, or during rapid weight gain still needs to be elucidated by systematic studies. Assessing levels may also be necessary for acute unplanned surgery, bleeding, or thrombotic complications, and to assess compliance. However, except for the reference PK ranges from adults used for the pediatric studies, no therapeutic target ranges validated by clinical outcomes are yet available for children, making interpretation of levels difficult.

Future Perspectives

A new group of anticoagulants, the factor IX and/or factor XII inhibitors, have the promise of anticoagulant activity with a decreased risk of bleeding. Several such agents are in early clinical development in adults, and if their improved benefit-risk balance is confirmed, these will be attractive for children, particularly for high-risk clinical settings. It will be important that future pediatric developments of such agents focus on the right populations, avoiding competition between different programs, and study designs build on the experience gained from the recent pediatric DOAC programs.

Conclusions

In conclusion, two DOACs have already received pediatric authorizations for treatment of acute VTEs and extended secondary prevention VTEs. Results from ongoing studies are pending that are expected to lead to pediatric authorizations of DOACs for thromboprophylaxis in certain high-risk situations. More real-life data will be necessary from postmarketing studies and registries to complement the evidence base for DOAC use in children, particularly in the youngest age group and special disease populations. Future pediatric studies on new anticoagulant agents, such as the factor XI and XII inhibitors, should build on the experience with the recent pediatric DOAC programs.

Conflict of Interest

C. M. has received personal funds and/or funds to institution from Anthos, Bayer, Boehringer Ingelheim, Bristol-Myers-Squibb, Janssen, and Pfizer.

References

- van Ommen CH, Heijboer H, Büller HR, Hirasing RA, Heijmans HS, Peters M. Venous thromboembolism in childhood: a prospective two-year registry in The Netherlands. *J Pediatr* 2001;139(05):676–681
- Setty BA, O'Brien SH, Kerlin BA. Pediatric venous thromboembolism in the United States: a tertiary care complication of chronic diseases. *Pediatr Blood Cancer* 2012;59(02):258–264
- Takemoto CM, Sohi S, Desai K, et al. Hospital-associated venous thromboembolism in children: incidence and clinical characteristics. *J Pediatr* 2014;164(02):332–338
- Sabapathy CA, Djouonang TN, Kahn SR, Platt RW, Tagalakakis V. Incidence trends and mortality from childhood venous thromboembolism: a population-based cohort study. *J Pediatr* 2016;172:175–180.e1
- Raffini L, Huang YS, Witmer C, Feudtner C. Dramatic increase in venous thromboembolism in children's hospitals in the United States from 2001 to 2007. *Pediatrics* 2009;124(04):1001–1008
- Mahajerin A, Branchford BR, Amankwah EK, et al. Hospital-associated venous thromboembolism in pediatrics: a systematic review and meta-analysis of risk factors and risk-assessment models. *Haematologica* 2015;100(08):1045–1050
- Newall F, Branchford B, Male C. Anticoagulant prophylaxis and therapy in children: current challenges and emerging issues. *J Thromb Haemost* 2018;16(02):196–208
- Monagle P, Barnes C, Ignjatovic V, et al. Developmental haemostasis. Impact for clinical haemostasis laboratories. *Thromb Haemost* 2006;95(02):362–372
- Monagle P, Chan AKC, Goldenberg NA, et al. Antithrombotic therapy in neonates and children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141(2, Suppl):e737S–e801S
- Monagle P, Cuello CA, Augustine C, et al. American Society of Hematology 2018 Guidelines for management of venous thromboembolism: treatment of pediatric venous thromboembolism. *Blood Adv* 2018;2(22):3292–3316
- Monagle P, Cochrane A, Roberts R, et al; Fontan Anticoagulation Study Group. A multicenter, randomized trial comparing heparin/warfarin and acetylsalicylic acid as primary thromboprophylaxis for 2 years after the Fontan procedure in children. *J Am Coll Cardiol* 2011;58(06):645–651
- Baker AL, Vanderpluym C, Gauvreau KA, et al. Safety and efficacy of warfarin therapy in Kawasaki disease. *J Pediatr* 2017;189:61–65
- Vidal E, Sharathkumar A, Glover J, Faustino EV. Central venous catheter-related thrombosis and thromboprophylaxis in children: a systematic review and meta-analysis. *J Thromb Haemost* 2014;12(07):1096–1109
- Sharathkumar AA, Biss T, Kulkarni K, et al; SSC Subcommittee on Pediatrics and Neonatal T&H of the ISTH. Epidemiology and outcomes of clinically unsuspected venous thromboembolism in children: a systematic review. *J Thromb Haemost* 2020;18(05):1100–1112
- Jones S, Monagle P, Newall F. Do asymptomatic clots in children matter? *Thromb Res* 2020;189:24–34
- Goldenberg NA, Kittelson JM, Abshire TC, et al; Kids-DOTT Trial Investigators and the ATLAS Group. A six-week versus three-month duration of anticoagulation for acute provoked venous thromboembolism in patients < 21 years old: results of the Multinational Kids-DOTT Randomized Controlled Trial [abstract]. *Res Pract Thromb Haemost* 2021;5(Suppl 2)
- Greiner J, Schrappe M, Claviez A, et al; THROMBOTECT Study Investigators. THROMBOTECT - a randomized study comparing low molecular weight heparin, antithrombin and unfractionated heparin for thromboprophylaxis during induction therapy of acute lymphoblastic leukemia in children and adolescents. *Haematologica* 2019;104(04):756–765
- Giglia TM, Massicotte MP, Tweddell JS, et al; American Heart Association Congenital Heart Defects Committee of the Council on Cardiovascular Disease in the Young, Council on Cardiovascular and Stroke Nursing, Council on Epidemiology and Prevention, and Stroke Council. Prevention and treatment of thrombosis in pediatric and congenital heart disease: a scientific statement from the American Heart Association. *Circulation* 2013;128(24):2622–2703
- Hanslik A, Kitzmüller E, Tran US, et al. Monitoring unfractionated heparin in children: a parallel-cohort randomized controlled trial comparing 2 dose protocols. *Blood* 2015;126(18):2091–2097
- Kuhle S, Eulmesekian P, Kavanagh B, et al. Lack of correlation between heparin dose and standard clinical monitoring tests in treatment with unfractionated heparin in critically ill children. *Haematologica* 2007;92(04):554–557
- Yee DL, O'Brien SH, Young G. Pharmacokinetics and pharmacodynamics of anticoagulants in paediatric patients. *Clin Pharmacokinet* 2013;52(11):967–980
- Streif W, Andrew M, Marzinotto V, et al. Analysis of warfarin therapy in pediatric patients: a prospective cohort study of 319 patients. *Blood* 1999;94(09):3007–3014
- US Food and Drug Administration. Dalteparin sodium approval for pediatric patients. 2019. Accessed October 2021 at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020287s072lbl.pdf
- Male C, Thom K, O'Brien SH. Direct oral anticoagulants: what will be their role in children? *Thromb Res* 2019;173:178–185
- Albisetti M. Use of direct oral anticoagulants in children and adolescents. *Hamostaseologie* 2020;40(01):64–73
- Branstetter JW, Kiskaddon AL, King MA, et al. Efficacy and safety of non-vitamin K antagonist oral anticoagulants in pediatric venous thromboembolism treatment and thromboprophylaxis: a systematic review of the literature. *Semin Thromb Hemost* 2021;47(06):643–653
- Male C, Monagle P, Chan AK, Young G. Pediatric/Neonatal Hemostasis and Thrombosis Scientific and Standardization Subcommittee of the International Society on Thrombosis and Haemostasis. Recommendations for the development of new anticoagulant drugs for pediatric use: communication from the SSC of the ISTH. *J Thromb Haemost* 2015;13(03):481–484
- Halton JM, Lehr T, Cronin L, et al. Safety, tolerability and clinical pharmacology of dabigatran etexilate in adolescents. An open-label phase IIa study. *Thromb Haemost* 2016;116(03):461–471
- Monagle P, Lensing AWA, Thelen K, et al; EINSTEIN-Jr Phase 2 Investigators. Bodyweight-adjusted rivaroxaban for children with venous thromboembolism (EINSTEIN-Jr): results from three multicentre, single-arm, phase 2 studies. *Lancet Haematol* 2019;6(10):e500–e509
- European Medicines Agency. Reflection paper on the use of extrapolation in the development of medicines for paediatrics. 2018. Accessed October 2021 at: https://www.ema.europa.eu/documents/scientific-guideline/adopted-reflection-paper-use-extrapolation-development-medicines-paediatrics-revision-1_en.pdf
- Willmann S, Becker C, Burghaus R, et al. Development of a paediatric population-based model of the pharmacokinetics of rivaroxaban. *Clin Pharmacokinet* 2014;53(01):89–102
- Kubitza D, Willmann S, Becka M, et al. Exploratory evaluation of pharmacodynamics, pharmacokinetics and safety of rivaroxaban in children and adolescents: an EINSTEIN-Jr phase I study. *Thromb J* 2018;16:31

- 33 Male C, Lensing AWA, Palumbo JS, et al; EINSTEIN-Jr Phase 3 Investigators. Rivaroxaban compared with standard anticoagulants for the treatment of acute venous thromboembolism in children: a randomised, controlled, phase 3 trial. *Lancet Haematol* 2020;7(01):e18–e27
- 34 Young G, Lensing AWA, Monagle P, et al; EINSTEIN-Jr. Phase 3 Investigators. Rivaroxaban for treatment of pediatric venous thromboembolism. An Einstein-Jr phase 3 dose-exposure-response evaluation. *J Thromb Haemost* 2020;18(07):1672–1685
- 35 European Medicines Agency. Xarelto product information. 2021. Accessed October 2021 at: <https://www.ema.europa.eu/en/medicines/human/EPAR/xarelto#product-information-section>
- 36 Pina LM, Dong X, Zhang L, et al. Rivaroxaban, a direct Factor Xa inhibitor, versus acetylsalicylic acid as thromboprophylaxis in children post-Fontan procedure: rationale and design of a prospective, randomized trial (the UNIVERSE study). *Am Heart J* 2019;213:97–104
- 37 McCrindle BW, Michelson AD, Van Bergen AH, et al; UNIVERSE Study Investigators. Thromboprophylaxis for children post-Fontan procedure: insights from the UNIVERSE study. *J Am Heart Assoc* 2021;10(22):e021765
- 38 European Medicines Agency. Pradaxa product information. 2021. Accessed October 2021 at: <https://www.ema.europa.eu/en/medicines/human/EPAR/pradaxa#product-information-section>
- 39 Halton JML, Albisetti M, Biss B, et al. Phase IIa study of dabigatran etexilate in children with venous thrombosis: pharmacokinetics, safety, and tolerability. *J Thromb Haemost* 2017;15(11):2147–2157
- 40 Halton JML, Picard AC, Harper R, et al. Pharmacokinetics, pharmacodynamics, safety and tolerability of dabigatran etexilate oral liquid formulation in infants with venous thromboembolism. *Thromb Haemost* 2017;117(11):2168–2175
- 41 Halton J, Brandão LR, Luciani M, et al; DIVERSITY Trial Investigators. Dabigatran etexilate for the treatment of acute venous thromboembolism in children (DIVERSITY): a randomised, controlled, open-label, phase 2b/3, non-inferiority trial. *Lancet Haematol* 2021;8(01):e22–e33
- 42 Brandão LR, Albisetti M, Halton J, et al; DIVERSITY Study Investigators. Safety of dabigatran etexilate for the secondary prevention of venous thromboembolism in children. *Blood* 2020;135(07):491–504
- 43 Röshammar D, Huang F, Albisetti M, et al. Pharmacokinetic modeling and simulation support for age- and weight-adjusted dosing of dabigatran etexilate in children with venous thromboembolism. *J Thromb Haemost* 2021;19(05):1259–1270
- 44 Bristol-Myers-Squibb. Study to evaluate a single dose of apixaban in pediatric participants at risk for a thrombotic disorder (NCT01707394). 2012. Accessed October 2021 at: <https://clinicaltrials.gov/ct2/show/NCT01707394>
- 45 O'Brien SH, Li D, Mitchell LG, et al. PREVAPIX-ALL: apixaban compared to standard of care for prevention of venous thrombosis in paediatric acute lymphoblastic leukaemia (ALL)-rationale and design. *Thromb Haemost* 2019;119(05):844–853
- 46 Payne RM, Burns KM, Glatz AC, et al; Pediatric Heart Network Investigators. A multi-national trial of a direct oral anticoagulant in children with cardiac disease: design and rationale of the Safety of ApiXaban On Pediatric Heart disease On the prevention of Embolism (SAXOPHONE) study. *Am Heart J* 2019; 217:52–63
- 47 Pfizer. Apixaban for the acute treatment of venous thromboembolism in children (NCT02464969). 2015. Accessed October 2021 at: <https://clinicaltrials.gov/ct2/show/NCT02464969>
- 48 Daiichi-Sankyo. Phase 1 pediatric pharmacokinetics/pharmacodynamics (PK/PD) study (NCT02303431). 2014. Accessed October 2021 at: <https://clinicaltrials.gov/ct2/show/NCT02303431>
- 49 Daiichi-Sankyo. Edoxaban for prevention of blood vessels being blocked by clots (thrombotic events) in children at risk because of cardiac disease (NCT03395639). 2018. Accessed October 2021 at: <https://clinicaltrials.gov/ct2/show/NCT03395639>
- 50 van Ommen CH, Albisetti M, Chan AK, et al. The Edoxaban Hokusai VTE PEDIATRICS Study: an open-label, multicenter, randomized study of edoxaban for pediatric venous thromboembolic disease. *Res Pract Thromb Haemost* 2020;4(05):886–892