

Use of Direct Oral Anticoagulants in Children and Adolescents

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Abstract

While the need for anticoagulation in children has increased over the last decades, dose regimens of currently used anticoagulants, including low-molecular-weight heparin (LMWH) and vitamin K antagonist (VKA), are still extrapolated from adult guidelines because well-designed clinical trials were never performed in children. This approach is not optimal due to specific pediatric features of the hemostatic system and pathophysiology of thrombosis. These anticoagulants also present several disadvantages that further hamper optimal anticoagulation of pediatric patients, especially newborns and infants. The new direct oral anticoagulants (DOACs), which have the potential to overcome these disadvantages, were extensively investigated in adults and have become a valid alternative to LMWH and VKA for anticoagulation in the adult population. Several pediatric trials on all approved DOACs are currently ongoing, providing specific pediatric formulations and age- and weight-adjusted dose guidelines. First results of phase III trials indicate that DOACs are at least as efficient and safe as LMWH and VKA for the treatment and prevention of thrombotic events in children with different clinical conditions. This review article summarizes available data from terminated and ongoing controlled trials on DOACs in children and adolescents.

Keywords

- ▶ direct oral anticoagulants
- ▶ anticoagulation
- ▶ children
- ▶ thrombosis

Zusammenfassung

Während der Bedarf an Antikoagulation bei Kindern in den letzten Jahrzehnten zugenommen hat, werden die Therapierichtlinien der derzeit verwendeten Antikoagulantien, einschließlich niedermolekularem Heparin (LMWH) und Vitamin K-Antagonisten (VKA), immer noch aus den Empfehlungen für Erwachsene extrapoliert, da nie gut konzipierte klinische Studien an Kindern durchgeführt wurden. Dieser Ansatz ist aufgrund spezifischer pädiatrischer Merkmale des hämostatischen Systems und der Pathophysiologie der Thrombose nicht optimal. Diese Antikoagulantien weisen auch mehrere Nachteile auf, die eine optimale Antikoagulation von pädiatrischen Patienten, insbesondere von Neugeborenen und Säuglingen, weiter behindern. Die neuen direkten oralen Antikoagulantien (DOACs), die das Potenzial haben, diese Nachteile zu überwinden, wurden bei Erwachsenen umfassend untersucht und stellen eine valide Alternative zu LMWH und VKA für die Antikoagulation in der Erwachsenenpopulation dar. Derzeit laufen mehrere pädiatrische Studien mit allen zugelassenen DOACs, die spezifische pädiatrische Formulierungen sowie alters- und gewichtsangepasste Dosisrichtlinien enthalten. Erste Ergebnisse der Phase-III-Studien zeigen, dass DOACs zur Behandlung und Prävention thrombotischer Ereignisse bei Kindern mit unterschiedlichen Grundkrankheiten mindestens so effizient und sicher sind wie LMWH und VKA. Dieser Übersichtsartikel fasst die verfügbaren Daten aus abgeschlossenen und laufenden kontrollierten Studien zu DOACs bei Kindern und Jugendlichen zusammen.

Schlüsselwörter

- ▶ direkte orale Antikoagulantien
- ▶ Antikoagulation
- ▶ Kinder
- ▶ Thrombose

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Introduction

Venous thromboembolism (VTE) in children and adolescents has dramatically increased over the last two decades.¹ The rise is mostly due to the increase of improved invasive methods for the diagnosis and treatment of severe and complex medical conditions such as cancer, congenital heart disease, and other congenital malformations involving several organs.^{1,2} In these children, VTE is usually secondary to the use of a central venous catheter.^{1,2} In adolescents, one of the most common cause of VTE is the use of oral contraceptive.³

Current standard of care (SOC) for the treatment of VTE in pediatrics includes the use of unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and vitamin K antagonists (VKA).^{4,5} These anticoagulants have several disadvantages that make anticoagulation in children very challenging, particularly in newborns and infants. Disadvantages include unpredictable pharmacokinetic response, several drug and food interactions, and the need for parenteral administration and frequent monitoring, which is problematic in children with poor venous access. Due to the lack of randomized controlled studies performed in children with these agents, dosage and duration of anticoagulation is extrapolated from adult guidelines; no pediatric, age-specific formulations are available; and all agents are used off-label.^{4,5}

Direct oral anticoagulants (DOACs) have proven at least as efficient and safe as SOC for most indications in adults, including treatment and prophylaxis of deep venous thrombosis (DVT), pulmonary embolism, and atrial fibrillation.⁶ DOACs have clearly overcome limitations of SOC in adults and have thus the potential to be of benefit for children, too. Several phase I–III trials are currently ongoing to assess efficacy and safety of DOACs in children and adolescents for several indications.

This review summarizes available data information from completed and ongoing trials on the use of DOACs in the pediatric population.

Direct Thrombin Inhibitors

Dabigatran Etexilte

Dabigatran is a 3-((2-[(4-(amino[(E) hexyloxy-carbonylimino]methyl)phenylamino) methyl]-1-methyl-1H-benzimidazole-5-carbonyl)pyridine-2-yl-amino) propionic acid ethyl ester compound that specifically and reversibly inhibits thrombin.⁷ Dabigatran is orally administered as the prodrug, dabigatran etexilate, which differs from dabigatran by an ethyl group at the carboxylic acid and a hexyloxy-carbonyl side chain at the amidine.⁸ Once absorbed from the gastrointestinal tract, dabigatran etexilate is converted to its active metabolite, dabigatran.⁹ Dabigatran is available in three different pharmaceutical formulations: capsule, pellets, and oral liquid formulation.

Pharmacodynamics (PD) and pharmacokinetics (PK) of dabigatran were investigated in a double-blind, randomized, placebo-controlled study in 40 healthy adult volunteers.¹⁰ In this study, dabigatran etexilate was rapidly absorbed with peak plasma concentrations of dabigatran reached within 2 hours of administration. Absorption was followed by a

rapid distribution/elimination phase and a terminal phase with associated estimated half-lives between 8 and 10 hours with single and 14 and 17 hours with multiple dose administrations (–Table 1).¹⁰ Further population PK analyses showed that renal function has the most important, clinically relevant impact on dabigatran exposure.^{11,12}

Preclinical Pediatric Studies

The anticoagulant effect of dabigatran in children was first assessed in vitro using pooled plasma sample from healthy children aged birth to <1, 1 to <5, 5 to <10, 10 to <17 years, and adults.¹³ Plasma samples were spiked with increasing concentrations of dabigatran and the effect tested in five coagulation assays (prothrombin time [PT], activated partial thromboplastin time [aPTT], diluted thrombin time [dTT], ecarin clotting time [ECT], and thrombin time [TT]). The coagulation assay response to dabigatran for all of the tests was similar in pediatric plasma compared with adult plasma. The PT values were relatively insensitive, but displayed a linear response to increasing dabigatran concentrations. The aPTT was moderately sensitive to increasing dabigatran concentrations with approximately threefold prolongation over baseline at the highest concentration, although the response was not linear. The TT, dTT, and ECT were linearly correlated with dabigatran concentrations; however, the ECT and TT were overly sensitive. In the overall hemostasis potential assay, which quantifies the plasma capacity to generate a fibrin clot, increasing dabigatran concentrations delayed the initiation of clot formation and reduced the time to 50% clot lysis. The responses to initiation of clot formation and clot lysis were consistent across all pediatric groups and comparable to responses in adults.¹³

Pediatric Dosing Regimen

Optimal dosing regimen for clinical studies of dabigatran in children was estimated from adult regimens using the Hayton model, which applies to renally eliminated drugs.¹⁴ Taking into consideration the maturation and growth of the renal function, this model estimates pediatric dosing regimens by adjusting adult doses to the age and weight of the child.¹⁴ Based on this equation, an age- and weight-adjusted nomogram for different weight ranges was established.

Clinical Pediatric Studies

Several phase IIa studies assessed pharmacokinetics, safety, and tolerability of dabigatran capsules and oral liquid formulation in children (–Table 2).^{15–19} In one study, nine adolescents aged 12 to 18 years received dabigatran capsules at a dose of 1.71 ($\pm 10\%$) mg/kg followed by 2.14 ($\pm 10\%$) mg/kg twice daily for 3 days.¹⁶ No patients had bleeding events, deaths, or drug-related serious adverse events. Two patients developed dyspepsia. The dabigatran PK/PD relationship observed in these adolescent patients was similar to that in adult patients.¹⁶ In a second study, six patients aged 1 to 2 years (mean age, 1.4 years) and nine patients aged 2 to 12 years (mean age, 5.2 years) were treated with a single dose of dabigatran oral liquid formulation. Three other infants received dabigatran twice daily for 3 days.¹⁷ No patients

Table 1 Pharmacologic characteristics of direct oral anticoagulants

Characteristic	Direct thrombin inhibitor	Direct FXa inhibitors			
	Dabigatran	Apixaban	Betrixaban	Edoxaban	Rivaroxaban
Oral bioavailability, %	3–7	52.3	34	62	66–100
Plasma protein binding, %	35	87	60	55	92–95
Renal excretion, %	80	27	17.8	50	50
Median T _{max} , h					
Single dose	1.25–1.5	1.5–1.8 ^a /2.5–3.3 ^b	3–4	1.0–1.5	0.5–0.6 ^a /1.5–3 ^b
Multiple dose	1.5			1.0–3.5	
Mean t _{1/2} , h					
Single dose	7–9	3.6–6.8 ^a /11.1–26.8 ^b	19–27	5.79–10.7	3.24–4.15 ^a /7–17 ^b
Multiple dose	14–17			8.75–10.4	
Interactions					
P-gp substrate					
Inducers	Decrease exposure	Decrease exposure	Decrease exposure	Not relevant	None
Inhibitors	Increase exposure	Increase exposure	Increase exposure	Increase exposure	Increase exposure
CYP3A4 substrate					
Inducers	None	Decrease exposure	None	None	Decrease exposure
Inhibitors	None	Increase exposure	None	None	Increase exposure

Abbreviations: t_{1/2}, half-life; T_{max}, time to peak plasma concentration; P-gp, P-glycoprotein; CYP, cytochrome P450.

^aOral solution.

^bTablet.

showed drug-related adverse events, and the PK profile was similar to adults and adolescents.¹⁷ In a third phase IIa study, eight infants at a mean age of 88.6 days (range, 41–169 days) received a single dose of dabigatran oral liquid formulation.¹⁸ There were no treatment-related adverse events, no deaths, and no treatment discontinuations. The PK/PD relationships were consistent with the observed profiles in adults and older children.¹⁸

Interim results of two phase III trials on dabigatran in children were presented at the Annual Meeting of the International Society on Thrombosis and Haemostasis (ISTH), July 6 to 19, 2019, in Melbourne.^{20,21} In the open-label, randomized, active-controlled, multicenter, phase IIb/III trial (DIVERSITY study), 234 children aged 12 to < 18, 2 to < 12, and 0 to < 2 years with confirmed diagnosis of VTE and initially treated with UFH or LMWH were randomized (2:1) to dabigatran (capsules, pellets, or oral liquid solution) twice a day or SOC and treated for 3 months. Results of this study indicate that dabigatran is noninferior to SOC in terms of efficacy and safety, and demonstrate the appropriateness of the age- and body-weight-adjusted dosing algorithm for dabigatran to use in children aged between 0 and < 18 years (→Table 2).²⁰ In the open-label, single-arm prospective cohort, phase III trial, 203 children aged 12 to < 18, 2 to < 12, and 0 to < 2 years with VTE, who were treated with SOC for ≥ 3 months or completed study treatment in the DIVERSITY study, and had an unresolved

clinical risk factor requiring further anticoagulation, were treated with dabigatran for a maximal duration of 12 months. Results of this study indicate that dabigatran has a favorable safety profile in children with persistent VTE risk factors. Few children developed recurrent VTE and few children experienced major bleeding events and/or clinically relevant non-major bleeding.²¹ In both studies, dabigatran PK/PD relationships were comparable to previous adult data (→Table 2).^{20,21} Further studies on dabigatran in the pediatric population are depicted in →Table 2.¹⁵

Direct Factor Xa Inhibitors

Apixaban

Apixaban is a 1-(4-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide compound with potent, reversible, and highly selective inhibitory activity against coagulation FXa.²² Apixaban inhibits free and clot-bound FXa, as well as prothrombinase activity.²³ Apixaban is available in two different pharmaceutical formulations: tablet and oral solution.

In healthy adult subjects, peak plasma levels of apixaban after a single ascending oral dose were observed at 1.5 to 1.8 hours for the oral solution (0.5, 1.0, and 2.5 mg) and at 2.5 to 3.3 hours for the tablet form (5, 10, 25, and 50 mg).²⁴ The half-life of apixaban was 4.3 to 6.8 hours when administered

Table 2 Clinical pediatric studies on the direct oral thrombin inhibitor, dabigatran etexilate

Study	Condition	Intervention	Duration of initial treatment with SOC	Phase	Age	Number enrolled	Status	Completion
Open-label, single-dose, tolerability, PK/PD, and safety study of dabigatran etexilate given at the end of standard anticoagulant therapy	VTE	Dabigatran	Completed course of anticoagulation	II	≤12 mo	8	Completed	February 2016
Single-dose open-label PK/PD, safety and tolerability study of dabigatran etexilate given at the end of standard anticoagulant therapy	VTE	Dabigatran	Completed course of anticoagulation	II	1 to <12 y	18	Completed	February 2016
Open-label safety and tolerability study of dabigatran etexilate given for 3 d at the end of standard anticoagulant therapy	VTE	Dabigatran	Completed course of anticoagulation	II	12–18 y	9	Completed	February 2012
Open-label, single-arm safety prospective cohort study of dabigatran etexilate for secondary prevention of VTE	Secondary VTE prevention	Dabigatran	Completed course of anticoagulation with SOC or dabigatran	III	≤18 y	203	Active, not recruiting	November 2019
Open-label, randomized, parallel-group, active-controlled, multicenter noninferiority study of dabigatran etexilate vs. SOC for VTE treatment	VTE	Dabigatran SOC	minimum 5–7 d, but not longer than 21 d	III	0–18 y	234	Active, not recruiting	November 2019

Abbreviations: PK/PD, pharmacokinetic/pharmacodynamics; SOC, standard of care (usually referring to unfractionated heparin, low-molecular-weight heparin, fondaparinux, and/or VKA); VTE, venous thromboembolism.

Source: <https://clinicaltrials.gov/ct2/results?cond=children&term=dabigatran&entry=&state=&city=&dist.> Assessed August 8, 2019.

as an oral solution and 11 to 26.8 hours when administered in tablet form (► **Table 1**).²⁴

Preclinical Pediatric Studies

Yetman et al. performed in vitro assays to explore the potential effect of apixaban in the pediatric population using umbilical cord, children, and adult plasma samples spiked with apixaban concentrations of 30 and 110 ng/mL.²⁵ Both apixaban concentrations were expected to correspond with peak and trough apixaban concentrations following administration of 2.5 or 5 mg twice daily.²⁵ In this study, apixaban demonstrated consistent concentration-related FXa inhibition across all age groups. However, FXa inhibition with apixaban 110 ng/mL was greater in plasma from children aged 6 months or younger than in plasma from adults.²⁵

Clinical Pediatric Studies

The PK/PD profile of a single-dose apixaban is currently investigated in a phase I study on 44 pediatric patients at risk for a venous or arterial thrombotic disorder.²⁶ Further studies on apixaban in the pediatric population are depicted in ► **Table 3**.²⁶

Betrixaban

Betrixaban is an anthranilamide-based compound 1,N-(5-chloropyridin-2-yl)-2-(4-(N,N-dimethylcarbamimidoyl)-benzamido)benzamide with potent FXa inhibitory activity.²⁷

At a dose of 80 mg, betrixaban is rapidly absorbed and reaches plasma concentration peaks after 3 to 4 hours.²⁸ The half-life of betrixaban ranges between 19 and 27 hours (► **Table 1**).²⁸

Ongoing pediatric studies on betrixaban are listed in ► **Table 3**.²⁹

Edoxaban

Edoxaban is a N-(5-chloropyridin-2-yl)-N'-[(1S,2R,4S)-4-(N,N-dimethylcarbamoyl)-2-(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamido)-cyclohexyl]ethanediamide p-toluenesulfonate monohydrate compound that is highly specific and directly inhibits FXa activity.³⁰ Edoxaban is available in two different pharmaceutical formulations: tablet and oral suspension.

In healthy adult subjects, peak plasma levels of edoxaban were observed at 1.0 to 1.5 hours after a single ascending oral dose (10, 30, 60, 90, 120, and 150 mg).³¹ The half-life of edoxaban ranged from 5.79 to 10.7 hours (► **Table 1**).³¹ Overall, increasing edoxaban dose resulted in consistent and predictable plasma concentrations.³¹

Preclinical Pediatric Studies

Sinegre et al. compared the hemostatic response and coagulation assay results in plasma samples from adults and children of different age spiked in vitro with specific concentrations of edoxaban.³² In this study, edoxaban anti-FXa activity accurately reflected plasma levels in both children and adults, and the in vitro effects were similar at all ages, with the exception of children younger than 2 years in whom the anticoagulant effect was increased.³²

Table 3 Clinical pediatric studies on the direct oral FXa inhibitors

Study	Condition	Intervention	Duration of initial treatment with SOC	Phase	Age	Number enrolled	Status	Completion
Apixaban^a								
Multiple-dose study to evaluate the PK, PD, safety, and tolerability of apixaban in pediatric subjects with an indwelling CVC	CVC	Apixaban	NK	I	12–17 y	13	Terminated	July 2012
Single-dose study to evaluate the PK, PD, safety, and tolerability of apixaban in pediatric subjects at risk for a venous or arterial thrombotic disorder	VTE Arterial thrombosis	Apixaban	NK	I	37 wk to 18 y	44	Recruiting	December 2019
A pilot study of apixaban for the treatment of VTE	VTE	Apixaban	NK	II	Children and adolescents weighing ≥ 40 kg	25	Recruiting	May 2021
A prospective, randomized, open-label, multicenter study of the safety and PK of apixaban vs. VKA or LMWH in pediatric subjects with congenital or acquired heart disease requiring chronic anticoagulation for thromboembolism prevention	Congenital or acquired heart disease VTE prophylaxis	Apixaban VKA LMWH	NK	II	34 wk to 17 y	150	Recruiting	October 2021
A randomized, open-label, multicenter study of the safety and efficacy of apixaban for VTE prevention vs. no systemic anticoagulant prophylaxis during induction chemotherapy in children with newly diagnosed ALL or lymphoma (T or B cell) treated with asparaginase	ALL, Lymphoma	Apixaban No systemic anticoagulant prophylaxis	NK	III	1–17 y	500	Recruiting	April 2021
A randomized, open-label, active-controlled, safety, and descriptive efficacy study in pediatric subjects requiring anticoagulation for the treatment of VTE	VTE	Apixaban SOC	NK	IV	3 mo to 17 y	150	Recruiting	April 2021
Betrixaban^b								
An open-label, single-dose, nonrandomized study to evaluate PK, PD, and safety of betrixaban in pediatric patients	VTE prophylaxis	Betrixaban	Completed course of anticoagulation	I	≤ 17 y	60	Recruiting	April 2022

Table 3 (Continued)

Study	Condition	Intervention	Duration of initial treatment with SOC	Phase	Age	Number enrolled	Status	Completion
Edoxaban^c								
An open-label, single-dose, nonrandomized study to evaluate PK and PD of edoxaban in pediatric patients	VTE, DVT	Edoxaban	NK	I	≤18 y	60	Recruiting	December 2019
An open-label, randomized, parallel-group, multicenter, observational trial to evaluate safety and efficacy of edoxaban in children with cardiac diseases at risk of thromboembolic events	Cardiac disease VTE prevention	Edoxaban SOC	NA	III	≤17 y	150	Recruiting	December 2020
An open-label, randomized, multicenter, controlled trial to evaluate the PK and PD of edoxaban and to compare the efficacy and safety of edoxaban with SOC in pediatric subjects with confirmed VTE	VTE Pulmonary embolism DVT	Edoxaban SOC	At least 5 d	III	≤17 y	274	Recruiting	March 2021
Rivaroxaban^d								
Single-dose study testing rivaroxaban granules for oral suspension formulation in children with previous thrombosis	Thrombosis	Rivaroxaban	Completed anticoagulant treatment and at least 10 d prior to the planned study drug administration	I	2 mo to 12 y	47	Completed	May 2018
Single-dose pilot study of oral rivaroxaban in pediatric subjects with VTE	VTE	Rivaroxaban	Completed treatment course of anticoagulation	I	6 mo to 18 y	59	Completed	July 2015
7-d study of the safety, efficacy, and the PK and PD properties of oral rivaroxaban in children with arterial or venous thrombosis	Arterial or venous thrombosis	Rivaroxaban	At least 5 d	I/II	0–6 mo	10	Completed	December 2017
30-d, single-arm study of the safety, efficacy, and the PK and PD properties of oral rivaroxaban in young children with various manifestations of VTE	VTE	Rivaroxaban	At least 2 mo or 6 wk for CVL-related VTE	II	6 mo to 5 y	46	Completed	April 17

(Continued)

Table 3 (Continued)

Study	Condition	Intervention	Duration of initial treatment with SOC	Phase	Age	Number enrolled	Status	Completion
30-d, single-arm study of the safety, efficacy, and the PK and PD properties of oral rivaroxaban in children with various manifestations of VTE	VTE	Rivaroxaban	At least 2 mo or 6 wk for CVL-related VTE	II	6–17 y	65	Completed	September 2016
Multicenter, open-label, active-controlled, randomized study to evaluate the efficacy and safety of an age- and body-weight-adjusted rivaroxaban regimen compared with SOC in children with acute VTE	VTE	Rivaroxaban SOC	6–9 d	III	0–17 y	500	Completed	January 2019
A prospective, open-label, active-controlled study to evaluate the PK, PD, safety, and efficacy of rivaroxaban for thromboprophylaxis in pediatric subjects after the Fontan procedure	Fontan procedure Thromboprophylaxis	Rivaroxaban Acetylsalicylic acid	NA	III	2–8 y	112	Recruiting	October 2020

Abbreviations: ALL, acute lymphoblastic leukemia; CVC, central venous catheter; DVT, deep vein thrombosis; NA, not applicable; NK, data not available; PD, pharmacodynamics; PK, pharmacokinetics; SOC, standard of care (usually referring to unfractionated heparin, low-molecular-weight heparin, fondaparinux, and/or VKA); VKA, vitamin K antagonists; VTE, venous thromboembolism.

^aFrom <https://clinicaltrials.gov/ct2/results?cond=&term=apixaban+children&cntry=&state=&city=&dist>. Assessed August 8, 2019.

^bFrom <https://clinicaltrials.gov/ct2/results?cond=&term=betrixaban+children&cntry=&state=&city=&dist>. Assessed August 8, 2019.

^cFrom <https://clinicaltrials.gov/ct2/results?cond=&term=edoxaban+children&cntry=&state=&city=&dist>. Assessed August 8, 2019.

^dFrom <https://clinicaltrials.gov/ct2/results?cond=&term=rivaroxaban+children&cntry=&state=&city=&dist>. Assessed August 8, 2019.

The PK/PD profile of a single-dose edoxaban is currently investigated in a phase I study on 60 pediatric patients aged 0 to 18 years requiring anticoagulant therapy.³³ Further studies on edoxaban in the pediatric population are depicted in [Table 3](#).³³

Rivaroxaban

Rivaroxaban is a 5-Chloro-N-((5S)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl)methylthiophene-2-carboxamide compound with a highly potent and selective direct FXa inhibitory activity.³⁴ Rivaroxaban is available in two different pharmaceutical formulations: tablet and oral suspension.

PK/PD profiles of rivaroxaban were first investigated in a single-center, randomized, placebo-controlled study in 108 healthy adult volunteers.³⁵ In this study, peak plasma levels of rivaroxaban after a single escalating oral dose were observed at 0.5 to 0.6 hours for the oral solution (5, 10 mg) and at 1.5 to 3.0 hours for the tablet form (1.5, 5, 10, 20, 40, and 80 mg).³⁶ The half-life of rivaroxaban was 3.24 to 4.15 hours when administered as an oral solution. For rivaroxaban tablets at doses greater than 10 mg, the half-lives ranged from 7 to 17 hours ([Table 1](#)).³⁵

Preclinical Pediatric Studies

Two studies investigated the age-related anticoagulant effect of rivaroxaban *in vitro*.^{36,37} In both studies, plasma pools from neonates, children aged 28 days to 23 months, 2 to 6 years, 7 to 11 years, 12 to 16 years, and adults were spiked with increasing concentrations of rivaroxaban (0–500 ng/mL). While rivaroxaban caused a significant increase in the clotting time (PT and aPTT) as well as an increase in lag time (as measured by thrombin generation) in neonates, no significant differences in rivaroxaban effect was observed across the older pediatric age groups when compared with adults. Overall, rivaroxaban demonstrated a predictable and a dose-dependent PK profile in all age groups.^{36,37}

Pediatric Dosing Regimen

To assess the optimal dosing regimen for clinical studies of rivaroxaban in children, a physiologically based PK model for rivaroxaban doses of 10 and 20 mg in adults was developed.³⁸ This model was subsequently scaled to the pediatric population (0–18 years) by including anthropometric and physiological information, age-dependent clearance, and age-dependent protein binding.³⁸ The body-weight-related dosing regimen led to a large overlap of the simulated plasma PK parameters for all age ranges with the values obtained in the corresponding adult reference simulation. However, PK values in infants and preschool children (body weight: <40 kg) were lower than the 90% confidence interval threshold of the adult reference model, indicating that in these groups increased doses would be required to achieve the same plasma levels as in adults.³⁸

Clinical Pediatric Studies

The PK of a single rivaroxaban dose in children using population PK modeling was assessed in a phase I study.^{39,40} In this

study, two rivaroxaban dose levels equivalent to adult doses of rivaroxaban 10 and 20 mg, and two different formulations (tablet and oral suspension), were tested in 59 children aged 0.5 to 18 years who had completed treatment for VTE.^{39,40} The observed plasma concentration-time profiles in all subjects receiving body-weight-adjusted doses were mostly within the 90% prediction interval, irrespective of dose or formulation.³⁹ The PD assessment based on PT and aPTT demonstrated that the anticoagulant effect of rivaroxaban was not affected by development hemostasis ([Table 3](#)).⁴⁰

Three phase II studies were performed to confirm or adapt the predicted body-weight-adjusted rivaroxaban regimens from the phase I study in 93 children (10 children younger than 6 months; 15 children aged 6 months to 1 year; 25 children aged 2–5 years; 32 children aged 6–11 years; and 11 children aged 12–17 years).⁴¹ Therapeutic rivaroxaban exposures with once-daily dosing in children with bodyweights of at least 30 kg and with twice-daily dosing in children with bodyweights of at least 20 kg and less than 30 kg were confirmed. However, children with low body weights (<20 kg, particularly <12 kg) showed low or subtherapeutic exposure. From these results, rivaroxaban dosages to be adopted for the phase III studies were increased to twice-daily administrations in those with a body weight of at least 12 kg but less than 20 kg and three times daily administrations in those weighing less than 12 kg.⁴¹ None of the children had a major bleed, and four (4%) of these children had a clinically relevant non-major bleed (three children aged 12–17 years with menorrhagia and one child aged 6–11 years with gingival bleeding). No symptomatic recurrent VTE was observed. Of 75 patients having repeat imaging, the thrombotic burden was resolved in 24 (32%), improved in 43 (57%), and unchanged in 8 (11%) patients. No patient deteriorated.⁴¹

Results of a phase III study comparing the efficacy and safety of rivaroxaban with standard anticoagulants for the treatment of acute VTE in children aged from birth to 17 years were presented at the Annual Meeting of the ISTH, July 6 to 19, 2019, in Melbourne.⁴² In this study, 500 children were randomized to receive open-label rivaroxaban in tablet or suspension form in body-weight-adjusted 20 mg equivalent dose regimens or a standard anticoagulant. Children <12 kg body weight were given rivaroxaban three times a day, children between 12 and 30 kg body weight two times a day, and children > 30 kg body weight once a day. The main treatment period was 3 months, with the exception of 1 month for children younger than 2 years with a catheter-related thrombosis. Results of this study indicate that children with VTE treated with rivaroxaban showed a low recurrence risk and a reduced thrombotic burden without increased bleeding compared with standard anticoagulants ([Table 3](#)).^{42,43} Further studies on rivaroxaban in the pediatric population are listed in [Table 3](#).⁴³

Concluding Remarks

This is an exciting moment for the pediatric hematology community. Several well-designed, controlled trials providing PK/PD, efficacy, and safety data on DOACs in children are ongoing and in part completed. First data from these studies

are very promising, indicating that DOACs have consistent PK/PD relationships and may show at least comparable efficacy and safety as LMWH and VKA over all pediatric age groups. These studies will help establishing evidence-based guidelines for the treatment and prevention of thromboembolic events in children and adolescents with various underlying conditions in a very near future. Nevertheless, study data from children and adolescents fulfilling inclusion criteria may not necessarily apply for all pediatric patients developing VTE in the daily clinical life. This is, for example, especially true for severely ill newborns and infants or for unstable children at intensive care units who are at increased risk of bleeding. For this reason, collection of real-life data providing insights on the use of DOACs in difficult clinical situations not covered by the studies will be extremely important.

Conflict of Interest

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References

- 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
- Trenor CC III, Chung RJ, Michelson AD, et al. Hormonal contraception and thrombotic risk: a multidisciplinary approach. *Pediatrics* 2011;127(02):347–357
- 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
- Khachatryan T, Hauschild C, Hoff J, et al. Review of direct oral anticoagulants and guide for effective drug utilization. *Am J Cardiovasc Drugs* 2019. Doi: 10.1007/s40256-019-00344-6. [Epub ahead of print]
- Hauel NH, Nar H, Priepke H, Ries U, Stassen JM, Wienen W. Structure-based design of novel potent nonpeptide thrombin inhibitors. *J Med Chem* 2002;45(09):1757–1766
- Eriksson BI, Smith H, Yasothan U, Kirkpatrick P. Dabigatran etexilate. *Nat Rev Drug Discov* 2008;7(07):557–558
- Blech S, Ebner T, Ludwig-Schwelling E, Stangier J, Roth W. The metabolism and disposition of the oral direct thrombin inhibitor, dabigatran, in humans. *Drug Metab Dispos* 2008;36(02):386–399
- Stangier J, Rathgen K, Stähle H, Gansser D, Roth W. The pharmacokinetics, pharmacodynamics and tolerability of dabigatran etexilate, a new oral direct thrombin inhibitor, in healthy male subjects. *Br J Clin Pharmacol* 2007;64(03):292–303
- Liesenfeld KH, Lehr T, Dansirikul C, et al. Population pharmacokinetic analysis of the oral thrombin inhibitor dabigatran etexilate in patients with non-valvular atrial fibrillation from the RE-LY trial. *J Thromb Haemost* 2011;9(11):2168–2175
- Dansirikul C, Lehr T, Liesenfeld KH, Haertter S, Staab A. A combined pharmacometric analysis of dabigatran etexilate in healthy volunteers and patients with atrial fibrillation or undergoing orthopaedic surgery. *Thromb Haemost* 2012;107(04):775–785
- Dietrich K, Stang L, van Ryn J, Mitchell LG. Assessing the anticoagulant effect of dabigatran in children: an in vitro study. *Thromb Res* 2015;135(04):630–635
- Hayton WL. Maturation and growth of renal function: dosing renally cleared drugs in children. *AAPS PharmSci* 2000;2(01):E3
- U.S. National Library of Medicine. Available at: <https://clinicaltrials.gov/ct2/results?cond=children&term=dabigatran&cntry=&state=&city=&dist>. Assessed August 8, 2019
- 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
- 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
- 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
- Maas H, Gropper S, Huang F, et al. Anticoagulant effects of dabigatran in paediatric patients compared with adults: combined data from three paediatric clinical trials. *Thromb Haemost* 2018;118(09):1625–1636
- Albisetti M, Brandao L, Bomgaars L, et al. Efficacy and safety of dabigatran etexilate for treatment of venous thromboembolism in paediatric patients – results of the DIVERSITY trial. Abstract presented at the Annual Meeting of the International Society on Thrombosis and Haemostasis (ISTH); July 6–19, 2019; Melbourne, Australia
- Brandao L, Albisetti M, Halton J, et al. Safety of dabigatran for secondary prevention of venous thromboembolism in paediatric patient. Abstract presented at the Annual Meeting of the International Society on Thrombosis and Haemostasis (ISTH); July 6–19, 2019; Melbourne, Australia
- Pinto DJ, Orwat MJ, Koch S, et al. Discovery of 1-(4-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide (apixaban, BMS-562247), a highly potent, selective, efficacious, and orally bioavailable inhibitor of blood coagulation factor Xa. *J Med Chem* 2007;50(22):5339–5356
- Byon W, Garonzik S, Boyd RA, Frost CE. Apixaban: a clinical pharmacokinetic and pharmacodynamic review. *Clin Pharmacokinet* 2019;58(10):1265–1279
- Frost C, Wang J, Nepal S, et al. Apixaban, an oral, direct factor Xa inhibitor: single dose safety, pharmacokinetics, pharmacodynamics and food effect in healthy subjects. *Br J Clin Pharmacol* 2013;75(02):476–487
- Yetman RJ, Barrett YC, Wang Z, et al. Apixaban pharmacodynamic activity in umbilical cord, paediatric, and adult plasma. *Thromb Haemost* 2017;117(08):1518–1527
- <https://clinicaltrials.gov/ct2/results?cond=&term=apixaban+children&cntry=&state=&city=&dist>. Assessed August 8, 2019
- Zhang P, Huang W, Wang L, et al. Discovery of betrixaban (PRT054021), N-(5-chloropyridin-2-yl)-2-(4-(N,N-dimethylcarbamimidoyl)benzamido)-5-methoxybenzamide, a highly potent, selective, and orally efficacious factor Xa inhibitor. *Bioorg Med Chem Lett* 2009;19(08):2179–2185
- Huisman MV, Klok FA. Pharmacological properties of betrixaban. *Eur Heart J Suppl* 2018;20(Suppl E):E12–E15
- <https://clinicaltrials.gov/ct2/results?cond=&term=betrixaban+children&cntry=&state=&city=&dist>. Assessed August 8, 2019
- Furugohri T, Isobe K, Honda Y, et al. DU-176b, a potent and orally active factor Xa inhibitor: in vitro and in vivo pharmacological profiles. *J Thromb Haemost* 2008;6(09):1542–1549

- 31 Ogata K, Mendell-Harary J, Tachibana M, et al. Clinical safety, tolerability, pharmacokinetics, and pharmacodynamics of the novel factor Xa inhibitor edoxaban in healthy volunteers. *J Clin Pharmacol* 2010;50(07):743–753
- 32 Sinegre T, Zlobecki M, Doré E, Pereira B, Grèze V, Lebreton A. In vitro assessment of edoxaban anticoagulant effect in pediatric plasma. *Thromb Res* 2019;178:112–118
- 33 <https://clinicaltrials.gov/ct2/results?cond=&term=edoxaban+children&cntry=&state=&city=&dist>. Assessed August 8, 2019
- 34 Roehrig S, Straub A, Pohlmann J, et al. Discovery of the novel antithrombotic agent 5-chloro-N-((5S)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-ylmethyl)thiophene-2-carboxamide (BAY 59-7939): an oral, direct factor Xa inhibitor. *J Med Chem* 2005;48(19):5900–5908
- 35 Kubitzka D, Becka M, Voith B, Zuehlsdorf M, Wensing G. Safety, pharmacodynamics, and pharmacokinetics of single doses of BAY 59-7939, an oral, direct factor Xa inhibitor. *Clin Pharmacol Ther* 2005;78(04):412–421
- 36 Attard C, Monagle P, Kubitzka D, Ignjatovic V. The in vitro anticoagulant effect of rivaroxaban in children. *Thromb Res* 2012;130(05):804–807
- 37 Attard C, Monagle P, Kubitzka D, Ignjatovic V. The in-vitro anticoagulant effect of rivaroxaban in neonates. *Blood Coagul Fibrinolysis* 2014;25(03):237–240
- 38 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
- 39 Willmann S, Thelen K, Kubitzka D, et al. Pharmacokinetics of rivaroxaban in children using physiologically based and population pharmacokinetic modelling: an EINSTEIN-Jr phase I study. *Thromb J* 2018;4:16:32
- 40 Kubitzka 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
- 41 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
- 42 Male C, Lensing A, Kubitzka D, et al. Rivaroxaban for the treatment of acute venous thromboembolism in children. Abstract presented at the Annual Meeting of the International Society on Thrombosis and Haemostasis (ISTH); July 6–19, 2019; Melbourne, Australia
- 43 <https://clinicaltrials.gov/ct2/results?cond=&term=rivaroxaban+children&cntry=&state=&city=&dist>. Assessed August 8, 2019