Efficacy and Safety of Non-Vitamin K Antagonist Oral Anticoagulants in Pediatric Venous Thromboembolism Treatment and Thromboprophylaxis: A Systematic Review of the Literature

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Abstract

Venous thromboembolism (VTE) in children can lead to significant morbidity and mortality. Traditionally, treatment for thrombotic events in pediatric patients has been limited mainly to unfractionated heparin, low-molecular-weight heparin (LMWH), or vitamin K antagonists. Since the first non–vitamin K antagonist oral anticoagulant (NOAC) was approved for adult use, these agents have gained popularity for a variety of indications. This is largely due to their ease of administration, favorable pharmacokinetic and pharmacodynamic profile, decreased food interactions, and decreased need for therapeutic drug monitoring. Treating and preventing VTE with traditional anticoagulants in pediatric patients presents many challenges. This systematic review evaluated the current literature regarding pediatric NOAC trials. Additionally, based on an up-to-date query of *clinicaltrials.gov*, we detail current ongoing and as-yet unpublished clinical trials, study outcomes, and projected completion dates. Published pediatric NOAC trials have included 1,007 total children to date and have ranged from phase 1 to 4, with "indications" including both thromboembolism prophylaxis and VTE treatment. Three recent phase 3 trials, specifically involving rivaroxaban and dabigatran, have shown the agents to be at least as effective as traditional

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anticoagulants for acute and/or extended VTE treatment, with low frequency of recurrent thrombosis and clinically significant bleeding rates. Additionally, specially developed and tested pediatric formulations have allowed for accurate and reliable dosing, oral administration, stable pharmacokinetics and pharmacodynamics, and fewer drug or food interactions. Ongoing trials, anticipated for completion in the next few years, will reveal important information with regard to thromboembolism prophylaxis in special pediatric subpopulations and settings.

Venous thromboembolism (VTE) in children can lead to significant morbidity and mortality. Adverse outcomes of VTE in young patients include recurrent VTE, postthrombotic syndrome (PTS), and VTE-related mortality. Although VTE-related death is rare in the pediatric patient population, recurrent VTE has been reported in 3% of children within 12 months of a provoked VTE, and in 11% within 24 months after provoked VTE.[1,2] For children who develop spontaneous VTE, recurrent VTE within a median time of 3.5 years is reportedly as high as 21.3% after withdrawal of anticoagulation.[3] The incidence of PTS has been reported to be approximately one out of every four children when the limb/vena cava is involved.[4] Thrombotic events occurring in hospitalized children at tertiary care facilities increased from 34 cases per 10,000 hospital admissions in 2001 to 58 cases per 10,000 hospital admissions in 2007.[5] Traditionally, treatment for thrombotic events in pediatric patients has been limited mainly to unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), or vitamin K antagonists (VKAs).[6,7] The 9th edition of the CHEST Guidelines for Antithrombotic Therapy in Neonates and Children made no recommendations for anticoagulation in pediatric patients outside of UFH, LMWH, and VKA.[6] However, complications with these agents such as heparin-induced thrombocytopenia (HIT), lack of access to anti-Xa laboratory monitoring, poor international normalized ratio (INR) control, and medication dosage considerations often complicate the management of pediatric anticoagulation. Since the approval of the first non–vitamin K antagonist oral anticoagulant (NOAC), dabigatran, by the Food and Drug Administration (FDA) in 2010, this class of medications has gained popularity in adults. This is largely due to a comparative efficacy and safety profile compared with standard of care (SOC) with beneficial dosage forms and monitoring.[8] NOACs provide an ease of administration compared with heparin products, which require intravenous or subcutaneous administration. Additionally, NOACs offer advantages over VKA, which include fewer food interactions and decreased laboratory monitoring.[4,6,7]

Currently, there are several NOACs on the market with two different mechanisms of action. Apixaban, edoxaban, and rivaroxaban are oral factor Xa inhibitors. Factor Xa inhibitors work by directly inhibiting both free and clot-bound Xa and prothrombinase activity, as well as indirectly inhibiting thrombin-induced platelet aggregation, leading to a reduction in thrombin generation.[9] The only approved oral direct thrombin inhibitor on the market today is dabigatran, which works by competitively inhibiting thrombin and subsequently preventing the conversion of fibrinogen to fibrin. Based on their chemical properties and direct effect, NOACs provide a more consistent pharmacokinetic (PK) and pharmacodynamic (PD) profile compared with VKA. They possess FDA approval in adult patients for varying indications, such as atrial fibrillation, VTE prophylaxis following hip or knee replacement, VTE prophylaxis following hip or knee replacement, VTE treatment, and acute coronary artery disease.[7,10,11]

Treating and preventing thrombotic events in children presents unique challenges not observed in adults, including variations in PK properties, difficulty in monitoring, variation in endogenous antithrombin concentrations in younger patients resulting in unpredictable heparin effects, and challenges in achieving a therapeutic effect. There is a paucity of systematic data reflecting age-specific PK/PD, safety, efficacy, and appropriate monitoring of heparin products and VKA in the pediatric population.[12] Additionally, thromboprophylaxis with subcutaneous UFH or LMWH may cause stress, anxiety, and pain in children, making subsequent medication administration difficult. Enoxaparin is commonly used for outpatient deep vein thrombosis (DVT) treatment and prophylaxis in pediatric patients.[5,12] Although effective, it can be an unfavorable choice for long-term anticoagulation in children due to subcutaneous administration and the need for frequent anti-Xa monitoring. The challenges with current therapy options have led to the interest in NOACs as potential therapeutic options within the pediatric patient population. The aim of this review article is to evaluate the current literature regarding the safety and efficacy of NOACs in pediatrics.

Methods

A systematic review of the literature was conducted via PubMed query utilizing the indexed medical subject heading (MeSH) terms as follows: [children OR pediatrics] AND [direct oral anticoagulant OR apixaban OR edoxaban OR rivaroxaban OR dabigatran], with query limited to English language, human subjects, and publication date range from January 1, 2002, to April 1, 2020. The objective was to describe overall trial experience and population by age with an emphasis on phase 2 and phase 3 trial designs and findings. Case reports, case series, commentaries, opinion articles, review articles, and nonclinical articles were excluded. Two independent reviewers assessed bibliographies

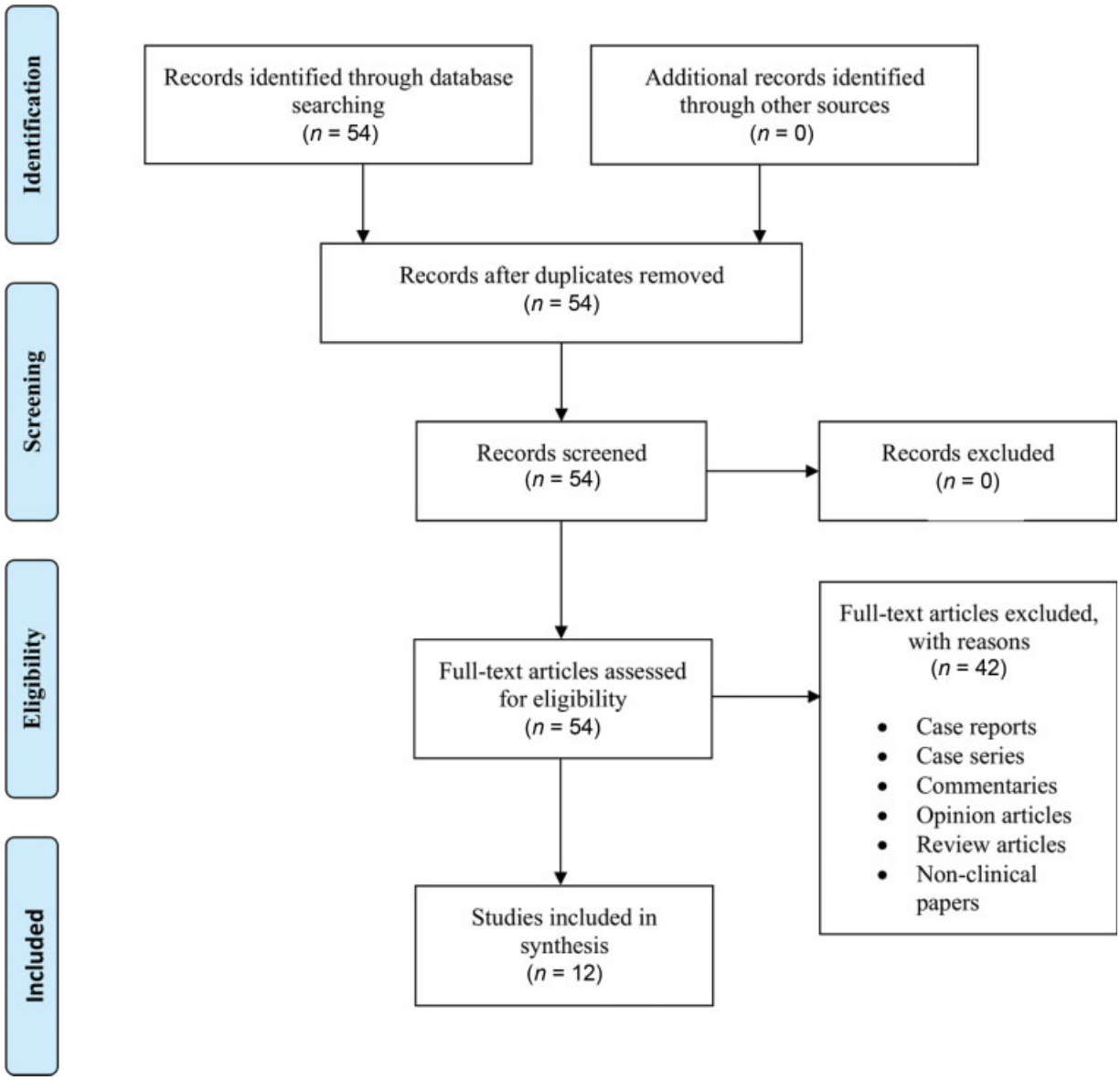

Fig. 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram. Number of studies identified by the search strategy, number of studies excluded and included during primary and secondary screening, and final number of studies included.

belonging to included articles to identify additional studies for inclusion (►**Fig. 1**). Additionally, ClinicalTrials.gov was searched for ongoing clinical trials involving apixaban, edoxaban, rivaroxaban, and dabigatran.

Results

The search (see "Methods" section) generated 54 unique abstracts, of which 12 published studies were found to meet eligibility criteria for inclusion. Phase 1 in vitro studies for the NOACs with published phase 2/3 studies were included for a comprehensive evaluation of dosing strategies. In addition, nine ongoing (or as yet unpublished) trials were identified (►**Table 1**). For NOACs which did not have published phase 2/3 studies at the time of this review, phase 1 in vitro studies were not included. The total number of pediatric patients included in published studies was 1,007. As shown in ►**Table 2**, this included 128 children in phase 2 trials and 779 in phase 3 trials. Furthermore, the published NOAC trials to date have included 16 neonates, 152 non-neonatal infants (>30 days to <2 years), 351 children, and 488 adolescents.

Direct Thrombin Inhibitors

Dabigatran

Dabigatran received FDA approval in 2010 (European Medicines Agency [EMA] approval in 2008) for adult patients and is unique in that it directly inhibits thrombin and does not rely on endogenous coagulation proteins or coagulation inhibitors for its anticoagulant effect.[13] Dabigatran is currently indicated in adults for the treatment and prevention of DVT and pulmonary embolism (PE), as well as for stroke prevention in nonvalvular atrial fibrillation, and VTE

Table 1 Overview of ongoing studies included

NCT	Indication	Intervention	Age	Phase	Primary outcome	Expected completion[a]
Rivaroxaban						
NCT02846532	VTE prophylaxis after the Fontan procedure	Rivaroxaban vs. acetylsalicylic acid	2–8 y	III	12-mo incidence of major bleeding events and incidence of thrombotic events	Jul 2020
Apixaban						
NCT01707394	VTE prophylaxis for CVAD or condition with risk for thrombosis	Single dose of apixaban	34 WGA to < 18 y	I	Estimated AUC, Cmax, and Tmax up to 26 h post dose	Jun 2020
SAXOPHONE	TE prophylaxis for congenital or acquired heart diseases	Apixaban vs. LMWH or VKA	34 WGA to < 18 y	II	14-mo incidence of bleeding events	Oct 2021[b]
PREVAPIX-ALL	VTE prophylaxis during induction chemotherapy including asparaginase for ALL	Apixaban vs. no systemic thromboprophylaxis	1 y to < 18 y	III	1-mo composite of nonfatal DVT, PE, cerebral venous sinus thrombosis, and VTE-related death	Sept 2021[b]
CANINES	VTE treatment	Apixaban vs. standard of care (UFH, LMWH, or VKA)	Birth to < 18 y	IV	12-wk composite of major and clinically relevant non-major bleeding	Apr 2023[b]
NCT04041843	VTE treatment within 72 h of diagnosis	Apixaban 10 mg twice daily for 7 d followed by 5 mg twice daily	Children with body-weight ≥ 40 kg	II	90-d new VTE formation	May 2022
Edoxaban						
ENNOBLE	VTE prophylaxis in children with cardiac disease at risk for thromboembolic complications	Edoxaban vs. standard of care (LMWH, UFH, VKA)	38 WGA to < 18 y	III	4 and 13 mo combined major and non-major bleeding events per ISTH definition	June 2021[b]
HOKUSAI-Jr	VTE treatment after receiving at least 5 prior days of heparin therapy	Edoxaban vs. standard of care (LMWH, VKA, UFH, or fondaparinux)	38 WGA to < 18 y	III	3-mo composite of symptomatic recurrent VTE, death from VTE, and no change or extension of thrombotic burden	Dec 2021[b]
NCT02303431	PK study in pediatric patients requiring anticoagulant therapy	Edoxaban low and high dose in 5 cohorts: 0–6 mo, 6 mo to < 2 y, 2 to < 6 y, 6 to < 12 y, 12 to < 18 y	Birth to < 18 y	I	Apparent systemic clearance, VD, and AUC within 36 h post-dose	Sept 2020

Abbreviations: ALL, acute lymphoblastic lymphoma; AUC, area under the concentration time curve; Cmax, maximum observed plasma concentration; CVAD, central venous access device; DVT, deep vein thrombosis; ISTH, International Society on Thrombosis and Haemostasis; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; PK, pharmacokinetics; TE, thromboembolism; Tmax, time that maximum plasma concentration occurs; UFH, unfractionated heparin; VD, volume of distribution; VKA, vitamin K antagonist; VTE, venous thromboembolism; WGA, week-adjusted gestational age.
[a]Last patient, last visit, based on current estimate from Clinicaltrials.gov unless otherwise noted.
[b]N.A. Goldenberg, personal written communication on November 17, 2020 (with sponsor's permission).

Table 2 Patient numbers per age group included in completed studies (DIVERSITY phase 1–3, EINSTEIN Jr phase 1–3) [14–17,20,25,27,28]

	Phase 1	Phase 2	Phase 3	Total
Neonate[a]	–	–	16[b]	16
Infant[c]	28	39[d]	85	152
Child[e]	47	69	235	351
Adolescent[f]	25	20	443	488
Total	100	128	779	1,007

[a] ≤ 30 days old.
[b]Unpublished information from EINSTEIN-Jr phase 3 and DIVERSITY phase 3.
[c] > 30 days to <2 years old.
[d]EINSTEIN-Jr phase 2 studies included 10 patients aged birth to < 6 months; however, the study does not indicate whether any of these patients were neonates.
[e]2 to <13 years old.
[f]13 to <18 years old.

prophylaxis after total hip arthroplasty.[13] Of note, dabigatran is primarily renally excreted and requires dose adjustments in the setting of renal dysfunction (►**Table 3**).

To date, there are five studies assessing the use of dabigatran in the pediatric patient population and one additional analysis.

Various phase studies have been completed in pediatric patients evaluating dabigatran. The basis for pediatric doses evaluated in clinical studies was an in vitro, multiple-age group dose evaluation study performed by Dietrich et al.[14] Plasma samples were pooled from the following groups: 10 to 17 years ($n = 12$), 5 to <10 years ($n = 11$), 1 to < 5 years ($n = 9$), and 0 to < 1 year ($n = 9$). There were no differences in responses to dabigatran over all pediatric age groups and responses were consistent and comparable to those of adults throughout all tested age groups.[14]

Halton et al performed a series of three nonrandomized phase 2 trials in infants, children, and adolescents, respectively, with the goal to evaluate the PK/PD, safety, and

Table 3 Pharmacologic characteristics of non–vitamin K antagonist oral anticoagulants[a,9,13,22,45]

	MOA target	Oral bioavailability (%)	T Max (h)	Half-life (h)	Renal excretion (%)	Documented pediatric interactions
Apixaban	Xa	50	3–4	9–14	26	P-gp substrates, CYP 3A4[b]
Dabigatran	Thrombin	7	0.5–2	12–17	80	P-gp substrates
Edoxaban	Xa	62	1–2	10–14	50	Rifampin
Rivaroxaban	Xa	66–100	2–4	5–11	66	P-gp substrates, CYP 3A4

Abbreviations: CYP, cytochromes P450; MOA, mechanism of action; P-gp, P-glycoprotein.
[a]Pharmacokinetics are based on manufacturer-labeled information.
[b]Dose reduction is recommended in the setting of combined P-gp and CYP3A4 substrates.

tolerability of dabigatran in patients with prior VTE. All three studies enrolled children with prior VTE who had completed standard anticoagulant therapy with either UFH, LMWH, or VKA prior to dabigatran administration.[15–17] Pediatric doses were derived based on Hayton's equation, a formula used for dosing renally excreted drugs in children of various ages, which accounts for differences in kidney function during the maturation process. Additionally, a dose conversion factor of 0.646 was utilized to adjust for higher bioavailability of dabigatran liquid. However, a larger bioavailability study identified a lower dabigatran exposure difference between drug formulations, and the conversion factor was no longer applied in the last phase 2 and all subsequent studies.[18]

In the first of the three studies, nine adolescents were enrolled between the ages of 13 and 17 years with a mean age of 15.7 years.[15] Participants were given 3 days of twice daily dosing of dabigatran using 50 and 75 mg capsules, targeting doses of 1.71 and 2.14 mg/kg ($\pm$10%) for initial and subsequent doses, respectively. These doses correlated with 80 and 100% of the recommended adult dose, respectively, utilizing Hayton's equation based on a 70-kg patient. Additionally, dabigatran peak and trough levels were drawn based on a weight-only-based dosing regimen, which found no supratherapeutic levels, but identified low trough levels. This set the stage for the remaining studies, where their dosing algorithm became weight and age based, where age was utilized as a surrogate for renal function. The subsequent phase 2 studies in younger children were single-dose studies for feasibility. The second study enrolled 18 children and divided into the following age groups for dosing: 1 to $<$ 2 years of age with a mean age of 1.4 years and 2 to $<$ 12 years of age with a mean age of 5.2 years.[16] In the third study, eight infants were included with a mean age of 88.6 days (range, 41–169 days).[17] Full-term neonates ($>$ 37-week gestational age) and infants aged $<$ 1 year were eligible for inclusion to receive a single dose of study medication. The results of these studies largely showed a similar PK/PD profile and relationship in children as in previous adult studies evaluating VTE treatment. Subsequently, dosing based on renal function resulted in similar drug exposures as is observed in adults with VTE. The doses of dabigatran used, although for a limited duration, appeared to be safe and well tolerated. There were no reported treatment-related adverse effects, thromboembolic, or bleeding events.

These three studies were further analyzed by Maas et al with the primary goal of comparing the PK/PD data to adult populations from the RE-COVER and RE-NOVATE II studies.[19] These findings regarding comparability to adults found the dilute thrombin time (dTT)/plasma concentration ratio was similar across all age groups. Additionally, it was confirmed that absolute activated partial thromboplastin time and Ecarin clotting time (ECT), when accounting for a higher physiologic baseline for these tests in younger patients, were similar to results previously exhibited in adults with a nonlinear and linear relationship to circulating dabigatran trough concentrations, respectively.

The findings of these three studies established the dosing for two pediatric phase 3 studies with dabigatran.

First, the DIVERSITY study is a randomized, controlled, open-label, parallel-group, phase 2b/3 noninferiority trial comparing dabigatran and SOC for acute VTE.[20] Two-hundred and sixty-seven children younger than 18 years with a diagnosis of VTE, treated initially with 5 to 21 days of parenteral therapy, and expected to required anticoagulation for at least 3 months were eligible for randomization. Patients were then further stratified by age group (12 to $<$18 years; 2 to $<$12 years; birth to $<$2 years). The primary endpoint was a composite of the proportion of children with complete thrombus resolution, freedom from recurrent VTE, and VTE-related death. Secondary endpoints included major bleeding events, all bleeding events, tolerability of therapy, all-cause mortality, and PK/PD assessment. Of the 267 children enrolled in the DIVERSITY study, 90 were randomly assigned to SOC, while 177 were assigned to the dabigatran arm. Of the 267 randomized patients, 38 (42%) in the SOC compared with 81 (46%) in the dabigatran group met the primary outcome (risk difference, $p < 0.0001$ for noninferiority). Additionally, all bleeding events, 22 (24%) versus 38 (22%); $p = 0.61$, and major bleeding events, 2 (2%) versus 4 (2%); $p = 0.95$, were similar among SOC and dabigatran, respectively. The DIVERSITY study showed dabigatran was noninferior to SOC and might be a suitable alternative anticoagulant for the management of VTE in children.[20]

Second, an open-label, single-arm, phase 3 study by Brandão et al enrolled 203 patients with a goal to assess the safety of dabigatran for long-term secondary prevention of VTE.[21] Patients who previously had been treated for VTE with SOC or patients from the dabigatran arm in the

Table 4 A summary of published pediatric comparative phase III trials on the treatment and prevention of VTE with non-VKA oral anticoagulants

Identifier	Indication	Intervention	Comparator	Age	Efficacy (*n*, %)	Safety (*n*, %)
DIVERSITY phase 3 trial	VTE treatment	Dabigatran etexilate	SOC (LMWH, VKA, or fondaparinux)	Birth to <18 y	Composite efficacy score[a]: 81 (46%) vs. 38 (42%), *p*-value[b] = 0.001; complete thrombus resolution: 81 (46%) vs. 38 (42%); recurrent VTE 7 (4%) vs. 7 (8%); VTE-related mortality: 0 (0%) vs. 1 (1%)	MBEs[c]: 4 of 176 (2%) vs. 2 of 90 (2%), $p = 0.95$
EINSTEIN Jr phase 3 trial	VTE treatment	Rivaroxaban	SOC (heparin, LMWH, fondaparinux, or VKA)	Birth to 17 y	Symptomatic recurrent VTE: 4 of 335 (1.2%) vs. 5 of 165 (3.0%), HR: 0.40 (95% CI: 0.11–1.41); mortality 1 (<1%) vs. 0 (0%)	MBEs: 0 (0%) vs. 2 (1%); MBEs or CRNMBEs[d]: 10 (3%) vs. 3 (2%), HR: 1.58 (95% CI, 0.51–6.27)

Abbreviations: CI, confidence interval; CRNMBEs, clinically relevant non-major bleeding events; HR, hazard ratio; LMWH, low-molecular-weight heparin; MBEs, major bleeding events; SOC, standard of care; VKA, vitamin K antagonist; VTE, venous thromboembolism.
[a]Composite efficacy score: combined endpoint of complete thrombus resolution, freedom from recurrent VTE, and freedom from VTE-related mortality.
[b]*p*-Value relates to a test for noninferiority.
[c]MBEs: fatal bleeding, clinically overt bleeding (decrease in hemoglobin of at least 20 g/L in a 24-hour period), bleeding that is retroperitoneal, pulmonary, intracranial, or otherwise involves the central nervous system.
[d]Overt bleeding not meeting the criteria for major bleeding, but associated with medical intervention, or unscheduled contact (visit or telephone call) with a physician, or (temporary) cessation of study treatment, or discomfort for the child such as pain or impairment of activities of daily life.

DIVERSITY study treated for 3 months or longer and who had unresolved clinical risk factors for VTE were treated for up to 12 additional months or until resolution of clinical risk factors. Patients were divided into three age cohorts: children aged > 3 months to < 2 years, 2 to < 12 years, and 12 to < 18 years. Multiple dabigatran dosage forms were utilized in the study including capsules and pellets (►**Table 5**).

The study demonstrated that 2 of 203 patients (1%) experienced recurrent VTE. With regard to safety, 3 (1.5%) patients experienced major bleeding events, 2 (1%) experienced clinically relevant non-major bleeding events, and 37 (18.2%) experienced minor bleeding events. Adverse events were reported in 152 children (74.9%), with the most common being nasopharyngitis (16.7%), headache (16.3%), and abdominal pain (10.3%). PK/PD findings confirmed a linear association for dTT and ECT. These findings were consistent with previous adult and pediatric studies. Overall, the study showed favorability for use of dabigatran in the study population.[21]

Collectively, the studies to date regarding dabigatran in pediatric patients provide high-quality safety and efficacy data. The DIVERSITY study, one of largest randomized pediatric anticoagulant studies, showed noninferiority to SOC for the treatment of VTE with similar PK/PD relationships as seen in adults. Currently, a challenge to the potential implementation of dabigatran in this population includes complex dose-conversion calculations using Hayton's formula; however, an age and weight-based dosing guide along with an educational video will accompany the medication packaging. Additionally, dyspepsia is a common side-effect among adult patients taking dabigatran affecting quality of life with a reported incidence as high as 8%.[13] In the pediatric phase 3 studies, dyspepsia was not reported in any patients younger than 12 years and was reported 6 to 13% in patients aged 12 to 18 years, with most cases being classified as mild.[20,21] Thus, dabigatran provides a suitable alternative to traditional SOC. Additional postmarket evaluation will be needed to fully evaluate the benefit–risk in all age subsets for special indications in children.

Factor Xa Inhibitors

Rivaroxaban

Rivaroxaban, an oral factor Xa inhibitor, received initial FDA approval in 2011 (EMA approval in 2008) and is now approved for various conditions in adults, including nonvalvular atrial fibrillation, coronary or peripheral artery disease, and VTE treatment or prophylaxis.[22] Of note, rivaroxaban is primarily renally excreted and may require dose adjustments based on renal function (►**Table 3**). Currently, there are multiple published studies and one ongoing clinical trial evaluating rivaroxaban in pediatric patients (►**Table 1**).

Various phase studies of the EINSTEIN-Jr program (rivaroxaban vs. standard anticoagulation for acute VTE in childhood) have been conducted evaluating rivaroxaban use in pediatric patients. The basis for pediatric doses evaluated in clinical studies was a pediatric physiologically based PK model evaluating rivaroxaban 10 and 20 mg doses in adults scaled to the pediatric population (0–18 years), which found similar PK parameters, except in infants and young children, who were found to require increased doses.[23] Additionally, an in vitro study assessing rivaroxaban in the plasma of children of various age groups to test for age-related differences in concentration response noted no significant difference in the effects of rivaroxaban when age-specific plasma pools were created for 28 days to 23 months, 2 to 6 years, 7 to 11 years, 12 to 16 years, and adults.[24]

The EINSTEIN-Jr phase 1 study was a multinational, single-dose, open-label study describing the PK/PD and safety of a single, body weight–adjusted rivaroxaban dose

Table 5 NOAC formulations and dosing utilized in clinical trials

NOAC	Formulations studied	Study identifier	Notes
Dabigatran	Capsules, pellets, and oral liquid	NCT01895777	Capsules for 8–18 y; pellets for 6 mo to < 8 y (or ≥ 8 to < 12 y if unable to swallow capsules); oral liquid for 0 to < 6 mo (or 6 to < 12 mo if unable to take pellets)
Dabigatran	50, 75, and 110 mg capsules, pellets, and oral liquid	NCT02197416, Brandão et al[21]	Capsules for 8 to < 18 y, pellets for < 8 y (or 8 to < 12 y if unable to swallow capsules), oral solution for > 3 to < 12 mo if unable to swallow pellets
Dabigatran	Oral liquid	Halton et al[15]	Dose conversion used due to probable bioavailability differences between oral liquid and capsules. Oral liquid taste assessment: 11% of patients rating as "bad," 17% rating as "very bad," 28% rating as "bitter," and 22% rating as "sour"
Rivaroxaban	5, 10, 15, and 20 mg tablets, and 1 mg/mL oral suspension	Monagle et al[27]	Tablets for 6 to 17 y and suspension for those < 6 y (or < 11 y if unable to swallow tablets)
Rivaroxaban	1 mg/mL oral suspension	NCT02846532	
Rivaroxaban	5, 10, 15, and 20 mg tablets and 1 mg/mL granules for oral suspension	NCT02234843, Male et al,[28] Young et al[29]	Oral suspension taste and texture questionnaire: 83% like the taste and 79% willing to take the suspension again and 50% described the oral suspension as "sweet" (oral suspension is fruit flavored)
Apixaban	0.5 mg dissolvable tablets, 2.5 mg tablets, and 0.4 mg/mL oral solution	NCT02369653	Only children ≥ 5 y were eligible to receive oral solution due to high excipient concentration
Apixaban	Tablets and oral solution	NCT02464969	Neonates are eligible for PK subanalysis and have separate dosing strategy
Apixaban	0.5 mg tablets and 0.4 mg/mL oral solution	NCT02981472	Only children ≥ 5 y are eligible to receive oral solution
Edoxaban	15 and 30 mg tablets and oral suspension	NCT03395639, NCT02798471	Tablets for 12 to < 18 y and suspension for < 12 y (optional for ≥12 y)

Abbreviations: NOAC, non–vitamin K antagonist oral anticoagulant; PK, pharmacokinetics.

in children aged 6 months to 18 years.[25] This study sought to determine weight-based dosing of rivaroxaban for VTE treatment in children. It concluded that the PK/PD relationship for rivaroxaban in children is similar to that in adults, and the anticoagulant effect of rivaroxaban is not affected by developmental hemostasis in patients aged 6 months to 18 years.[25] PK data were further analyzed in a separate population PK study to guide dose selection for phase 2 and phase 3 trials. The PK parameters from this analysis provided two modeling and simulation approaches to support a rivaroxaban dosing nomogram.[26]

EINSTEIN-Jr phase 2 study was designed to evaluate rivaroxaban treatment in 93 children aged 6 to 17 years, 6 months to 5 years, and less than 6 months with VTE.[27] In this multicenter, single-arm study, the aim was to develop pediatric dosing regimens for the treatment of VTE. Oral rivaroxaban was administered orally in body weight–adjusted 20 mg equivalent doses, based on the PK modeling predictions and EINSTEIN-Jr phase 1 data. Patients received doses once daily (6 years to 17 years), twice daily (6 months to 11 years), or three times daily (younger than 6 months). It was noted in this study that treatment with body weight–adjusted rivaroxaban was safe in children, with no reported major bleeds and a 4% occurrence of a clinically significant minor bleeds. Furthermore, dosing in infants weighing less than 12 kg was adjusted based on the results of this study, resulting in higher weight-relative doses and three times daily dosing to be used in the phase 3 study.[27]

The EINSTEIN-Jr phase 3 study is the largest trial to date evaluating NOAC use in the pediatric population (►**Table 4**).[28] In this phase 3 study, the aim was to evaluate the efficacy and safety of rivaroxaban compared with SOC anticoagulants for the treatment of VTE in the pediatric population. This multicenter, parallel-group, open-label, randomized study included 500 children (0–17 years of age) with documented acute VTE.[28] Of the 500 children randomized in the EINSTEIN-Jr trial, 335 were assigned to the rivaroxaban arm, while 165 were assigned to SOC. Rivaroxaban treatment with tablets or a newly developed granules-for-oral suspension formulation was body weight adjusted and administered once daily, twice daily, or three times daily for children with body weights of ≥ 30 kg, ≥ 12 to < 30 kg, and < 12 kg, respectively (►**Table 5**). Treatment with body weight–adjusted rivaroxaban tablets or oral suspension for acute VTE in pediatric patients resulted in a similarly low recurrence risk and reduced thrombotic burden without increased bleeding risk compared with SOC.[28,29]

Based on the collective results of the EINSTEIN-Jr studies, rivaroxaban appears to be an attractive anticoagulant option for the management of VTE in pediatric patients. Additionally, while adult doses utilizing 15 and 20 mg dosage forms require administration with food for improved absorption, food has less effect on absorption with pediatric dosages and dosage forms. In the EINSTEIN-Jr studies, rivaroxaban was given with or shortly after a meal.[28]

The UNIVERSE study is an ongoing, two-part, prospective, open-label, randomized, multicenter study designed to evaluate the PK/PD profiles, safety, and efficacy of rivaroxaban for thromboprophylaxis in children aged 2 to 8 years with single ventricle physiology after Fontan palliation.[30] The study aims to provide dosing, PK/PD, safety, and efficacy data comparing rivaroxaban versus aspirin. Primary endpoints include PK parameters, major bleeding events, and the incidence of thrombotic events over a 12-month period of time. The study was completed in July 2020 without published results to date.

Apixaban

Apixaban, an oral factor Xa inhibitor, received initial FDA approval in 2012 (EMA approval in 2011) for adult patients.[9] Apixaban is indicated in adult patients for the treatment of DVT and PE, as well as for thromboprophylaxis in patients with nonvalvular atrial fibrillation or after total knee or hip arthroplasty.[31–34] Additionally, it may be used as secondary prophylaxis after initial therapy to prevent recurrent DVT/PE in high-risk patients.[35,36] Of note, apixaban has predictable PK and may require renal and hepatic adjustments in certain patient populations (►**Table 3**).

To date, there are five ongoing trials assessing the use of apixaban in pediatric patients (►**Table 1**).

A single-dose, parallel, phase 1 study evaluated the PK/PD parameters of prophylactic apixaban in patients at risk for a venous or arterial thrombotic disorder.[37] Inclusion criteria included neonates $\geq$ 34 weeks of gestational age or $\geq$ 37 weeks of postconceptual age to children and adolescents younger than 18 years and any stable disease that places them at risk for venous or arterial thrombotic disorder. This study was completed in June 2020 and results have not yet been published.[37]

The PREVAPIX-ALL (APIXaban compared with standard of care for PREVention of venous thrombosis in pediatric Acute Lymphoblastic Leukemia [ALL]) trial also has published information regarding the study rationale and design.[38] The goal of this prospective, randomized, multinational, open-label, SOC-controlled phase 3 trial is to compare the outcomes of prophylactic apixaban versus no anticoagulation in 500 children with ALL or T/B cell lymphoblastic lymphoma undergoing standard induction chemotherapy with asparaginase and who have a central venous access device. Apixaban is initiated on the day of randomization and continued through day 28 of induction chemotherapy. Dosing for this study is based on population PK modeling of adult PK data in conjunction with pediatric Phase 1 data accounting for age and weight.[38,39]

The SAXOPHONE (Safety of ApiXaban On Pediatric Heart disease On the preventioN of Embolism) study has published information regarding study design and rationale.[40,41] The goal of this prospective, randomized, open-label, multicenter, multinational, phase 2 trial is a PK/PD surrogate and safety study of apixaban compared with SOC for thromboprophylaxis in pediatric patients with congenital and acquired heart disease.[40,41] This study included approximately 200 children aged more than 1 month up to 18 years with congenital or acquired heart disease (i.e., cardiomyopathy, Kawasaki's disease with coronary aneurysm) requiring thromboembolic prophylaxis or currently receiving thromboembolic prophylaxis with SOC. Dosing of apixaban in this study is based on a fixed-dose, body weight–tiered regimen ranging from 1 mg twice daily to 5 mg twice daily. Whether a patient receives a 0.5-mg dissolvable tablet or 0.4 mg/mL solution will be determined based on patient's age.[40,41] This clinical trial is anticipated to complete late 2021.

The CANINES study is a randomized, open-label phase 4 study that is also ongoing, with the goal to assess the safety and efficacy of apixaban for the treatment of acute VTE in pediatric patients.[42] Inclusion criteria include patients younger than 18 years, with a minimum weight of 2.6 kg, who have confirmed VTE, who tolerate oral or enteral feeds, and have planned VTE treatment lasting at least 6 to 12 weeks. Patients between birth and $<$18 years will be dosed on a body weight–tiered regimen with doses ranging from 0.2 to 5 mg BID.[42] This trial has an estimated completion date of April 2023.

Additionally, there is an open-label, single group pilot study evaluating apixaban for the treatment and prevention of secondary VTE in children and adolescents without initial parenteral therapy (NCT04041843).[43] Inclusion criteria are children and adolescents weighing $\geq$ 40 kg and who have confirmed VTE.[43] This study is currently recruiting with an estimated completion date of 2022.

The dosage forms available with apixaban are of particular interest. In addition to the commercially available tablet, there is a 0.4-mg/mL liquid formulation that was developed for pediatric patients. Of note, children younger than 5 years are not eligible to receive the apixaban oral solution due to excessive excipient (lactose) in the solution relative to age.[39,44] A dissolvable apixaban mini-tablet (0.5 mg) formulation was subsequently developed for further administration in pediatric patients. In the PREVAPIX-ALL study, children $\geq$5 years and weighing $\geq$35 kg are eligible to receive the 2.5-mg tablets, 0.5-mg tablets, or oral solution apixaban, while patients younger than 5 years and weighing less than 35 kg may only be administered the 0.5-mg tablets due to the concern with the oral solution in young children.[38] In the SAXOPHONE study, participants younger than 5 years will receive 0.5-mg dissolvable tablets and participants older than 5 years will receive either 0.5-mg dissolvable tablets or a 0.4-mg/mL oral solution (►**Table 5**).[40,41] The CANINES study notes that a tablet or solution will be utilized but does not specify limitations for the solution.[42]

The ongoing trials will provide safety and efficacy data for prophylaxis and treatment of VTE in pediatric patients with varying risk factors. This will be of particular benefit with regard to available dosage forms for apixaban. Although

there is an oral solution available, the inability to utilize it in children younger than 5 years is a disadvantage. While there are not currently any formalized recommendations regarding the utilization of apixaban in pediatric patients, the information from the aforementioned trials will expand knowledge for its use in those with congenital heart disease and those requiring thromboembolism prophylaxis. Furthermore, apixaban has the widest spectrum of indications among pediatric NOAC trials including prophylaxis and acute treatment of thromboembolism.[38–42]

Edoxaban

Edoxaban received initial FDA and EMA approval in adults in 2015.[45] Edoxaban is currently indicated in adults for stroke prevention in nonvalvular atrial fibrillation and for the treatment of DVT or PE.[45] Edoxaban is primarily renally excreted and requires dose adjustment in the setting of renal dysfunction (►**Table 3**). There are not any published studies to date assessing the use of edoxaban in the pediatric patient population, but there are currently three ongoing clinical studies (►**Table 1**).

An open-label, single-dose, nonrandomized phase 1 study is ongoing to evaluate the PK/PD of edoxaban in pediatric patients.[46] Eligible patients are randomized to one of six age cohorts with the primary and secondary endpoints all PK/PD related. The study is currently recruiting and has an expected completion date of September 2021.

The ENNOBLE-ATE trial is an ongoing, phase 3 open-label, randomized, multicenter trial evaluating the safety and efficacy of edoxaban for thromboprophylaxis in children with cardiac disease at risk for thromboembolic events.[47] Inclusion criterion includes patients from 38 weeks of gestational age to 18 years of age with cardiac disease and at risk for thromboembolic complications, requiring antithrombotic prophylaxis for a minimum of 3 months, or who have a history of shunt thrombosis with a shunt currently in place.[47] The primary endpoints are a composite of bleeding events within the main treatment period (4 months) and a composite of bleeding events during the entire study period (13 months). The key secondary objective is to compare the efficacy of edoxaban against SOC with regard to the occurrence of symptomatic thromboembolic events in the systemic arterial or venous pathways.[47] ENNOBLE-ATE is currently recruiting with anticipated results in the near future.

The HOKUSAI-Jr trial is an ongoing, open-label, randomized, multicenter, phase 3 trial evaluating the PK/PD, safety, and efficacy of edoxaban for pediatric patients with confirmed VTE.[48,49] Children aged 38 weeks of gestational age to 18 years of age with a confirmed VTE requiring anticoagulation for a minimum of 90 days and who have received at least 5 days of SOC are included in the trial. Patients are randomized to either edoxaban or SOC.[48,49] The primary endpoints are a composite of recurrent VTE, death related to VTE, and a composite of no change or extension of thrombotic burden. The study is currently recruiting and has an expected completion date of March 2021.

Edoxaban is the second newest NOAC on the market and has no published data to support its use in pediatric patients. Collectively, these three ongoing studies aim to provide the initial data necessary to develop future studies describing the use of edoxaban in the pediatric patient population.

Conclusion

NOACs provide advantages compared with current recommended options of anticoagulation therapy, namely, ease of oral administration, less frequent laboratory monitoring, and a relatively stable PK/PD profile. Findings to date from published trials on the use of NOACs in a total of 1,007 children are promising. The low frequency of recurrent VTE and of clinically relevant bleeding rates in combination with minimal laboratory monitoring requirements in phase 3 trials such as DIVERSITY and EINSTEIN-Jr suggests suitability of NOACs for VTE treatment in children and also provide optimism for the potential for primary thromboprophylaxis in at-risk children. There are several ongoing studies assessing the use of apixaban and edoxaban for thromboprophylaxis in patients with distinct blood rheology such as in cardiac conditions (SAXOPHONE, ENNOBLE), in patients undergoing repetitive procedures and need for temporary drug interruption such as in leukemia with a central venous catheter (PREVAPIX-ALL), and for the treatment of acute VTE (CANINES, HOKUSAI-Jr; ►**Table 1**). The impact of these agents in the setting of primary thromboprophylaxis and VTE treatment will provide efficacious and safe options for clinical utilization in the pediatric patient population.

A limitation of this systematic review is that the initial query was conducted utilizing a single database; however, each article identified from the single database search had its references evaluated by two independent reviewers for additional articles to meet inclusion criteria. Further issues including the optimal duration of VTE treatment, use for prophylaxis, and specific pediatric settings and subpopulations (including patients with antiphospholipid antibodies) remain to be further investigated. In addition, further studies will be beneficial in establishing dosing, efficacy, and safety parameters in real-life pediatric patient population. Other open questions that remain to be answered in pediatrics include the comparative efficacy between the available NOACs, the need for therapeutic drug monitoring, and the efficacy of reversal agents. Nevertheless, recent experience in the field suggests that NOAC therapy is likely to become the new SOC for pediatric VTE treatment. As additional pediatric-specific dosage forms are developed and approved for varying indications in this young patient population, continued PK/PD data and clinical experience will refine how these agents are utilized in the pediatric clinical practice setting.

Conflict of Interest
L.B. reports other from Boehringer Ingelheim (BI), specifying research support and participation as a board study member; C.M. reports grants and personal fees from Bayer AG, Boehringer-Ingelheim, Bristol Myers Squibb, and Pfizer; N.A.G. reports other from Bayer, outside the

submitted work; and N.A.G. receives research support and salary support from the National Institutes of Health, National Heart Lung, and Blood Institute for clinical and translational investigation in venous thromboembolism in patients younger than 21 years. N.A.G. receives consultancy fees from Daiici Sankyo Inc., Anthos Therapeutics Inc., and the Academic Research Organization CPC Clinical Research for roles in clinical trial oversight committees (e.g., steering, data and safety monitoring) in pharmaceutical industry–sponsored pediatric clinical trials of antithrombotic agents. J.W.B., C.C., H.F., K.M.G., M.A.K., and A.L.K. do not have any conflicts of interest to disclose.

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