ABSTRACT

Common treatment options for deep vein thrombosis and venous thromboembolism in the pediatric population include unfractionated heparin, low molecular weight heparin, and warfarin. Other alternatives are bivalirudin, argatroban, and fondaparinux. Warfarin is the only approved oral option, but an oral agent without frequent monitoring would be optimal for pediatric patients. Thus, there is an increasing need for new anticoagulation options in this population. None of the current direct oral anticoagulants have FDA-approved indications and dosing in children. The two classes of DOACs and the drugs they are comprised of are factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) and direct thrombin inhibitor (dabigatran). Off-label usage of these agents is largely based on adult doses. By far, rivaroxaban and dabigatran have the most published data and ongoing trials in pediatric patients compared to edoxaban and apixaban. After evaluating the current literature available on these agents, it is, however, still too early to make any definitive recommendations on their usage in this special population.

Keywords: Anticoagulants; Apixaban; Dabigatran; Edoxaban; Pediatrics

INTRODUCTION

The need of anticoagulation in pediatric patients is increasing, and certain patient populations can be at an increased risk of developing deep vein thrombosis (DVT) and require venous thromboembolism (VTE) prophylaxis or treatment [1]. In neonates, anticoagulation is often needed when the thromboembolism is caused by a central venous access device or an umbilical venous catheter. The use of anticoagulation is also warranted in neonates with unilateral or bilateral renal vein thrombosis that extends into the inferior vena cava and with evidence of
renal impairment, respectively. Many indications exist for thromboprophylaxis in the neonatal population, and these include but are not limited to patients post congenital cardiac surgery (e.g., modified Blalock–Taussig shunts) and patients with peripheral or umbilical arterial catheters who are at high risk of developing clots [2].

Similarly, children may also require anticoagulation after cardiac surgery (e.g., Glenn procedure or bilateral cavopulmonary shunt). Some children with moderate or giant coronary aneurysms following Kawasaki disease are also warranted to be on therapeutic doses of anticoagulants. Children with cancer are overall at an increased risk of developing VTE and can sometimes be seen on low molecular weight heparin for the treatment of deep vein thrombosis. A more detailed list of indications for antithrombotic therapy in neonates and children can be found in the CHEST guideline [2].

Unfractionated heparin (UFH), low molecular weight heparin (LMWH), or warfarin is often the anticoagulant of choice in the pediatric population [2]. If UFH and LMWH cannot be used due to heparin-induced thrombocytopenia and if warfarin is not an option due to the lack of oral access, other alternatives such as bivalirudin, argatroban, and fondaparinux can be used. Published literature exist in supporting the use of these three latter anticoagulants in pediatric patients [3–10]. Lepirudin has also been studied in children [11] but is not recommended by many clinicians because this anticoagulant appears to cause more bleeding in this population [12].

In recent years, direct oral anticoagulants (DOACs) have gained interest in their potential usage in pediatric patients. Factor Xa inhibitors and direct thrombin inhibitor comprise the DOACs. Rivaroxaban, apixaban, and edoxaban are the factor Xa inhibitors and dabigatran is the direct thrombin inhibitor. DOACs should be avoided in patients who are pregnant and patients with mechanical heart valves, rheumatic mitral stenosis, and stage V chronic kidney disease (except in patients on stable hemodialysis who desire to be on apixaban) [13–18]. Limited data exists on the use of these DOACs in pediatric patients, and none of them have Food and Drug Administration (FDA)-approved pediatric labeling. Off-label use of these DOACs in pediatrics is largely extrapolated from adult dosing guidelines. Fortunately, there are many clinical trials currently recruiting pediatric patients and are underway to assess their effects and efficacy in this special population. This article will attempt to summarize the current data and the ongoing trials being performed on their usage in pediatric patients.

Compliance with Ethical Guidelines

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

FACTOR Xa INHIBITORS

In the coagulation cascade, factor X is positioned at the convergence of the extrinsic and intrinsic pathways [13]. Its activation to factor Xa along with its binding with factor Va to form prothrombinase is essential for the conversion of prothrombin to thrombin [13]. Factor Xa inhibitors therefore directly decrease the amount of thrombin being produced in coagulation. Rivaroxaban, apixaban, and most recently edoxaban, are oral factor Xa inhibitors currently on the market in Europe and the United States.
Rivaroxaban

Rivaroxaban, the first-approved DOAC, reversibly inhibits free and bound factor Xa as well as that in the prothrombinase complex ultimately preventing clot formation and growth [19]. Rivaroxaban has been shown to be non-inferior to low molecular weight heparin and warfarin in multiple studies in the adult population [20–24]. It is approved for use in adult patients to reduce the risk of thromboembolic complications associated with nonvalvular atrial fibrillation (NVAF), to treat and prevent recurrent DVT and pulmonary embolism (PE), and for preventing DVT in patients who underwent knee or hip replacement surgery [14]. Dosing in adults for the treatment and reduction in the risk of recurrent DVT and PE is 15 mg by mouth twice daily with food for 21 days followed by 20 mg by mouth once daily with food for the remainder of the treatment duration [14]. Along with the outcomes found in the adult non-inferiority studies, rivaroxaban carries additional advantages including once-daily dosing, high bioavailability, minimal drug interactions, and a limited need for laboratory monitoring [25]. These factors make rivaroxaban an appealing alternative to the currently recommended anticoagulants (i.e., warfarin, UFH, and LMWH) in the pediatric population.

Completed Studies

Currently, there are only four completed studies assessing the pharmacokinetic and pharmacodynamic (PK/PD) effects of rivaroxaban in the pediatric population [19, 25, 26]. The first of these studies was an in vitro analysis of the differences in the pharmacodynamic effects of rivaroxaban in healthy children versus adults [25]. Plasma samples were obtained from healthy children ages 28 days to 16 years without a family history of coagulation disorders admitted to the hospital for minor day surgery. Plasma samples were grouped into age-specific pools, which were spiked with six different concentrations of rivaroxaban (0, 25, 50, 100, 250, and 500 ng/ml) to match therapeutic levels of 100–300 ng/ml in plasma. Outcomes included the differences between measured activated partial thromboplastin time (aPTT), prothrombin time (PT), anti-factor Xa activity, and endogenous thrombin potential (ETP). The results of this trial failed to show a difference in age-related effect of rivaroxaban on any of the above-mentioned monitoring assays [25].

The second of these studies involved the development of a pharmacokinetic model for rivaroxaban 10 and 20 mg in adults scaled to the pediatric population [19]. This study was conducted via physiologically-based pharmacokinetic (PBPK) simulation software, which considered lipophilicity, hepatic and renal clearance processes, gastrointestinal transit and absorption, as well as the effects food had on the medication. Using the adult model, a pediatric model was designed that included anthropometric and physiological information, age-dependent clearance processes of and protein binding in virtual children from term neonates to adolescents aged 18 years. Based on an average adult weight of 70 kg, a pediatric weight-based dose was used. These included pediatric doses of 0.143 mg/kg (1/7th mg/kg) and 0.286 mg/kg (2/7th mg/kg), which would be equivalent to a 10- and 20-mg dose, respectively, in adult patients. The results of this study showed similar maximum concentration (C_{max}), area under the curve (AUC), and 24-h concentration (C_{24h}) values versus body weight. In children with body weight >70 kg, the simulated AUC
and $C_{24h}$ were much higher than the adult reference [i.e., >90% confidence interval (CI)] so the weight-based doses for these children may be much higher than the 10 or 20 mg used in adults. On the other hand, these values for either doses (i.e., 0.143 or 0.286 mg/kg) in infants and children up to 40 kg of body weight were much lower than the adult reference population (i.e., <90% CI) so higher doses in this weight group may be necessary [19].

Another study was presented as an abstract at the XXV Congress of the International Society on Thrombosis and Haemostasis and 61st Annual Scientific and Standardization Committee Meeting that recently took place in Toronto, Canada in June of 2015 [26]. The aim of this study was to determine a dose of rivaroxaban in pediatric patients aged 12–18 years that would result in an equivalent exposure seen with a 20-mg dose in adult patients for the treatment of VTE. By using a PBPK model, a weight-adjusted dose of rivaroxaban taken once daily was established for the cohort. The researchers initially performed a phase I single-dose PK/PD study comparing the predicted and observed plasma concentrations and AUC for the 10- ($n = 4$) and 20-mg ($n = 5$) equivalent doses. Both the observed concentrations and the AUC were similar to the prediction made by the PBPK model. Dose linearity was also observed between the 10- and 20-mg equivalent doses. This phase I study was followed by a 30-day multiple-dose PK/PD phase II study comparing the predicted and observed plasma concentrations and AUC for the 20-mg equivalent dose and evaluating the PD changes to the observed concentrations by measuring markers such as PT and aPTT. Eleven children with a mean age of 15.5 years were enrolled in this second study. Similar to the phase I study, the observed concentrations and the AUC were similar to the predicted model. Both the aPTT and PT showed an almost-linear relationship with the drug’s plasma concentration. No major bleeding was observed in the study. From this data, the researchers concluded that pediatric patients weighing 30–50 kg will probably need 15 mg daily and those weighing >50 kg, 20 mg daily of rivaroxaban, for the treatment of VTE. This dosing regimen is currently being studied in a phase III clinical trial with a similar cohort [26].

The last of these completed studies was recently completed and was a phase I trial assessing the pharmacokinetic and pharmacodynamic properties of oral rivaroxaban in the pediatric population [27]. The subjects included in this trial were those aged 6 months to <18 years who had completed treatment for venous thromboembolism but were considered to be at risk of recurrence. These subjects were given a single dose of weight-adjusted rivaroxaban equivalent to 10- or 20-mg dose in adults. The primary outcomes included AUC, $C_{\text{max}}$, PT, aPTT, and anti-factor Xa from day 1 to day 2 post administration of rivaroxaban. The investigators also evaluated the safety and tolerability of this DOAC on day 1, 2, and 7 post dose. Even though this study was completed, the results have not yet been published on clinicaltrials.gov [27].

**Ongoing Studies**

Current ongoing studies evaluating the effects of rivaroxaban in the pediatric population include EINSTEIN Junior which is recruiting patients for two phase II and one phase III studies [28–30]. There are two phase II trials underway, which are both 30-day, open-label, active-controlled randomized studies of the safety/efficacy and pharmacokinetic/
pharmacodynamic properties of oral rivaroxaban in children with various manifestations of venous thrombosis [28, 29]. The difference between these two studies is the age of the participants. One of these studies includes participants ages 6 months to <6 years and the other includes participants ages 6 to 17 years. Participants enrolled in either trial are those entering their last month of anticoagulant therapy after having been treated with LMWH, fondaparinux and/or vitamin K antagonist (VKA) for at least 2 months or for at least 6 weeks in patients who have had catheter-related thrombosis [28, 29].

Similarly, the phase III trial is an open-label, active-controlled, randomized study assessing the safety and efficacy of rivaroxaban in comparison to the standard of care including subcutaneous LMWH, fondaparinux and/or oral VKA in patients with confirmed acute venous thromboembolism [30]. Children included in this trial are those ages 6 months to <18 years who were initially treated with unfractionated heparin, LMWH, or fondaparinux and required anticoagulant therapy for at least 90 days. In this trial, rivaroxaban will be provided according to an age- and body weight-adjusted dosing schedule to achieve concentrations similar to those observed in adult patients on 20 mg of rivaroxaban. It will be provided as a 20-mg equivalent tablet given once daily for children 12–18 years of age and subsequently as a 20-mg equivalent oral suspension given twice daily for children ages 6 months to <12 years [30] (Fig. 1). The results of all of these ongoing studies are pending and yet to be published.

Another ongoing study is a multicenter, international, phase I study evaluating a rivaroxaban dry powder suspension in pediatric patients ages 6 months to 12 years with previous history of thrombosis [31]. Subjects will be included if they have finished treatment with an anticoagulant at least 10 days and have normal PT and aPTT within 10 days before enrolling into the study. The primary outcomes will be the measurement of AUC and \( C_{\text{max}} \) 20 to 24 h after the administration of the studied suspension. This study will also evaluate the PT, aPTT, and anti-Xa activity of rivaroxaban between the aforementioned timeframe and will be compared to baseline values that will be obtained within 5 h prior to drug administration [31]. Similar studies evaluating the bioavailability of a rivaroxaban oral suspension have recently been completed in adults. [32, 33]. It will be interesting to compare theses adult data with the pediatric data when they become available. Establishing a bio-equivalent oral suspension of rivaroxaban will be a vital step in potentially administering this DOAC to younger pediatric patients.

The last ongoing study is both a phase I and phase II study that will assess the safety, efficacy, and pharmacokinetic/pharmacodynamic properties of oral rivaroxaban in patients less than 6 months of age with catheter-related thrombosis who have been treated for at least 2 weeks of standard therapy with heparin and/or warfarin [34]. This study will take place in 11 countries such as Australia, France, Israel, and the United States. The subjects will be given a 7-day treatment of an age- and body weight-adjusted oral rivaroxaban given twice daily as a 1-mg/ml oral suspension to achieve similar exposures as those observed with 20-mg daily dosing in adults. The primary outcome will be the plasma concentration of rivaroxaban in this cohort from day 1 to day 8. As secondary endpoints, the investigators will assess the incidence of major bleeding, clinically relevant non-major bleeding, and symptomatic recurrent thromboembolism on days 1 to 7.
The incidence of asymptomatic worsening of thrombotic burden will also be evaluated on day 8 post administration of rivaroxaban.[34]. The results of all these ongoing studies will be vital to the approval of rivaroxaban use in the pediatric population.

**Apixaban**

Similar to rivaroxaban, apixaban is a reversible factor Xa inhibitor that inhibits free, bound, and complexed factor Xa.[15]. It has gained approval for the prevention of thromboembolic...
complications in adult patients who have undergone hip or knee replacement [35, 36]. It was also found to be superior to warfarin for the risk reduction of stroke and systemic embolism in patients with atrial fibrillation [37]. Most recently, it has been approved for the treatment of DVT and PE and the reduction in the risk of recurrent DVT and PE following initial therapy [38, 39]. The recommended dosing for the treatment of DVT and PE in adults is 10 mg by mouth twice daily for 7 days, followed by 5 mg by mouth twice daily [15]. Dosing for the prevention of DVT following hip or knee replacement surgery or for the reduction in the risk of recurrent DVT and PE following initial therapy is 2.5 mg by mouth twice daily [15].

**Completed Study**

Currently, there are not any published trials assessing the efficacy of apixaban in the pediatric population. In 2012, a multi-dose study of apixaban in the pediatric population was terminated for unknown reasons [40]. This study was designed to assess the pharmacokinetic and pharmacodynamic properties of apixaban in patients aged 12 to <18 years with a functioning central venous catheter. The study drug was given at a low dose of 0.66 mg/m² twice daily for 10 days or a high dose of 1.32 mg/m² as an oral solution twice daily for 10 days [40]. No other information was published or available on this trial and the researchers did not mention a reason for the early discontinuation of this study.

**Ongoing Studies**

To date, there are three ongoing studies assessing the potential use of apixaban in pediatric patients [41–44]. The first of these studies is a phase I single-dose, parallel study evaluating the PK and PD parameters of apixaban as a preventive regimen in subjects ages 37 weeks to 18 years at risk for a venous or arterial thrombotic disorder [41]. Five different groups are assigned in this study. Group 1 includes neonates who are given an unspecified dose of apixaban. Group 2 is divided into two arms: 9 months to 2 years given 2.43 mg/m² of apixaban and 28 days to <9 months given 1.08 mg/m² of the drug. Group 3 includes patients 2 years to <6 years old who are given a single-dose of apixaban at 1.17 mg/m². Children ages 6 years to <12 years are assigned to Group 4 and are given apixaban 1.8 mg/m², whereas adolescents in Group 5 are given 2.19 mg/m² of apixaban. The primary outcomes of this study include the measurement of AUC, Cmax, and Tmax of apixaban up to 26 h post drug administration. As secondary outcomes, the researchers monitor adverse events up to 26 h and 30 days post dose and evaluate the pharmacodynamic effect of apixaban by measuring anti-factor Xa level up to 26 h post dose [41].

The second study was recently presented as a poster at the previously mentioned XXV Congress of the International Society on Thrombosis and Haemostasis and 61st Annual Scientific and Standardization Committee Meeting [42, 43]. This is a phase III, multicenter, international, open-label, study that randomizes pediatric patients (ages 1 to <18 years) with acute lymphoblastic leukemia or lymphoma treated with L-asparaginase to either the placebo group or the intervention group. Patients who are 2 years old and above weighing less than 35 kg are given 0.05 mg/kg twice daily of apixaban as a 0.4 mg/ml solution and patients weighing ≥35 kg are given a 2.5-mg tablet twice daily. Per the researchers, dosage for 12–23 months has yet to be determined. The primary endpoint of this study is a composite of non-fatal DVT/PE, cerebral venous sinus thrombosis, and VTE-related death up to
1 month after therapy. The researchers are planning to recruit a total of 700 subjects. If this recruitment is successful, this will be the first adequately powered phase III clinical trial evaluating DOAC in the pediatric population [42, 43].

The last ongoing study will be a randomized, phase IV, open-label study evaluating the use of apixaban as a treatment option for acute venous thromboembolism in pediatric patients less than 18 years of age [44]. Subjects will be given either the standard of care (e.g., heparin or enoxaparin) or apixaban. Children 12 to <18 years old weighing less than 40 kg will receive an apixaban dose of 0.2 mg/kg twice daily for 7 days followed by 0.1 mg/kg twice daily, whereas children at the same age weighing more than 40 kg will receive the adult VTE treatment dose (i.e., 10 mg twice daily for 7 days followed by 5 mg twice daily). Dosages for patients less than 12 years old have not been mentioned. The primary outcomes of this study consist of the composite of major and non-major bleeding and the composite of confirmed symptomatic and asymptomatic recurrent VTE and mortality related to the VTE up to 12 weeks post treatment. Apixaban and anti-Xa levels will also be obtained as secondary endpoints. This study is estimated to be completed in October 2020 [44] (Fig. 2).

Edoxaban

Edoxaban is the most recently approved [January 2015 in the United States (US) and June 2015 in Europe] factor Xa inhibitor. Even though edoxaban does not have a novel mechanism of action, it exhibits some pharmacodynamic/pharmacokinetic advantages in anticoagulation. It has the fastest time to maximum effect (1–2 h) and offers options for once-daily dosing and for patients with renal impairment [45]. Also, its absorption is not affected by the presence of food [45]. Edoxaban is currently approved for the prevention of VTE in patients undergoing orthopedic surgery of the lower extremities, DVT/PE treatment 5–10 days after a parenteral anticoagulant has been used, as well as for stroke and systemic embolism risk reduction in NVAF. In the adult population, 60 mg once daily is used for DVT/PE treatment, with a dose reduction to 30 mg once daily if the patient’s creatinine clearance is between 15 and 50 ml/min, on a concomitant P-glycoprotein (Pg-P) inhibitor, or weight is ≤60 kg [16]. The ENGAGE AF-TIMI 48 trial [46], which was a randomized, double-blind, non-inferiority study of high- and low-dose edoxaban (60 and 30 mg, respectively) compared to warfarin, showed that edoxaban was non-inferior to warfarin in preventing the primary end point of systemic embolism or stroke. In addition, edoxaban had a lower bleeding rate and death from cardiovascular causes in comparison to warfarin [46].

Ongoing Study

The only current pediatric study involving edoxaban is a phase I, open-label, preliminary pharmacodynamic and pharmacokinetic trial in patients 0–18 years old [47]. The dose matched to low and high adult doses (30 and 60 mg, respectively) will be given to children requiring oral anticoagulation as a single dose. There are currently eight arms in this study divided by age and low/high dose of edoxaban. The primary outcome is clearance between days 1 and 3 post dose, and the secondary outcomes include pharmacodynamic parameters that are measured with PT, aPTT, and anti-Xa levels, safety and tolerability, and metabolite exposure. This trial is currently recruiting patients and is expected to be completed in 2016 [47].
Of note, from the ENGAGE AF-TIMI 48 study and the observation that about 50% of the dose of edoxaban is cleared by the kidneys [46], there is a direct correlation between serum drug levels and outcomes expected from edoxaban (i.e., decrease in the risk of stroke). The ENGAGE study proved this when it showed that patients with NVAF with CrCL >95 ml/min had a statistically higher rate of ischemic stroke with edoxaban in comparison to patients receiving warfarin. This observation resulted in a black box warning in the US for edoxaban.

**Fig. 2** Design of apixaban for the acute treatment of venous thromboembolism in children (Phase IV Study) [44]
recommending healthcare providers not to use this oral anticoagulant in patients with NVAF whose CrCL is >95 ml/min [46]. However, this is listed only as a precaution, not a restriction, in the European drug label for edoxaban [17]. Even though this US warning is only in patients with NVAF and atrial fibrillation is an irrelevant diagnosis in pediatric patients, it will still be interesting to assess if edoxaban will be efficacious as an anticoagulant in this population, especially those ≥2 years old, since they very well can have a CrCL >95 ml/min/1.73 m² [48]. With that being said, it is, however, not clear how the concentration of edoxaban may relate in these two different populations with different methods to assess renal function so clinicians should be cautious when trying to extrapolate this finding to children based on normalized body surface area.

DIRECT THROMBIN INHIBITOR

Thrombin converts fibrinogen to fibrin in the final step of the coagulation cascade. Inhibiting this step of the coagulation cascade inhibits free and bound thrombin, ultimately resulting in anticoagulation [18]. Dabigatran is currently the only oral medication in this class of anticoagulant.

Dabigatran

In the adult population, dabigatran is approved to treat DVT/PE as well as to reduce the risk of stroke/systemic embolism in NVAF. Approved doses for these indications are 150 mg twice a day for CrCL >30 ml/min, with a dose adjustment to 75 mg twice a day for CrCL 15–30 ml/min (i.e., for stroke reduction in NVAF only). Dabigatran is transported via the Pg-p efflux protein, and reaches $C_{\text{max}}$ in about 1 h if taken on an empty stomach. If given with a high-fat meal, the $C_{\text{max}}$ increases to 2 h, but there is not any change in the bioavailability of the medication [18]. In the RE-LY trial, 100 and 150 mg of dabigatran were compared to warfarin in patients with NVAF. In this study, dabigatran was noninferior to warfarin for stroke and systemic embolism reduction [18]. Being a direct thrombin inhibitor, dabigatran binds to thrombin directly and is not dependent on the availability of antithrombin which can be very variable among patients, specifically pediatric patients [49]. In addition, there is also not any drug monitoring required with dabigatran, making it also a favorable option to explore in pediatric patients.

Completed Studies

A study was recently published assessing the effect of dabigatran in vitro using plasma samples and an assay with increasing concentrations of dabigatran [1]. The five clotting assays in this study included thrombin time (TT), dilute thrombin time (dTT), ecarin clotting time (ECT), aPTT, and PT. When evaluating response to increasing dabigatran concentrations (0, 50, 250, and 450 ng/ml), there was not any difference among the different age groups of children (0 to $<$1, 1 to $<$5, 5 to $<$10, and 10 to $<$17 years). However, longer clotting times with respect to aPTT, ECT, and TT were observed in children compared to adults with increasing concentrations of dabigatran. Of all the assays, the dTT, TT, and ECT were most linearly correlated with increasing plasma concentrations, and the study concluded that dTT was the best assay for measuring dabigatran concentration in pediatric patients. The author concluded that this assay may be necessary to measure dabigatran concentrations until there
are more studies looking into the pharmacodynamic and pharmacokinetic effects of this anticoagulant in the pediatric population [1].

Another open-label, phase II study was also completed in February 2012 in Canada in which the investigators aimed to evaluate the safety and tolerability of dabigatran given for 3 days to adolescents who had finished a course of standard anticoagulation for the primary diagnosis of VTE [50]. Nine subjects (mean age, 15.7 ± 1.3 years; six of them were female) were initially enrolled in this study. One of these subjects did not finish the study due to withdrawal, but he or she was included in the final analysis. All patients were given an initial dose of 1.71 mg/kg [75 mg (three patients); 100 mg (three patients); 125 mg (three patients)], which was 80% of the adult 150-mg dose adjusted for a weight of 70 kg. Thrombin time was then obtained and the dabigatran was adjusted to a target dose of 2.14 mg/kg twice daily (BID) [100 mg BID (three patients); 125 mg BID (three patients); 150 mg BID (two patients)]. None of these subjects had a major or minor bleeding event, but two of them experienced drug-related adverse events while on treatment and one subject reported a serious adverse event 72 h post-treatment (exact descriptions of these events were not documented). Free and total dabigatran concentrations were also obtained in six of the subjects. The subjects who received a final dosage of 100 mg BID had a mean free and total dabigatran concentration of 28 and 34.2 ng/ml, respectively; whereas the 125 mg BID, 41.6 and 58.2 ng/ml, respectively [50].

Even though this particular study had a small sample size, the results can potentially add to the body of literature and provide other investigators a plausible initial dosage of dabigatran for adolescents involved in larger future studies.

Ongoing Studies
Currently, there are three phase II trials being conducted on the use of an oral dabigatran liquid formulation in the pediatric population [51–53]. Two of these studies aim to evaluate the pharmacokinetic/pharmacodynamic data, safety, and tolerability of this solution in children who are at the end of their standard anticoagulation course for a VTE diagnosis [51, 52]. The first study is enrolling infants less than 1 year of age (excluding <3 kg) [51], whereas the other study is evaluating the use of this solution in children 1 to 2 years old (excluding <9 kg) [52]. Patients will be given an age- and weight-adjusted equivalent dose of dabigatran. The exact doses being used in these studies, however, are not currently available. Some common primary endpoints between these two studies include the measurement of total plasma concentrations of dabigatran, ECT, and aPTT. The study with infants <1 year of age is also looking at anti-factor IIa activity 2 and 12 h post dose [51], whereas the other study is also evaluating the incidence of bleeding and adverse events as additional primary endpoints [52]. The global assessment of tolerability of the liquid medication is also being assessed as one of the secondary endpoints [51, 52]. The last of this phase II trial [53] has similar primary and secondary endpoints to the one being conducted in children 1 to 2 years old [52], but the former is an international study and the investigators are evaluating the use of this oral dabigatran solution in children 1 to 12 years old [53]. The results of all these three previously mentioned studies are vital to establishing a bio-equivalent oral suspension of dabigatran in the pediatric population.

\(\Delta\) Adis
On the other hand, there are currently two phase III trials evaluating the safety and efficacy of dabigatran in pediatric patients [54, 55]. The first study is an open-label, non-inferiority study comparing dabigatran with standard of care (i.e., warfarin, UFH, or LMWH) to treat patients with VTE. It has a co-primary endpoint of thrombus resolution with freedom from recurrent VTE in addition to freedom from major bleeding events. The VTE must have been diagnosed and already been treated with UFH or LMWH for 5–7 days with an indication to treat with anticoagulants for at least 3 months post diagnosis [54] (Fig. 3). In another open-label study, dabigatran is being evaluated as a secondary prophylaxis for VTE in children ages 0–18 years [55]. The endpoints for this study include VTE recurrence, bleeding events (major and minor), and mortality associated with thrombotic events. These patients must have finished their previous course of anticoagulants for the initial VTE to be eligible for this study [55]. The results of all of these ongoing studies are pending and yet to be published. Table 1 summarizes the information on the completed trials and those being performed on the use of DOACs in the pediatric population.

### CLINICAL APPLICATION

Current anticoagulants recommended for the use in pediatric patients with VTE include UFH, LMWH, and warfarin [2]. There are several limitations to the use of these agents that make the DOACs desirable. Disadvantages to the use of unfractionated heparin include the need for continuous intravenous access and frequent therapeutic drug level monitoring. Although LMWH does not require intravenous access, it requires twice-daily subcutaneous administration, which may not be ideal for pediatric patients who are often afraid of needles/injections. Also, anti-Xa levels are often required to be monitored in pediatric patients on LMWH [2]. Finally, warfarin, although it has the advantage of being a once-daily oral anticoagulant, it requires frequent international normalized ratio (INR) monitoring and carries multiple drug and food interactions that may require frequent dose adjustments [56].

The DOACs, including rivaroxaban, apixaban, dabigatran, and most recently edoxaban, offer the possibility of improved dose stability, oral routes of administration, infrequent drug monitoring, and fewer drug and food interactions [56]. A disadvantage to the use of these agents in comparison to the standard therapies is the lack of an established reversal agent for pediatric patients in the case of a major bleeding event or accidental/intentional overdose [57]. Fortunately, it seems that accidental or intentional one-time, low-dose ingestion of rivaroxaban and dabigatran does not lead to clinically significant bleeding as demonstrated by cases called into the California Poison Control system from January 2011 to July 2013 [58]. Nonetheless, an effective reversal agent for pediatric patients is indicated. Idarucizumab was recently approved in the US in October 2015 for the reversal of dabigatran in adults [59–61]. Currently, two additional reversal agents are in development: andexanet alfa and ciraparantag. Both of these agents can potentially reverse the oral factor Xa inhibitors as a class, and the latter may also reverse the effect of dabigatran [62]. Even though efficacy data on these reversal agents do not currently exist in pediatric patients, it will be really important for these agents to be evaluated in this population in the near future.
Based on the current literature, treatment of VTE in the pediatric population should always be initiated with UFH, LMWH, or warfarin. It is still too early to recommend one of the DOACs as an initial alternative for such indication due to the lack of published clinical trials. More data

Fig. 3 Design of the efficacy and safety comparison of dabigatran etexilate to standard of care in pediatric patients with venous thromboembolism (Phase III Study) [54]
| Class of anticoagulant | Medication | Authors/investigators | NCT # | Treatment | Dose |
|------------------------|------------|-----------------------|-------|-----------|------|
| Factor Xa inhibitors   | Rivaroxaban| Attard et al.         | –     | Age-specific plasma pools (i.e., 28 days to 16 years) spiked with increasing concentrations of rivaroxaban | 0–500 ng/ml |
|                        |            | Willmann et al.       | –     | Simulated PK properties of rivaroxaban in virtual populations of children | 0.143 mg/kg (10-mg adult equivalent) and 0.286 mg/kg (20-mg adult equivalent) once daily |
|                        |            | Young et al.          | –     | Phase I and phase II PK/PD study of a rivaroxaban dosing regimen for the treatment of VTE in patients 12 to 18 years of age | Weight-adjusted dose equivalent to 20-mg dose in adults |
| Bayer                  |            | 01145859              |       | Phase I PK/PD profile of single-dose rivaroxaban in patients 6 months to 18 years of age | Weight-adjusted dose equivalent to 10- or 20-mg doses in adults |
| Bayer                  |            | 01684423              |       | Phase II safety, efficacy and PK/PD properties of oral rivaroxaban compared to standard anticoagulant therapy in patients ages 6 to <18 years | Experimental: rivaroxaban 20-mg equivalent tablet once daily for children 12–18 years and 20-mg equivalent PO suspension twice daily for children aged 6 to <12 years |
| Bayer                  |            | 02497716              |       | Phase I study on rivaroxaban dry powder suspension in patients 6 months to 12 years old with previous thrombosis | Single weight-adjusted dose of the reconstituted dry powder suspension |
| Bayer                  |            | 02564718              |       | Phase I and II safety, efficacy and PK/PD properties of oral rivaroxaban in patients less than 6 months old | 7-day treatment of an age- and body weight-adjusted oral rivaroxaban given twice daily as an 1 mg/ml oral suspension to achieve similar exposures as those observed with 20 mg daily dosing in adults |
| Bayer                  |            | 02309411              |       | Phase II safety, efficacy and PK/PD properties of oral rivaroxaban compared to standard anticoagulant therapy in patients ages 6 months to <6 years | Experimental: rivaroxaban PO suspension age and body weight adjusted twice daily to achieve similar exposure as adult 20-mg once daily |
| Bayer                  |            | 02234843              |       | Efficacy and safety of rivaroxaban compared to standard of care in children ages 6 months to <18 years with acute VTE | Experimental: rivaroxaban 20-mg equivalent tablet once daily for children 12–18 years and 20-mg equivalent PO suspension twice daily for children aged 6 months to <12 years |
| Bayer                  |            |                      |       |           | Active comparator: continuation of anticoagulant used prior to randomization (i.e., UFH, LMWH, fondaparinux, VKA) |

Table 1 Published and ongoing studies on DOACs in pediatric patients [27–31, 34, 40–44, 47, 50–55]
| Class of anticoagulant | Medication | Authors/investigators | NCT # | Treatment                                                                 | Dose                                                                 |
|-----------------------|------------|-----------------------|-------|---------------------------------------------------------------------------|----------------------------------------------------------------------|
| Apixaban              | Bristol-Myers Squibb | 01195727 | Multiple dose apixaban PK/PD study in pediatric subjects aged 12 to <18 years with a central venous catheter | Low-dose group: 0.66 mg/m² PO solution BID × 10 days  
High-dose group: 1.32 mg/m² PO solution BID × 10 days |
| Bristol-Myers Squibb  | 01707394 | Single-dose apixaban PK/PD study in subjects 37 weeks to 18 years at risk for thrombotic disorder | Neonates: dose not mentioned  
28 days to <9 months: 1.08 mg/m²  
9 months to <2 years: 2.43 mg/m²  
2 years to <6 years: 1.17 mg/m²  
6 years to <12 years: 1.8 mg/m²  
12 years to <18 years: 2.19 mg/m² |
| Bristol-Myers Squibb  | 02369653 | Safety and efficacy of apixaban to prevent clots in leukemic patients ages 1–17 years treated with PEG-asparaginase | 12–23 months: dose not yet determined  
≥2 years and <35 kg: 0.05 mg/kg BID (0.4 mg/ml solution)  
≥35 kg: 2.5 mg tablet BID |
| Pfizer                | 02464969 | Efficacy of apixaban for the treatment of VTE in pediatric patients less than 18 years old | <12 years: dose not yet determined  
12 to <18 years and ≤40 kg: 0.2 mg/kg BID × 7 days, then 0.1 mg/kg BID  
12 to <18 years and >40 kg: 10 mg BID × 7 days, then 5 mg BID |
| Edoxaban              | Daiichi Sanyoko Inc. | 02303431 | Phase I PK/PD study in subjects 0 to <18 years after single dose of edoxaban | Low-dose group: matched to 30-mg exposure in adults  
High-dose group: matched to 60-mg exposure in adults |
| Class of anticoagulant | Medication | Authors/investigators | NCT #      | Treatment                                                                                           | Dose                                                                                       |
|------------------------|------------|-----------------------|------------|-----------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| Direct thrombin inhibitor | Dabigatran | Boehringer Ingelheim | 00844415   | Phase II study evaluate the safety and tolerability of dabigatran for 3 days in patients 12–18 years old who had finished standard anticoagulation for primary VTE | 1.71 mg/kg × 1, then adjusted to a target dose of 2.14 mg/kg BID based on TT and clinical assessment |
|                        |            | Dietrich et al.       | –          | Optimal coagulation assay for dabigatran and anticoagulant effect of dabigatran in vitro in pediatric patients 0 to <18 years old | 0, 50, 250, 450 ng/ml                                                                 |
|                        |            | Boehringer Ingelheim  | 01083732   | Phase II study evaluating the safety & tolerability of a dabigatran oral solution in 1 to 12 years old | Age- and weight-adjusted equivalent of adult dose                                            |
|                        |            | Boehringer Ingelheim  | 01773174   | Phase II study evaluating the PK, safety, and tolerability of a dabigatran oral solution in 1–2 years old | Age- and weight-adjusted equivalent of adult dose                                            |
|                        |            | Boehringer Ingelheim  | 02223260   | Phase II study evaluating the PK/PD, safety and tolerability of a dabigatran oral solution in <1 year old | Age- and weight-adjusted equivalent of adult dose                                            |
|                        |            | Boehringer Ingelheim  | 01895777   | Phase III study evaluating dabigatran vs. SOC for VTE treatment in children 0 to <18 years old       | Dabigatran group: age- and weight-appropriate dose BID × 3 months (capsules, pellets, or liquid formulation) SOC: LMWH or VKA × 3 months |
|                        |            | Boehringer Ingelheim  | 02197416   | Phase III study evaluating dabigatran for secondary prevention of VTE in patients 0 to <18 years old | Dabigatran group: age- and weight-appropriate capsule                                         |
Table 1 continued

| Class of anticoagulant | Medication | Authors/investigators | NCT # | 1st Outcome(s) | 2nd Outcome(s) | Anticipated end date/published date |
|------------------------|------------|-----------------------|-------|----------------|----------------|-----------------------------------|
| Factor Xa inhibitors   | Rivaroxaban| Attard et al. – –     | N/A   | No significant in vitro differences in rivaroxaban effect across the age groups | –              | Published July 2012               |
|                        |            | Willmann et al. – –   |       | AUC, C<sub>max</sub> and C<sub>24h</sub> throughout the investigated age ranges largely overlapped with adult reference ranges | Infants and children <40 kg: AUC, C<sub>max</sub> and C<sub>24h</sub> were <90% CI threshold of adult | Published January 2014           |
|                        |            | Young et al. – –      |       | Observed plasma concentrations and AUC were similar to predicted model | Adolescents >70 kg: AUC and C<sub>24h</sub> were higher than the 90% CI of adult | Published June 2015              |
|                        |            | Bayer 01145859 PK: AUC, C<sub>max</sub> (day 1–2) | 01145859 | Safety and tolerability (day 1, 2, and 7) | Completed July 2015 |                        |
|                        |            | Bayer 01684423 PD: PT, aPTT, anti-factor Xa (day 1–2) | 01684423 | Recurrent VTE and asymptomatic deterioration after 31 days | Recurrent VTE and asymptomatic deterioration after 60 days | Published January 2016           |
|                        |            | Bayer 02497716 AUC and C<sub>max</sub> between 20 and 24 h after administering medication | 02497716 | PT, aPTT, and anti-factor Xa activity of rivaroxaban compared between 5 h prior to drug administration and 20–24 h post exposure | Recurrent VTE and asymptomatic deterioration in thrombotic burden on repeat imaging | April 2016                     |
|                        |            | Bayer 02564718 Plasma concentration of rivaroxaban from day 1 to day 8 | 02564718 | Incidence of major bleeding, clinical relevant non-major bleeding and symptomatic recurrent thromboembolism on days 1 to 7 | Incidence of asymptomatic worsening of thrombotic burden on day 8 post dose | October 2016                  |
|                        |            | Bayer 02309411 Major bleeding and clinically relevant non-major bleeding | 02309411 | Recurrent symptomatic VTE | Recurrent symptomatic VTE | March 2017                  |
|                        |            | Bayer 02234843 Composite symptomatic recurrent VTE up to 3 months | 02234843 | Composite symptomatic recurrent VTE and asymptomatic deterioration on repeat imaging up to 3 months | – | November 2018                |
Table 1 continued

| Class of anticoagulant | Medication         | Authors/investigators | NCT #     | 1ª Outcome(s)                                      | 2ª Outcome(s)                                      | Anticipated end date/published date |
|------------------------|--------------------|-----------------------|-----------|---------------------------------------------------|---------------------------------------------------|------------------------------------|
| Apixaban               | Bristol-Myers      | 01195727              | C<sub>max</sub>, AUC, T<sub>max</sub> | Anti-Xa PD analysis                               |Terminated July 2012                           |
|                        | Squibb             |                       |           | Plasma concentration vs. time                     |                                                    |                                    |
|                        |                    | 01707394              | C<sub>max</sub>, T<sub>max</sub> up to 26 h post dose | Safety                                           |August 2016                                      |
|                        |                    | 02369653              | Composite of non-fatal DVT/PE, CVST and VTE-related death (up to 1 month post treatment) | Anti-Xa PD analysis                               |                                                    |                                    |
|                        |                    |                       |           | Major bleeding                                     |Non-major bleeding                                | May 2019                           |
| Pfizer                 | 02464969           | Composite of major and non-major bleeding | Apixaban concentration and anti-Xa levels on day 14 |                                                    |                                    |
|                        | Daichi Sanyoko Inc. | 02303431              | Clearance (days 1–3) | PT, aPTT, anti-Xa levels, safety/tolerability (AE, VS, heme), metabolite exposure, palatability of liquid oral suspension | December 2016                                      |
| Direct thrombin inhibitor | Dabigatran         | 00844415              | No major and minor bleeding events | Centrally measured aPTT: | Completed February 2012                           |
|                        | Boehringer Ingelheim |                       | 2 patients with DRAE on-treatment and 1 patient with SAE 72 h post treatment | 100 mg (38.6 ± 2.94 s) |                                                    |
|                        |                     |                       | Free dabigatran levels: | 125 mg (47.4 ± 4.42 s) |                                                    |
|                        |                     |                       | 100 mg (~28 ng/ml) | Ecarin clotting time: |                                                    |
|                        |                     |                       | 125 mg (~41.6 ng/ml) | 100 mg (43.3 ± 1.31 s) |                                                    |
|                        |                     |                       | Total dabigatran levels: | 125 mg (49.6 ± 11.6 s) |                                                    |
|                        |                     |                       | 100 mg (~34.2 ng/ml) | No patient with clinical significant changes in vital signs, ECG, and other labs |                                                    |
|                        |                     |                       | 125 mg (~58.2 ng/ml) | 1 patient had a recurrent VTE within 3 days of dabigatran |                                                    |
|                        |                     |                       | Centrally measured TT: |                                                                      |                                                    |
|                        |                     |                       | 100 mg (36.9 ± 3.61 s) |                                                                      |                                                    |
|                        |                     |                       | 125 mg (37.4 ± 3.97 s) |                                                                      |                                                    |
| Class of anticoagulant | Medication Authors/investigators | NCT # | 1* Outcome(s) | 2* Outcome(s) | Anticipated end date/published date |
|------------------------|----------------------------------|-------|---------------|---------------|-----------------------------------|
|                        | Dietrich et al.                  | –     | No difference in response to dabigatran in different pediatric age groups; dTT best assay to measure dabigatran concentrations in pediatric patients | – | Published April 2015 |
|                        | Boehringer Ingelheim 01083732    | Ecarin clotting time, factor IIa inhibition and aPTT | Plasma levels of total and free dabigatran and of BIBR 1048 BS, BIBR 951 BS, and BIBR 1087 SE | Tolerability, taste assessment, and change in clinical parameters and labs | November 2015 |
|                        | Boehringer Ingelheim 01773174    | Ecarin clotting time, factor IIa inhibition and aPTT | Plasma levels of total and free dabigatran and of BIBR 1048 BS, BIBR 951 BS, and BIBR 1087 SE | Tolerability, taste assessment, and change in clinical parameters and labs | December 2015 |
|                        | Boehringer Ingelheim 02223260    | Ecarin clotting time, anti-factor IIa activity, aPTT and total dabigatran level 2 and 12 h post dose | | Tolerability and PK/PD relationship, Incidence of bleeding and adverse events | April 2016 |
|                        | Boehringer Ingelheim 01895777    | Combined efficacy of complete thrombus resolution and freedom from recurrent VTE and VTE mortality for 3 months | Freedom from major bleeding events for 3 months | Plasma concentration of dabigatran, frequency of dose adjustments, freedom from recurrence of VTE, all bleeding events, all-cause mortality, frequency of switching anticoagulation therapy | March 2018 |
|                        | Boehringer Ingelheim 02197416    | Recurrence of VTE (6–12 months), major and minor bleeding events, overall mortality and related to thromboembolic events | | Number of dose adjustments needed in treatment period, occurrence of post thrombotic syndrome, aPTT, ECT | June 2018 |

*AE* adverse effects, *aPTT* activated partial thromboplastin time, *AUC* area under the curve, *BID* twice daily, *C_{max}* maximum concentration, *C_{24h}* 24-h concentration, *CI* confidence interval, *CSVT* cerebral venous sinus thrombosis, *DOAC* direct oral anticoagulant, *DRAE* drug-related adverse events, *dTT* dilute thrombin time, *DVT* deep vein thrombosis, *ECG* electrocardiogram, *ECT* ecarin clotting time, *LMWH* low molecular weight heparin, *NCT* national clinical trial, *PE* pulmonary embolism, *PK/PD* pharmacokinetic/pharmacodynamic, *PO* oral, *PT* prothrombin time, *SAE* serious adverse event, *SOC* standard of care, *TT* thrombin time, *UFH* unfractionated heparin, *VKA* vitamin K antagonist, *VS* vital signs, *VTE* venous thromboembolism
are needed to determine the appropriate dosing of these agents in different age groups. For example, the evidence available for the use of rivaroxaban in this population only includes the outcomes of four completed studies assessing its pharmacokinetic and pharmacodynamic effects in a simulated model as well as an in vitro analysis. The outcomes of these trials suggested that there are minimal age-related differences in pharmacokinetic and pharmacodynamic effects of rivaroxaban except in children less than 40 kg of body weight [19, 25]. In this specific population, serum concentrations were found to be significantly reduced, suggesting the need for higher doses. These data also presented that children more than 70 kg had significantly different AUC and $C_{24h}$, and therefore, using adult-based dosing of rivaroxaban can lead to very different pharmacokinetic and pharmacodynamic results in these children [19]. On the other hand, pharmacokinetic and pharmacodynamic results of apixaban and edoxaban should surely drive their use in children since the available data suggested different dosing in patients less than 60 kg, as would be the case in most pediatric patients. In summary, clinicians should wait for more clinical studies to be completed before recommending the use of DOAC in this special population.

CONCLUSIONS

Pediatric thromboembolic complications requiring the use of anticoagulation continues to be a concern for this patient population especially in regard to its associated morbidity and mortality. Due to the lack of clinical evidence on the use of DOACs in this population, their use should not be considered as first-line therapy. Instead, UFH, LMWH, or warfarin should first be initiated. Since many studies related to DOACs are ongoing, clinicians should wait for them to be completed before making any definitive recommendations on using these agents in children. When the results of the multiple ongoing phase III studies are completed and published, a revised pediatric anticoagulation guideline will surely be warranted.

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Compliance with ethical guidelines. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

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