The Use of DOACs in Pediatrics: Current Therapeutic and Prophylactic Indications, Cardiac Indications, and Real-World Evidence—A Review

Alessandra Bosch[1] Martin Olivieri[2] Susanne Holzhauer[3]

[1] Department of Haematology, University Children's Hospital Zurich – Eleonore Foundation, Zurich, Switzerland
[2] Paediatric Thrombosis and Haemostasis Unit, Dr. Von Hauner Children's Hospital, LMU Clinic, LMU Munich, Germany
[3] Department of Paediatric Haematology and Oncology, Paediatric Haemostasis Centre, Charité University Medicine, Berlin, Germany

Address for correspondence Alessandra Bosch, MD, MSc, Universitäts Kinderspital Zürich, Hämatologie, Lenggstr. 30, 8008 Zürich, Switzerland (e-mail: Alessandra.Bosch@kispi.uzh.ch).

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Abstract

Based on clinical trials that have been conducted and published in the past decade, direct oral anticoagulants (DOACs) are increasingly being used as an antithrombotic treatment in children with venous thrombotic events and to prevent thrombotic events in children at risk. In this review, current indications and standards for the initiation of DOACs in children are summarized for the treatment of venous thrombotic events and for the primary and secondary prevention in children at risk of developing thromboses based on the published randomized controlled trials (RCT). Similarly, indications for DOACs in children with underlying cardiac disease are portrayed based on RCT findings. Lastly, available real-world data are reviewed for the use of DOACs in pediatric patients with a focus on patients at higher risk of both thrombosis and bleeding who were primarily excluded from the RCTs. DOACs contribute largely to the evolving individualization of care of thrombotic events in children, but at-risk patient populations remain underrepresented regarding DOAC experience, such as preterm infants, and children with severe renal or hepatic disease. Real-world data from observational studies and registries will continue to be necessary to establish DOACs' effectiveness and safety in children in everyday clinical use.

Keywords
- DOAC
- pediatrics
- heart disease
- VTE treatment
- thromboprophylaxis

Introduction

The incidence of pediatric thromboembolic complications has steadily increased over the past 20 years. As a result, the need for both effective prophylaxis and treatment has risen.[1,2] Until recently, the standard anticoagulation therapies for pediatric thrombotic events included unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), vitamin K antagonists (VKAs), and additionally antiplatelet agents such as acetylsalicylic acid (ASA) for arterial thrombosis or thromboprophylaxis in cardiac disease.[3,4] In the past decade, direct oral anticoagulants (DOACs) have been studied in pediatric clinical trials for various indications.[5–12] These trials not only delivered controlled data on the safety and efficacy of DOACs but also on the standard-of-care anticoagulants in children.

DOACs are small molecules that directly inhibit coagulation factor Xa (rivaroxaban, apixaban, edoxaban) or thrombin (dabigatran).[5–12] DOACs have become an attractive alternative to the standard-of-care anticoagulants, especially in the outpatient setting.

After the completion of phase 3 clinical trials in children with venous thromboembolic events (VTE), three DOACs have been licensed for use in children across varying medical licensing agencies and authorities (rivaroxaban, dabigatran, apixaban).[5–8] Further trials and subgroup analyses were conducted to

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Georg Thieme Verlag KG,
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evaluate DOACs (rivaroxaban, edoxaban, apixaban) for VTE prevention in pediatric patients with leukemia and in patients with congenital or acquired heart disease.[9–12] The DOAC dose used in the thrombosis-prevention differed: some used therapeutic or full-dose DOACs, and others used reduced-dose DOACs (=50% dosage). Based on the trial results, the various DOACs are being widely used, and the real-world experience with these new medications is growing. This review will summarize the clinical practices of usage of DOACs in pediatric populations based on clinical trials and real-world data in three parts: Part A—Current indications for use of DOACs in VTE treatment and prophylaxis; Part B—Current indications for use of DOACs in patients with cardiac indication; and Part C—The real-world use of DOACs in pediatric patients.

A: Current Indications for Use of DOACs in Children

Treatment of Venous Thromboembolic Events

The treatment of VTE includes the treatment of deep vein thrombosis, pulmonary embolism, and cerebral sino venous thrombosis in children. Recent DOAC randomized controlled trials (RCTs) have provided significant contributions to the available evidence in the treatment of pediatric VTE (►Fig. 1).[5–8] Dabigatran and rivaroxaban have both been studied and results have been reported for VTE treatment in pediatric patients. They have become an attractive alternative to the previous standard-of-care anticoagulants—especially in the outpatient setting. Physicians' level of comfort and confidence in the prescription of DOACs in children with VTE is based largely on the highly selected patient group who participated in clinical DOAC trials. These are reviewed in detail below and summarized in the text box (►Fig. 2).

The clinical trial results for edoxaban and apixaban for VTE in children are still pending publication.

Rivaroxaban

The phase I EINSTEIN Jr trial assessed the pharmacokinetics, pharmacodynamics, and safety of weight-adjusted rivaroxaban dosing in 59 children.[13] Phase II EINSTEIN Jr trials studied the safety of rivaroxaban across different age groups in 93 children, adjusting dosing recommendations based on measured drug levels for the subsequent phase III trial.[14] In the phase III EINSTEIN Jr randomized controlled trial (RCT), 335 children with VTE were treated with rivaroxaban after an initial 5- to 9-day course of parenteral anticoagulation. The age groups included were 0 to <2 years (11%), 2 to <12 years (34%), and 12 to <18 years (54%). Inclusion and exclusion criteria are shown in ►Table 1. The primary efficacy outcome was the absence of symptomatic VTE recurrence. The efficacy and safety of rivaroxaban were comparable to standard anticoagulants, but the study was not powered to show superiority. No major bleeding events occurred in the rivaroxaban group.[5] Results from subanalysis studies on central venous line (CVL) VTE, cerebral sino venous thrombosis, and cancer-related thrombosis were consistent with those of the main trial.[8,15,16] However, heavy menstrual bleeding was reported slightly more often in the rivaroxaban group as compared with the standard-of-care group.[5,17] Available rivaroxaban formulations include tablets (for children weighing >12 kg) or liquid suspension. Rivaroxaban is licensed for VTE treatment and secondary prevention in the European Medicines Agency region (EMA), Switzerland, the United States, and Canada.

Dabigatran

The safety, pharmacokinetics, and pharmacodynamics of dabigatran were studied in phase IIa trials with pharmacokinetic/pharmacodynamic findings consistent with those observed in adults.[18–21] The phase III DIVERSITY RCT included 177 patients with VTE who were treated with dabigatran. The age groups included were 0 to <2 years (12%), 2 to <12 years (24%), and 12 to <18 years (63%). Again, initial anticoagulation was administered parenterally or subcutaneously for 5 to 21 days before patients were switched to dabigatran (►Table 1). The primary efficacy outcome was a composite of thrombus resolution, freedom from symptomatic VTE recurrence, and VTE-related death. Both the efficacy and safety of dabigatran were noninferior to the standard-of-care arm. There were four (2.3%)

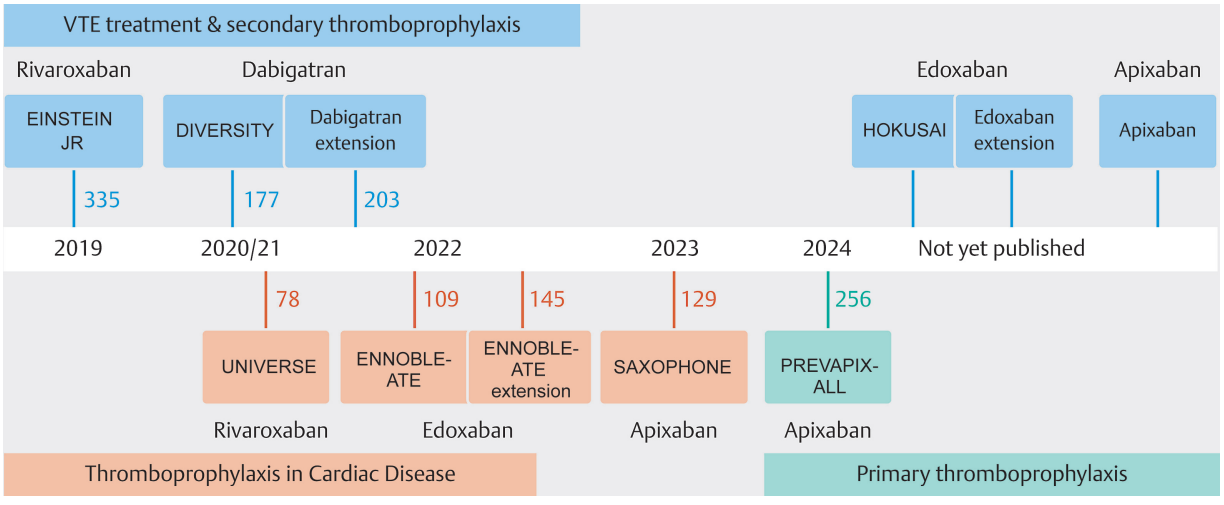

Fig. 1 Clinical trials of DOACs in pediatric patients published over time. Numbers indicate number of patients receiving DOAC in each trial. DOAC, direct oral anticoagulant; VTE, venous thromboembolic events.

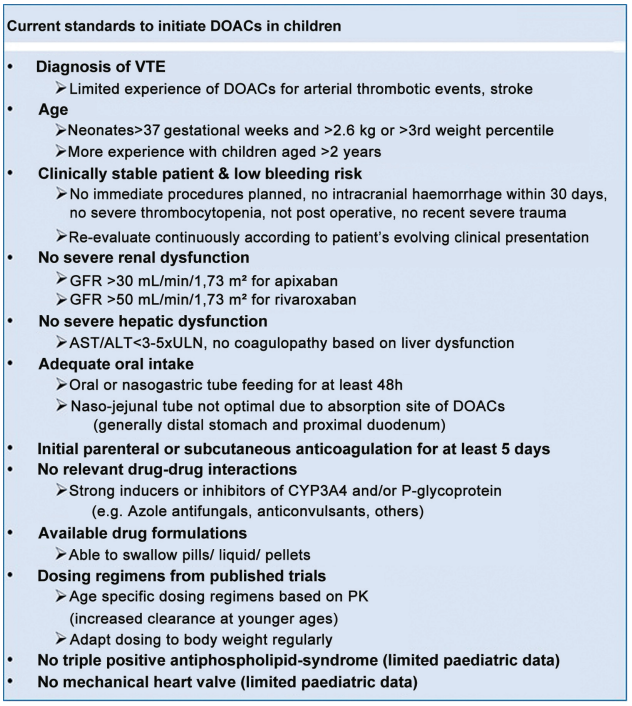

Fig. 2 Current standards to initiate DOACs in children—based on inclusion and exclusion criteria of clinical trials. DOAC, direct oral anticoagulant; VTE, venous thromboembolic events; GFR, glomerular filtration rate; AST, aspartate transaminase; ALT, alanine aminotransferase; PK, pharmacokinetics; ULN, upper limit of normal.

major bleeding events as compared with 2.2% in the standard-of-care arm. Subgroup analyses were performed for patients with thrombophilia and patients with congenital heart disease.[22,23] Results did not differ from the main study findings. Dabigatran was discontinued early in 10% of patients, due to below-target drug levels as per study protocol.[24] Dabigatran was overall well tolerated, but there were more gastrointestinal adverse events such as abdominal pain, vomiting, or dyspepsia than in the SOC arm, consistent with reports in adults.[6,17,25]

Currently available formulations for dabigatran are capsules (studied in children from 8 years of age). Pellets (studied in children from 3 months of age) or liquid suspensions have not been made available for usage in all jurisdictions. Dabigatran is licensed for pediatric VTE treatment and secondary prevention in the EMA region, and the United States, but not in Switzerland or Canada.

Thromboprophylaxis—Primary and Secondary Prevention of VTE

The increasing incidence of thrombosis in the last decades also emphasizes the awareness of thrombosis prevention in the pediatric population. However, RCTs on the use of primary thromboprophylaxis in children for preventing thrombotic events in specific situations are lacking. The aim of secondary thromboprophylaxis is to prevent thrombosis recurrence or progression after completed treatment of an initial VTE, in the presence of ongoing thrombotic risk. Dabigatran and edoxaban were studied in extension studies for secondary prevention. The results for dabigatran have been published, but edoxaban results are still pending.[22] The PREVAPIX-ALL trial investigated apixaban as primary prophylaxis in pediatric patients with hematological malignancies specifically acute lymphatic leukemia and lymphoma.[11] Thromboprophylaxis in patients with congenital or acquired heart disease is discussed in part B of this review.

Dabigatran—Secondary Prevention

Dabigatran was studied in a DIVERSITY extension study after the VTE treatment period of 3 months had been completed. A total of 203 patients who required ongoing anticoagulation for secondary VTE prevention were included. The age groups included were 0 to <2 years (4%), 2 to <12 years (21%), and 12 to <18 years (75%). Patients received dabigatran for up to 12 months, with a median exposure time of 36.3 weeks.[7] Inclusion and exclusion criteria as well as efficacy and safety outcomes were similar to the DIVERSITY trial (►Table 1). Indications for secondary thromboprophylaxis included ongoing risk factors such as congenital heart disease, hematologic malignancy, the presence of a CVL, thrombophilia (protein C, protein S, antithrombin deficiency, antiphospholipid syndrome), or recurrent unprovoked VTE. Dabigatran was administered at the same therapeutic dose as in the original phase III DIVERSITY trial, with no dose reduction occurring. Similar to the DIVERSITY trial, 12% of patients discontinued dabigatran in the extension study due to low measured drug levels as per protocol.[24] Efficacy and safety outcomes were satisfactory with low VTE recurrence (1%), low major bleeding rates (1.5%), and clinically relevant non-major (CRNM) bleeding rates (1%).[22] Of note, the study duration was up to 1 year only, and long-term effects of DOACs are not known for the pediatric population. Additionally, reduced-dose secondary prophylaxis has not been studied in the pediatric population—it is unknown whether a lower dose DOAC would be safe and effective.

Apixaban—Primary Thromboprophylaxis

The safety, pharmacokinetics, and pharmacodynamics of apixaban were studied in phase IIa trials.[12,26] Apixaban drug levels were comparable to those in the adult studies at a dosing equivalent of 2.5 mg.[26] The PREVAPIX-ALL trial compared primary prophylaxis with reduced-dose apixaban compared with the standard of care of no thromboprophylaxis in pediatric patients newly diagnosed with acute lymphoblastic leukemia or lymphoma and a CVL throughout the induction phase of chemotherapy. A total of 256 patients received apixaban for a median of 27 days. The age groups included were 0 to <2 years (0.4%), 2 to <12 years (80%), and 12 to <18 years (19%). See ►Table 1 for inclusion and exclusion criteria. The primary efficacy outcome was a composite measure of both symptomatic and clinically unsuspected VTE, detected by ultrasound and echocardiography screening at the end of treatment. The safety outcomes were major and CRNM bleeding events. VTE occurred in 12% of patients receiving apixaban versus 18% in the SOC group—the difference was statistically not meaningful. There were two major bleeding events in each group. However, there

Table 1 DOAC trials for VTE treatment and prophylaxis

	Rivaroxaban	Dabigatran	Dabigatran	Apixaban
Trial name and design	EINSTEIN Jr[5] VTE treatment	DIVERSITY[6] VTE treatment	DIVERSITY extension[7] Secondary VTE prophylaxis	PREVAPIX-ALL[11] Primary VTE prophylaxis
Number of patients receiving DOAC	$n = 335$	$n = 177$	$n = 203$	$n = 256$
Inclusion criteria	• Children birth to <18 y with VTE • Anticoagulation required for at least 90 d (children aged <2 y for CVL-related VTE for at least 30 d) • Initially treated with UFH, LMWH, or fondaparinux for 5–9 d • Gestational age at least 37 wk; weight >2,600 g. • Oral feeding/nasogastric/gastric feeds for at least 10 d	• Children birth to <18 y with VTE • Anticoagulation required for at least 90 d; • initially treated with UFH or, LMWH for 5–21 d • Gestational age at least 37 wk; weight >3rd percentile. • Enteral feeding	• Age birth to <18 y • Previous diagnosis of VTE • Completed VTE treatment anticoagulation for ≥3 mo • Presence of risk factor requiring further anticoagulation (CVL, thrombophilia, underlying disease, etc.)	• Ages ≥1 y to <18 y • New diagnosis of acute lymphoblastic leukemia or lymphoblastic lymphoma (B or T cell) • Planned chemotherapy 3–4 drugs including corticosteroid, vincristine, asparaginase +/− daunorubicin • Functioning central venous line, placed before the start of apixaban • Tolerate oral medication +/− nasogastric tube
Exclusion criteria	• Age group 0–6 mo: gestational age <37 wk and/or body weight <2.6 kg • Active bleeding or high bleeding risk • Sustained uncontrolled hypertension (systolic and/or diastolic bp >95th percentile) • GFR <30 mL/min/1.73 m^2 or creatinine >97.5th percentile • Hepatic disease (coagulopathy, ALT >5× ULN, bilirubin >2× ULN) • Pregnancy or post-menarche females without contraception • Platelets < 50 G/L • Life expectancy <3 mo • Concomitant use of strong inhibitors of both cytochrome P450 isoenzyme 3A4 (CYP3A4) and P-glycoprotein, including but not limited to all human immunodeficiency virus protease inhibitors and the following azole-antimycotics agents:	• Age group 0 to <2 y old if gestational age at birth <37 wk or body weight <3rd percentile • Active bleeding or high bleeding risk, including ICH, intracranial or intraspinal surgeries within 6 mo of start of DOAC; major surgeries within 4 wk of start of DOAC (intracranial, chest, abdomen, pelvis). CVL removal is not considered a major surgery; GI hemorrhage within 1 y of the start of DOAC. Hemorrhagic disorder or bleeding diathesis (vWD, hemophilia, hereditary bleeding disorder). Fibrinolytic agents within 48 h of dabigatran administration. • Sustained uncontrolled hypertension (systolic and/or diastolic bp >ULN for age) • GFR < 50 mL/min/1.73 m^2 • Active infective endocarditis; • Heart valve prosthesis needing	• Age group 0 to <2 y old if gestational age at birth <37 wk or body weight <3rd percentile • Active bleeding or high bleeding risk, including ICH, intracranial, or intraspinal surgeries within 6 mo of start of DOAC; major surgeries within 4 wk of start of DOAC (intracranial, chest, abdomen, pelvis). CVL removal is not considered a major surgery; GI hemorrhage within 1 y of start of DOAC. Hemorrhagic disorder or bleeding diathesis (vWD, hemophilia, hereditary bleeding disorder). Fibrinolytic agents within 48 h of dabigatran administration. • Sustained uncontrolled hypertension (systolic and/or diastolic bp >ULN for age) • eGFR < 60 or 80 mL/min/1.73 m^2 • Active infective endocarditis; • Heart valve prosthesis needing	• Age <1 y old • Bleeding disorder (inherited or acquired); INR >1.4 and aPTT >3 s above the upper limit of normal 1 wk prior to enrolment • Uncontrolled severe hypertension (>5 mm Hg above 95th percentile diastolic or systolic bp) • Extreme hyperleukocytosis, WBC >200,000 G/L; any patients with leukapheresis excluded • Schedule of >3 lumbar punctures over treatment period (days 1–29) • Major surgery within 7 d prior to enrolment • VTE in the past 3 mo • Hepatic disease (ALT and/or AST >5× ULN, direct bilirubin >2× ULN) • Renal function <30% of normal for age and size—Schwartz formula • Concurrent anticoagulation with LMWH, UFH, other oral

Table 1 (*Continued*)

	Rivaroxaban	Dabigatran	Dabigatran	Apixaban
	ketoconazole, itraconazole, voriconazole, posaconazole, if used systemically (fluconazole allowed); concomitant use of strong inducers of CYP3A4, including but not limited to rifampicin, rifabutin, phenobarbital, phenytoin, and carbamazepine	anticoagulation • Hepatic disease (hepatitis A,B, C, coagulopathy, ALT/AST/ALP >3× ULN) • Pregnancy or post-menarche females without contraception • Platelets < 80 G/L, hemoglobin <80 g/L • Concomitant use of inhibitors of P-glycoprotein	anticoagulation • Hepatic disease (hepatitis A,B, C, coagulopathy, ALT/AST/ALP >3× ULN) • Pregnancy or post-menarche females without contraception • Platelets < 80 G/L, hemoglobin <80 g/L • Concomitant use of inhibitors of P-glycoprotein	anticoagulant or systemic tPA; concurrent antiplatelet therapy (including aspirin, thienopyridines), concurrent use of NSAIDs >7 d • Concomitant systemic treatment with strong inhibitors of CYP3A4 or P-glycoprotein (e.g., voriconazole or ketoconazole) • Concomitant systemic treatment with strong inducers of CYP3A4 or P-glycoprotein (e.g., rifampin, carbamazepine, phenytoin, and St John's Wort)
Age groups	• 0 to <2 y: $n = 37$ • 2 to <12 y: $n = 114$ • 12 to <18 y: $n = 184$	• 0 to <2 y: $n = 22$ • 2 to <12 y: $n = 43$ • 12 to <18 y: $n = 112$	• 0 to <2 y: $n = 8$ • 2 to <12 y: $n = 42$ • 12 to <18 y: $n = 153$	• 1 to <2 y: $n = 1$ • 2 to <12 y: $n = 206$ • 12 to <18 y: $n = 49$
Indication for treatment	• CVL-related VTE: $n = 90$ (27%) • CSVT: $n = 74$ (22%) • Non-CVL VTE: $n = 171$ (53%) • Pulmonary embolism: $n = 49$ (29%) • Cancer $n = 40$ (12%)	• CVL-related VTE: $n = 27$ (15%) • CSVT: $n = 20$ (11%) • Non-CVL: $n = 110$ (62%) • Pulmonary embolism: $n = 20$ (11%) • Cancer: $n = 18$ (10%)	• Inherited thrombophilia, $n = 91$ (45%) • Recurrent VTE, $n = 29$ (14%) • Structural venous abnormality, $n = 26$ (13%) • Antiphospholipid syndrome, $n = 20$ (10%) • Congenital heart disease, $n = 12$ (6%) • Hematologic cancer $n = 11$ (5.5%) • CVL, $n = 11$ (5.5%) • Recent immobilization $n = 7$ (3.5%) • Other	• B cell ALL/L: $n = 224$ (88%) • T cell ALL/L: $n = 29$ (11%) • Standard risk: $n = 168$ (66%) • High risk: $n = 81$ (32%)
Licensed as per 10/2024 (DACH)	• EMA: licensed for VTE treatment and secondary thromboprophylaxis in patients • Switzerland: licensed for VTE treatment and secondary thromboprophylaxis	• EMA: licensed for VTE treatment • Switzerland: not licensed	• EMA: licensed for secondary thromboprophylaxis • Switzerland: not licensed	• EMA: not licensed for primary thromboprophylaxis (licensed for VTE treatment and secondary thromboprophylaxis) • Switzerland: not licensed
Formulation available in trial	• Suspension, tablets	• Pellets, capsules, oral solution	• Pellets, capsules, oral solution	• Tablets, oral solution

Abbreviations: ALL, acute lymphoblastic leukemia; AST, aspartate transaminase; ALT, alanine aminotransferase; CSVT, cerebral sino venous thrombosis; CVL, central venous line; CYP3A4, cytochrome P450 isoenzyme 3A4; DACH, Germany, Austria, Switzerland; DOAC, direct oral anticoagulant; EMA, European Medicines Agency; GFR, glomerular filtration rate; ICH, intracranial hemorrhage; LMWH, low-molecular-weight heparin; NSAID, nonsteroidal anti-inflammatory drugs; UFH, unfractionated heparin; ULN, upper limit of normal; VKA, vitamin K antagonist; VTE, venous thromboembolic events.

was a higher rate of CRNM bleeding in the apixaban group (4 vs. 1% in the SOC group), as well as minor bleeding (14 vs. 8%). In a post hoc analysis, CRNM bleeding rates were similar between groups for children aged >10 years. In a subanalysis of patients with obesity, apixaban decreased VTE risk, but these results have not yet been published.

Overall, adverse events were reported in 91% of participants, which is expected in a population of patients undergoing treatment for malignancy. However, 5% of participants discontinued the study medication due to apixaban-related adverse events. The study was powered to demonstrate superiority, but apixaban did not meet this endpoint. Therefore, primary thromboprophylaxis with apixaban is not recommended in all patients with newly diagnosed acute lymphoblastic leukemia or lymphoblastic lymphoma. The authors did, however, conclude that thromboprophylaxis with apixaban could be considered in patients at higher VTE risk, based on individual patient factors and risk assessment. The formulations studied were oral solution and tablets; currently, only tablets are available. Apixaban has been licensed by the EMA for treatment and secondary prophylaxis in pediatric patients, but not for primary prophylaxis.

B: Current Indications for DOACs in Patients with Underlying Cardiac Disease

Thrombotic complications in congenital and acquired heart disease are reported in up to 8% of children post–cardiac surgery,[27] and contribute considerably to morbidity and mortality in this patient population.[28] Risk factors for thrombosis include blood flow abnormalities, thrombogenic exogenic materials (stents, valves, sutures, shunts), coagulation derangement due to cardiopulmonary bypass procedures, polycythemia secondary to cyanotic heart disease or inherited thrombophilia. Additionally, these patients most often have CVLs, especially in the acute peri- and postoperative time period. Due to the presence of multiple prothrombotic risk factors, thromboprophylaxis is often indicated to prevent first thrombotic events or recurrent thrombotic events. Each individual patient is assessed based on their specific cardiac physiology and thrombosis risk factors. A team of cardiac surgeons, cardiologists, intensivists, and/or hematologists then decide which anticoagulant, antiplatelet, or treatment combination is indicated based on current guidelines, and mainly expert opinion or local preference.[29] The antithrombotic agents used are antiplatelet agents such as acetylsalicic acid or clopidogrel, and/ or anticoagulation. The standard-of-care anticoagulants have been UFH, LMWH, and VKA until recently. Subcutaneous application, frequent laboratory monitoring, narrow therapeutic range, and drug and dietary interactions lead to a high treatment burden for patients.[28] However, recently three large DOAC clinical trials were conducted comparing rivaroxaban, apixaban, and edoxaban to the respective standard of care for the specific cardiac populations. ►Table 2 shows an overview of the three clinical trials. The study populations consisted mainly of children with congenital or acquired heart disease (single ventricle conditions, Kawasaki disease, and other heart defects) comparing the safety and efficacy of apixaban, edoxaban, and rivaroxaban to standard-of-care treatments (ASA, VKA, and LMWH).[9,10,12] The UNIVERSE trial included only patients from 2 to 8 years of age with a single ventricle condition after the Fontan procedure and compared rivaroxaban to the control group treated with ASA.[9] The ENNOBLE-ATE trial included children of all ages with various cardiac diseases at risk of thromboembolism, similar to the SAXOPHONE trial that involved pediatric patients with diverse cardiac conditions aged 28 days to 18 years. The proportion of patients with single ventricle and Fontan procedures in both studies is high (74 vs. 73%) and allows for comparison of outcomes with the UNIVERSE study.[10,12]

The UNIVERSE trial utilized a reduced dose (50% of therapeutic dosage) of rivaroxaban, while in the SAXOPHONE trial and the ENNOBLE-ATE trial a full/therapeutic dose of edoxaban and apixaban was used respectively. The aim of all three studies was to assess the safety and efficacy of the different DOACs used for primary and secondary thrombosis prevention in cardiac diseases.[9,10,12]

All three trials showed low major bleeding rates (SAXOPHONE: 0.8% [95% CI: 0.0–4.3%]; ENNOBLE-ATE: 0.9% [95% CI: 0.24–0.25%]; UNIVERSE 2% and low numbers of thrombotic events [SAXOPHONE 0%; ENNOBLE-ATE 0%, UNIVERSE 2%]) in the intervention group. A post hoc subgroup analysis of the DIVERSITY trial on the use of dabigatran in patients with congenital heart disease ($N = 48$, 21 dabigatran, 27 SOC) also showed low major bleeding rates (0) and high efficacy for the endpoints thrombus resolution, VTE recurrence, and VTE-related death. However, this trial showed a significantly higher rate of minor bleeds (14.3%).[23,30]

According to the systematic review of Guan et al,[30] the DOAC trials including patients with congenital heart disease were shown to be safe and effective, although it must be mentioned that all trials were underpowered to demonstrate superiority over the SOC. In total, 471 participants were included in the studies. A limitation of the systematic review was that the study populations of all trials were different and thus not directly comparable. This precluded a meta-analysis. However, several nonrandomized case series show the real-world safety and efficacy of DOACs in patients with underlying cardiac disease (see also part C of this review).[30] The safety and efficacy profile of DOACs in this high-risk patient group represents an alternative to SOC and additionally offers several advantages with reduced treatment burden for patients. To date and in the EMA region, none of the three DOACs is licensed for use in patients with congenital heart disease, while in Switzerland and the United States rivaroxaban is licensed for primary and secondary thromboprophylaxis in Fontan patients.

C: Real-World Experiences of DOACs in Pediatric Patients

Despite the growing number of pediatric investigational programs for DOACs, and data published thus far, the range of indications and pediatric populations studied remains limited. Younger age groups, particularly neonates, were

Table 2 DOAC trials for cardiac indication

	Apixaban	Edoxaban	Rivaroxaban	Dabigatran
Trial name and design	SAXOPHONE[12]	ENNOBLE-ATE[10]	UNIVERSE[9]	DIVERSITY[6,23]
Licensed for thromboprophylaxis as per 10/2024 (DACH) + available formulation	Not licensed	Not licensed	Switzerland: reduced-dose post-Fontan thromboprophylaxis (oral suspension in children >10 kg; 10 mg tablets for children >50 kg) Germany/Austria: not licensed	Not licensed
Number of patients receiving DOAC in RCT	129	109	88	48
Inclusion criteria	Children with congenital heart disease requiring thromboprophylaxis	Congenital/acquired heart disease	Children with single-ventricle physiology who had Fontan procedure within 4 mo before enrolment	
Exclusion criteria	Thromboembolism, severe hypertension, gastrointestinal ulcer, coagulopathy, active bleeding, intracranial vascular malformation or tumor, pregnancy, renal or liver dysfunction, thrombocytopenia, ECMO, LVAD, antiplatelets, CYP450 inducers/inhibitors, NSAIDs	Thromboembolism, active/high-risk bleeding, contraindication to LMWH, VKA, Fontan procedure with possible protein-losing enteropathy, rifampicin requirement, GFR < 30%	Thrombosis, gastrointestinal disease or surgery with impaired absorption, active/high risk of bleeding	Conditions associated with an increased risk of bleeding, renal dysfunction, active infective endocarditis, subjects with a heart valve prosthesis requiring anticoagulation, hepatic disease, and pregnant or breastfeeding females. Females who have reached menarche and are not using a medically accepted contraceptive method per local guidelines
Age groups	Children of all ages 28 d to <2 y: $n = 8$ 2 y to <12 y: $n = 89$ 12 y to <18 y: $n = 32$	Children of all ages Birth to <2 y: $n = 8$ 2 y to <12 y: $n = 73$ 12 y to <18 y: $n = 28$	2–8 years: $n = 76$	Birth to 18 y: Birth to <2 y: $n = 12$ 2 y to <12 y: $n = 6$ 12 y to <18 y: $n = 3$
Risk factors requiring thromboprophylaxis	Single ventricle, Kawasaki disease, other heart disease	Kawasaki disease, Fontan surgery, heart failure, other	Single ventricle physiology with Fontan procedure	Diagnosis of acute thromboembolism
Therapeutic or reduced dose used for thromboprophylaxis	Full dose	Full dose	Reduced dose/50% dose	Full dose

Abbreviations: CYP450, cytochrome P450; d, day; DACH, Germany, Austria, Switzerland; DOAC, direct oral anticoagulant; ECMO, extracorporeal membrane oxygenation; GFR, glomerular filtration rate; LMWH, low-molecular-weight heparin; LVAD, left ventricular assist device; *n*, number; NSAID, nonsteroidal anti-inflammatory drugs; UFH, unfractionated heparin; VKA, vitamin K antagonist; y, year.

underrepresented, and preterm neonates and children with significant comorbidities were frequently excluded from the RCTs. This is a critical limitation, as it means that children who are at high risk for both thrombosis and bleeding complications have not yet been adequately studied regarding the performance of DOACs.[31] Given the apparent advantages of DOACs over VKAs or LMWH, we anticipate a growing DOAC utilization in vulnerable patient groups, such as those with impaired renal or liver function, cancer, or neonates.

First practical experience with DOACs for the treatment of venous thrombosis in pediatric patients confirms the effectiveness and safety of these anticoagulants (for details, see ►Table 3).[32–35] A novel insight is the comparison of different DOACs regarding bleeding complications. The "American Thrombosis and Hemostasis Network 15" reported the use of DOACs in 233 patients younger than 21 years from 15 specialized hemostasis centers in the United States.[33] This study found that heavy menstrual bleeding was experienced by significantly more adolescent females treated with rivaroxaban compared with those treated with apixaban (45.6 vs. 18.9%). Similarly to previously reported RCTs, most patients in these case series were adolescents; high-risk patient groups, such as multimorbid patients and those with impaired kidney or liver function were not represented. Thus, while these early real-world data support the outcomes of clinical trials, they leave important knowledge gaps unaddressed.

Cardiac Disease

Most of the DOAC real-world data for specific patient groups pertains to primary or secondary prophylaxis in children with congenital or acquired heart defects and originated in the Boston Children's Hospital. Vander Pluym and colleagues developed a protocol to treat pediatric cardiology patients with apixaban for both prophylactic and therapeutic purposes before results from the RCT and before liquid formulations were available. Unlike the "one dose per weight fits all" model used in the earlier-described RCTs, the authors opted to regularly measure apixaban-specific anti-Xa chromogenic levels in their patients and adjust dosages based on peak levels.[36–39] This approach was aimed at determining the "correct" and "safe" dose for each patient based on age, weight, and renal function while allowing for varying levels or doses that may be more appropriate for different clinical indications. Similar to findings in adults, the authors found in 219 pediatric patients that apixaban has a wide margin of safety and effectiveness, resulting in clot resolution and absence of bleeding and adverse events across a broad range of apixaban levels. Although apixaban levels tended to be higher in patients who experienced adverse events (median 178 ng/mL, range: 48–450) compared with those without adverse events (median: 155 ng/mL, range: 23–474), the difference was not statistically significant.[36] The authors report having adjusted the dosage in 25% of patients overall. Adkins et al added information on the use of apixaban for the specific indication of thromboprophylaxis in children post–Fontan cardiac surgery.[39] With this, the authors underline the safety and effectiveness of DOAC in this patient group but fail to show that peak level-based dosing is superior to fixed regimens as used in both the UNIVERSE and SAXOPHONE trials.[9,12] Initial results on long-term experiences have been published by Sagiv et al, showing that prophylaxis with edoxaban in children with large aneurysms following Kawasaki disease was safe and effective during a median observation period of 48 months.[40] For details see ►Table 3.

Cancer-Associated Thrombosis

Although thrombotic events are frequent in children with cancer, only a few children with cancer and associated VTE have been included in the DOAC RCTs. In the EINSTEIN Jr study, 11% of included patients had cancer in the trial.[5,16] To date, two retrospective case series involving a total of 27 pediatric oncology patients have been published on DOAC therapy.[41,42] Barg and Kenet published the first case series of 16 pediatric patients with active or recurrent cancer treated with rivaroxaban for cancer-associated thrombosis.[41] The authors confirmed that drug levels in that specific patient group and recanalization rates were comparable to those published in the EINSTEIN JR study. However, adverse events, including major bleeding and thrombotic complications, were more frequent with CRNM bleeding reported in nearly 20% of the patients. Sultan et al recently described their experience on 11 children treated with rivaroxaban for hematological malignancy at two pediatric oncology centers in Quebec, Canada.[42] Here, major or CRNM bleeding, which is a major concern in leukemia and lymphoma patients, was observed in none of the patients, while recurrent thrombotic events occurred in 9% of patients. However, no information on dose adjustments or interruption of therapy based on platelet count or co-medications that may influence drug levels is reported in either of the retrospective analyses. Consequently, although these early reports generally support the use of DOACs for the treatment of cancer-associated thrombosis, prospective and cancer-specific observational studies along the lines of clinical oncology studies are needed to define patient groups that benefit from DOAC treatment or prophylaxis.

Renal Impairment

No evidence is currently available for the use of DOACs in children with a GFR <30 mL/min/1.73 m^2 or patients on hemodialysis. Unlike heparin or VKAs, there are no established therapeutic or prophylactic drug levels to guide DOAC dosing in these cases; consequently, DOACs are currently contraindicated in children with severe renal impairment. Although children with a GFR >50 mL/min/1.73 m^2 were not excluded from the RCTs, very few children with mild to moderate renal impairment participated in published trials and no real-world data have been published so far. Among the available DOACs, there are important differences in their renal elimination rate (apixaban 27%; rivaroxaban 35%; edoxaban 50%; and dabigatran 80%).[43–47] Dabigatran has the highest renal elimination as an active metabolite, while apixaban has the lowest. As drug exposure increases with declining renal function—corresponding to the proportion of the drug excreted via the kidneys—careful consideration

Table 3 Real-world evidence on DOAC use in children

Authors	Number of patients	DOAC	Indication	Age group Median (range)	Dosing regimen	Monitoring	Safety	Effectiveness	Duration Median (range)
Cardiac Indications									
Adkins et al[39]	62	Apixaban	Prophylaxis for early postsurgical Fontan thromboprophylaxis	3.2 y (2.1–10.5)	Weight 3–9 kg: 0.625 mg 2 ×/d >9–15 kg: 1.25 mg 2 ×/d >15–22 kg: 1.875 mg 2 ×/d >22–30 kg: 2.5 mg 2 ×/d >30–50 kg: 3.75 mg 2 ×/d >50 kg: 5 mg 2 ×/d > 100 kg: consideration for starting dose at 7.5 mg 2 ×/d	Peak apixaban levels 3–4 hour	Bleeding Any 9.7% Major 1.6% CRNM 3.2% Number of CRNM or major bleeding events per 1,000 person-days on apixaban 0.22	Thrombotic events any 3.2% Number of thrombotic events per 1,000 person-days on apixaban 0.15	93 d (7–1,421 d)
Benvenuto et al[38]	19	Apixaban	Prophylaxis ($n = 18$) or therapy ($n = 1$) awaiting heart transplantation	13.5 y (6.1–15.8)	Drug levels: Standard-risk prophylaxis 80–150 ng/mL Treatment of thrombosis 100–300 ng/mL High-risk prophylaxis 200–300 ng/mL (i.e., ventricular assist devices, Kawasaki with giant coronary aneurysm, mechanical valves, etc.)	Peak apixaban levels 3–4 h	Bleeding Major 0% CRNM 0%	No thrombotic events	114.6 d (38.5–174.5)
Kobayashi et al[37]	5	Apixaban	Prophylaxis for HeartMate 3 ventricular assist device	17 y (12–23)	5 mg 2 ×/d Adjustment based on anti Xa levels for peak apixaban level 150–250 ng/mL with a high-risk bleeding target reduced to 80–150 ng/mL with a high-risk of thrombosis target 250–350 ng/mL	Peak apixaban levels 3–4 h	Bleeding CRNM 20%	Thrombotic events 20%	1,589 d Sum of all patients
Vander Pluym et al[36]	219	Apixaban	Prophylaxis ($n = 172$) or therapy ($n = 47$) for cardiac disease	6.8 y (0.3–19)	Weight 4–9 kg: 0.625 mg 2 ×/d >9 to 18 kg: 1.25 mg 2 ×/d >18 to 29 kg: 2.5 mg 2 ×/d >29 to 35 kg: 3.75 mg 2 ×/d >35 kg: 5 mg 2 ×/d Exceptions: Treatment of acute pulmonary embolism: 10 mg twice daily × 7 d, then 5 mg twice daily Weight >100 kg and high-risk thrombosis indication: consider 7.5 mg 2 ×/d starting dose In 60% concomitant low-dose aspirin	Peak apixaban levels 3–4 h	Bleeding Major, $n = 1$ CRNM, $n = 3$ Combined rate: 2.9/100 patient-years	Prophylaxis: Thrombotic events 0% Therapy: Resolution 95%	162 d (4–1,217)
Sagiv et al[40]	16	Edoxaban	Prophylaxis for Kawasaki disease	7 (1–17) y	<6 y 1.4 mg/kg 1 ×/d 6 to <12 y 1.2 mg/kg 1 ×/d (<max. 45 mg) 12 to <18 y 30 to <60 kg/45 mg >60 kg/60 mg And 30 mg if patient <5th percentile or indication for dose reduction. All patients additionally received low-dose aspirin	Peak-and-trough levels, no dose adjustment based on levels	Bleeding Major: 0% CRNM: 0%	Thrombosis incidence 16% at 48 mo on edoxaban therapy	48.8 mo (5.6 60.4 mo)

(*Continued*)

Table 3 (*Continued*)

Authors	Number of patients	DOAC	Indication	Age group Median (range)	Dosing regimen	Monitoring	Safety	Effectiveness	Duration Median (range)
Cancer									
Sultan et al[42]	11	Rivaroxaban (91%)	Therapy (91%) secondary prophylaxis (9%) for VTE and hematological malignancies	13 y (IQR 10–16.5)	Not reported	Not reported	Bleeding Major 0% CRNM 0%	Recurrent VTE 9% Resolution *Complete 81%*	50.7 mo sum of all patients
Barg et al[41]	16	Rivaroxaban	Therapy for VTE and cancer Hematologic malignancies 56% Solid tumors 44%	14 y (7.5–17)	Not reported	Peak and trough levels, no dose adjustment based on levels	Bleeding Major 6.3% CRNM 12.5% *2 deaths unrelated to VTE or treatment.*	Recurrent VTE 19% Resolution *Complete 62.5%* *Partial 25%* *No change 12.5%*	7 mo (IQR 5–13)
VTE treatment									
Hassan et al[34]	58	Rivaroxaban	Therapy or secondary prophylaxis for VTE	25 patients <2 y 6 patients <1 mo	<30 kg bodyweight-adjusted liquid formulation ≥30 kg tablets 15 mg/20 mg	Not reported	Bleeding Major 0% CRNM 0%	Therapy Recurrent VTE 3.8% Resolution *Complete 35%* *Partial 40.3%* *No change 9.6%.* *Prophylaxis*	
Hou et al[35]	46	Rivaroxaban	Therapy for VTE associated with orthopedic surgery	17 (15–18) y	10 mg/20 mg 1 ×/d	Not reported			39 d (IQR 18.8–49.3)
Valenti[32]	65	Apixaban (37%) Rivaroxaban (61%) Dabigatran (2%)	Therapy for VTE	17 y (4–22)	Not reported	Not reported	Bleeding All 17% Major 1.5% CRNM 9%	Recurrent VTE 9% Resolution *Complete 57%* *Partial 20%* *No change 19%*	33 mo (11–120)
Corrales-Medina et al[33]	233	Apixaban (39%) Rivaroxaban (59%) Dabigatran (1.3%) Edoxaban (0.9%)	Therapy for VTE	16.5 y (1–21)	Not reported	Not reported	Bleeding All 13.8% Major 0.4% CRNM 2.2% HMB *Rivaroxaban 46%* *Apixaban 19%*	Recurrent VTE 4% Resolution not reported	Up to 6 mo

Abbreviations: CRNM, clinically relevant non major; d, day; DOAC, direct oral anticoagulant; HMB, heavy menstrual bleeding; IQR, interquartile range; n, number; VTE, venous thromboembolism; VAD, ventricular assist device; y, year.

Notes: Real-world studies on prophylaxis or treatment with DOACs in pediatric patients. Studies were identified by the following search in PubMed: (DOAC or Apixaban or Edoxaban or Dabigatran or Rivaroxaban) and (Children or child* or pediatric* or neonate*).

must be given to the choice of anticoagulant. Still, since long-term use of LMWH is difficult to tolerate, and VKAs have been linked to accelerated progression of chronic kidney disease, DOACs may be an option for selected children with severe renal impairment, provided that drug levels are carefully monitored and adjusted as needed.[48,49]

Advanced Liver Disease

Pediatric patients with liver disease were excluded from clinical trials; precise exclusion criteria differed between trials, for details see ►Table 1. Real-world data to guide the management of VTE in children with advanced liver disease are not available. As introduced in the context of renal function, DOACs undergo varying degrees of non-renal elimination; consequently, it can be expected that children with advanced liver disease will experience altered pharmacokinetic and clinical effects secondary to reductions in coagulation factors, plasma protein binding, metabolism, and renal excretion in hepatorenal syndrome. As DOACs gain importance in the treatment of adult patients with advanced liver disease and thrombotic events are common in liver disease, a key focus of the International DOAC Registry of the ISTH is the systematic monitoring of pediatric patients with impaired liver function and VTE.[50–52]

Neonates and Preterm Infants

Neonates and children younger than 2 years are underrepresented in published RCTs. Additionally, published real-world evidence on the effectiveness and safety of DOACs at this early age group is limited. Recently, a clinical experience was published with 25 patients younger than 2 years, showing that 87.5% of neonates and infants showed a reduction in the thrombotic burden with either normalized or improved reimaging and no bleeding complications were reported.[34]

Unmet Needs

The expanded use of DOACs has resulted in a growing number of patients presenting for elective and urgent procedures while on therapeutic DOACs. Interventional clinicians are increasingly expected to be knowledgeable about DOAC management. Currently, strategies for managing and reversing DOACs in pediatric patients during the perioperative period are based solely on case studies or extrapolated data from adults.[53] RCTs on DOAC reversal for emergency surgeries are unlikely to be conducted in the near future due to the rarity of such events. The safety and efficacy of andexanet alfa for rivaroxaban, apixaban, or edoxaban as well as idarucizumab for dabigatran have not been studied in pediatric patients and are not approved for pediatric use. Additionally, there are currently no dosing recommendations for pediatric patients.[54]

While foregoing drug level measurements when prescribing DOACs is generally appealing, it remains unclear whether this approach is safe and effective for all patient populations. Specifically, further research is needed to determine the viability of this approach for patients with conditions such as short bowel syndrome, protein loss, or those concurrently taking medications that might lead to significant drug interactions. Furthermore, it is unknown which specific DOACs might be most appropriate for these patient subgroups. Systematically documenting experiences and outcomes in these patients, potentially alongside drug-level monitoring, is crucial to optimize DOAC selection and ensure safety and efficacy.

Finally, DOACs offer new possibilities for the prevention of thrombosis in children with severe thrombophilia such as protein C, protein S, and antithrombin deficiency. Here too, clinical studies will be critical in assessing long-term effectiveness and safety.[55]

Outlook and Conclusion

DOACs contribute largely to the evolving individualization of care of thrombotic events in children. Through the results of the clinical trials, DOACs have become a part of the standard of care for the treatment of pediatric VTE in children. Recent studies on pediatric thromboprophylaxis suggest that DOACs are also suitable for thrombosis prevention for children with cardiac disease. However, DOACs are not yet approved for this prophylactic indication across all jurisdictions.

Although available real-word data confirm the results of the RCTs, significant gaps remain regarding the efficacy and safety of the different DOACs for prophylaxis and treatment in higher-risk scenarios. Future studies should focus on specific patient populations such as preterm infants and children with kidney or liver diseases. Important questions include the optimal choice of DOACs based on indications, appropriate dosages, and whether therapeutic drug monitoring is beneficial or necessary for certain indications. Furthermore, it will be essential to further study, gain experience, and establish guidance regarding periprocedural and bleeding management of pediatric patients with DOAC therapy. Real-world data from observational studies and registries will continue to be necessary to establish DOACs' effectiveness and safety in children in everyday clinical use.[52,56]

Conflict of Interest

AB: Consultancy/Speaker fees: CSL Behring, Roche, Sobi. MO: Consultancy/Speaker fees: Bayer, Biomarin, Biotest, Chugai, CSL Behring, LFB, NovoNordisk, Octapharma, Pfizer, Roche, Sobi, Stago, Takeda. Grants/Research support: Bayer, CSL Behring, NovoNordisk, Pfizer, Roche, Sobi, Takeda. SH: Consultancy/speaker fees: BioMarin, Pfizer, Roche, Sobi. Grants/Research support: Pfizer, Sobi.

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