# Direct Oral Anticoagulants in the Field of Paediatric Thrombosis

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## Keywords
Anticoagulants ; Administration, Oral ; Thrombosis ; Child

## Abstract
Direct oral anticoagulants (DOACs) have largely replaced traditional anticoagulants in adults for many years. However, their use in children has only emerged more recently. In this narrative review, we provide an overview on the current knowledge regarding DOACs in paediatric thrombosis.

Rivaroxaban and dabigatran have been shown to be safe and effective options for the treatment of venous thromboembolic events in children. In addition, apixaban, edoxaban and rivaroxaban can be used safely for thromboprophylaxis in children with congenital heart disease who are at high risk for thrombosis. In contrast, the benefits of DOACs in the treatment of arterial thrombosis, stroke, or in the prevention of thromboembolic events in children with leukaemia remain less well established. Owing to their oral administration, predictable pharmacokinetics, fixed dosing, and minimal monitoring requirements, DOACs represent an important advancement in paediatric anticoagulation and offer effective, practical alternatives to traditional therapies. Ongoing research and real-world data will be essential to further define their role across the full spectrum of paediatric thromboembolic disease.

## Introduction

Thrombo-embolic events (TEs) are an increasingly recognized clinical problem in children, due to improvements in diagnostic imaging, increased clinical awareness, and better survival of children with complex medical conditions. The treatment and prevention of TEs have long relied on traditional anticoagulants, including unfractionated heparin (UFH), low molecular weight heparin (LMWH), and vitamin K antagonists (VKAs). However, most practices for use of these drugs in children were extrapolated from adult data or based on observational studies and small-scale trials. Moreover, these anticoagulants require injections and/or regular monitoring and dose adjustments, which can be burdensome for both patients and providers.

In recent years, direct oral anticoagulants (DOACs) have emerged as a promising alternative and are increasingly used in paediatric patients (1). These drugs offer oral administration, predictable pharmacokinetics, and fixed dosing regimens, potentially simplifying care and improving quality of life for the patients. Additionally, clinical trials to establish the safety, efficacy, and appropriate use of DOACs in children are available. Thus, DOACs are expected to replace traditional anticoagulants for many indications, making it important for clinicians to become well-acquainted with their characteristics and use.

This review aims to provide an overview of the available evidence on the use of DOACs in the treatment and prevention of thrombosis in children.

## Classification, pharmacology, bleeding complications and reversal of DOACs

DOACs fall into two classes based on their mechanism of action: direct thrombin inhibitors and factor Xa inhibitors. Dabigatran (Pradaxa®) is currently the only direct thrombin inhibitor, while factor Xa inhibitors include apixaban (Eliquis®), rivaroxaban (Xarelto®), and edoxaban (Lixiana®). These drugs differ in pharmacokinetics and renal clearance with apixaban being less dependent on renal excretion, potentially making it safer for patients with impaired renal function. Although serum drug levels can be measured for DOACs, their clinical significance is unclear. For example, only a weak correlation between apixaban levels and clinical effect was observed in paediatric cardiac patients (2). Nevertheless, measuring levels could be considered in special situations, such as renal dysfunction, post-pyloric feeding, possible drug–drug interactions.

Overall, clinical trials have demonstrated that DOACs are safe for use in paediatric populations. The most common bleeding symptoms in children treated with DOACs include epistaxis (8.4%), subcutaneous hematoma (6.4%), and wound haemorrhage (3.7%) but major and clinically relevant non-major (CRNM) bleeding episodes are rare (2.4%) (3). In a comparative analysis, 9.4% of the 9,470 patients on rivaroxaban, apixaban or edoxaban reported one or more relevant bleeding events at least 7 days after their first prescription, while higher rates were observed among patients treated with LMWH (14.1%; n=51,330) and warfarin (16.1%; n=6,330)

(4). Notably, neonates, thrombocytopenic cancer patients or those at high risk for bleeding, and patients with renal or liver failure were underrepresented or excluded from trials, limiting information on the use of DOACs in these patient groups. Moreover, reversing DOACs remains challenging. Idarucizumab is under investigation in children as a reversal agent for dabigatran, while andexanet alfa, approved in adults for factor Xa inhibitors, is expensive, not widely available, and lacks paediatric data. Prothrombin complex concentrates could serve as an alternative option, though they are not specifically approved for this purpose. In case elective surgery is scheduled, DOACs should be discontinued 24-48 hours before, depending on the renal function and type of surgery (risk of bleeding).

## The use of DOACs in the treatment of venous thrombo-embolic events

Rivaroxaban and dabigatran have emerged as the most studied DOACs in the treatment of paediatric venous thrombo-embolic events (VTEs) (5). Overall, a meta-analysis of 3 randomized clinical trials including 790 children with a VTE, demonstrated that DOACs were associated with a reduced risk of VTE recurrence compared to standard anticoagulation (risk difference = -3%, p = 0.04), while there was no significant difference in mortality or bleeding events (6). Based on this evidence, both rivaroxaban and dabigatran received EMA approval for treatment of paediatric VTE in 2020. To date, available data on the efficacy and safety of apixaban in the treatment of VTE in children are limited to adolescents, whereas results of a randomized trial with edoxaban are still awaiting publication. It should also be noted that the use of DOACs is contra-indicated in patients with confirmed antiphospholipid syndrome, due to the increased risk of TEs shown in adults (7). Table 1 provides an overview of studies of DOACs in children.

### Rivaroxaban (EINSTEIN-Jr)

Thrombus resolution occurred in a similar frequency in patients treated with rivaroxaban (47%) compared to those receiving standard-of-care (SOC) (42%) and recurrence rates were similarly low (1% and 3% respectively). Major and CRNM bleeding events occurred in 0% and 3%, respectively, in the rivaroxaban group compared to 1% and less than 1% in the SOC group (8). After completing the initial 3-month treatment phase, patients could continue with secondary prophylaxis for up to 1 year. During the extended-phase treatment, recurrent VTE occurred in three of the 214 children (1%; cumulative incidence 3%; 95% CI 0.9-9.8). No major bleeding events were reported and CRNM bleeding episodes occurred in 3 children on rivaroxaban (2%). No deaths were observed during the study (9).

### Dabigatran (DIVERSITY)

This study demonstrated that dabigatran was non-inferior to SOC for thrombus resolution (46% for dabigatran; 42% for SOC) and recurrent VTE (4% for dabigatran; 8% for SOC). No deaths were reported in either group. The incidence of bleeding symptoms were the same for both groups (major and CRNM bleeding in 2% and 1% respectively, in each group) (10). In a subgroup analysis, Brandão et al. demonstrated that among patients with inherited thrombophilia, thrombus resolution and recurrence-free interval was better in those who received dabigatran (36%) than in those treated with SOC (22%) (11). For patients requiring secondary prophylaxis (n=203), dabigatran was administered for up to 12 months and was associated with 1.0% recurrence rate, 1.5% major bleeding events, and 1.0% CRNM bleeding events. There were no deaths reported (12).

### Apixaban

In this open-label phase 2 study, 63.6% (14 of 22) of adolescents with a VTE achieved a complete response after 3 months of treatment, while the others demonstrated a partial response. No patients experienced a new VTE and no major or CRNM bleeding events occurred (13). In a separate case report, Manis et al. documented the successful use of apixaban in combination with thrombectomy in a 17-year-old boy with Paget-Schroetter syndrome complicated by VTE (14).

### Edoxaban (Hokusai VTE PEDIATRICS Study (NCT02798471))

Preliminary data available on ClinicalTrials.gov show that recurrent VTE occurred in 3.4% and 4.8% of patients treated with edoxaban for 3 months and 12 months respectively, compared to 1.4% and 1.4% in the SOC group at both time points. The difference was not significant at 3 months but the analysis is not yet available for the 12 months' time point. Major and CRNM bleeding were reported in 2.1% for the edoxaban group versus 3.5% in the SOC group.

### Real-world data

A single-centre retrospective review provided real-world evidence on the use of DOACs in 65 children with VTE (rivaroxaban in 61.5%, apixaban in 37%, and dabigatran in 1.5%). The median duration of follow-up was 11.5 months (ranging from 12-120 months). Among these patients, six (9.2%) experienced recurrent VTE (one on apixaban and five on rivaroxaban). A major bleeding episode occurred in one surgical patient (2%), while six patients (9%) had CRNM bleeding. These findings indicate a higher risk of recurrent VTE compared to randomized trials, likely due to ongoing risk factors (including anti-phospholipid syndrome and systemic lupus erythematosus in 1 patient each) and longer follow-up. Nevertheless, bleeding rates were consistent with findings from previous trials (15).

## The use of DOACs in the treatment of arterial thrombosis and stroke

The use of DOACs in the treatment of paediatric arterial thrombosis and/or stroke is limited to a few cases, hence lacking evidence. Gupta et al. described a 6-year old boy with inherited thrombophilia who was treated with rivaroxaban for a posterior a. basilaris stroke (16). He experienced no recurrence during the first 6 months of treatment. In addition, apixaban was used for the treatment of an intracardiac thrombus in 3 patients (2-6 years old) with congenital heart disease (17). Complete resolution was obtained in 2 of them, a partial resolution in the other patient. No clinical bleeding events occurred.

## DOACs as thromboprophylaxis in acute lymphoblastic leukaemia and lymphoblastic lymphoma

During induction therapy for acute lymphoblastic leukaemia or lymphoblastic lymphoma, children face an increased risk of TEs. The Phase 3 PREVAPIX-ALL trial tested apixaban in this high-risk population, in a randomization to no anticoagulation. VTE occurred in 12% (31/256) of the apixaban group versus 18% (45/256) in the control group (p = 0.080), a non-significant difference. One death in the SOC group was attributed to a haemorrhagic cerebral sinus vein thrombosis. Major bleeding was equal (2 patients per group),

**TABLE 1:** Overview of studies investigating the use of DOACs in children.

| DOAC | Phase/design/ comparator | Age, number (n) | Efficacy | Safety |
|---|---|---|---|---|
| **Treatment of VTE** | | | | |
| **Rivaroxaban (8) (EINSTEIN-Jr)** | Phase 3, randomized, SOC | > 37 wks. GA; n = 500 | CR: 47% vs 42%<br>Improvement: 29% vs 33%<br>Recurrence: 1% vs 3% | Major bleed: 0% vs 1%<br>CRNMB: 3% vs 1% |
| **Dabigatran (10,11) (DIVERSITY)** | Phase 2b/3, randomized, SOC | 3 mo. – 18 y; n = 267 | Resolution:<br>46% vs 42%<br>36% vs 22% (inherited thrombophilia)<br>Recurrence:<br>4% vs 8% | Major bleed: 2% in each group<br>CRNMB: 1% in each group |
| **Apixaban (13)** | Phase 2, open-label | Adolescents > 40 kg; n = 26 | CR: 64%<br>PR: 36%<br>Recurrence: 0% | No bleeding events |
| **Edoxaban (Hokusai VTE PEDIATRICS Study)** | Phase 3, randomized, SOC | n = 290 | Recurrence:<br>3% vs 1% at 3 mo.<br>5% vs 1% at 12 mo. | Major and CRNMB:<br>2.1% vs 3.5% |
| **Rivaroxaban, apixaban or dabigatran (15)** | Real-world | n = 65 | Recurrence:<br>9% | Major bleed: 2%<br>CRNMB: 9% |
| **Thromboprophylaxis in ALL and LBL** | | | | |
| **Apixaban (18) (PREVAPIX-ALL)** | Phase 3, randomized, no anticoagulation | 1-18 y; n = 265 | VTE occurrence:<br>12% vs 18% | Major bleed: 0.8%<br>CRNMB: 4% vs 1% |
| **Thromboprophylaxis in congenital heart disease** | | | | |
| **Rivaroxaban (19)* (UNIVERSE)** | Phase 3, randomized, aspirin | 2-8 y; n = 100 | TE occurrence:<br>2% vs 9% | Bleeding: 36% vs 41% |
| **Apixaban (23)*** | Real-world | ≤ 18 y n = 62 | TE occurrence:<br>0.07 per 1000 person-days | Major or CRNMB: 0.22 per 1000 person-days |
| **Apixaban (22) (SAXOPHONE)** | Phase 2, randomized, SOC | 28 d – 18 y; n = 192 | TE occurrence:<br>0% | Major or CRNMB: 0.8% vs 4.8% |
| **Apixaban (2)** | Real-world | < 19 y; n = 172 | TE occurrence:<br>0% | Major bleed: 0.5%<br>CRNMB: 1.7% |
| **Edoxaban (27) (ENNOBLE-ATE)** | Phase 3, randomized, SOC | < 18 y, n = 167 | TE occurrence:<br>0% vs 1.7% | Major or CRNMB: 0.9% vs 1.7% |
| **Edoxaban (28)** | Real-world | < 18 y, n = 1651 | Event-free survival 88% at 10 y, 70% at 12 y | none |

* included only Fontan patients; ALL: acute lymphoblastic leukemia; CR: complete resolution; CRNMB: clinically relevant non-major bleed; DOAC: direct oral anticoagulant; GA: gestational age; LBL: lymphoblastic lymphoma; PR: partial resolution; SOC: standard-of-care; (V)TE: (venous) thrombo-embolic event; y: years

but CRNM bleeding was higher with apixaban (4% vs. 1%, p = 0.030). Overall, these findings demonstrate that apixaban is safe but did not significantly reduce VTE in these children, limiting its routine use for thromboprophylaxis (18).

## DOACs as thromboprophylaxis in congenital heart disease

Beyond malignancies, children with congenital heart disease are also at increased risk for thrombosis. This is especially true after a Fontan procedure in single-ventricle patients, where thrombosis remains a common complication. Other high-risk conditions include heart failure, giant coronary artery aneurysms due to Kawasaki disease, ventricular assist devices, and mechanical heart valves. Standard prophylaxis for these patients includes LMWH, VKA, and/or platelet antagonists, but their limitations have led to growing interest in DOACs as a more convenient and potentially effective alternative. Several clinical trials and real-world studies on rivaroxaban or apixaban have indeed highlighted their potential for the prevention of thrombosis after a Fontan procedure. Furthermore, evidence for the use of DOACs in children with other cardiac conditions is also growing. Particularly, apixaban and edoxaban have been studied in these patients.

### Rivaroxaban

In the phase 3 UNIVERSE study (19), patients within 4 months of a Fontan procedure had similar TE rates with rivaroxaban (2%; 1/66) compared to aspirin (9%; 3/34) during a 12 month treatment. Moreover, the proportion of bleeding events was similar in both groups (36% vs 41%).

The use of rivaroxaban in non-Fontan paediatric cardiac patients is limited. Montanez et al. described an 8-year-old boy with a dilated coronary artery aneurysm secondary to Kawasaki disease in whom rivaroxaban appeared to be a safe and effective option for thromboprophylaxis (20). Additionally, a small real-world case series reported no new thrombus formation and few complications in 15 children on rivaroxaban (including those with Fontan circulation, high-risk surgical shunts and high-risk stent angioplasty) (21).

### Apixaban

The phase 2 SAXOPHONE study evaluated apixaban for 1 year in children with single ventricle physiology (74%), Kawasaki disease (14%), and other congenital or acquired heart conditions (22). Major or CRNM bleeding occurred in 0.8% (1/129) with apixaban compared to 4.8% (3/63) with SOC. However, overall bleeding events were more frequent with apixaban (100 vs. 58.2 events per 100 patient-years), primarily due to 12 participants with ≥4 minor bleeding events. Importantly, no TEs or deaths occurred in either group. Real-world evidence further supports the efficacy and safety of apixaban in 219 cardiac patients ≤19 years (median age of 6.8 years). This retrospective single-centre analysis demonstrated no clinical signs or imaging evidence of new thrombus formation in any of the 172 patients requiring thromboprophylaxis post-cardiac surgery (42%), for failing Fontan physiology (13%), Kawasaki disease (8%), cardiomyopathy and heart failure (9%), and other cardiac reasons (21%) (2). There were 1 major and 3 CRNM bleeding events. The efficacy and safety of apixaban in patients with Fontan is also supported by another real-world study that reported only 1 TE (0.07 per 1000 person-days) and 3 serious or CRNM bleeding events (0.22 per 1000 person-days) (23).

Furthermore, apixaban was administered prophylactically to 18 children awaiting a heart transplant. Of these, 3 patients had a ventricular assist device. No increased perioperative bleeding, no major or CRNM bleeding episodes nor TEs were reported (24). Similarly, Kobayashi et al. as well as Van Edom et al. demonstrated in small case series that apixaban can be used in children and adolescents supported with the HeartMate 3 ventricular assist device (25,26).

### Edoxaban

The Phase 3 ENNOBLE-ATE trial demonstrated the efficacy and safety of oral edoxaban once daily for 3 months with an open-label extension up to 1 year in patients with Fontan circulation (44%), Kawasaki disease (22%), heart failure (4%) and other cardiac disorders (30%). No TEs were reported with edoxaban versus 1.7% with SOC (27). Bleeding rates were similarly low in both groups. Real-world data on edoxaban use in children and adolescents with a history of Kawasaki disease and giant coronary artery aneurysms demonstrated event-free survival rates of 88% at 10 years and 70% at 12 years from diagnosis (28). These outcomes are comparable to the expected risk for thrombosis of 18 +/- 2% per 10 patient-years, as calculated from the International Kawasaki Disease Registry (29).

### Mechanical and bioprosthetic valves

To date, only 1 single-centre study in adults with bioprosthetic aortic or mitral valves (ENAVLE) is available, demonstrating non-inferiority of edoxaban compared to warfarin for the prevention of TEs (30). On the contrary, a higher incidence of both thrombotic and bleeding events compared to warfarin has been reported in adults with mechanical valves receiving dabigatran (RE-ALIGN study) (31). Although the use of DOACs in patients with either mechanical or bioprosthetic valves is increasing (32), evidence is limited and the use of DOACs in these patients therefore remains relatively contra-indicated.

## Anticoagulation using DOACs in congenital vascular malformations

DOACs are increasingly adopted to treat painful venous malformations (VMs) in adults. However, limited data exist regarding their use in paediatric patients. In 2017, Yasumoto et al. reported the first successful use of dabigatran to treat consumptive coagulopathy in a 17-year-old adolescent (33). More recently, a case series involving seven children with painful VMs and chronic intravascular consumptive coagulopathy, demonstrated that treatment with DOACs (dabigatran in 2 patients, rivaroxaban in 5 patients) resulted in effective pain relief and improved coagulation profiles, with no reported adverse events. These findings suggest that DOACs may represent a viable treatment option for children with VMs complicated by intravascular coagulopathy (34).

## Conclusion

DOACs are increasingly being studied in the paediatric population and have been shown to be effective and safe in treating VTE as well as preventing TEs in children with congenital heart disease who have a high risk of thrombosis. However, the benefit of DOACs in treating arterial thrombosis or stroke has not yet been fully established. Further research and real-world data are urgently needed to better define the role of DOACs for all possible indications in children.

## Statement

The author has no conflicts of interest to disclose relating to the topic discussed in this manuscript.

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