

# New Anticoagulants in Neonates, Children, and Adolescents

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## Abstract

### Keywords

- ▶ pediatric medicine
- ▶ thrombosis
- ▶ heparins
- ▶ vitamin K antagonists
- ▶ direct oral anticoagulants

Thrombotic events are an increasing challenge in pediatrics. Standard-of-care anti-coagulants for pediatric thrombosis have several disadvantages which could be overcome by using direct oral anticoagulants (DOACs). Until recently, there was not enough evidence from clinical trials to recommend for or against the use of any of the four DOACs in children with thrombosis. In this literature review, we looked at the latest clinical trials in this field. On [clinicaltrials.gov](https://clinicaltrials.gov), we found 13 current studies with published results. For two of the four DOACs, namely dabigatran and rivaroxaban, we found successful phase III studies which led to the approval for the use in children. The results of these pivotal phase III studies allow to finally recommend rivaroxaban and dabigatran for the prophylaxis and treatment of thrombotic events in children.

## Zusammenfassung

### Schlüsselwörter

- ▶ Kinderheilkunde
- ▶ Thrombose
- ▶ Heparin
- ▶ Vitamin-K-Antagonisten
- ▶ direkte orale Antikoaganzien

Thrombotische Ereignisse stellen in der Kindermedizin eine zunehmende Herausforderung dar. Die Standardantikoaganzien für pädiatrische Thrombosen haben mehrere Nachteile, die durch den Einsatz direkter oraler Antikoaganzien (DOACs) überwunden werden könnten. Bis vor kurzem war aber noch nicht ausreichend Evidenz aus klinischen Studien verfügbar, um evidenzbasierte Empfehlungen für den Einsatz einer der vier DOACs bei Kindern mit Thrombosen zu geben. In dieser Literaturübersicht haben wir die neuesten klinischen Studien auf diesem Gebiet untersucht. Auf [clinicaltrials.gov](https://clinicaltrials.gov) fanden wir 13 aktuelle Studien mit veröffentlichten Ergebnissen. Für zwei der vier DOACs, namentlich Dabigatran und Rivaroxaban, fanden wir erfolgreiche Phase-III-Studien, die zur Zulassung für den Einsatz bei Kindern führten. Die Evidenz aus diesen zulassungsrelevanten Phase-III-Studien gestattet es daher jetzt, Rivaroxaban und Dabigatran für die Vorbeugung und Behandlung von thrombotischen Ereignissen bei Kindern zu empfehlen.

## Introduction

There is a strong and increasing need for new anticoagulants in pediatric medicine. For this, there are two reasons. The first reason is the progress in pediatric intensive care. In

children, thrombotic events occurred almost exclusively as complications of underlying diseases and/or their treatment.<sup>1</sup> Most of the affected pediatric patients had at least one severe underlying disease, such as congenital heart

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defects or cancer among other. Raffini et al showed a 70% increase in thrombotic events in children in U.S. hospitals for the years 2001–2007.<sup>1</sup> As thrombotic event become more common in pediatric clinical care, the need for anticoagulation suitable for children is also growing. The second reason is that the current standard of care (SoC) anticoagulant drugs mostly used in children, including unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and vitamin K antagonists (VKAs), have several disadvantages.

### Standard of Care in Pediatric Anticoagulation

The SoC in pediatric anticoagulation consists mainly of three types of drugs: UFH, LMWH, and VKAs like phenprocoumon and warfarin. Currently available recommendations on the use of these anticoagulants include the ones by Monagle et al for the American College of Chest physician,<sup>2</sup> Monagle et al for the American Society of Hematology,<sup>3</sup> and Chalmers et al for the British Society for Haematology.<sup>4</sup>

### Heparins in Children

Both types of heparins, UFH and LMWH, need to be administered parenterally. Frequent injections cause stress and anxiety, especially in small children, making subsequent administration increasingly difficult.<sup>5</sup> Heparins exert only an indirect anticoagulant effect by enhancing the action of endogenous antithrombin. However, antithrombin levels are often too low in neonates and critically ill children.<sup>6</sup>

### Unfractionated Heparin in Children

Since the pharmacokinetic (PK) and pharmacodynamic (PD) properties of UFH in children are strongly influenced by their age and health status, UFH effects show a high variability and therefore require intensive monitoring via intravenous access, which is very inconvenient for children.<sup>7</sup> This monitoring is based on the interpretation of two assays: activated partial thromboplastin time (aPTT) and heparin assay (anti-Xa). However, due to the high variability of their values, the interpretation of these assays is limited, especially in severely ill children.<sup>8</sup> Target therapeutic levels are extrapolated from the values of adult patients, because there are no reference values for children.<sup>9</sup>

Moreover, heparin-induced thrombocytopenia (HIT) may occur. In 2012, a systematic review found an HIT incidence of 2.3 to 3.7% in children receiving UFH treatment.<sup>10</sup> Nevertheless, UFH has a short half-life, and with protamine sulfate, an antidote is available<sup>11</sup>; therefore, it still has its place in short-term prophylaxis (procedures, intensive care, and surgery) and in the treatment of acutely ill children at risk of bleeding.<sup>12</sup>

### Low-Molecular-Weight Heparin in Children

The PD and PK properties of LMWH show less variance than those of UFH. It has a longer half-life. Though the incidence of HIT with LMWH is probably lower than with UFH, the exact numbers are unknown.<sup>13</sup> LMWH requires twice-daily subcutaneous administration and often monitoring of anti-Xa

levels via intravenous access, with the same monitoring challenges as UFH. Because of risk of liver dysfunction and bone deterioration in children undergoing long-term LMWH therapy, it is suggested to carefully monitor bone density and liver function after 3 months of use.<sup>13</sup> LMWHs have more stable, though age-dependent, PK/PD properties; require less frequent monitoring; have longer half-lives than UFH; and are therefore well-suited for longer-term use and the outpatient setting in children.<sup>12</sup>

### Vitamin K Antagonists in Children

VKAs like Sintrom, Marcumar, and warfarin have only a narrow therapeutic range.<sup>14</sup> In 2012, a pediatric retrospective study with 4,883 patients identified independent risk factors such as Asian race, drug interactions, mitral valve replacement, and length of hospital stay for readmission of patients to hospitals within 30 days due to warfarin-associated bleeding.<sup>14</sup> VKAs take about 3 days to build their anticoagulant effect, which is often too slow in the context of intensive care.<sup>15</sup>

Long-term use of VKAs requires international normalized ratio (INR) monitoring and therefore frequent visits to a healthcare provider, which is inconvenient and time consuming. Infants and many small children have difficulties to swallow pills. Though VKAs have the advantage of oral administration, they are available only as pills, not as liquids. VKAs show interactions with vitamin K-containing foods. This causes problems, especially for infants, because breast milk contains little vitamin K and also because breast milk substitutes and parenteral nutrition for infants are usually fortified with vitamin K.<sup>16,17</sup>

### Eight Criteria for New Anticoagulants in Pediatric Care

The increasing need for new anticoagulants in pediatric care may be specified as a need for anticoagulant drugs, which meet the following eight criteria, compared with current anticoagulation:

1. Exert their effect directly, not via antithrombin.
2. Have a faster onset than VKAs.
3. Have more predictable PKs and PDs.
4. No or minimal need for laboratory monitoring.
5. Administer orally, preferably in liquid form.
6. Have fewer interactions with drugs and foods.
7. Have a comparable or higher effectiveness and safety.
8. Are approved for use in children by regulatory authorities such as the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA).

### Pediatric Investigation Plans for Direct Oral Anticoagulants

Direct oral anticoagulants (DOACs) such as dabigatran (Pradaxa), rivaroxaban (Xarelto), apixaban (Eliquis), and edoxaban (Lixiana) have been shown in numerous studies to meet the first seven of the above eight criteria for the treatment of thrombosis, but so far only in adult patients.<sup>13,14</sup>

To address this, “pediatric investigation plans” (PIPs) for dabigatran, rivaroxaban, apixaban, and edoxaban have been developed and published by the EMA and pharmaceutical companies.<sup>18</sup>

These PIPs describe in detail how age-appropriate pediatric formulations are to be developed, to ensure reliable and accurate administration of the medicine to children of different ages, and what kind of studies have to be done for this.<sup>12</sup>

The necessary phase I to III studies have already been completed for dabigatran and rivaroxaban and only the phase IV postmarketing studies are missing, while the PIPs for edoxaban and apixaban are still ongoing. Therefore, this clinical review will focus on dabigatran and rivaroxaban.

## Aim of this Review

To evaluate the extent to which DOACs will be able to meet the growing need for new anticoagulation agents in pediatric care, we will describe the latest results of the current pediatric studies on rivaroxaban and dabigatran.

## Characteristics of DOACs in Adults

The DOACs can be divided into two main classes: direct oral thrombin inhibitors and direct oral factor Xa inhibitors. Dabigatran belongs to the first class, and all other DOACs belong to the second class.

All DOACs are small molecules, which were artificially designed to specifically and reversibly inhibit certain coagulation factors in the coagulation pathway and are orally administered. Anticoagulant effects do not rely on endogenous cofactors; hence, they are called “direct” anticoagulants.<sup>12</sup>

## Pharmacological Characteristics of DOACs in Adults

The pro-drug dabigatran etexilate differs from dabigatran by an ethyl group at the carboxylic acid and a hexyloxycarbonyl side chain at the amidine. In the gastrointestinal tract, dabigatran etexilate is converted into the active metabolite, dabigatran.<sup>19</sup> In a study on 40 male adults, dabigatran etexilate onset was fast, the peak plasma concentration was reached within 2 hours of administration, and half-life was at 8 to 10 hours.<sup>20</sup> As Albisetti<sup>21</sup> pointed out, studies have shown that renal function has the most important, clinically relevant impact on dabigatran exposure.<sup>22,23</sup>

In a study on 108 healthy adults, peak plasma levels of rivaroxaban after a single escalating oral dose were observed at 0.5 to 0.6 hours by the liquid and at 1.5 to 3.0 hours for the tablet formulation, with a half-life of 3.24 to 4.15 hours for the liquid solution and 7 to 10 hours for the tablets.<sup>24</sup>

## Drug–Drug Interaction of DOACs

The currently available data on drug–drug interaction (DDI) of DOACs come from studies in adults only.

## Interaction of Dabigatran in Adults

Because of the increased risk of bleeding, dabigatran should not be coadministered with any other anticoagulant/anti-

platelet drugs, such as aspirin and diclofenac.<sup>25</sup> Clopidogrel increases the absorption rate of dabigatran; therefore, it should also not be coadministered.<sup>26</sup>

According to a review on drug interaction with DOACs by Di Minno et al,<sup>27</sup> both rivaroxaban and dabigatran interact with drugs that are inducers or inhibitors of cytochrome P450 isoenzyme (CYP3A4) or of P-glycoprotein (P-gp). Therefore, in dabigatran users, there are at least eight drugs to be avoided: carbamazepine, cyclosporine, dronedarone, ketoconazole, verapamil, phenytoin, rifampicin, and St. John’s worth. Drugs to be used with caution in dabigatran users are quinidine, quinine, and verapamil. Proton-pump inhibitors impair the effect of dabigatran.<sup>27</sup>

## Interactions of Rivaroxaban in Adults

In contrast to dabigatran, rivaroxaban can in principle be coadministered with aspirin<sup>28</sup> and clopidogrel,<sup>29</sup> although the later does prolong the mean bleeding time of patients treated with rivaroxaban.<sup>30</sup> Any other anticoagulant drug should not be coadministered with rivaroxaban because of the increased bleeding risk.<sup>26,31</sup> Simultaneous treatment of rivaroxaban with strong inhibitors of both CYP3A4 and P-gp should also be avoided, because they affect the rivaroxaban–plasma concentrations.<sup>32</sup>

There are at least 11 drugs that should be avoided in rivaroxaban users: amiodarone, chloramphenicol, clarithromycin, cyclosporine, dronedarone, itraconazole, ketoconazole, quinidine, quinine, ritonavir, and verapamil. The following five drugs should be used with caution in rivaroxaban users: carbamazepine, hypericum, perforatum, phenytoin, and rifampicin. The following six drugs impair the effect of rivaroxaban: carbamazepine, hypericum, perforatum, phenobarbital, phenytoin, and rifampicin.<sup>27</sup>

## DOACs–Food Interaction

The little knowledge of DOACs–food interaction (DFI) that we already have is based on the modulation of P-gp activity, which can either enhance or inhibit the effectiveness of DOACs and comes from three sources: (1) pharmacological studies in adults, (2) animal studies, (3) in vitro studies. According to these, the following 13 foods inhibit effects of DOACs: ginkgo biloba, berberine, black pepper, grape fruit, apigenin, rutin, capsaicin, lemon, soybean extract, notoginsenoside R1, curcumin, green tea, fisetin, and honokiol. The following eight foods are considered inducers of effects of DOACs: St. John’s wort, quercetin, *Scutellaria*, soy milk and miso, sucralose, licorice root, genipin, and mango.<sup>27</sup>

## Results of Current Pediatric Trials on DOACs

We searched pediatric studies on DOACs on clinicaltrials.gov<sup>33</sup> and current literature on the findings of pivotal studies for DOACs in children. We found that 30 pediatric DOACs studies have been registered so far; 18 of these studies have been completed, and 13 of these had their results published. We could not find any published pivotal studies on apixaban and edoxaban.

For the evaluation of the efficacy and safety of pediatric DOACs and thus for the implementation of the PIPs<sup>34</sup> of the EMA mentioned at the beginning, there were three large, multinational, and thus multicenter studies: the DIVERSITY trial for dabigatran<sup>35</sup> and the EINSTEIN and the UNIVERSE trials for rivaroxaban.<sup>34,36</sup> In addition, there was also a single-arm phase III study assessing dabigatran for extended secondary venous thromboembolism (VTE) prevention.<sup>37</sup>

In further DOACs studies they identified, Branstetter et al counted 16 neonates, 152 non-neonatal infants (>30 days to <2 years), 351 children, and 488 adolescents.<sup>38</sup>

In the following summary of the results of the three trials, we will describe only the pivotal phase III trials, that is, the trials that ultimately led to the approval of both dabigatran and rivaroxaban for the treatment of children. In all three trials, there were two types of endpoints: primary endpoints on the efficacy of the two DOACs compared with standard therapy and secondary endpoints related to adverse effects and the need for therapy adjustments.<sup>35,36,39</sup>

The DIVERSITY and EINSTEIN trials were in children with acute VTE, and the UNIVERSE trial was in children post Fontan procedure.

### DIVERSITY Trial

The randomized, controlled, open-label, multicenter, phase IIb/III DIVERSITY trial represented the execution of a PIP jointly developed by the EMA and the FDA and was conducted in 65 centers in 26 countries.<sup>35</sup>

In the phase III study, after enrolment, eligibility screening was performed during initial parenteral anticoagulation. Subsequently, children were randomized in a 1:2 ratio (standard treatment vs. dabigatran) to receive either standard treatment or dabigatran. The SoC was defined as treatment with LMWHs, UFH, VKAs, or fondaparinux, at the discretion of the investigators and standard clinical practice. The patients were assigned to three age groups: birth to 2 years, 3 to 12 years, and 13 to 18 years. The doses in the dabigatran group were extrapolated from

the usual doses of adult patients based on the weight and age of the children. Extrapolations were based on Hayton's nomogram, in which estimated renal function is derived from age and weight to achieve similar exposure to dabigatran-treated adults.<sup>40</sup> Ninety patients were in the SoC control group and 177 patients were in the dabigatran group.

The study results in all three primary endpoints: (1) complete thrombus resolution, (2) freedom from recurrent VTE, and (3) freedom from VTE-related death—were at least equal in the dabigatran group comparing to SoC.<sup>35</sup>

As shown in **Table 1**, almost all relative numbers of adverse events were lower in the dabigatran group, except for the relative and absolute numbers of adverse events leading to treatment discontinuation.

The DIVERSITY trial was thus able to prove that dabigatran is at least equal to the SoC in terms of efficacy and safety.

### EINSTEIN Trial

The EINSTEIN-Jr phase III study compared the efficacy and safety of body weight-adjusted rivaroxaban treatment regimens with those of standard anticoagulation in 500 children with acute VTE. Children in the rivaroxaban group received a body weight-adjusted 20 mg equivalent dose, which corresponds to the therapeutic exposure range of young adults. Rivaroxaban was administered once daily in children weighing more than 30 kg, twice daily in children weighing 12 to 30 kg, and three times daily in children weighing less than 12 kg. Young children were given a specially developed liquid formulation, while older children were given film-coated tablets.<sup>41</sup>

**Table 2** summarizes the efficacy and safety outcomes of the EINSTEIN-Jr phase III trial.

The successful implementation of the DIVERSITY phase III study led to the approval of dabigatran for use in children by the EMA in November 2020 and by the FDA in June 2021. Dabigatran is therefore the first and only approved oral direct thrombin inhibitor for children in the European Union and the United States.<sup>38,42,43</sup>

**Table 1** Summary of adverse events in the DIVERSITY trial, according to Halton et al<sup>35</sup>

	Standard-of-care group, n = 90			Dabigatran group, <sup>a</sup> n = 176		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Children with any adverse event	31 (34%)	21 (23%)	8 (9%)	89 (51%)	33 (19%)	13 (7%)
Children with serious adverse events <sup>a</sup>	0	10 (11%)	8 (9%)	3 (2%)	8 (5%)	11 (6%)
Leading to death	0	0	2 (2%)	0	0	0
Life-threatening	0	1 (1%)	1 (1%)	0	0	2 (1%)
Requiring hospitalization	0	4 (4%)	7 (8%)	2 (1%)	5 (3%)	10 (6%)
Prolonged hospitalization	0	1 (1%)	0	0	2 (1%)	3 (2%)
Other	0	5 (6%)	1 (1%)	2 (1%)	1 (1%)	3 (2%)
Children with adverse events of special interests	0	0	1 (1%)	1 (1%)	0	1 (1%)
Children with adverse events leading to treatment discontinuation	0	1 (1%)	2 (2%)	5 (3%)	3 (2%)	5 (3%)

**Table 2** Efficacy and safety outcomes of the EINSTEIN-Jr phase 3 trial, according to Cohen et al<sup>41</sup>

	Rivaroxaban	Comparator	Hazard ratio (95% CI)
<b>Efficacy population</b>			
Number of patients assessed	335	165	
Primary efficacy outcome	4 (1%)	5 (3%)	0.4 (0.11–1.41)
Primary efficacy outcome or progression of thrombosis repeat imaging	5 (1%)	6 (4%)	0.41 (0.12–1.36)
Primary efficacy outcome or major bleeding	4 (1%)	7 (4%)	0.3 (0.08–0.93)
Mortality	1 (< 1%)	0	
Cancer related	1	0	
<b>Safety population</b>			
Number of patients assessed	329	162	
Major bleeding or CRNMB	10 (3%)	3 (2%)	1.58 (0.51–6.27)
Major bleeding	0	2 (1%)	
Pulmonary	0	1	
Intracranial	0	1	
CRNMB	10 (3%)	1 (<1%)	
GI	4	0	
Urogenital	2	0	
Skin	1	0	
Nasal or mouth	3	1	

Abbreviations: CI, confidence interval; CRNMB, clinically relevant non-major bleeding.

–**Table 3** summarizes the DIVERSITY and EINSTEIN phase III trials, according to Branstetter et al.<sup>38</sup>

The rivaroxaban phase III trials were also successful and led to EMA approval for VTE treatment in children, while FDA approval is still pending. Rivaroxaban was approved by the EMA in January 2021.<sup>44</sup> In the United States,

rivaroxaban was submitted for approval in children in June 2021.

#### UNIVERSE Trial

The UNIVERSE trial was a randomized, multicenter, two-part, open-label trial of rivaroxaban for thromboprophylaxis in

**Table 3** Summary of the DIVERSITY and EINSTEIN phase III trials, according to Branstetter et al<sup>38</sup>

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

Abbreviations: CI, confidence interval; CRNMBEs, clinically relevant non-major bleeding events, HR, hazard ratio; LMWH, low-molecular-weight heparin; MBEs, major bleeding events, SOC, standard of care; VKA, vitamin K antagonist; VTE, venous thromboembolism.

<sup>a</sup>Composite efficacy score: combined endpoint of complete thrombus resolution, freedom from recurrent VTE, and freedom from VTE-related mortality.

<sup>b</sup> $p$ -Value relates to a test for noninferiority.

<sup>c</sup>MBEs: fatal bleeding, clinically overt bleeding (decrease in hemoglobin of at least 20 g/L in a 24-hour period), bleeding that is retroperitoneal, pulmonary, intracranial, or otherwise involves the central nervous system.

<sup>d</sup>Overt bleeding not meeting the criteria for major bleeding, but associated with medical intervention, or unscheduled contact (visit or telephone call) with a physician, or (temporary) cessation of study treatment, or discomfort for the child such as pain or impairment of activities of daily life.

children following a Fontan procedure. The aim of the study was to investigate the dosing regimen, safety, and efficacy. The first, single-arm part of the UNIVERSE study assessed the PKs/PDs and safety of rivaroxaban in 12 participants.<sup>41</sup>

In the second part of the UNIVERSE trial, participants were randomized in a 2:1 ratio (rivaroxaban vs. SoC) (open-label). A total of 112 participants were enrolled in the study at 35 sites in 10 countries.

–Table 3 summarizes the bleeding events in the UNIVERSE phase III trial.

Therefore, the safety profile compared with the SoC was similar and, in the efficacy results, a trend toward less thrombotic events could be demonstrated in the rivaroxaban group (–Table 4).<sup>36</sup>

The UNIVERSE study (thromboprophylaxis for children post-Fontan procedure) has been submitted for approval in the United States. As this study was not part of the PIP agreed with the EMA, it has not yet been submitted in the European Union.<sup>45</sup>

The dosing regimens for dabigatran and rivaroxaban in children and neonates are so complex that their detailed presentation is beyond the scope of this review. We recommend that you refer to the EMA- and FDA-approved package inserts for dosing information.

## Ongoing Pediatric DOACs Studies

According to Branstetter et al,<sup>38</sup> there are currently nine ongoing phases I to IV pediatric DOACs studies, for rivaroxaban (one phase III study), apixaban (five studies, phases I–IV), and edoxaban (three studies, one phase I and two phase III studies). Therefore, it is at least possible that similarly meaningful pivotal studies will be published in the future for apixaban and edoxaban as for rivaroxaban and dabigatran.

## Discussion

If we assess the described results from the pivotal studies on dabigatran and rivaroxaban against the eight criteria for new anticoagulants in pediatrics described at the beginning, it becomes clear that both dabigatran and rivaroxaban meet these eight criteria. Both rivaroxaban and dabigatran:

1. Exert their effect directly, not via antithrombin.
2. Have a faster onset than VKAs.
3. Have more predictable PKs and PDs.
4. Require only minimal need for laboratory monitoring.
5. Are administered orally, and, for rivaroxaban, even in liquid form.

**Table 4** Summary of bleeding events in the UNIVERSE trial, according to McCrindle et al<sup>36</sup>

Bleeding events	Rivaroxaban		ASA
	Part A (N = 12)	Part B (N = 64)	Part B (N = 34)
Participant with $\geq 1$ on-treatment bleeding events	4 (33%)	23 (36%)	14 (41%)
Major bleeding	0	1 (2%)	0
Clinically relevant non-major bleeding	1 (8%)	4 (6%)	3 (9%)
Gastrointestinal	0	2 (3%)	1 (3%)
Lower gastrointestinal	0	2 (3%)	1 (3%)
Gingival	0	1 (2%)	0
Hematoma	0	0	1 (3%)
Skin	1 (8%)	1 (2%)	1 (3%)
Subconjunctival	0	0	1 (3%)
Trivial bleeding	3 (25%)	21 (33%)	12 (35%)
Epistaxis	0	7 (11%)	3 (9%)
Gastrointestinal	0	1 (2%)	1 (3%)
Lower gastrointestinal	0	0	1 (3%)
Upper gastrointestinal	0	1 (2%)	1 (3%)
Gingival	1 (8%)	3 (5%)	1 (3%)
Hematoma	2 (17%)	7 (11%)	2 (6%)
Skin	0	14 (22%)	8 (24%)
Vascular access site	0	2 (3%)	0

Notes: Percentages were calculated with the number of participants in each group as denominator. Incidence is based on the number of subjects, not the number of events. A participant may appear in different sites/categories. Safety analysis set: all participants in part A who received at least 1 dose of study drug and all participants in part B who were randomized and received at least 1 dose of study drug. The primary safety outcome is major bleed that meets the International Society on Thrombosis and Haemostasis definition: overt bleeding and associated with a decrease in hemoglobin of  $\geq 2$  g/dL; leading to a transfusion of the equivalent of  $\geq 2$  units of packed red blood cells or whole blood in adults; occurring in a critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal; or contributing to death. ASA indicates acetylsalicylic acid.<sup>36</sup>

6. Have fewer interactions with drugs and foods, although data on DDI in children are still missing and the DDI are more common than initially expected.
7. Have shown to probably have at least the same effectiveness and safety as the SoC, although all of these studies lack in power to provide a high level of evidence.
8. Were therefore approved for use in children by regulatory authorities such as the EMA and the FDA.

Although the number of severe bleeding events in the pivotal studies was small, the lack of established reversal agents for pediatric patients in the case of a major bleeding event or accidental/intentional overdose remains a major disadvantage of DOACs in pediatric anticoagulation.<sup>46</sup> Promising candidates for this are currently the reversal agent idarucizumab/Praxbind and Ondexxya/andexanet alfa—currently, there are just anecdotal reports of its use in children; therefore, it can only be used off-label for the time being.<sup>47</sup> For rivaroxaban, the antidote Ondexxya (andexanet alfa) was granted EMA-approval for use in adults in 2019.<sup>48</sup>

Though the three phase III trials we described here evaluated adverse events, we still lack knowledge of possible pediatric DDI and DFI. From the discussion of the advantages of DOACs over conventional anticoagulation in children, we already know that the responses of the child and adult metabolism to anticoagulants are not always the same.<sup>6</sup> Although DDI and DFI studies are routinely conducted in drug development, due to ethical, logistical, and methodological challenges, they are ever conducted only in healthy adult volunteers, never in multimorbid and severely morbid pediatric patients. Because pediatric DDI and DFI assessments are therefore lacking, adult DDI and DFI data are extrapolated to pediatric patients.<sup>49</sup>

A systematic literature search on DDI reported in pediatrics but not in adults from 1945 to 2011 by Salem et al found 145 corresponding reports on 20 victim drugs and 25 interacting drugs. This study showed that children younger than 2 years were particularly affected by pediatric DDI.<sup>50</sup>

None of the phase I to IV studies discussed in this review specifically looked for pediatric DOACs-DDI, so we still know far too little about this and therefore need to be particularly cautious in children younger than 2 years.

Events involving pediatric DOACs-DDI can and should be reported to the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) in Germany,<sup>51</sup> to EudraVigilance in the European Union,<sup>52</sup> and to the FDA's Adverse Event Reporting System (FAERS) in the United States.<sup>53</sup>

In their 2016 review of pediatric DOACs, von Vajna et al<sup>46</sup> concluded that it was too early to make recommendations. After reviewing these three latest trials, it is now possible to recommend dabigatran etexilate and rivaroxaban for the treatment of pediatric thrombosis—with the two caveats, there might be a lack of reversal agents and the possible occurrence of DDI and DFI. These will probably be avoided by taking the DDI and DFI into account, which we already know from adult patients, animal experiments, and in vitro studies.

Finally, we would like to emphasize that, in our experience, the decision between SoC and DOACs in the prevention and treatment of VTE in children still requires careful clinical case-by-case evaluation, as the treatment situation in phase III trials differs in some respects from everyday clinical practice.

#### Conflict of Interest

The authors declare that they have no conflict of interest.

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