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Anticoagulant prophylaxis and therapy in children: current challenges and emerging issues

F. NEWALL,* B. BRANCHFORD† and C. MALE‡

**Clinical Haematology & Nursing Research, Royal Children's Hospital, Haematology Research Group, Murdoch Childrens Research Institute and Departments of Paediatrics and Nursing, The University of Melbourne, Melbourne, Australia; †Department of Pediatrics, Section of Hematology/Oncology/Bone Marrow Transplant and the Hemophilia and Thrombosis Center, School of Medicine and Center for Cancer and Blood Disorders, Children's Hospital Colorado, University of Colorado, Aurora, CO, USA; and ‡Haemostasis and Thrombosis Unit, Department of Paediatrics and Adolescent Medicine, Medical University of Vienna, Vienna, Austria*

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Summary. This review is aimed at describing the unique challenges of anticoagulant prophylaxis and treatment in children, and highlighting areas for research for improving clinical outcomes of children with thromboembolic disease. The evidence presented demonstrates the challenges of advancing the evidence base informing optimal management of thromboembolic disease in children. Recent observational studies have identified risk factors for venous thromboembolism in children, but there are few interventional studies assessing the benefit–risk balance of using thromboprophylaxis in risk-stratified clinical subgroups. A risk level-based framework is proposed for administering mechanical and pharmacological thromboprophylaxis. More research is required to refine the assignment of risk levels. The anticoagulants currently used predominantly in children are unfractionated heparin, low molecular weight heparin, and vitamin K antagonists. There is a paucity of robust evidence on the age-specific pharmacology of these agents, and their efficacy and safety for prevention and treatment of thrombosis in children. The available literature is heterogeneous, reflecting age-specific differences, and the various clinical settings for anticoagulation in children. Monitoring assays and target ranges are not well established. Nevertheless, weight-based dosing appears to achieve acceptable outcomes in most indications. Given the limitations of the classical anticoagulants for children, there is great interest in the direct oral anticoagulants (DOACs), whose properties appear to be particularly suitable for children. All DOACs currently approved for adults have Pediatric Investigation Plans ongoing or planned. These are generating age-specific formulations and systematic dosing information. The ongoing pediatric studies still have to establish whether DOACs have a positive benefit–risk balance in the various pediatric indications and age groups.

Keywords: anticoagulants; child; drug evaluation; prevention; therapy.

Correspondence: Christoph Male, Department of Paediatrics and Adolescent Medicine, Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria
Tel.: +43 140 4003 2310
E-mail: christoph.male@meduniwien.ac.at

Introduction

The population of children requiring anticoagulant prophylaxis and treatment is evolving, corresponding to the increasing complexity evident within tertiary healthcare settings universally. The aims of this review are to describe the unique challenges of anticoagulation in children as compared with adult patients, and to highlight several areas of focus for research for improving the management of children with thromboembolic disease. The review is based on three presentations at the Pediatric State-of-the-Art session at the 2017 ISTH conference, discussing thromboprophylaxis, anticoagulant therapy, and the ongoing developments of direct oral anticoagulants (DOACs) for children.

Which risk groups of children should receive thromboprophylaxis?

The incidence of hospital-acquired venous thromboembolism (VTE) in children is increasing [1], along with associated concerns about increasing acute (pain, compartment syndrome, or pulmonary hypertension) and chronic (post-thrombotic syndrome) comorbidities, and mortality [2]. High-quality evidence from randomized controlled clinical trials (RCTs) of the safety and efficacy of thromboprophylaxis drive intervention strategies in adults [3]. Evidence-based guidelines are similarly needed

for children, but a paucity of robust evidence has slowed their development.

Risk profiles have been published based on small, single-institution studies, but they lack sufficient power to discern differences across important subgroups, such as types or length of surgery or cancer types. Therefore, the ISTH Pediatric/Neonatal Hemostasis and Thrombosis SSC convened a Working Group to develop recommendations for standardization and future research priorities regarding pediatric VTE risk assessment models. The group first published a meta-analysis, identifying intensive care unit (ICU) admission, central venous catheter (CVC) presence, mechanical ventilation and prolonged admission as independent risk factors for pediatric VTE [4]. Additionally, work has recently begun to differentiate risk profiles between clinical settings, such as non-critically ill children [5], and pediatric [6], cardiac [7] or neonatal [8] ICUs. An approach to pharmacological VTE prophylaxis in children is not likely to be as universally appropriate for children as it is in most hospitalized adults. This fact is more pertinent when we consider the age-based differences in hemostatic system maturity [9] and the potential effects on both VTE risk and the safety/efficacy of prophylaxis. Postpubertal age is a well-established risk factor for VTE in general, including healthcare-associated VTE (HA-VTE). Neonates comprise the other age group at risk, but it is unclear whether this risk is truly age-related or reflects the combined effects of many factors associated with sick newborns. Moreover, the risk–benefit balance of thromboprophylaxis is probably different, owing to differences in drug metabolism and an increased risk of intraventricular hemorrhage.

Registries exist whose primary utility is the development and validation of risk prediction tools, such as the multi-institutional Children's Hospital Acquired Thrombosis (CHAT) registry. A project involving this registry is underway to retrospectively develop, and then prospectively validate, a pediatric-specific risk score to identify high-risk children for involvement in future randomized clinical trials evaluating the safety and efficacy of various prevention strategies. An additional benefit may be decreased use of thromboprophylaxis in low-risk patients, thus decreasing their exposure to potentially harmful interventions.

Ongoing studies of clinical subgroups may help to determine the particular VTE risk associated with a specific clinical condition. The multi-institutional prospective observational Clot Incidence Rate in Central LinE (CIRCLE) [10] has reported preliminary data from almost 1100 children with CVCs, and is ultimately planning to include $\approx$2000 children. The CVC-related VTE rate was 5.7% across all of the children, but 85% of the events occurred in children with peripherally inserted central catheter lines.

A current example of an interventional study on thromboprophylaxis in specific clinical subgroups is the ongoing PREVAPIX-ALL trial through Children's Oncology Group [11]. It is a phase 3 RCT of the safety/efficacy of apixaban for VTE prevention in children with leukemia treated with asparaginase and the presence of a CVC.

Despite the robust pediatric-focused, clinical subgroup-specific information expected to be generated from these studies, further trials are needed. Collaborative, multi-institutional studies should be prioritized to increase enrollment and balance regional differences in underlying medical comorbidities. As the potential mechanical and pharmacological thromboprophylaxis interventions are not completely benign, studies should include considerations such as number needed to treat versus number needed to harm, and also discern between absolute risk reduction and relative risk reduction. The inherent trade-off between bleeding and VTE (i.e. net clinical benefit) can be modeled as a bivariate endpoint.

Patients aged > 18 years, even if hospitalized in a pediatric institution, should be subject to available standard adult VTE prevention guidelines [12–14].

With $\approx$85% of HA-VTEs occurring in patients with CVCs, this clinical characteristic deserves careful consideration, as it probably confers a high relative proportion of the overall HA-VTE risk in these patients [15]. This situation is more challenging, because previous studies of thromboprophylaxis for CVC-related VTE have not demonstrated clear benefit, as recently reviewed by Vidal *et al*. [16] It is important to clearly define CVC-specific features, including line type, material, insertion site, and tip placement location. Additionally, CVC insertion increasingly utilizes ultrasound guidance to decrease insertion attempts and more accurately estimate catheter-to-vessel diameter ratio, decreasing endothelial injury events and mechanical flow restriction, respectively. Identification of the characteristics that are most highly associated with CVC-related VTE will be critical for future risk stratification and mitigation strategies.

The children who are more likely to require CVCs for vascular access are those with malignancy, systemic infection, congenital heart disease, gastrointestinal failure, sickle cell disease, traumatic injury, and ICU admission. Besides the CVC, most patients have many other compounding risk factors, such as inflammation, decreased mobility, and exposure to thrombogenic medications such as steroids or asparaginase [17]. Table 1 lists relevant risk factors, many of which (CVC, infection, length of stay, etc.) are described further in the recent ISTH Pediatric SSC position paper from the VTE Prevention Working Group [18] and the associated meta-analysis of the literature for HA-VTE risk factors [4].

Mechanical prophylaxis may be instituted in most hospitalized children at moderate or high risk of VTE (Table 2). With specific relevance to lower-extremity thrombosis, data from adult studies suggest that sequential compression devices are preferred over compression stockings [19,20], with the exception of a known

thrombus, when only the latter may still be used. Additional risks (pressure ulcer or other skin irritation) and contraindications (acute VTE, fracture, burns, wound, postoperative site, peripheral intravenous access, or inappropriate fit) exist and must be considered. With the exception of some potential beneficial effect of increasing systemic fibrinolysis [21], the utility of mechanical prophylaxis has not been well established for upper and central venous system VTE, particularly if CVC-associated.

Pharmacological prophylaxis may be instituted in the following risk groups:

1 Children in an ICU with a CVC and one other risk factor from Table 1 fit a high-risk profile and may benefit from pharmacological thromboprophylaxis in the absence of strong contraindications.
2 For children with either a CVC or admission to an ICU (but not both), two risk factors from Table 1 are recommended prior to the initiation of pharmacological thromboprophylaxis.
3 For children with neither a CVC nor ICU admission, at least three risk factors from Table 1 should be present prior to the initiation of pharmacological thromboprophylaxis.

The applicability of the various prevention measures (mobilization, and mechanical or pharmacological thromboprophylaxis) in Table 2 will depend on the specific types of risk factor and their combinations (e.g. different for CVC and for altered mobility). Additionally, the risk factors in Table 1 (from which the risk categories in Table 2 are derived) are expected to be further refined, particularly with respect to 'weighting' in terms of relative risk, as more studies are completed in this area, generating more evidence. The current lack of evidence regarding any potential rank-ordering of these risk factors requires that this approach be used as general guidance only, and not for a concrete assignment of risk level. Specifically, these recommendations do not represent an evidence-based guideline, and solely reflect the expert opinion of the authors. Clinicians should interpret these recommendations with caution, and apply their own experience and knowledge on a case-by-case basis before implementation.

As the overall pediatric VTE prevention approach is still under active development, there are not yet different recommendations for medical and surgical patients (much less orthopedic versus non-orthopedic surgery) as there are in adults. The perioperative tactics, however, usually involve a truncated risk assessment (usually focused on postpubertal age, obesity, and underlying inflammatory disease, in addition to a personal or family history of thrombosis or thrombophilia) and a primary focus on intraoperative mechanical prophylaxis to help prevent venous stasis related to lack of extremity muscular contraction, as decreased mobility during the procedure is the key factor increasing risk in the acute period. Then, if the patient is discharged home after the procedure ('day surgery'), no further prophylaxis is needed, but if the patient is currently an inpatient or is admitted following the procedure, the approach discussed below can be applied (remembering that prolonged decreased mobility may occur, depending on the type and extent of surgery, as well as increased inflammation related to postsurgical tissue healing).

In all cases, pharmacological thromboprophylaxis should only be considered in the absence of contraindications (active or potential bleeding, severe thrombocytopenia, hemodynamic instability, or imminent/urgent surgical procedure). Owing to the lack of clear recommendations surrounding this topic, decisions about VTE prophylaxis made at the individual patient level (i.e. outside of any existing institutional guidelines) should involve input from

Table 1 Clinical characteristics associated with increased venous thromboembolism (VTE) risk in children (listed alphabetically, owing to the current lack of expert consensus or robust data regarding relative risk contributions)

Anticipated hospitalization > 72 h*,†
Cancer (active, not in remission)†
Central venous catheter presence*,†
Estrogen therapy started within the last 1 month
Inflammatory disease (newly diagnosed, poorly controlled, or flaring)
Intensive care unit admission*
Mechanical ventilation*
Mobility decreased from baseline (Braden *Q*-score < 2)†
Obesity (BMI > 99th percentile for age)
Postpubertal age
Severe dehydration, requiring intervention†
Surgery > 90 min within last 14 days†
Systemic or severe local infection (positive sputum/blood culture or viral test result, or empirical antibiotics)†
Trauma as admitting diagnosis

BMI, body mass index. *Risk factors identified by a recent meta-analysis of the pediatric healthcare-associated VTE literature [4]. †Risk factors defined in a recent publication from the ISTH Pediatric SSC [18].

Table 2 Suggested thromboprophylactic interventions by venous thromboembolism (VTE) risk category

	VTE low (0–1 RFs)*	VTE medium (2 RFs)*	VTE high (≥ 3 RFs)*
Bleed low (unlikely to bleed)	Early mobilization	Early mobilization Mechanical	Early mobilization Mechanical Pharmacological
Bleed medium (moderate bleeding potential)	Early mobilization	Early mobilization Mechanical	Early mobilization Mechanical ± Pharmacological
Bleed high (current bleeding or high bleeding potential)	Early mobilization	Early mobilization Mechanical	Early mobilization Mechanical

RF, risk factor. *Defined by number of RFs from Table 1.

a pediatric hematologist, especially if there is any question about dosing or balancing measures (skin disturbances for mechanical prophylaxis, or bleeding for pharmacological prophylaxis). Additionally, an important component after initiation of prophylaxis is evaluation for adverse effects or the balancing measures mentioned above. Finally, risk status should be assessed upon admission and then frequently re-evaluated (e.g. at least every 7 days) to incorporate any changes in clinical status that may mean moving into or out of the risk group for which prophylaxis is appropriate.

Anticoagulant therapy: which agent, intensity, and duration?

This section critiques evidence relating to the selection of agent, intensity and duration of the most commonly used anticoagulants (unfractionated heparin [UFH], low molecular weight heparin [LMWH], and warfarin) in children between 2007 and 2017. This review is not intended to be a stand-alone resource for therapeutic anticoagulation in children. Rather, this review is an adjunct to prior literature already informing treatment guidelines, and serves to highlight more recent knowledge published in this area. The search strategy and results for publications included in this article are detailed in Fig. 1A,B. Whereas there is clarity regarding dose discrimination between prophylactic and therapeutic doses of UFH and LMWH [22], the literature regarding therapeutic intensity for warfarin does not clearly discriminate between primary prophylactic, secondary prophylactic and therapeutic doses. Therefore, this review discusses any of these indications for warfarin, while focusing on therapeutic indications for UFH and LMWH. Owing to the complexity of antithrombotic regimens associated with extracorporeal circuits and ventricular assist devices, these indications are not included in this review. Similarly, owing to the space constraints of this State of the Art article, less frequently used anticoagulant agents are not included.

UFH

One systematic review [23], one RCT [24–26] and several observational studies were identified by the search. Across all study cohorts, UFH was predominantly used in critical care areas, including pediatric and neonatal intensive care and cardiac angiography suites, where its short half-life and full reversibility is of greatest value. The age-dependent variation in UFH dose requirements across childhood was supported by pharmacokinetic (PK) data for the first time in 2017, confirming age variation in half-life and clearance, with UFH pharmacokinetics varying between neonates, children, and adults [27].

Hanslik *et al*. concluded from their RCT of UFH in the angiography suite that 75 unit kg^{-1} may be the optimal dose of UFH for the prevention of thrombosis during angiography, based on clinical and laboratory outcomes [24–26]. This conclusion was based on the supratherapeutic laboratory parameters associated with the 100 unit kg^{-1} arm, the relatively quick clearance of UFH effect from the 50 unit kg^{-1} arm, and the lack of clinically significant difference in rates of thrombosis and hemorrhage between the two. Although UFH was administered for a different indication than the treatment of VTE, these data may inform bolus dose selection in the setting of commencing therapeutic UFH treatment [28].

Al Obary *et al*. [29] reported UFH clinical and laboratory outcomes, comparing historical controls with a prospective, nomogram-managed pediatric cohort [30]. Nomogram adherence resulted in a shorter time to therapeutic activated partial thromboplastin time (APTT) achievement and a reduced number of APTT tests. Infants required a greater number of APTT tests than older children, significant dose escalation as compared with older children, and a longer period of time to achieve target APTT ranges than older children [29,31]. Perhaps in recognition of this, Ryerson *et al*. reported the implementation of an antithrombin (AT) concentrate replacement protocol in a cohort of pediatric patients, predominantly aged < 1 year [32]. The study demonstrated that a single, high dose of AT concentrate increased target range achievement and reduced UFH requirements. However, this resulted in infants requiring a significantly lower UFH dose than expected based on age-related dosing recommendations (19 units kg^{-1} h^{-1} versus 28 units kg^{-1} h^{-1}). In the absence of evidence to suggest that UFH dose alone is associated with adverse outcomes, AT concentrate replacement and the resulting UFH dose reduction does not appear to be clinically significant, particularly in light of concerns raised regarding the non-hematological properties of by AT [33].

Laboratory monitoring of UFH with the APTT, the anti-activated factor X (FXa) and anti-activated FII (FIIa) assays, the thrombin clotting time and protamine titration has been reported [25–28,31,34,35]. Themes arising from these studies include the poor correlation between UFH dose and measures of UFH effect (APTT, anti-FXa, anti-FIIa, and TCT) [34], the lack of agreement between different measures of UFH effect [25,26,28,34–36], the lack of correlation between UFH concentration (protamine titration) and measures of UFH effect [28,35], and the variable influences that patient age and UFH concentration have upon measures of effect [25,26,28,35]. These data are somewhat in conflict with the often positive clinical outcomes achieved with UFH in cohorts of often critically ill children. For example, despite low rates of target range achievement (determined with APTT and anti-FXa assays), clinical outcomes in terms of clot resolution [31], thrombosis prevention [24] and low rates of UFH-associated major bleeding [24,29] suggest that the use of weight-based UFH dosing achieves outcomes that may be safe and

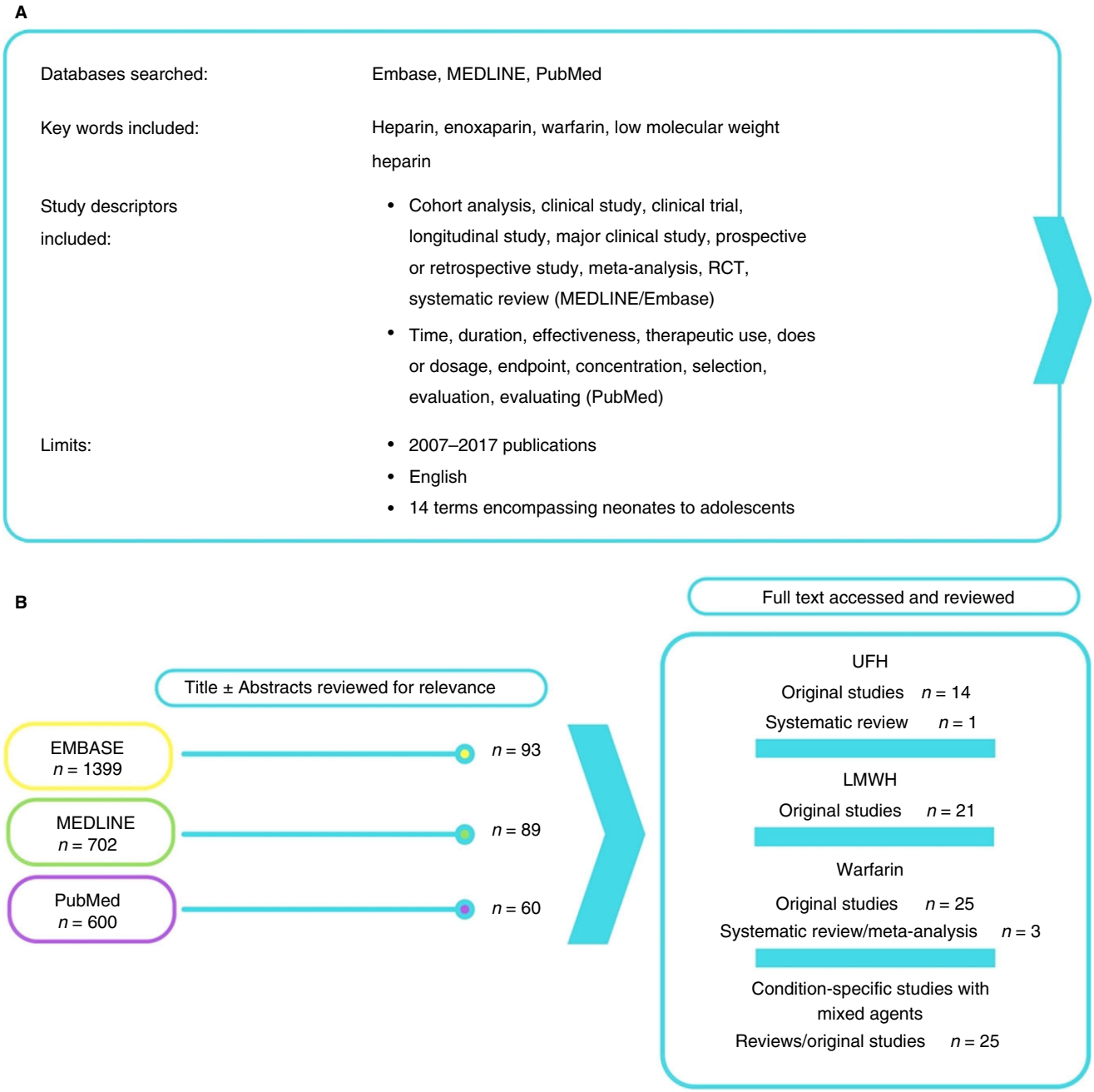

Fig. 1. Literature search strategy (A) and results (B): Anticoagulant therapy-which agent, intensity, and duration. LMWH, low molecular weight heparin; RCT, randomized controlled clinical trial; UFH, unfractionated heparin. [Color figure can be viewed at wileyonlinelibrary.com]

efficacious despite the lack of certainty regarding optimal laboratory management strategies.

LMWH

The cohort studies identified via this search strategy reported data regarding LMWH mode of administration, dose responsiveness, laboratory management and clinical outcomes associated with enoxaparin, dalteparin, and tinzaparin. The patients in these studies were often neonates, infants or very young children requiring anticoagulant therapy for the treatment of thromboses. Although LMWH is predominantly administered subcutaneously, twice daily, Diab *et al.* and Crary *et al.* both reported outcomes associated with intravenous LMWH administered either twice or three times daily [37,38]. The clinical outcomes associated with twice-daily intravenous LMWH administration were acceptable; however, more frequent intravenous dosing of LMWH may be required, as the majority of patients had subtherapeutic anti-FXa levels

6–8 h postdose [37,38]. Clearance of LMWH was explored in the PK study conducted by Trame *et al*., who reported comparable clinical outcomes between patients receiving once-daily enoxaparin and those receiving twice-daily enoxaparin [39]. With > 50% of patients having a 24-h trough level greater than the desired 0.1 IU mL^{-1}, the authors concluded that once-daily dosing was suitable for 50% of their cohort; however, no data were provided to aid in the selection of patients in whom once-daily dosing may produce acceptable outcomes.

Achieving therapeutic levels of LMWH effect is challenging in neonates and infants. Infants were less likely to achieve a therapeutic anti-FXa level on their first monitoring test [40–44], were more likely to require multiple dose escalations [40,43,45–48], and took more days of therapy to achieve a therapeutic anti-FXa level [43–45,47,48]. Several studies confirmed different mean dose requirements for neonates and infants, with neonates requiring between 1.62 mg kg^{-1} and 2 mg kg^{-1} twice daily, as compared with infants' requirements of 1.12–1.9 mg kg^{-1} twice daily [40,41,46–48], both of which are greater than the recommended starting doses of 1 mg kg^{-1} for children and 1.5 mg kg^{-1} for neonates and infants up to 2 months of age [22]. Compounding this age-related difference in dose requirements is the known assay-dependent variability reported by Greene *et al*. [49]. Assay-related differences were reported to impact on dose requirements and time to therapeutic range achievement. Given these concerns, the authors suggested that weight-based, unmonitored LMWH therapy may achieve outcomes comparable to those of laboratory-monitoring therapy [49,50]. This conclusion is somewhat reinforced by findings of multiple studies that have failed to confirm any association between achievement of a laboratory-confirmed target range and either thrombosis resolution or bleeding rates [42,47,48]. Adverse events associated with LMWH were predominantly reported in neonates. Malowany *et al*. reported a 56% adverse event rate (hematoma, induration, and blood leakage from insertion site) associated with subcutaneous catheters in their cohort of neonates receiving LMWH [48]. In addition, there were two LMWH-associated fractures secondary to osteopenia in this cohort of 16 neonates, raising an ongoing concern regarding the longer-term use of LMWH in neonates with respect to bone health.

Warfarin

The publications included in this review primarily reported warfarin use in children for primary and secondary thromboprophylaxis in the setting of cardiac disease, including Fontan surgery, prosthetic valves, cardiomyopathy, and Kawasaki disease. Two studies included children requiring warfarin therapy for the treatment of VTE or stroke [51,52]. Following the initiation of heparinoid therapy [22], warfarin is the agent of choice for longer-term (> 3 months) therapeutic-intensity anticoagulation in children. This recommendation relates to the complication of heparin-induced osteoporosis and fractures associated with longer-term LMWH therapy [48]. We acknowledge that cessation of LMWH therapy may not be feasible in some clinical scenarios, e.g. polypharmacy or when there are frequent requirements for interruption of anticoagulant therapy. Furthermore, one of the less frequently used anticoagulants in children, fondaparinux, or, in the future, some of the DOACs may become more widely recommended for use in children requiring longer-duration anticoagulant therapy, in order to preserve bone health.

Two studies, including one RCT, reported that warfarin is not superior to aspirin in children following the Fontan procedure [53,54]. However, the thrombosis event rates in both RCT arms were suboptimal (24% with warfarin; 21% with aspirin) [54]. The Iyengar study [53] reported a lower thrombosis rate (8%); however, no predetermined imaging or follow-up was used, so the true event rate could be higher. An interesting subanalysis of data from the RCT suggests that even a relatively modest rate of target therapeutic range achievement (> 30%) may confer a reduced thrombotic risk as compared with those children who achieved their target International Normalized Ratio (INR) range for < 30% of the time (hazard ratio 5.95; 95% confidence interval 2.01–31.9) [54].

Across the remaining cohorts of children, rates of target INR achievement ranged from 44% to 59% [55–58]. Reported risk factors associated with elevated INR levels include length of hospital stay, elevated baseline INR, cardiac surgery, obesity, Asian descent, and early commencement of warfarin therapy [51,52,59]. Only Crone *et al*. [59] investigated the possible impact of patient deconditioning and vitamin K intake or fasting upon the INR response to warfarin. Since 2010, 13 original studies [60–72] and two meta-analyses [73,74] focused on warfarin pharmacogenomics have been published, and these were identified with this search strategy. Data synthesis of these studies confirms that the identified vitamin K epoxide reductase complex subunit 1 (*VKORC1*) and cytochrome P450 2CP (*CYP2CP*) variants probably contribute to a reduction in warfarin dosing requirements as compared with wild-type alleles; however, all studies were conducted in patients with warfarin steady states, and most studies had small cohorts with limited ethnic diversity. In addition, the pharmacogenomics studies conducted to date have not adequately imputed the contribution of known common confounders of stable warfarin therapy, such as changes in diet, medications or wellness states, into their dosing algorithms.

Despite the modest rates of target INR achievement reported in these studies, the rate of thrombosis was zero in all studies [56–58], except for children with Kawasaki disease (22%) [55]. Major bleeding rates ranged from 1.3% to 12% in four studies [52,56–58], with Baker *et al*.

reporting, again, a higher rate of warfarin-related adverse events in children with Kawasaki disease, who had a rate of major bleeding of 33% (concomitant aspirin therapy) [55].

Anticoagulant therapy duration

Evidence regarding the optimal duration of anticoagulant therapy for the treatment of thrombotic disease in children is limited [75]. There is a growing school of thought that thromboses triggered by temporary factors, such as short-term CVCs, may require a shorter duration of treatment than unprovoked thromboses. This is the underlying premise behind the Kids-DOTT trial, investigating clinical outcomes associated with a shortened duration of anticoagulant therapy [76]. In the meantime, recommendations relating to the optimal treatment duration for thromboses in childhood remain largely based on data extrapolated from studies in the adult population.

DOACs – are we ready to use them in children?

The classical anticoagulants have several limitations for use in children [22]. For heparins, the anticoagulant effect is dependent on endogenous AT, the level of which which is physiologically low in neonates and may be decreased in sick children. Additionally, UFH has highly unpredictable PK and pharmacodynamic (PD) properties. Vitamin K antagonists have a slow onset and a slow offset, are strongly influenced by dietary intake, and show several drug interactions. All of these drugs require regular monitoring and dose adjustments. Finally, none of the classical anticoagulants has been systematically developed and licensed for children, so they lack age-appropriate formulations, and dosing, efficacy and safety are based on empirical evidence.

Recently, the DOACs have been developed for adults, and they are now approved for several indications for the prevention and treatment of thrombosis (Table 3) [77]. In adults, DOACs have established efficacy and safety in these indications that are at least non-inferior to those of the classical anticoagulants, without the need for monitoring of anticoagulant levels [78]. On the basis of their pharmacological properties and clinical results from adults, the DOACs have several potential advantages making them particularly suitable for children: oral administration, predictable pharmacokinetics, no AT dependence, little food interaction, few drug interactions, a wider therapeutic window, and possibly no monitoring requirements.

As a result of new legislation in the USA and EU concerning pediatric medicine development [79,80], all DOACs have Pediatric Investigation Plans (PIPs) agreed with the regulatory agencies [81], some of which have already progressed quite far [11]. Therefore, we may expect most DOACs to be eventually licensed for children, with pediatric formulations and systematic information regarding age-specific dosing, efficacy and safety available.

Pediatric investigation plans for DOACs

Table 4 lists the indications targeted by current PIPs for rivaroxaban, dabigatran, apixaban, edoxaban, and betrixaban, comprising prevention of VTE, prevention of arterial/cardiac thromboembolism (TE), and treatment of acute VTE. Details on individual PIPs and their timelines and current status are shown in Table S1 [11,81]. Generally, PIPs for DOACs consist of the following elements, as outlined by a recommendation by the Pediatric SSC of the ISTH [82].

An important element of a PIP is the development of pediatric formulation(s) that ensure reliable and accurate

Table 3 Indications and doses for direct oral anticoagulants currently approved for adults*

	Prevention of VTE	Prevention of cardiac, arterial TE	Treatment of VTE
Rivaroxaban (Xarelto)	Hip/knee replacement 10 mg once daily	Atrial fibrillation 20 mg once daily Acute coronary syndrome 2.5 mg twice daily and dual antiplatelet therapy	VTE treatment 15 mg twice daily for 3 weeks, 20 mg once daily
Dabigatran (Pradaxa)	Hip/knee replacement 110 mg (first dose), 220 mg once daily	Atrial fibrillation 150 (110) mg twice daily	VTE treatment LMWH for 1 week, 150 mg twice daily
Apixaban (Equilis)	Hip/knee replacement 2.5 mg twice daily	Atrial fibrillation 5 mg twice daily	VTE treatment 10 mg twice daily for 2 weeks, 5 mg twice daily
Edoxaban (Lixiana, Roteas)	–	Atrial fibrillation 60 mg once daily	VTE treatment LMWH for 1 week, 60 mg once daily
Betrixaban† (Bevyxxa)	Medical illness at risk for VTE 160 mg (first dose), 80 mg once daily	–	–

LMWH, low molecular weight heparin; TE, thromboembolism; VTE, venous thromboembolism. *Based on the EU marketing authorization. †Currently only approved by the US Food and Drug Administration (2017).

Table 4 Indications targeted by current Pediatric Investigation Plans for direct oral anticoagulants

	Prevention of VTE	Prevention of cardiac, arterial TE	Treatment of VTE
Rivaroxaban	–	Post-Fontan surgery, versus aspirin	Acute VTE
Dabigatran	–	–	1. Acute VTE 2. Extended secondary prevention
Apixaban	Acute leukemia with central venous catheter, versus placebo	Various cardiac diseases, versus LMWH/VKA	Acute VTE
Edoxaban	–	Various cardiac diseases	Acute VTE
Betrixaban	1. Medical illness or surgery 2. Neonates/preterms with umbilical catheter	–	–

LMWH, low molecular weight heparin; TE, thromboembolism; VKA, vitamin K antagonist; VTE, venous thromboembolism.

administration of the medicine to children of different ages, including studies to establish bioequivalence with the adult formulations. All pediatric developments are built upon existing data from adult studies. PK/PD studies in children should be optimized by incorporating information from adults and other sources using sophisticated tools such as physiologically based PK/PD models and population PK/PD modeling and simulations. A pediatric physiologically based PK model has been published for rivaroxaban, with PK data from adults and physiological information from children [83]. The model predicted that, in children with a body weight of < 40 kg, relatively higher weight-related doses will be required, owing to differences in medicine uptake, metabolization, and clearance. These predictions were eventually confirmed by actual PK data from children from the phase 1 and 2 pediatric rivaroxaban studies [84–86].

In vitro concentration–response studies performed with plasma from healthy children of different age groups spiked with the anticoagulant at increasing concentrations may be a means to explore whether differences in the coagulation system affect the age-specific drug concentration–anticoagulant effect (PD) relationship. *In vitro* studies have been published for rivaroxaban [87,88], dabigatran [89], and apixaban [90], and have essentially shown no relevant differences in concentration–response relationships between adults and children down to infant age, but some small differences in neonatal plasma [88,90].

Most DOAC PIPs perform single-dose PK/PD studies for initial dose-finding and safety assessment in children of all age groups. Only the dabigatran PIP involved a multiple-dose PK/PD study performed over a period of 3 days in adolescents [91], but it proceeded with single-dose assessments in younger children [11,81]. The rivaroxaban PIP has an intermediate step of a phase 2, dose-confirmation and safety study performed over the last 4 weeks of anticoagulation therapy for acute VTE [11,81], whereas all other programmes continue from their single-dose PK/PD studies immediately to phase 3 efficacy and safety studies. The PK/PD studies for rivaroxaban and dabigatran are almost completed, and have recently been reported as posters at the 2017 ISTH congress [84–86,92].

For phase 3, all PIPs targeting the indication of VTE treatment comprise open-label RCTs comparing the respective DOAC with standard-of-care (SOC) anticoagulants for the whole length of anticoagulant treatment after acute VTE, usually 3 months. Apart from treatment of acute VTE, the dabigatran PIP contains a long-term study targeting extended secondary prevention. These studies have rather limited patient numbers, i.e. between 150 and 270, and are not powered to independently demonstrate efficacy or safety in children. These approaches build on extrapolation from adults, based on the concept that VTE treatment is reasonably similar between children and adults. The pediatric trials aim to confirm the proof of efficacy from adults and account for potential differences in outcome frequencies.

For the indication primary prevention of VTE, the apixaban PIP has an ongoing study in children with acute leukemia or lymphoma, treatment with asparaginase, and the presence of a CVC (PREVAPIX-ALL). As there has never been a clear proof-of-concept for anticoagulant prophylaxis to prevent CVC-related VTE, in either in adults or children, apixaban is compared with placebo in a fully powered RCT ($n = 500$). The apixaban PIP is the most comprehensive, as it also runs a study targeting primary and secondary prevention in children with congenital and acquired cardiac diseases. This RCT compares apixaban with SOC anticoagulants for a duration of up to 1 year in 150 children. Prevention of cardiac TE, specifically in children after Fontan surgery, is also targeted by an ongoing study comparing rivaroxaban with aspirin [11]. A study for prevention of cardiac TE has also been agreed for the edoxaban PIP, but there is no public information available on its current status [11,81]. Betrixaban, which has a longer half-life than the other DOACs, has recently been approved by the US Food and Drug Administration for the prevention of VTE in medically ill adults [93]. A PIP has been agreed, but has not

started, which will target children with medical illness or surgery at risk of VTE, and neonates/preterms with umbilical vein/artery catheters [11,81].

Given the potent anticoagulant effect of DOACs, there is a need for agents to reverse anticoagulation for emergency surgical procedures or in case of major hemorrhages. A reversal agent specific for dabigatran, idarucizumab, has been (conditionally) approved for adults [94], and an agent specific for FXa inhibitors, and exanet alpha, is under development [95]. There is an ongoing PIP for idarucizumab, comprising a single-dose study of idarucizumab used as rescue medication in children, and a registry of all pediatric patients treated with idarucizumab [11,81]. Also, there is an agreed PIP, which is not yet ongoing, for andexanet alpha, with single-dose studies to evaluate the pharmacokinetics/pharmacodynamics of andexanet alfa, administered at the end of anticoagulant treatment with either enoxaparin, rivaroxaban, apixaban, edoxaban or betrixaban to children of all age groups [11,81].

Several PIPs target similar indications, particularly VTE treatment, and thus are competing for study patients worldwide, which aggravates the feasibility challenges inherently present with pediatric drug studies. There are ongoing efforts to streamline these parallel pediatric developments to ensure they target diverse indications and address the whole spectrum of pediatric needs [96].

Conclusions

Are we ready to use the DOACs in children? All of the currently approved DOACs have pediatric developments ongoing or planned, some of which have substantially progressed into phase 3 studies. Given the pharmacological properties of the DOACs and the special characteristics of children requiring anticoagulation, the DOACs have the potential to be of particular benefit for children. Pediatric formulations have been developed and are being tested in the ongoing studies. The key for use in children will be to have explicit age-appropriate dosing information available. Whether and in which situations there will be the need for therapeutic drug monitoring and dose adaption in children still has to be elucidated. The results of clinical studies in children will have to demonstrate whether there is a positive benefit–risk balance for DOACs in all targeted pediatric indications and age groups. This accounts particularly for indications that have not been explored in adults, such as prevention of CVC-related VTE, or pediatric cardiac indications such as Fontan surgery. Given the negative benefit–risk profile of DOACs in adults with mechanical heart valves [97], owing to insufficient suppression of thrombin generation [98], their efficacy could potentially be different in sick children with various intravascular artificial surfaces (CVC, shunts, stents, etc.). It will not be possible to answer all of these questions from pre-authorization studies in children, so post-authorization studies will be required to generate further data on long-term safety and efficacy, neonates/prematures, and other pediatric special disease populations.

A number of case reports of the use of DOACs in children have already appeared in the literature [99,100]. However, the DOACs should not be used off-label, which puts children at risk, because there is still insufficient systematic information available on dosing, efficacy, and safety. Moreover, off-label use jeopardizes the recruitment of children into comparative studies, through loss of equipoise. Given the unique chances of systematic pediatric developments of DOACs and the challenges of performing drug studies in children, all efforts should currently go into treating children within the ongoing studies. In conclusion, we are not yet ready to use the DOACs in children in clinical routine. On the basis of the time plans of current PIPs and their actual status, we may expect pediatric market authorizations for some of the DOACs by the early 2020s.

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Disclosure of Conflict of Interests

C. Male reports receiving consulting and speaker honoraria, travel support and study patient fees from Baxalta/Shire and Bayer; grants, speaker honoraria, travel support and study patient fees from CSL Behring; speaker honoraria, travel support and study patient fees from Biotest and Novo Nordisk; speaker honoraria, manuscript support and study patient fees from Boehringer Ingelheim; consulting honoraria and study patient fees from Bristol-Myers-Squibb; speaker honoraria from Sobi; and consulting fees and speaker honoraria from Roche, outside the submitted work. The other authors state that they have no conflict of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Current Pediatric Investigation Plans for direct oral anticoagulants.

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