Thrombosis Research 235 (2024) 186–193

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Anticoagulation of pediatric patients with venous thromboembolism in 2023

C. Heleen van Ommen *, Saskia E. Luijnenburg

Department of Pediatric Hematology, Sophia Children's Hospital, Erasmus MC, Rotterdam, the Netherlands

ARTICLE INFO

Keywords:
Pediatrics
Venous thromboembolism
Heparin
Vitamin K antagonist
Oral factor IIa inhibitor
Oral factor Xa inhibitor

ABSTRACT

Venous thromboembolism (VTE) is a rare and heterozygous disease in children. Management of VTE in children is complicated by age-related differences in epidemiology, recurrent VTE and bleeding risk, hemostatic proteins and pharmacokinetics of anticoagulants. Recently, the choice of anticoagulation has expanded to oral factor IIa and Xa inhibitors, which have been authorized for children for treatment of acute VTE and extended secondary prevention. These drugs have several properties that make them extremely suitable for use in children, including oral administration, antithrombin independence, less interactions with food and drugs and no need for monitoring. Unfortunately, the phase 3 studies had many exclusion criteria, and only a few term neonates and infants were included in these studies. Additional real-world data is needed to make evidence-based recommendations in these age and patient groups, as well.

1. Introduction

The management of venous thromboembolism (VTE) in pediatric patients is challenging. Pediatric VTE is uncommon (1 in 100.000), although its incidence is rising, mostly in hospitalized neonates and children with complex underlying diseases [1–3]. In addition, pediatric VTE is not only a rare, but also a heterogeneous disease regarding patient age, comorbidities, risk factors and anatomical locations, with each type of VTE having its unique pathophysiology, and short- and long-term consequences. Consequently, large clinical management trials are lacking in both neonates and children with VTE. Many recommendations for treatment of pediatric VTE are still extrapolated from adult studies despite several age-dependent differences, including differences in epidemiology of VTE, in pharmacokinetics and pharmacodynamics of anticoagulant drugs, in bleeding risk, and in hemostatic proteins, which vary over time from neonatal age to adulthood [4,5].

Anticoagulation is the standard-of-care for acute symptomatic pediatric VTE. The aims of anticoagulation are to prevent mortality and reduce the risk of extension, embolization, recurrent thrombosis and post thrombotic sequelae. Until recently, anticoagulation in pediatric VTE patients mainly consisted of unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and vitamin K antagonists (VKA) [6]. All these agents have drawbacks [7]. Both UFH and LMWH need to be administered parenterally. The anticoagulant function of heparins is accomplished by potentiating the inhibitory effects of endogenous antithrombin on several coagulation factors. Unfortunately, antithrombin levels may be very low in neonates and in critically ill children, causing heparin resistance. Heparin monitoring is challenging as measurement of anti-Xa levels and activated partial thromboplastin time (aPTT) require intravenous access, which can be very problematic for children. VKAs can be administered orally, but they show many interactions with food and drugs, and require frequent international normalized ratio (INR) monitoring. Furthermore, none of these anticoagulants has been authorized for children, with the exception of dalteparin in the United Stated, based on a small pediatric study [8]. Consequently, age-appropriate dose strengths and formulations, such as oral suspension or solutions, are not commercially available. Currently, the use of oral factor IIa and Xa inhibitors in children is increasing as dabigatran and rivaroxaban have shown to be as effective and safe as standard-of-care (SOC) for treatment of acute pediatric VTE and extended secondary prevention and are approved by regulatory authorities [9,10]. They have a fast onset and exert their effect directly (not via antithrombin), are administered orally, do not require monitoring, and have fewer interactions with drugs and food. However, they may not be ideal in every situation. In this review, we will give an overview about the current management options for VTE in pediatric patients, focusing on the use of dabigatran and rivaroxaban, reveal research gaps and discuss practical aspects of the most frequently used anticoagulants.

* Corresponding author at: Department of Pediatric Hematology, Erasmus MC Sophia Children's Hospital, Postbus 2060, 3015 CN Rotterdam, the Netherlands.
E-mail address: c.vanommen@erasmusmc.nl (C.H. van Ommen).

https://doi.org/10.1016/j.thromres.2023.12.019
Received 30 September 2023; Received in revised form 24 December 2023; Accepted 24 December 2023
Available online 10 February 2024

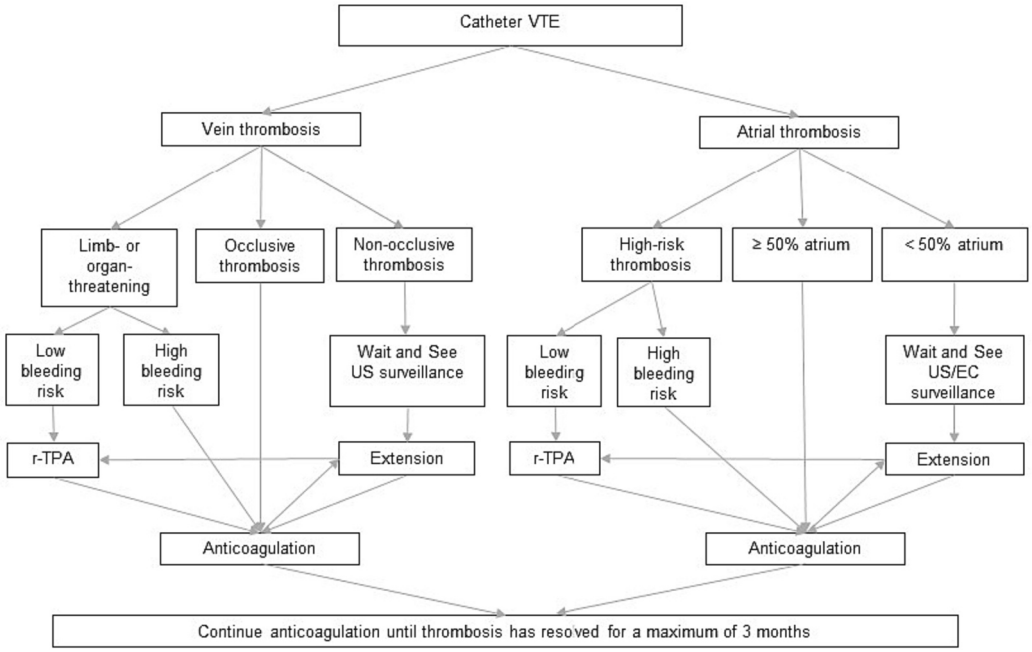

Fig. 1. Proposed management algorithm for neonatal catheter-related venous thrombosis. Abbreviations: r-tPA recombinant-tissue plasminogen activator, US ultrasonography, EC Echocardiography, VTE venous thromboembolism.

2. Management of venous thromboembolism in neonates

Neonatal venous thrombosis can roughly be divided into three groups: 1. neonatal catheter-related venous thrombosis (CVTE), 2. neonatal renal vein thrombosis (RVT) and 3. neonatal cerebral sinovenous thrombosis (CSVT). Studies evaluating the management of neonates with VTE are limited. Various treatment options have been recommended: 1. no antithrombotic therapy and monitoring, 2. anticoagulation (mainly UFH and LMWH), and 3. thrombolytic therapy [6,11]. Thrombectomy is rarely reported as experience with microsurgery is limited. The role of factor IIa and Xa inhibitors still need to be established in neonates, as will be discussed below. Before the start of antithrombotic treatment in neonates, it is important to consider the (bleeding) risks and benefits of all the above-mentioned options in each patient.

2.1. Neonatal catheter-related venous thromboembolism

CVTE is by far the largest group of neonatal VTE: >90 % of neonatal VTE is associated with central venous catheters [12]. The reported incidences of neonatal CVTE varied between 2.4 and 38 per 1000 admissions on the neonatal intensive care unit [13–15]. Presenting symptoms included unexplained thrombocytopenia, ongoing sepsis, swollen limb, and occlusion of the catheter [15]. Mortality and morbidity data are scarce. Mortality varied between 0.9 and 3.7 % [16,17]. Recurrent VTEs occurred in about 2 to 3 % in infants <3 months [18]. In about 16 % of neonates, mild post thrombotic syndrome (PTS) occurred with increased extremity circumference and the development of collateral veins [19].

In CVTE, the most recent American Society of Hematology (ASH) guideline recommends removal of the catheter if it is no longer required or dysfunctional, and suggests no removal, if the catheter is still required and functional [6]. Recent studies showed that the catheter can be removed without prior anticoagulation [15,20].

In 2014, Park et al. proposed an algorithm for diagnosis and management of CVTE in neonates based on their systematic review of published studies, which included case series and single case reports [21]. The treatment choice in this algorithm was especially based on the presence or absence of symptoms, thrombus propagation and the presence of limb or organ compromise. A wait-and-see policy was advised for asymptomatic VTE, anticoagulation (UFH or LMWH) for thrombus propagation and symptomatic VTE, and thrombolysis for major VTE with limb or organ compromise.

Recently, the results of the "NEOnatal Central-venous Line Observational study on Thrombosis (NEOCLOT): evaluation of a national guideline on management of neonatal CVT" were published [15]. This was a prospective multicenter observational study investigating the outcomes of implementation of the consensus based NEOCLOT guideline in the Netherlands. In the NEOCLOT guideline right atrium CVTE was distinguished from venous CVTE. Treatment choice depended on the obstruction of venous CVTE, the size of right atrium CVTE and the presence of high-risk VTE features. A wait-and see policy was advised for non-obstructive venous CVTE, and right atrium VTE obstructing less than half of the atrium. Anticoagulation (preferably LMWH) was advised in obstructive venous CVTE and right atrium VTE obstructing half or more of the right atrium. Thrombolysis with recombinant- tissue plasminogen activator (r-tPA) was advised for specifically defined high-risk VTE. The maximum duration of antithrombotic therapy was 3 months. However, if at an earlier stage ultrasonography showed that thrombosis had resolved, antithrombotic therapy could be stopped.

The NEOCLOT study included 115 infants <6 months old with CVTE (62 % male, 79 % preterm). The study showed a low rate of mortality ($n = 1$, 0.9 %) and recurrent VTE ($n = 2$, 1.7 %). Major bleeding occurred in 9 infants (7.8 %): 2 of 7 (29 %) infants on r-tPA and 7 of 63 (11 %) infants on LMWH. Five of 7 LMWH bleedings were complications of subcutaneous catheter use for administration. Seven of 9 infants with high-risk thrombi started on LMWH instead of thrombolysis as advised by the guideline because of increased bleeding risk as judged by the treating physicians. In 5 of them (71 %), the thrombi became smaller on LMWH and lost their high-risk features. In 2 infants, treatment was changed to thrombolysis after extension of thrombosis on LMWH, with good results. So, the safety of the NEOCLOT protocol can probably be improved by using LMWH with high initial doses as potential first choice treatment option for high-risk right atrium thrombosis and by frequent inspection or avoidance of subcutaneous catheters for LMWH administration (Fig. 1). In addition, radiologic follow-up in all infants with wait-

Table 1
Decision making in anticoagulant treatment of pediatric venous thromboembolism.

STEP 1				
Considerations	• Age group • Bleeding risk • Recurrence risk • Developmental hemostasis		• Renal function • Liver function • Diet • Prick fear	• Vascular access • Underlying conditions • Co-medication • Adherence

STEP 2	Anticoagulant	Route of administration	Indication	Disadvantages
Initial therapy	Low-molecular-weight heparin	Subcutaneous	All children	Subcutaneous injections Monitoring Renal excretion Antithrombin dependent
	Unfractionated heparin	Intravenous	In high-risk patients due to short half-life, available antidote, nonrenal clearance	Intravenous administration Monitoring Antithrombin dependent Risk of heparin-induced thrombocytopenia

STEP 3				
Maintenance therapy	Low molecular weight heparin	Subcutaneous	(Preterm) neonates, young infants Children without enteral feeding Children with frequent interruptions, such as lumbar punctures in leukemia	Subcutaneous injections Monitoring Renal excretion Antithrombin dependent
	Vitamin K antagonist	Oral	Children with enteral feeding Preferable not in neonates and young infants Children who cannot use direct factor IIa or Xa inhibitor	Frequent INR monitoring Frequent food and drug interaction No commercial liquid formulation Bridging needed Risk of osteoporosis with prolonged use
	Factor IIa inhibitor (dabigatran)	Oral	Children at least GA 37 weeks, weight > 3rd percentile WHO standards, minimum age 3 m (as soon as able to swallow soft foods) Children with enteral feeding Not in children with GFR < 50 mL/min per 1.73 m^2 or requiring dialysis Not in children with persistent elevated liver enzymes Not in antiphospholipid syndrome Not in patients with mechanical heart valves	Some drug interaction Renal excretion
	Factor Xa inhibitor (rivaroxaban)	Oral	Children at least GA 37 weeks and body weight >2600 g. Children with enteral feeding Not in children with GFR < 30 mL/min per 1.73 m^2 Not in infants <1 year with serum creatinine >97.5th percentile Not in children with persistent elevated liver enzymes Not in antiphospholipid syndrome Not in patients with mechanical heart valves	Some drug interaction Renal excretion

Abbreviations: GA gestational age, GFR Glomerular filtration rate, WHO World Health Organization, INR International Normalized Ratio, m months.

and-see policy is indicated to detect extension of thrombosis, specifically in infants with symptomatic CVTE.

2.2. Neonatal renal vein thrombosis

Renal vein thrombosis (RVT) is the most frequent non-catheter related VTE in neonates. Its incidence was estimated to be 2.2 to 2.6 per 100.000 live births [22]. The diagnosis is usually made within the first three days after birth [23,24]. The classical triad of presenting symptoms includes palpable flank mass, hematuria, and thrombocytopenia [23]. Associated risk factors are asphyxia, prematurity, dehydration, sepsis, maternal pre-eclampsia and diabetes mellitus [24–26]. Neonatal RVT seems to occur more frequently in males than females, is most often unilateral, with a left predominance. The mortality rate is low, but long-term kidney dysfunction is observed in about 70 % of the patients [23,24].

There is no consensus on the management of neonatal RVT. A registry showed that treatment varied greatly among centers [24]. It is not clear whether renal outcomes improve as result of anticoagulation or thrombolytic therapy. Nevertheless, the ASH guideline suggests using anticoagulation in neonates with unilateral RVT and thrombolysis followed by anticoagulation in neonates with bilateral RVT [6]. Neonates with RVT must be followed carefully for renal complications such as hypertension, atrophy, and chronic renal insufficiency. A prospective multicenter observational study with a standardized protocol might be helpful to identify the best treatment strategy for neonates with RVT.

2.3. Neonatal cerebral sinovenous thrombosis

The incidence of neonatal CSVT varied from 1 to 12 per 100.000 neonates in the Dutch registry to 47 per 100.000 neonates in the Canadian registry [27,28]. It occurs more often in males. Neonatal CSVT is a multifactorial disease and risk factors include pre-eclampsia, maternal diabetes, complicated delivery, perinatal asphyxia, sepsis, meningitis and dehydration. About 50 % of neonates with CSVT present within 48 h after birth with seizures or apneas, hypotonia, irritability or poor feeding. Another 25 % presents during the first week. About half of the patients develop some kind of impairment, especially in the presence of parenchymal infarctions [29,30].

Management strategies are based on case-series and expert

consensus. One cohort study of 68 neonates showed that neonatal CSVT may progress without anticoagulation (10/40 neonates, 25 %) compared with 1 of 28 neonates (3 %) on anticoagulation [31]. Anticoagulation seems to be safe, even in neonates with CSVT and thalamic bleeding [29,32]. Therefore, the ASH guideline recommends using anticoagulation in children with CSVT without bleeding and suggests using anticoagulation in children CSVT with intracerebral bleeding [6].

3. Management of venous thromboembolism in children

In children >1 month of age, VTE most frequently occurs in adolescents, with >150 VTE cases per 10,000 admissions in 2019 [2]. More than 90 % of children have one or more underlying clinical conditions with central venous catheters being the most common risk factor, accounting for about 50 % of VTE in children. Other risk factors include congenital heart disease, infection, oral contraception, surgery, malignancy, and immobility [33,34]. Thrombosis locations vary accordingly: in children until 12 years of age, VTE is most often located in the cerebral sinus, as result of asparaginase therapy for treatment of acute lymphoblastic leukemia, or mastoiditis. In adolescents, VTE is particularly located in the lower and upper extremities, and lung. In contrast to adults, spontaneous VTE is rare and occurs in about 2 to 9 % of pediatric patients, especially in adolescents [33]. Symptoms depend on the location of VTE. Each type of thrombosis, such as CVTE, or estrogen-related pulmonary embolism, or mastoiditis induced CSVT has its own acute and long-term sequelae. In general, mortality directly due to VTE is about 2 % in registry data [1,3]. Recurrent VTE occurs in 6 to 11 % of the patients [35–37]. The frequency of post thrombotic syndrome (PTS) varies between 10 and 70 % with a mean frequency of 26 % (95 % CI: 23–28 %) [38].

Overall, management of symptomatic VTE usually consists of anticoagulation unless the child is bleeding or has an increased risk of bleeding. The initial treatment of VTE comprises UFH or LMWH. Thrombolysis can be given in situations when fast clot resolution is needed, such as high-risk pulmonary embolism [39]. LMWH is the preferred initial anticoagulant agent, because it is administered subcutaneously, which allows outpatient management, and requires less monitoring. UFH is mainly given in critically ill patients due to its short half-life. Nowadays, maintenance therapy includes LMWH, rivaroxaban, dabigatran and VKA. The choice depends on many factors including indication, age, VTE recurrence risk, bleeding risk, renal and liver function, diet, co-medication, prick fear, and adherence (Table 1). The duration of treatment depends on the presence and persistence of an underlying risk factor, and the risks of recurrent VTE and bleeding. Until recently, most children with provoked VTE were treated with 3 months of anticoagulation, or longer if the causative risk factor was ongoing [6]. Shorter periods of anticoagulation might be appropriate in some patient groups. This was investigated in the multicenter evaluation of the duration of therapy for thrombosis in children (Kids-DOTT trial) [40]. In this study, 417 patients younger than 21 years of age with provoked VTE were randomized to 6 weeks ($n = 207$) or 12 weeks ($n = 210$) of anticoagulation, if they had no severe anticoagulant deficiencies, no persistent antiphospholipid antibodies and resolved or non-occlusive thrombi upon repeat imaging at 6 weeks after diagnosis. The primary efficacy outcome (symptomatic recurrent VTE within 1 year) occurred in 1 patient (0.65 %) in the 6-week group and in 2 patients (1.40 %) in the 3-month group. The primary safety outcome (clinically relevant bleeding events within 1 year) occurred in 1 patient (0.65 %) in the 6-week group and in 1 patient (0.70 %) in the 3-month group, demonstrating non-inferiority. For children with unprovoked thrombosis, the optimal duration of anticoagulant therapy is unknown. The ASH guideline suggests using anticoagulation for >6 months to 12 months, considering patient values and preferences [6].

4. Dabigatran and rivaroxaban pediatric phase 3 trials

4.1. Dabigatran

The efficacy and safety of dabigatran was studied in a phase 2b/3 trial (DIVERSITY) comparing dabigatran versus SOC in 2:1 ratio in 267 children aged 0 to <18 years of age with acute VTE [9] (Table 4). The study period was 3 months. The used formulations in this study included oral suspension for infants <12 months, oral pellets for children aged 3 months to <12 years and the adult capsules for children aged 8 to <18 years. The pediatric dabigatran dose regimens are age- and weight-based and extrapolated from the adult therapeutic dosage of 150 mg twice daily. Extrapolations were based on the Hayton formula, as dabigatran is predominantly renally excreted [41]. The primary composite efficacy endpoint of the DIVERSITY study included complete thrombus resolution, freedom from recurrent VTE, and freedom from VTE-related death. It was met by 38 of 90 (42 %) patients receiving SOC and 81 of 177 (46 %) receiving dabigatran, showing non-inferiority of dabigatran to SOC. The frequencies of any bleeding and major bleeding were similar in both arms (any bleeding: SOC 24 % vs dabigatran 22 %; major bleeding: SOC 2 % vs dabigatran 2 %).

In a single-arm phase 3 safety study, the outcomes of dabigatran treatment were assessed in 203 children who had an unresolved clinical risk factor requiring extended anticoagulation after anticoagulant treatment for 3 months [42]. The median exposure was 36.3 weeks. Overall, 2 children (1 %) developed recurrent VTE, and 3 (1.5 %) and 2 (1 %) children experienced major and clinically nonmajor bleeding complications, respectively.

4.2. Rivaroxaban

The Einstein-junior phase 3 study compared the efficacy and safety of rivaroxaban with SOC in a 2:1 ratio in 500 children aged 0 to <18 years of age with acute VTE [10] (Table 4). The study period was 1 month for children <2 years of age with CVTE and 3 months in the other children. Patients with extended anticoagulation could be treated with rivaroxaban for up to 12 months. Pharmaceutical formulations consisted of an oral solution for the young patients and film-coated tablets for children ≥12 kg. The pediatric rivaroxaban dose was a body weight-adjusted dose, corresponding to the adult 20 mg therapeutic dose. The primary efficacy outcome symptomatic recurrent VTE occurred in 4 of 335 (1 %) patients on rivaroxaban and in 5 of 165 (3 %) patients on SOC (hazard ratio [HR], 0.4; 95 % confidence interval [CI], 0.1–1.4). The principal safety outcome, major or clinically relevant nonmajor bleeding, occurred in 10 (3 %) of 329 children on rivaroxaban (all non-major) and in 3 of 162 (2 %) children (2 major and 1 non-major) on SOC (HR 1.58, 95 % CI 0.51–6.27). Complete resolution was more frequently observed on repeat imaging in the rivaroxaban group (38 %) than in the SOC group (26 %; odds ratio 1.70; 95 % CI 1.1–2.6).

4.3. Dabigatran and rivaroxaban in specific age and patient groups with venous thromboembolism

Thus, in the pediatric programs for dabigatran and rivaroxaban, pediatric formulations and age-appropriate dosing regimens have been developed, and efficacy and safety have been evaluated in phase 3 trials, leading to authorization of both drugs for treatment of acute VTE and extended secondary prophylaxis in children. However, the phase 3 studies had many exclusion criteria, and it appeared to be difficult to include neonates and young infants in these studies. Further real-life studies and registries, such as the Throm-PED registry of the International Pediatric Thrombosis Network (IPTN), will be helpful in determining efficacy and safety of these new anticoagulants in specific pediatric age and patient groups, some of which are discussed below [43].

4.4. Neonates and infants

Until now, LMWH is still the first choice for initial and prolonged anticoagulation in neonatal VTE. However, oral factor Xa or IIa inhibitors might be compelling alternatives for prolonged anticoagulation. In the DIVERSITY and Einstein-Junior studies, 89 infants <2 years of age were included: 35 infants in the DIVERSITY study (dabigatran $n = 22$; SOC $n = 13$), and 54 infants in the Einstein-Junior study (rivaroxaban $n = 37$; SOC $n = 17$) [9,10]. Preterm neonates, however, were excluded in both studies. Inclusion in the Einstein-Junior study for children younger than 0.5 years required a gestational age at birth of at least 37 weeks, a body weight above 2600 g, and oral feeding for at least 10 days. For inclusion in the DIVERSITY study, infants <2 years were required to have a gestational age ≥37 weeks and a body weight higher than the third percentile (according to the World Health Organization child growth standards). Thus, the results of the DIVERSITY study and Einstein-junior study are not applicable to preterm neonates.

In the DIVERSITY study, the percentage of infants <2 years of age with CVTE or CSVT was not separately reported. Seven of 13 (54 %) infants randomly assigned to standard of care and 13 of 22 (59 %) infants randomly assigned to dabigatran, met the composite efficacy endpoint of complete thrombus resolution and freedom from recurrent venous thromboembolism and venous thromboembolism-related death. None of the infants in both groups died or had recurrent VTE. One infant in the dabigatran group had major bleeding, an epistaxis requiring red blood cell transfusion. In the Einstein-Jr trial, 37 of 54 (69 %) infants <2 years of age had CVTE, and 9 (17 %) had CSVT. None of the infants in both arms died or had symptomatic recurrent VTE. Major bleeding occurred in in 1 of the 17 (6 %) infants in SOC arm (intracranial bleeding) and none of the 37 (0 %) infants in the rivaroxaban arm. Repeat imaging showed complete resolution in 5 (29 %) infants on SOC and in 16 (43 %) infants on rivaroxaban.

Thus, rivaroxaban and dabigatran have only been studied in 59 term infants <2 years of age. More real-life data from prospective cohort studies and registries is needed. The safety of both drugs in this age group will be further studied in two prospective observational post marketing studies (dabigatran: NCT05536791; rivaroxaban: NCT05900388).

4.5. Pediatric patients with catheter-related venous thromboembolism

Three predefined sub-analyses of the Einstein-junior study were published: sub-analyses of children with CVTE, CSVT, and cancer-associated VTE [44–46]. Although a central venous catheter is the most important risk factor for VTE in children, only 126 (25 %) of 500 patients enrolled in the Einstein-junior study had CVTE, symptomatic in 76 children and asymptomatic in 50 children [10]. In the sub-analysis of these 126 children with CVTE ($n = 90$ rivaroxaban, $n = 36$ SOC), no recurrent VTE or major bleeding occurred in either treatment group [44]. Three children in the rivaroxaban group had clinically relevant nonmajor bleeding. None of the children died. Complete or incomplete recanalization was present in 92 % of the symptomatic and 86 % of the asymptomatic CVTE. Unfortunately, because of the low sample size of this sub-study, statistical comparisons could not be made.

4.6. Pediatric patients with cerebral sinovenous thrombosis

In the Einstein-junior sub-analysis of children with CSVT, 114 children were included, 73 in the rivaroxaban group and 41 in the SOC group [45]. Recurrent VTE occurred in none of the rivaroxaban recipients and 1 (2.4 %) of the SOC recipients. Bleeding complications developed in 5 (6.8 %) patients on rivaroxaban (all nonmajor and noncerebral bleedings) and in 1 (2.5 %) patient on SOC (major subdural bleeding). In the DIVERSITY trial, 26 children with CSVT were included, 6 on SOC and 20 on dabigatran. Frequency of recurrent VTE and bleeding complications in these patients were not separately reported [9].

Table 2
Anticoagulants in neonates.

Medication	Dosing	Monitoring
LMWH Enoxaparin [51]	Preterm neonates: 2.0 mg/kg/12 h sc Term neonates: 1.7 mg/kg/12 h sc	Exclude ICH by US Check anti-FXa level 4 h after dose Target anti-FXa level: 0.5–1.0 U/mL Check platelets regularly
UFH [54,64]	Loading dose: none, unless risk or evidence of thrombus progression (25–100 U/kg in 10 min iv) Start maintenance: 28 U/kg/h iv	Exclude ICH by US Check aPTT and anti-Xa level 6 h after loading dose (if needed) and every change in therapy; otherwise check daily Target aPTT range, which corresponds to heparin level by anti-Xa of 0.3–0.7 U/mL Check platelets regularly
Rivaroxaban [59]	2.6–2.9 kg: 0.8 mg/8 h orally 3–3.9 kg: 0.9 mg/8 h orally 4–4.9 kg: 1.4 mg/8 h orally 5–6.9 kg: 1.6 mg/8 h orally	Not needed

Abbreviations: LMWH low-molecular weight heparin, UFH unfractionated heparin, ICH intracranial hemorrhage, US ultrasonography, aPTT activated partial thromboplastin time, iv intravenously, sc subcutaneously, hr hour, min minutes.

4.7. Pediatric patients with cancer

A total of 56 children (11 %) in the Einstein-junior study had cancer (hematologic 64 %; solid tumor 36 %), 40 in the rivaroxaban group and 16 in the SOC group [46]. Symptomatic recurrent VTE and major bleeding occurred in none of the children, whereas one clinically relevant nonmajor bleeding occurred in a child with rivaroxaban. In 26 (46.4 %) children, the anticoagulant treatment was interrupted 70 times (mean individual duration of interruption: 5.8 days). Anticoagulation was restarted after all treatment interruptions in therapeutic doses. Recurrent VTE, progression of existing thrombus, or clinically relevant bleeding did not occur. In the DIVERSITY trial, 19 patients had cancer associated thrombosis, 1 in the SOC group and 18 in the dabigatran group [9]. Outcomes in these 19 patients were not reported separately. In both studies children with cancer and an increased risk of bleeding, including thrombocytopenia $<50 \times 10^9$/L in the Einstein-junior study, were excluded.

4.8. Other patient groups

Children with severe renal dysfunction were excluded from DIVERSITY and Einstein-junior studies. Exclusion criteria included estimated glomerular filtration rate <50 mL/min per 1·73 m^2 using the Schwartz formula, or requirement for dialysis in DIVERSITY, and an estimated glomerular filtration rate <30 mL/min/1.73 m2 and children younger than 1 year with serum creatinine results above 97.5th percentile in Einstein-junior [9,10]. Children with abnormal liver function were also excluded. Exclusion criteria included persistent alanine aminotransferase (ALT) or aspartate transaminase or alkaline phosphatase >3× upper limit of normal (ULN) in the DIVERSITY study and ALT >5× ULN or total bilirubin >2× ULN with direct bilirubin >20 % of the total bilirubin in Einstein-junior study [9,10].

A few children with antiphospholipid syndrome (APS) were included in the DIVERSITY and Einstein-junior studies, 9 in the SOC arm and 12 in the dabigatran or rivaroxaban arm. Neither number and type of positive antiphospholipid antibodies nor separate outcomes of patients with APS were reported [9,10]. Based on current adult recommendations, dabigatran and rivaroxaban are not advised in children with APS.

Table 3
Anticoagulants in older children.

Medication	Dosing	Monitoring
LMWH Enoxaparin [65]	1 mg/kg/12 h sc	Check anti-Xa level 4 h after dose Target anti-Xa level: 0.5–1.0 U/mL Check platelets regularly
UFH [54]	Loading: 75 U/kg in 10 min iv Start maintenance: 20 U/kg/h iv	Check aPTT or anti-Xa level 6 h after loading dose and every change in therapy; target aPTT: 60–85 s, corresponding to heparin level by anti-Xa of 0.3–0.7 U/mL Check platelets regularly
VKA [62,63]	Warfarin: 0.2 mg/kg orally Phenprocoumon/ acenocoumarol: >5 years: 0.15 mg/kg orally once daily 1–5 years: 0.10 mg/kg orally once daily >5 years: 0.05 mg/kg orally once daily	Check INR Lower loading dose in patients with liver disease and Fontan circulation
Dabigatran [58]	Dose based on age and weight[a]	Not needed
Rivaroxaban [59]	4–4.9 kg: 1.4 mg/8 h orally 5–6.9 kg: 1.6 mg/8 h orally 7–7.9 kg: 1.8 mg/8 h orally 8–8.9 kg: 2.4 mg/8 h orally 9–9.9 kg: 2.8 mg/8 h orally 10–11.9 kg: 3 mg/8 h orally 12–29.9 kg: 5 mg/12 h orally 30–49.9 kg: 15 mg once daily ≥50 kg: 20 mg once daily	

Abbreviations: LMWH low-molecular weight heparin, UFH unfractionated heparin, aPTT activated partial thromboplastin time, iv intravenously, sc subcutaneously, INR international normalized ratio.

[a] See product information [58]; minimum starting age is 3 months (as soon as able to start swallow soft foods).

In all female adolescents with VTE, heavy menstrual bleeding (HMB) might be an important complication of anticoagulation [47]. Therefore, they should always be asked about past and present menstrual history to initiate adequate treatment if needed. In adult studies, a higher risk of HMB was found in women on rivaroxaban compared to warfarin [48]. Women with dabigatran may have a lower risk on HMB compared to warfarin [49]. The Einstein-junior study reported HMB in 23 (7 %) patients of the rivaroxaban arm and in 5 (3 %) of the SOC arm. HMB was not separately reported in the DIVERSITY study.

5. Practical aspects of anticoagulation in pediatric patients

5.1. Low-molecular-weight heparin

Neonates require higher dosages of LMWH to achieve therapeutic range than older children, with preterm neonates requiring the highest dosages, as result of low antithrombin levels and faster clearance (Tables 2 and 3) [50]. Enoxaparin is the most used and studied LMWH. A starting dose of 2 mg/kg twice daily in preterm, and 1.7 mg/kg twice daily in term neonates is suggested [51]. The therapeutic anti-Xa target range of 0.5–1.0 U/mL, 4 h after LMWH dose, is extrapolated from adult guidelines. Anti-Xa levels may change frequently due to weight changes, comorbidities and concomitant medications. At the moment, it is recommended to monitor anti-Xa levels weekly while neonates are in the hospital, and monthly after discharge [18]. Obtaining blood for anti-Xa levels is challenging in neonates. Studies did not show an association between achievement of the therapeutic target range and thrombosis resolution or bleeding complications [52,53]. So weight based, unmonitored LMWH therapy might accomplish the same outcomes as monitored LMWH therapy. This will be studied in the FiXET study (NCT02486666). The pain of (twice) daily subcutaneous injections can be diminished by topical anesthetics, such as lidocaine cream. The use of subcutaneous catheters should be avoided due to the risk of major bleeding [52].

5.2. Unfractionated heparin

UFH is especially used in critically ill patients due to its short half-life, available antidote (protamine sulfate) and nonrenal clearance. UFH is usually started with a loading dose of 75 U/kg over 10 min [54] (Tables 2 and 3). In neonates, a loading dose of UFH is not advised as the recurrence risk is very low in neonates, and the bleeding risk might be high [55]. After a loading dose of about 100 IU/kg, aPTT appeared to be >999 s in 3 of the 4 neonates for 30 min after the dose. Even after 102 min, the mean aPTT was still 312 ± 227 s in all 4 neonates [56]. A loading dose can be useful when there is an important risk or evidence of thrombus progression. Andrew et al. recommended a higher maintenance dose (28 U/kg/h) in neonates than in older children (20 U/kg/h) due to increased clearance, larger volumes of distribution and low antithrombin levels [54]. Monitoring of UFH may be difficult, especially in neonates. Commonly used tests include the anti-Xa assay and aPTT. The therapeutic anti-Xa level is extrapolated from that in adults, and is between 0.35 and 0.7 U/mL, which corresponds with a heparin concentration of 0.2–0.4 U/mL by protamine titration. In neonates, the anti-Xa level of 0.35–0.7 U/mL is associated with a higher baseline APTT and a larger variation of aPTT values (78–200 s) than in older children and adults [57]. Suggested approaches for UFH monitoring and adjustment in neonates are available in the publication of Bhatt et al. [55].

5.3. Dabigatran and rivaroxaban

Dosing recommendations for dabigatran are based on weight and age and can be found in the product information [58]. Dosing recommendations for rivaroxaban are shown in Tables 2 and 3 [59]. No dose recommendations for dabigatran and rivaroxaban are available for preterm neonates. Unfortunately, the oral solution of dabigatran for infants <12 months is not commercially available. As the oral pellets should be taken with soft foods, the minimum starting age of dabigatran is 3 months, as soon as infants are able to swallow soft foods. Dabigatran and rivaroxaban can be initiated after 5 days of parenteral anticoagulation in stable patients on enteral feeding, as in the phase 3 trials children required initial parenteral anticoagulation (UFH, LMWH or fondaparinux) to have time for informed consent and randomization [9,10]. Before the start of rivaroxaban and dabigatran, and yearly thereafter in case of prolonged anticoagulation, liver and renal functions should be examined. It is not recommended to use rivaroxaban and dabigatran in children with renal failure, hepatic impairment, APS and mechanical heart valves, following the recommendations for adults and the exclusion criteria in the pediatric phase 3 trials. For adolescents who are >120 kg, it seems reasonable to follow adult recommendations [60]. Be aware of potential medication interactions, which may occur when using medications that induce or inhibit cytochrome P450 enzyme (rivaroxaban) or permeability glycoprotein (rivaroxaban and dabigatran) [61]. In female patients with heavy menstrual bleeding while receiving rivaroxaban, alternative anticoagulant agents might be considered, including dabigatran, in addition to hormone therapies and antifibrinolytics.

Table 4
Summary of the Einstein junior and DIVERSITY phase 3 studies in children <18 years of age.

	Einstein junior	DIVERSITY
DOAC	Rivaroxaban	Dabigatran etexilate
Comparator	SOC (UFH, LMWH, fondaparinux, VKA)	SOC (UFH, LMWH, fondaparinux, VKA)
Duration prior parenteral anticoagulation	5–9 days	5–21 days
Patients enrolled	500	267
Study treatment period	3 months (1 month for children <2 years of age with CVC-related VTE)	3 months
Randomization (intervention:SOC)	2:1	2:1

	Intervention	SOC	Intervention	SOC
Primary efficacy outcome				
Patients (n)	335	165	177	90
Symptomatic recurrent VTE (n, %)	4 (1)	5 (3)		
Complete thrombus resolution, freedom from recurrent VTE and VTE-related death (n, %)			81 (46)	38 (42)
Principal safety outcome				
Patients (n)	329	162	176	90
Major or CRNM bleeding (n, %)	10 (3)[a]	3 (2)[b]		
Major bleeding (n, %)			4 (2)	2 (2 %)

Abbreviations: DOAC direct oral anticoagulant, SOC standard of care, LMWH low-molecular weight heparin, UFH unfractionated heparin, VKA vitamin K antagonist, CVC central venous catheter, VTE venous thromboembolism, CRNM clinically relevant non-major bleeding.

[a] All non-major bleedings.

[b] 2 major and 1 non-major bleedings.

5.4. Vitamin K antagonists

Although VKA can be orally administrated, they are not frequently used in neonates and infants as results of its interactions with food and many medications, and lack of a commercially available oral solution. For the older children, monitoring of INR can be inconvenient. For all types of VKAs initial and maintenance dosages are age dependent (Tables 2 and 3) [62,63]. VKA therapy can be initiated from day 2 after start of heparin therapy in stable patients on enteral feeding. As result of the narrow therapeutic index, frequent monitoring of the INR is required. The target INR for treatment of VTE is extrapolated from adults and between 2 and 3 for the majority of the cases. If INR is in the therapeutic range for >24 h, heparin therapy can be stopped (Table 4).

6. Future perspectives and conclusions

Currently, the efficacy and safety of two other oral factor Xa inhibitors edoxaban and apixaban are evaluated in phase 3 studies in children with acute VTE.(Edoxaban: NCT02798471; apixaban: NCT02464969) In addition, pediatric investigational plans are being developed with a new group of anticoagulants, the factor XI and XII inhibitors, which might have a better benefit-risk balance for prevention and/or treatment of VTE in the pediatric population. In the meantime, dabigatran and rivaroxaban will be increasingly used in children with acute VTE due to their advantages over standard anticoagulation and promising phase 3 study results. However, many questions are still unanswered in pediatric VTE management [6]. Focusing on factor IIa and Xa inhibitors, studies are needed to investigate 1. the efficacy and safety of these drugs in children who were excluded from or not frequently included in the studies, such as (premature) neonates, infants and other specific patient groups with VTE, 2. the need for monitoring of factor IIa and Xa inhibitors in specific situations or patient groups, 3. the efficacy and safety of reversal agents, 4. the management around procedures, 5. the effect on menstrual bleeding in female adolescents, and 6. adherence. Real-world prospective cohort studies and registries will be necessary to help answer these questions.

CRediT authorship contribution statement

C. Heleen van Ommen: Conceptualization, Writing – original draft. **Saskia E. Luijnenburg:** Conceptualization, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: CH van Ommen reports a relationship with Bayer BV that includes: consulting or advisory. CH van Ommen reports a relationship with Boehringer Ingelheim that includes: consulting or advisory.

References

[1] M. Andrew, M. David, M. Adams, K. Ali, R. Anderson, D. Barnard, et al., Venous thromboembolic complications (VTE) in children: first analyses of the Canadian Registry of VTE, Blood 83 (5) (1994) 1251–1257.
[2] S.H. O'Brien, J.R. Stanek, C.M. Witmer, L. Raffini, The continued rise of venous thromboembolism across US children's hospitals, Pediatrics 149 (3) (2022).
[3] C.H. van Ommen, H. Heijboer, H.R. Buller, R.A. Hirasing, H.S. Heijmans, M. Peters, Venous thromboembolism in childhood: a prospective two-year registry in The Netherlands, J. Pediatr. 139 (5) (2001) 676–681.
[4] M. Andrew, B. Paes, R. Milner, M. Johnston, L. Mitchell, D.M. Tollefsen, et al., Development of the human coagulation system in the healthy premature infant, Blood 72 (5) (1988) 1651–1657.
[5] M. Andrew, B. Paes, R. Milner, M. Johnston, L. Mitchell, D.M. Tollefsen, et al., Development of the human coagulation system in the full-term infant, Blood 70 (1) (1987) 165–172.
[6] P. Monagle, C.A. Cuello, C. Augustine, M. Bonduel, L.R. Brandao, T. Capman, et al., American Society of Hematology 2018 Guidelines for management of venous thromboembolism: treatment of pediatric venous thromboembolism, Blood Adv. 2 (22) (2018) 3292–3316.
[7] S. Halimeh, C. Male, U. Nowak-Goettl, New anticoagulants in neonates, children, and adolescents, Hamostaseologie 42 (2) (2022) 123–130.
[8] M. Merino, N. Richardson, G. Reaman, A. Ande, S. Zvada, C. Liu, et al., FDA approval summary: dalteparin for the treatment of symptomatic venous thromboembolism in pediatric patients, Pediatr. Blood Cancer 67 (12) (2020) e28688.
[9] J. Halton, L.R. Brandao, M. Luciani, L. Bomgaars, E. Chalmers, L.G. Mitchell, et al., Dabigatran etexilate for the treatment of acute venous thromboembolism in children (DIVERSITY): a randomised, controlled, open-label, phase 2b/3, non-inferiority trial, Lancet Haematol. 8 (1) (2021) e22–e33.
[10] C. Male, A.W.A. Lensing, J.S. Palumbo, R. Kumar, I. Nurmeev, K. Hege, et al., Rivaroxaban compared with standard anticoagulants for the treatment of acute venous thromboembolism in children: a randomised, controlled, phase 3 trial, Lancet Haematol. 7 (1) (2020) e18–e27.
[11] P. Monagle, A.K. Chan, N.A. Goldenberg, R.N. Ichord, J.M. Journeycake, U. Nowak-Gottl, et al., Antithrombotic therapy in neonates and children: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, Chest 141 (2 Suppl) (2012) e737S–e801S.
[12] E.K. Amankwah, C.M. Atchison, S. Arlikar, I. Ayala, L. Barrett, B.R. Branchford, et al., Risk factors for hospital-sssociated venous thromboembolism in the neonatal intensive care unit, Thromb. Res. 134 (2) (2014) 305–309.
[13] W. El-Naggar, E.W. Yoon, D. McMillan, J. Afifi, S. Mitra, B. Singh, et al., Epidemiology of thrombosis in Canadian neonatal intensive care units, J. Perinatol. 40 (7) (2020) 1083–1090.
[14] B. Schmidt, A. Zipursky, Thrombotic disease in newborn infants, ClinPerinatol 11 (2) (1984) 461–488.
[15] C.H. van Ommen, K.A. Bergman, M. Boerma, H.A. Bouma, A.E. Donker, M. Gouvernante, et al., NEOnatal Central-venous Line Observational study on Thrombosis (NEOCLOT): evaluation of a national guideline on management of neonatal catheter-related venous thrombosis, J. Thromb. Haemost. 21 (4) (2023) 963–974.
[16] U. Nowak-Gottl, V. Janssen, D. Manner, G. Kenet, Venous thromboembolism in neonates and children—update 2013, Thromb. Res. 131 (Suppl. 1) (2013) S39–S41.

[17] P. Saracco, R. Bagna, C. Gentilomo, M. Magarotto, A. Viano, F. Magnetti, et al., Clinical data of neonatal systemic thrombosis, J. Pediatr. 171 (60–6) (2016) e1.
[18] J. Ting, K. Yeung, B. Paes, A.K.C. Chan, J.A. Petropoulos, L. Banfield, et al., How to use low-molecular-weight heparin to treat neonatal thrombosis in clinical practice, Blood Coagul. Fibrinolysis 32 (8) (2021) 531–538.
[19] M.L. Avila, L. Duan, A. Cipolla, A. Kim, W.H. Kahr, S. Williams, et al., Postthrombotic syndrome following upper extremity deep vein thrombosis in children, Blood 124 (7) (2014) 1166–1173.
[20] J. Jaffray, L. Baumann Kreuziger, B. Branchford, C.P. Wee, E.V.S. Faustino, N. A. Zakai, et al., Symptomatic pulmonary embolus after catheter removal in children with catheter related thrombosis: a report from the CHAT Consortium, J. Thromb. Haemost. 20 (1) (2022) 133–137.
[21] C.K. Park, B.A. Paes, K. Nagel, A.K. Chan, P. Murthy, Thrombosis, et al., Neonatal central venous catheter thrombosis: diagnosis, management and outcome, Blood Coagul. Fibrinolysis 25 (2) (2014) 97–106.
[22] A. Bokenkamp, R. von Kries, U. Nowak-Gottl, U. Gobel, P.F. Hoyer, Neonatal renal venous thrombosis in Germany between 1992 and 1994: epidemiology, treatment and outcome, Eur. J. Pediatr. 159 (1–2) (2000) 44–48.
[23] B. Ndoudi Likoho, R. Berthaud, C. Dossier, J.D. Delbet, O. Boyer, V. Baudouin, et al., Renal vein thrombosis in neonates: a case series of diagnosis, treatment and childhood kidney function follow-up, Pediatr. Nephrol. 38 (9) (2023) 3055–3063.
[24] K.K. Lau, J.M. Stoffman, S. Williams, P. McCusker, L. Brandao, S. Patel, et al., Neonatal renal vein thrombosis: review of the English-language literature between 1992 and 2006, Pediatrics 120 (5) (2007) e1278–e1284.
[25] A.C. Ouellette, E.K. Darling, B. Sivapathasundaram, G. Babe, R. Perez, A.K.C. Chan, et al., Incidence, risk factors, and outcomes of neonatal renal vein thrombosis in Ontario: population-based cohort study, Kidney360 1 (7) (2020) 640–647.
[26] L.R. Brandao, E.A. Simpson, K.K. Lau, Neonatal renal vein thrombosis, Semin. Fetal Neonatal Med. 16 (6) (2011) 323–328.
[27] G. deVeber, M. Andrew, C. Adams, B. Bjornson, F. Booth, D.J. Buckley, et al., Cerebral sinovenous thrombosis in children, N. Engl. J. Med. 345 (6) (2001) 417–423.
[28] M.M. Raets, J.J. Sol, P. Govaert, M.H. Lequin, I.K. Reiss, A.A. Kroon, et al., Serial cranial US for detection of cerebral sinovenous thrombosis in preterm infants, Radiology 269 (3) (2013) 879–886.
[29] J.Y. Yang, A.K. Chan, D.J. Callen, B.A. Paes, Neonatal cerebral sinovenous thrombosis: sifting the evidence for a diagnostic plan and treatment strategy, Pediatrics 126 (3) (2010) e693–e700.
[30] M.R. Golomb, Outcomes of perinatal arterial ischemic stroke and cerebral sinovenous thrombosis, Semin. Fetal Neonatal Med. 14 (5) (2009) 318–322.
[31] M.D. Moharir, M. Shroff, D. Stephens, A.M. Pontigon, A. Chan, D. MacGregor, et al., Anticoagulants in pediatric cerebral sinovenous thrombosis: a safety and outcome study, Ann. Neurol. 67 (5) (2010) 590–599.
[32] F.J. Berfelo, K.J. Kersbergen, C.H. van Ommen, P. Govaert, H.L. van Straaten, B. T. Poll-The, et al., Neonatal cerebral sinovenous thrombosis from symptom to outcome, Stroke 41 (7) (2010) 1382–1388.
[33] E.A. Chalmers, Epidemiology of venous thromboembolism in neonates and children, Thromb. Res. 118 (1) (2006) 3–12.
[34] J. Jaffray, A. Mahajerin, G. Young, N. Goldenberg, L. Ji, R. Sposto, et al., A multi-institutional registry of pediatric hospital-acquired thrombosis cases: The Children's Hospital-Acquired Thrombosis (CHAT) project, Thromb. Res. 161 (2018) 67–72.
[35] M.P. Massicotte, D. Dix, P. Monagle, M. Adams, M. Andrew, Central venous catheter related thrombosis in children: analysis of the Canadian Registry of Venous Thromboembolic Complications, J. Pediatr. 133 (6) (1998) 770–776.
[36] P. Monagle, M. Adams, M. Mahoney, K. Ali, D. Barnard, M. Bernstein, et al., Outcome of pediatric thromboembolic disease: a report from the Canadian Childhood Thrombophilia Registry, Pediatr. Res. 47 (6) (2000) 763–766.
[37] C.H. van Ommen, H. Heijboer, E.J. van den Dool, B.A. Hutten, M. Peters, Pediatric venous thromboembolic disease in one single center: congenital prothrombotic disorders and the clinical outcome, J. Thromb. Haemost. 1 (12) (2003) 2516–2522.
[38] N.A. Goldenberg, M.P. Donadini, S.R. Kahn, M. Crowther, G. Kenet, U. Nowak-Gottl, et al., Post-thrombotic syndrome in children: a systematic review of frequency of occurrence, validity of outcome measures, and prognostic factors, Haematologica 95 (11) (2010) 1952–1959.
[39] C. Ross, R. Kumar, M.C. Pelland-Marcotte, S. Mehta, M.E. Kleinman, R. R. Thiagarajan, et al., Acute management of high-risk and intermediate-risk pulmonary embolism in children: a review, Chest 161 (3) (2022) 791–802.
[40] N.A. Goldenberg, J.M. Kittelson, T.C. Abshire, M. Bonaca, J.F. Casella, R.A. Dale, et al., Effect of anticoagulant therapy for 6 weeks vs 3 months on recurrence and bleeding events in patients younger than 21 years of age with provoked venous thromboembolism: the kids-DOTT randomized clinical trial, JAMA 327 (2) (2022) 129–137.
[41] D. Roshammar, F. Huang, M. Albisetti, L. Bomgaars, E. Chalmers, M. Luciani, et al., Pharmacokinetic modeling and simulation support for age- and weight-adjusted dosing of dabigatran etexilate in children with venous thromboembolism, J. Thromb. Haemost. 19 (5) (2021) 1259–1270.
[42] L.R. Brandao, M. Albisetti, J. Halton, L. Bomgaars, E. Chalmers, L.G. Mitchell, et al., Safety of dabigatran etexilate for the secondary prevention of venous thromboembolism in children, Blood 135 (7) (2020) 491–504.
[43] C.H. van Ommen, M. Albisetti, M. Bhatt, M. Bonduel, B. Branchford, E. Chalmers, et al., International pediatric thrombosis network to advance pediatric thrombosis research: communication from the ISTH SSC subcommittee on pediatric and neonatal thrombosis and hemostasis, J. Thromb. Haemost. 19 (4) (2021) 1123–1129.
[44] K. Thom, A.W.A. Lensing, I. Nurmeev, F. Bajolle, D. Bonnet, G. Kenet, et al., Safety and efficacy of anticoagulant therapy in pediatric catheter-related venous thrombosis (EINSTEIN-Jr CVC-VTE), Blood Adv. 4 (19) (2020) 4632–4639.
[45] M. Sanchez van Kammen, C. Male, P. Connor, P. Monagle, J.M. Coutinho, A.W. A. Lensing, et al., Anticoagulant treatment for pediatric infection-related cerebral venous thrombosis, Pediatr. Neurol. 128 (2022) 20–24.
[46] J.S. Palumbo, A.W.A. Lensing, L.R. Brandao, H.L. Hooimeijer, G. Kenet, H. van Ommen, et al., Anticoagulation in pediatric cancer-associated venous thromboembolism: a subgroup analysis of EINSTEIN-Jr, Blood Adv. 6 (22) (2022) 5821–5828.
[47] E. DeLoughery, B.S. Bannow, Anticoagulant therapy for women: implications for menstruation, pregnancy, and lactation, Hematology Am. Soc. Hematol. Educ. Program 2022 (1) (2022) 467–473.
[48] R. Godin, V. Marcoux, V. Tagalakis, Abnormal uterine bleeding in women receiving direct oral anticoagulants for the treatment of venous thromboembolism, Vasc. Pharmacol. 93-95 (2017) 1–5.
[49] M.V. Huisman, M. Ferreira, M. Feuring, M. Fraessdorf, F.A. Klok, Less abnormal uterine bleeding with dabigatran than warfarin in women treated for acute venous thromboembolism, J. Thromb. Haemost. 16 (9) (2018) 1775–1778.
[50] I.L.M. Klaassen, J.J. Sol, M.H. Suijker, K. Fijnvandraat, M.D. van de Wetering, C. Heleen van Ommen, Are low-molecular-weight heparins safe and effective in children? A systematic review, Blood Rev. 33 (2019) 33–42.
[51] J.I. Malowany, P. Monagle, D.C. Knoppert, D.S. Lee, J. Wu, P. McCusker, et al., Enoxaparin for neonatal thrombosis: a call for a higher dose for neonates, Thromb. Res. 122 (6) (2008) 826–830.
[52] J. Sol, M. Boerma, I. Klaassen, S. Simons, B. Witjes, E. Wildschut, et al., Effectiveness and safety of nadroparin therapy in preterm and term neonates with venous thromboembolism, J. Clin. Med. 10 (7) (2021).
[53] J.I. Malowany, D.C. Knoppert, A.K. Chan, D. Pepelassis, D.S. Lee, Enoxaparin use in the neonatal intensive care unit: experience over 8 years, Pharmacotherapy 27 (9) (2007) 1263–1271.
[54] M. Andrew, V. Marzinotto, P. Massicotte, V. Blanchette, J. Ginsberg, P. Brill-Edwards, et al., Heparin therapy in pediatric patients: a prospective cohort study, Pediatr. Res. 35 (1) (1994) 78–83.
[55] M.D. Bhatt, B.A. Paes, A.K. Chan, How to use unfractionated heparin to treat neonatal thrombosis in clinical practice, Blood Coagul. Fibrinolysis 27 (6) (2016) 605–614.
[56] F. Newall, V. Ignjatovic, L. Johnston, R. Summerhayes, G. Lane, N. Cranswick, et al., Age is a determinant factor for measures of concentration and effect in children requiring unfractionated heparin, Thromb. Haemost. 103 (5) (2010) 1085–1090.
[57] V. Ignjatovic, J. Furmedge, F. Newall, A. Chan, L. Berry, C. Fong, et al., Age-related differences in heparin response, Thromb. Res. 118 (6) (2006) 741–745.
[58] Pradaxa product information, European Medicines Agency (2021). Available from: https://www.ema.europa.eu/en/documents/product-information/pradaxa-epar-product-information_en.pdf.
[59] Xarelto product information, European Medicines Agency (2021). Available from: https://www.ema.europa.eu/en/documents/product-information/xarelto-epar-product-information_en.pdf.
[60] K.A. Martin, J. Beyer-Westendorf, B.L. Davidson, M.V. Huisman, P.M. Sandset, S. Moll, Use of direct oral anticoagulants in patients with obesity for treatment and prevention of venous thromboembolism: updated communication from the ISTH SSC Subcommittee on Control of Anticoagulation, J. Thromb. Haemost. 19 (8) (2021) 1874–1882.
[61] S.R. Vazquez, Drug-drug interactions in an era of multiple anticoagulants: a focus on clinically relevant drug interactions, Blood 132 (21) (2018) 2230–2239.
[62] N. Spoor, F.J. Smiers, F.J. van der Meer, B.A. Hutten, C.H. van Ommen, Phenprocoumon and acenocoumarol treatment in paediatric patients, Thromb. Haemost. 108 (6) (2012) 1238–1241.
[63] C. Law, L. Raffini, A guide to the use of anticoagulant drugs in children, Paediatr. Drugs 17 (2) (2015) 105–114.
[64] M.J. Manco-Johnson, How I treat venous thrombosis in children, Blood 107 (1) (2006) 21–29.
[65] P. Massicotte, M. Adams, V. Marzinotto, L.A. Brooker, M. Andrew, Low-molecular-weight heparin in pediatric patients with thrombotic disease: a dose finding study, J. Pediatr. 128 (3) (1996) 313–318.