CLINICAL GUIDELINES

blood advances

# American Society of Hematology/International Society on Thrombosis and Haemostasis 2024 updated guidelines for treatment of venous thromboembolism in pediatric patients

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**Background:** The American Society of Hematology (ASH) guidelines on treatment of pediatric venous thromboembolism (VTE) were published in 2018. In the last 6 years, there has been a 10-fold increase in the number of children involved in VTE treatment trials.

**Objective:** The ASH Committee on Quality and Guidelines agreed to update the pediatric guidelines in conjunction with the International Society on Thrombosis and Haemostasis (ISTH). These ASH/ISTH evidence-based guidelines are intended to support patients, clinicians, and other health care professionals in the management of pediatric patients with VTE.

**Methods:** ASH/ISTH formed a multidisciplinary guideline panel to minimize potential bias from conflicts of interest. An unconflicted patient representative was not identified. The University of Kansas Health System supported the guideline development process, updating or performing systematic evidence reviews up to 2024. The panel focused specifically on the 2018 questions for which there was the greatest amount of interim data. The panel used the GRADE (Grades of Recommendation,

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Assessment, Development, and Evaluation) approach, including GRADE Evidence-to-Decision frameworks, to assess evidence and make recommendations, which were subject to public comment.

**Results:** The panel agreed on 20 recommendations and also provided implementation guidance on the optimal use of anticoagulants in pediatric patients. Key recommendations of these guidelines include the role of DOACs in the treatment of a variety of pediatric VTEs.

**Conclusions:** Further research is required. Key priorities are understanding the natural history of clinically unsuspected thrombosis across a range of patient subpopulations and obtaining real-world data on the use of DOACs in children.

## Summary of recommendations

These guidelines are based on updated[1] and original systematic reviews of evidence conducted under the direction of the University of Kansas Health System. The panel followed best practice for guideline development recommended by the Institute of Medicine and the Guidelines International Network (GIN).[1-3] The panel used the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach[4-10] to assess the certainty in the evidence and formulate recommendations.

The incidence of venous thromboembolism (VTE) in children at a population level is very low, reported to be 0.07 to 0.14 per 10 000 children.[11-13] However, in hospitalized children, the rate is 100- to 1000-times increased, up to at least 106 per 10 000 admissions.[14,15] Thus, despite some exceptions, VTE should be considered a disease of sick children. The most common age groups for VTE are neonates and adolescents, and this reflects the pattern of associated underlying diseases and interventions. The most common precipitating factor is the presence of central venous access devices (CVADs), which are related to 80% to 85% of pediatric VTE.[16,17] Although rare, spontaneous thrombosis in previously healthy children can often present the most challenging treatment dilemmas. The natural history of many types of VTE in children remains unclear. There are major differences between adults and children in the epidemiology and pathophysiology of thrombosis, the physiology of the coagulation system, and the subsequent impact on the pharmacology of antithrombotic agents.

The questions addressed in these guidelines were judged to be those for which there were new data available to update the questions addressed in 2018. In addition, the panel added new questions regarding the use of direct oral anticoagulants (DOACs) compared with standard-of-care (SOC) anticoagulants for VTE treatment. The inclusion of questions in this guideline revision did not automatically mean that recommendations were expected to change from 2018 but that there were sufficient new data to warrant a renewed consideration of the question. The recommendations within the guidelines address questions predominantly of whether to treat or not to treat, and which type of treatment is optimal for a given clinical situation. The guidelines are predominantly concerned with the treatment of acute thrombosis. On occasions, thrombosis at diagnosis is believed to be chronic due to the review of previous scans or timing of likely precipitant factors (such as central venous access). The decision to treat or not treat in these situations, requires individual consideration of the risk-to-benefit ratio and is beyond the scope of these guidelines. In addition, specific information is given about the use of various anticoagulants in pediatric patients for the treatment of VTE. Apixaban and edoxaban were not considered in these guidelines because phase 3 clinical trial data regarding use of these drugs for the treatment of VTE in children are yet to be published. Subsequent guidelines related to prophylaxis for VTE in pediatric patients will include all drugs for which there are pediatric data, and further specific guidance as to the use of drugs in the prophylaxis setting may be provided with those guidelines. Of note, in 2018, there were recommendations about the management of homozygous protein C deficiency. These recommendations were not considered in this effort' in light of the recent International Society on Thrombosis and Haemostasis (ISTH) comprehensive guidance on this topic.[18,19]

Throughout these recommendations, the panel, at times, considers neonates (age, birth to day 28), infants (age, day 29 to 1 year), children (age, 1-11 years), and adolescents (age, 12-18 years) separately. At times, the terms pediatric patients (encompassing all age groups) or neonates and pediatric patients (separating neonates from all other age groups) are used.

### Interpretation of strong and conditional recommendations

The strength of a recommendation is expressed as either strong ("the guideline panel recommends…") or conditional ("the guideline panel suggests…") and has the following interpretation:

#### *Strong recommendation*

- For patients: most individuals in this situation would want the recommended course of action, and only a small proportion would not.
- For clinicians: most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.
- For policymakers: the recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.
- For researchers: the recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty in the evidence. In such instances, further research may provide important information that alters the recommendations.

#### *Conditional recommendation*

- For patients: most individuals in this situation would want the suggested course of action, but many would not. Decision aids

may be useful in helping patients to make decisions consistent with their individual risks, values, and preferences.

- For clinicians: clinicians should recognize that different choices will be appropriate for individual patients and that they must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values, and preferences.
- For policymakers: policymaking will require substantial debate and involvement of various stakeholders. Performance measures about the suggested course of action should focus on whether an appropriate decision-making process is duly documented.
- For researchers: this recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help identify possible research gaps.

## Recommendations

***Recommendation 1.*** For pediatric patients with symptomatic deep vein thrombosis (DVT) or pulmonary embolism (PE), the ASH/ISTH guideline panel *suggests* using anticoagulation rather than no anticoagulation (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

**Remarks:** Although there remains limited direct evidence in pediatric patients, there is strong indirect evidence in adults that symptomatic VTE requires treatment. However, based on recently published observational studies in pediatric patients, there may be specific clinical scenarios such as neonatal central venous catheter–associated VTE or trauma-associated VTE in which anticoagulation may result in either no significant benefit or potentially an increased risk of harm. Outside of these specific clinical scenarios, the panel agrees that in most pediatric patients with symptomatic DVT and PE, anticoagulation is warranted. Therefore, the panel made a conditional recommendation with low certainty in the evidence.

***Recommendation 2.*** For pediatric patients with clinically unsuspected (previously termed asymptomatic) DVT or PE, the ASH/ISTH guideline panel *suggests* either using anticoagulation or no anticoagulation (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

**Remarks:** The natural history of clinically unsuspected DVT or PE in pediatric patients appears to carry a lower risk (compared with symptomatic DVT or PE) of acute and long-term sequelae, especially in certain pediatric subpopulations. The recommendation is based on studies that report outcomes for pediatric patients with clinically unsuspected DVT or PE. Single institution, observational, and retrospective studies in select subpopulations of pediatric patients suggest that not using anticoagulation for clinically unsuspected DVT or PE does not lead to severe outcomes. The benefits or harms of anticoagulation or no anticoagulation vary for different populations including neonates, pediatric patients who are critically ill, patients with cardiac disease, or patients who have experienced trauma. However, if clinically unsuspected DVT or PE is detected, the decision to treat or not treat should be individualized. Research to better understand the natural history of clinically unsuspected DVT or PE, benefits, and harms of treatment in a variety of subgroups and clinical settings in pediatrics is a high priority.

***Recommendation 3.*** For select pediatric patients with provoked VTE, the ASH/ISTH guideline panel *suggests* 6 weeks rather than 3 months of anticoagulation. Exclusions to this recommendation include (1) PE, (2) recurrent VTE, (3) persistent occlusive thrombus at 6 weeks, (4) cancer-associated thrombosis, (5) patients with persistent antiphospholipid antibodies (APAs) or major thrombophilia, and (6) ongoing VTE risk factors (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

**Remarks:** This recommendation is based mainly on the Kids-DOTT randomized clinical trial (RCT) that evaluated the duration of anticoagulation therapy in pediatric patients with provoked VTE. Importantly, the criteria for inclusion and randomization were stringent, and many pediatric patients with provoked VTE were excluded. The recommendation reflects the population that was studied and cannot be extrapolated to all patients with provoked VTE. For patients with provoked VTE not meeting these low-risk criteria, the panel suggests the use of anticoagulation therapy for 3 months, and for those with persistent provoking VTE risk factors, longer duration of anticoagulation may be considered.

***Recommendation 4.*** For pediatric patients with unprovoked DVT or PE, the ASH/ISTH guideline panel *suggests* using anticoagulation for 6 to 12 months rather than indefinite anticoagulation (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

**Remarks:** Unprovoked VTE is rare in pediatrics. Although studies suggest that rates of recurrent VTE in children and adolescents with age of >1 year with unprovoked VTE are relatively high (21%-36% at 3.5 years follow up), there are no pediatric studies evaluating duration of therapy in this cohort.[20,21] Although extrapolation of adult data might favor prolonged treatment in terms of VTE recurrence, in the absence of pediatric data, the panel felt that the impact of indefinite anticoagulation on bleeding risk and quality of life (QOL) would more negatively affect pediatric patients compared with adults. Patient values and preferences should be considered when making this decision.

***Recommendation 5.*** For pediatric patients with cerebral sinus venous thrombosis (CSVT) with and without hemorrhage secondary to venous congestion, the ASH/ISTH guideline panel *suggests* using anticoagulation rather than no anticoagulation (conditional recommendation based on very low certainty in the evidence based on pediatric data ⊕◯◯◯).

**Remarks:** Observational studies suggest lower mortality and improved neurologic outcomes in patients with CSVT treated with anticoagulation. However, the panel recognized different populations of patients with CSVT (eg, neonates, and those with infection-associated CSVT, who have experienced trauma, have had surgery, and have cancer) may have different risks for bleeding and neurologic outcomes that should be considered in the decision to use anticoagulation. Evidence of venous congestion secondary to thrombus obstruction with or without hemorrhage should be managed with anticoagulation. The panel

notes that when anticoagulation is prescribed, it is important that appropriate therapy for additional associated conditions (eg, surgical interventions for infection-associated CSVT) be used.

***Recommendation 6.*** For pediatric patients with CSVT, the ASH/ISTH guideline panel *suggests* using anticoagulation alone rather than thrombolysis followed by anticoagulation (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

**Remarks:** The evidence is sparse for the balance of benefits and harms of thrombolysis compared with anticoagulation in pediatric patients with CSVT. Based on the experience of the panel members, the panel suggests use of anticoagulation rather than thrombolysis for children with CSVT who have no evidence of ischemia. However, thrombolysis may be considered when there is neurologic deterioration despite anticoagulation and, in such or similar instances, reperfusion therapies may be considered depending on local resources or experiences.

***Recommendation 7a.*** For neonates and pediatric patients with right atrial thrombosis (RAT), the ASH/ISTH guideline panel *suggests* anticoagulation rather than no anticoagulation for patients with high-risk features and low perceived risk of bleeding (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

**Remarks:** Insufficient data are available for formal risk stratification of RAT and bleeding from anticoagulation. Based on available literature and experience of panel members, high-risk features of RAT to consider include large size, shape (snake-shaped or pedunculated), mobility, location (eg, involvement of tricuspid valve or restricting blood flow), presence of intracardiac right-to-left shunt, presence of a central venous catheter, or associated with symptoms (arrhythmias, hemodynamic compromise, etc). The decision to start anticoagulation should be individualized based on the risk of thrombotic complications and the perceived risk of bleeding from anticoagulation.

***Recommendation 7b.*** For neonates and pediatric patients with RAT and the absence of high-risk features or with unacceptable perceived risk of bleeding, the ASH/ISTH guideline panel *suggests* no anticoagulation over anticoagulation (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

**Remarks:** Studies in patients without high-risk features treated with anticoagulation do not demonstrate clinical benefits compared with patients not treated with anticoagulation. The studies are not randomized, are small, and are subject to significant bias. Study participants treated with anticoagulation had an increased risk of bleeding.

***Recommendation 8.*** For neonates and pediatric patients with RAT requiring antithrombotic treatment, the ASH/ISTH guideline panel *suggests* using anticoagulation alone over thrombolysis followed by anticoagulation (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

**Remarks:** In most cases, anticoagulation alone is adequate. However, there are individual cases in which the hemodynamic status, size, and mobility of the thrombus might dictate more aggressive therapy. The choice to use thrombolysis will depend on feasibility or the intervention and patient and family acceptability of the anticipated risks and benefits of thrombolysis.

***Recommendation 9.*** For neonates with renal vein thrombosis (RVT), the ASH/ISTH guideline panel *suggests* using anticoagulation rather than no anticoagulation (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

**Remarks:** The panel considers the intervention to have a potential beneficial effect if the long-term outcomes of avoiding hypertension, chronic kidney disease, and renal failure are considered. Anticoagulation is likely more important with bilateral renal vein involvement compared with unilateral involvement with or without extension to the inferior vena cava (IVC). Severity of disease, gestational age, presence of intraventricular hemorrhage, underlying comorbidities, and degree of thrombocytopenia may affect bleeding risk with treatment.

***Recommendation 10a.*** For neonates with non–life-threatening RVT, the ASH/ISTH guideline panel *recommends* anticoagulation alone vs thrombolysis followed by anticoagulation (strong recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

**Remarks:** Available evidence is derived from observational studies in which patients treated with thrombolysis were critically ill, and because the studies did not adjust for this bias, causation is difficult to ascertain. The panel placed a high value on avoiding the potential bleeding risks of thrombolysis, especially in neonates, and therefore, made this recommendation for cases with low mortality risk (ie, unilateral RVT or unilateral RVT with IVC extension). The panel made a strong recommendation, considering high-quality evidence for harm and high costs, despite very low quality evidence for benefit.

***Recommendation 10b.*** For neonates with life-threatening RVT, the ASH/ISTH guideline panel *suggests* using thrombolysis followed by anticoagulation, rather than anticoagulation alone (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

**Remarks:** When RVT is life threatening (ie, bilateral thrombosis), the panel considered that the beneficial effects of thrombolysis may outweigh the undesirable consequences of the intervention. Gestational age, presence of intraventricular hemorrhage, underlying comorbidities, and degree of thrombocytopenia may affect bleeding risk with thrombolysis.

***Recommendation 11a.*** For neonates and children with occlusive portal vein thrombosis (PVT) and for children with nonocclusive PVT, post–liver transplant PVT, or unprovoked PVT, the ASH/ISTH guideline panel *suggests* using anticoagulation rather than no anticoagulation (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

***Recommendation 11b.*** For neonates with nonocclusive PVT, and for children who have already developed portal hypertension (PHTN) secondary to PVT, the ASH/ISTH guideline panel *suggests* no anticoagulation rather than using anticoagulation (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

**Remarks:** For recommendations 11a and 11b: neonates and pediatric patients who did not receive anticoagulation warrant follow-up monitoring, because extension of thrombus or organ dysfunction may require reconsideration of treatment options. Evidence from the available observational studies describes (complete or partial) PVT resolution in patients who did receive anticoagulation, as well as those who did not receive anticoagulation, and therefore, does not allow for assessment of the degree of benefit from anticoagulation. However, the panel placed value on avoiding the potential increased risk of long-term complications associated with persistent occlusive thrombus, and therefore, favored treatment in this setting. The panel also recognized the potential increased risk of bleeding in pediatric patients with PHTN and development of esophageal varices, and therefore, did not recommend anticoagulation in that setting.

***Recommendation 12a.*** For pediatric patients with superficial vein thrombosis (SVT) secondary to IV cannulation in the upper limb, the ASH/ISTH guideline panel *suggests* no anticoagulation rather than using anticoagulation. (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

***Recommendation 12b.*** For pediatric patients with SVT in the upper limb, which is not cannula related, or in the lower limbs associated with cancer or varicose veins, the ASH/ISTH guideline panel *suggests* anticoagulation rather than no anticoagulation (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

**Remarks:** There were no direct and only limited indirect data upon which to base this recommendation. The panel members experience suggested that, in most instances (eg, peripheral IV [PIV]– or CVAD-related events in the upper extremity), no anticoagulation may be required. However, anticoagulation could be considered in select patients with symptomatic SVT (eg, non–PIV-/PICC (peripherally inserted central catheter)-related, cancer, varicose vein, and lower limb events) or scenarios (eg, PIV/long-term PICC and/or symptom progression). The panel notes that when anticoagulation is prescribed, there is uncertainty about the optimal intensity (eg, prophylactic vs full dose) and duration of therapy.

***Recommendation 13.*** For pediatric patients with proximal DVT, the ASH/ISTH guideline panel *suggests* using anticoagulation alone rather than thrombolysis followed by anticoagulation (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

**Remarks:** The panel considered characteristics such as the extent and clinical impact of VTE, as important in determining the risk to benefit ratio of thrombolysis. In most cases, the risks seem higher than the potential benefit; however, there may be individuals for whom the opposite is true. In this clinical scenario, extrapolation from adult data was difficult. There are insufficient data to address the risk to benefit ratio of local thrombolysis via interventional radiology compared with systemic thrombolysis, and the panel noted that the centers with access to pediatric interventional radiology were often stronger advocates of thrombolysis.

***Recommendation 14.*** For pediatric patients with PE and echocardiographic or biochemical evidence of right ventricular dysfunction but without hemodynamic compromise, the ASH/ISTH guideline panel *suggests* using anticoagulation alone rather than thrombolysis followed by anticoagulation (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

**Remarks:** The panel considered submassive PE to represent pediatric patients with PE who do not have hemodynamic compromise (ie, systemic hypotension or other signs of shock) but who do have echocardiographic (eg, right ventricular dilation or intraventricular septal bowing into the left ventricle, etc) or biochemical (eg, elevated troponin or brain natriuretic peptide, etc) evidence of right ventricular dysfunction.[22] There were minimal pediatric data, and recent international adult guideline panels have recommended anticoagulation alone rather than thrombolysis followed by anticoagulation in this situation (based on low certainty in the evidence of effects).[23,24] These same adult guidelines, however, have suggested that thrombolysis may be reasonable to consider for younger patients with submassive PE at low risk of bleeding and those who have evidence of both echocardiographic and biochemical evidence of right ventricular dysfunction, which may be extrapolated to select pediatric patients. Patients with submassive PE should be monitored closely for the development of hemodynamic compromise.[22,23] The panel concluded that the risks of thrombolysis outweighed the benefits in most cases, hence the conditional recommendation for anticoagulation alone.

***Recommendation 15.*** For pediatric patients with PE and hemodynamic compromise the ASH/ISTH guideline panel *suggests* using thrombolysis followed by anticoagulation rather than anticoagulation alone (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

**Remarks:** The panel considered massive PE to represent pediatric patients with PE who do have hemodynamic compromise that may be life threatening, with limited time to respond to standard anticoagulation, and therefore, conditionally recommended thrombolysis followed by anticoagulation, based predominantly on extrapolation from recent adult guidelines and 3 small pediatric studies that suggested a trend toward decreased mortality with thrombolysis.[23-27]

***Recommendation 16.*** For pediatric patients with symptomatic CVAD-related thrombosis who no longer require venous access or whose CVAD is nonfunctioning, the ASH/ISTH guideline panel *suggests* either immediate removal or delayed removal of the CVAD (conditional recommendation based on low certainty in the evidence about effects ⊕⊕◯◯).

**Remarks:** Recent observational studies provided data that >48 hours of anticoagulation before CVAD removal vs immediate CVAD removal are comparable in terms of potential risk of emboli leading to PE or paradoxical stroke. The panel recognized that some clinical scenarios, such as children with a large thrombotic burden or those with right-to-left cardiac shunts, may benefit from a few days

of anticoagulation before CVAD removal to decrease the risk of embolism.

***Recommendation 17.*** For pediatric patients with VTE, the ASH/ISTH guideline panel *suggests* using DOACs (rivaroxaban/dabigatran) over SOC anticoagulants (low molecular weight heparin [LMWH], unfractionated heparin [UFH], vitamin K antagonists [VKAs], and fondaparinux; conditional recommendation based on low certainty in the evidence about effects ⊕◯◯◯).

**Remarks:** The panel concluded that there was a small benefit of DOACs over SOC, in relation to reduced thrombus recurrence rate and increased rate of thrombus resolution. The undesirable effects of DOACs vs SOC were felt to be small, with a reduction in major bleeding albeit with an increase in clinically relevant non major bleeding (CRNMB). The panel acknowledged the limitations of these data when evaluating the outcomes of mortality, recurrence, postthrombotic syndrome (PTS), and major/CRNMB due to the small number of events reported. Given the natural history of PTS and thrombus recurrence, evaluation at 3 to 6 months was considered to be too soon to provide accurate representation of these outcomes. The monitoring of drug level and dose adjustment of dabigatran during the DIVERSITY trial raised concern about the potential effect on efficacy and safety of routine use according to current approvals, which do not require such monitoring. Although data on QOL, cost-effectiveness, and acceptability of an oral agent that does not require monitoring were lacking, the panel felt that these were important factors when making this recommendation.

***Recommendation 18.*** For pediatric patients with VTE the ASH/ISTH guideline panel *suggests* using rivaroxaban over SOC anticoagulants (LMWH, UFH, VKA, and fondaparinux; conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

**Remarks:** The panel concluded that there was a small benefit of rivaroxaban over SOC, in relation to reduced thrombus recurrence and improved thrombus resolution. The undesirable effects of rivaroxaban vs SOC were felt to be small, with a reduction in major bleeding countered by an increase in CRNMB. These data were limited by the small number of important outcomes that were reported, that is mortality, recurrence, PTS, and major bleeding/CRNMB. The panel noted that some individuals were excluded from the EINSTEIN-Junior trial, including those aged <6 months with low birth weight and those with severe liver or renal impairment. The panel also noted reports of heavier menstrual bleeding while on rivaroxaban and felt that this was an important consideration when choosing an anticoagulant.

***Recommendation 19.*** For pediatric patients with VTE, the ASH/ISTH guideline panel *suggests* using dabigatran over SOC anticoagulants (LMWH, UFH, VKA, and fondaparinux; conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

**Remarks:** The panel concluded that there was a small benefit of dabigatran over SOC, in relation to reduced thrombus recurrence and improved thrombus resolution. The undesirable effects were felt to be trivial, with major bleeding reported in fewer patients treated with dabigatran and an equivalent frequency of CRNMB. The panel noted that some individuals were excluded from the DIVERSITY trial, including those aged <2 years with low body weight, and those with severe liver or renal impairment. The monitoring and dose adjustment of dabigatran during the DIVERSITY trial raised concern about the potential effect on efficacy and safety of routine use according to current approvals, which do not require such monitoring. The panel also noted reports of gastrointestinal side effects while on dabigatran and felt that this was an important consideration when choosing an anticoagulant.

***Recommendation 20.*** For pediatric patients with VTE, the ASH/ISTH guideline panel *suggests* using either rivaroxaban or dabigatran, although there may be individual populations or jurisdictional availability that would lead clinicians to choose 1 agent over the other (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

**Remarks:** The panel undertook an exercise to review the evidence-to-decisions (EtDs) for rivaroxaban vs SOC and dabigatran vs SOC to examine if 1 of these agents (given the available data) would be a preferred agent to use in treatment of pediatric VTE. To accomplish this, the panel first assigned weights to the summary of judgments. Balance of effects, certainty in the evidence, and acceptability and feasibility of implementation were given the highest weighting, with resources required given moderate weighting, and cost-effectiveness and equity given the lowest weighting.

### Good practice statements

The panel agreed that a pediatric hematologist or a pediatrician in consultation with a hematologist will be best suited to implement these recommendations given the complexity of the care involved in children with VTE.

For pediatric patients who are at high risk of bleeding (eg, CSVT and associated hemorrhage secondary to venous congestion, immediately after or anticipated invasive procedures), consider the use of a short half-life agent such as UFH rather than LMWH or DOACs if anticoagulation is required, to decrease the risk of worsening hemorrhage or bleeds.

***Values and preferences.*** This updated guideline used a formal exercise to determine the utility and disutility of the patient important outcomes from the previous iteration by surveying the panel members as performing a systematic review on disutility from the adult population. Based on this exercise, overall, these recommendations placed a higher value on PE, proximal DVT, and major bleeding, and placed a relatively lower value on CRNMB and distal DVT.

## Introduction

### Aims of these guidelines and specific objectives

The purpose of these guidelines is to provide evidence-based recommendations on the treatment of VTE in pediatric patients. The primary goals of these guidelines are to review, critically appraise, and implement evidence-based recommendations that will assist clinicians in deciding which pediatric patients with VTE require antithrombotic treatment and which agent/agents to use.

Furthermore, the implementation guidance section aims to assist clinicians in optimizing the use of anticoagulants in pediatric patients. Through improved provider and patient education of the available evidence and evidence-based recommendations, these guidelines aim to provide clinical decision support for shared decision-making that will result in best care of pediatric patients with VTE.

The target audience includes patients, hematologists, general practitioners, pediatricians, other clinicians, and decision-makers. Policymakers interested in these guidelines include those involved in developing local, national, or international plans with the goal to improve the care of pediatric patients. This article may also serve as the basis for adaptation by local, regional, or national guideline panels.

### Description of the health problem

Pediatric VTE is considered a major clinical problem because of the potential for associated mortality and significant complications including PE, cerebrovascular events, as well as PTS.[28,29] VTE occurs when ≥1 components of the Virchow triad are activated: stasis of blood flow, injury to the endothelial lining, or hypercoagulability of blood components. Virchow triad remains the most useful pathophysiological construct for thinking about thromboembolism in children.[30]

Since the publication of the 2018 ASH pediatric VTE treatment guidelines, there has been a dramatic increase in available information, knowledge, and expertise in relation to the appropriate diagnosis, prevention, and clinical management of VTE in pediatric patients. However, there remain many unknowns and large data registries, and ongoing studies will hopefully continue to improve our knowledge.

## Methods

The guideline panel developed and graded the recommendations and assessed the certainty of the supporting evidence following the GRADE approach.[4,5,7-10,31] The overall guideline development process, including funding of the work, panel formation, management of conflicts of interest, internal and external review, and organizational approval, was guided by ASH policies and procedures derived from the GIN-McMaster guideline development checklist http://cebgrade.mcmaster.ca/guidecheck.html[32] and was intended to meet recommendations for trustworthy guidelines by the Institute of Medicine and the GIN.[1-3]

### Organization, panel composition, planning, and coordination

The work of this panel was coordinated by ASH, ISTH, and the University of Kansas Health System (funded by ASH and ISTH under a partner agreement). Project oversight was provided by the ASH guideline oversight subcommittee, which reported to the ASH Committee on Quality and the ISTH guidelines and guidance committee, which reported to ISTH council. ASH vetted and appointed individuals to the guideline panel. The University of Kansas Health System vetted and retained researchers to conduct systematic reviews of evidence and coordinate the guideline development process including the use of the GRADE approach.

The membership of the panels and the systematic review team are described in supplement 1 of the supplemental Data.

The panel included both adult and pediatric hematologists, a pediatric cardiologist, a pediatric critical care expert, a pharmacist, a pediatric hematology and cardiology nurse, and a biostatistician, who all had clinical and research expertise on the guideline topic. One co-chair was a content expert; the other co-chair was an expert in guideline development methodology.

In addition to synthesizing evidence systematically, the University of Kansas Health System supported the guideline development process, including determining methods, preparing meeting materials, and facilitating panel discussions. The panel's work was done using web-based tools (www.surveymonkey.com and www.gradepro.org), and in-person and online meetings.

### Guideline funding and management of conflicts of interest

Development of these guidelines was jointly funded by ASH, a nonprofit medical specialty society that represents hematologists; and ISTH, a nonprofit international medical specialty society committed to the understanding and treatment of all conditions related to thrombosis and hemostasis. Most members of the guideline panel were members of ASH and ISTH. ASH staff supported panel appointments and coordinated meetings but had no role in choosing the guideline questions or determining the recommendations.

Members of the guideline panel received travel reimbursement for attendance at in-person meetings. Through the University of Kansas Health System, some researchers who contributed to the systematic evidence reviews received salary or grant support. Other researchers participated to fulfill requirements of an academic degree or program.

Conflicts of interest of all participants were managed according to ASH policies based on recommendations of the Institute of Medicine[33] and the GIN.[3] Participants disclosed all financial and nonfinancial interests relevant to the guideline topic. ASH staff and the ASH guideline oversight subcommittee reviewed the disclosures and composed the guideline panel to include a diversity of expertise and perspectives in order to avoid most of the panel having the same or similar conflicts. Greatest attention was given to direct financial conflicts with for-profit companies that could be directly affected by the guidelines. Most of the guideline panel, including the co-chairs, had no such conflicts. None of the University of Kansas Health System researchers who contributed to the systematic evidence reviews or who supported the guideline development process had any such conflicts.

Recusal was used to manage certain conflicts.[5,34-36] During deliberations about recommendations, any panel member with a current, direct financial conflict in a commercial entity that marketed any product that could be affected by a specific recommendation participated in discussions about the evidence and clinical context but was recused from making judgments or voting on individual domains (eg, magnitude of desirable consequences) and the direction and strength of the recommendation. The EtD framework for each recommendation describes which individuals were recused from making judgments about each recommendation.

Supplement 2 provides the complete disclosure-of-interests forms of all panel members. In part A of the supplement, individuals disclosed direct financial interests for 2 years before appointment; in part B, indirect financial interests are covered; and in part C, other interests that are not mainly financial are discussed. Part D describes new interests disclosed by individuals after appointment. Part E summarizes ASH decisions about which interests were judged to be conflicts and how they were managed, including through recusal.

Supplement 3 provides the complete disclosure of interest forms of researchers who contributed to these guidelines.

## Formulating specific clinical questions and determining outcomes of interest

Given that this is an update of previous guidelines, the panel commenced with the questions used in the 2018 pediatric VTE guidelines and then used the GRADEpro guideline development tool (www.gradepro.org)[37] and Google form (docs.google.com/forms) to brainstorm and then prioritize the questions described in Table 1. The recommendations from the 2018 ASH guidelines for treatment of pediatric VTE that were not addressed in the 2024 ASH/ISTH guideline on treatment of pediatric VTE are shown in Table 2.

The panel selected outcomes of interest for each question a priori, following the approach described in detail elsewhere.[38] In brief, the panel first brainstormed all possible outcomes before rating their relative importance for decision-making following the GRADE approach.[38] Although acknowledging considerable variation in the impact on patient outcomes, the panel considered the outcomes listed in Table 1 as critical for clinical decision-making for the respective questions.

## Evidence review and development of recommendations

For each guideline question, the University of Kansas Health System prepared a GRADE EtD framework, using the GRADEpro guideline development tool (www.gradepro.org).[4,10] The EtD table summarized the results of systematic reviews of the literature that were updated or performed for this guideline. The EtD table addressed effects of interventions, resource use (cost-effectiveness), values and preferences (relative importance of outcomes), equity, acceptability, and feasibility. The guideline panel reviewed draft EtD tables before, during, or after the guideline panel meeting, and made suggestions for corrections and identified missing evidence. To ensure that recent studies were not missed, searches (supplement 4) were updated twice, once in June 2023 and again in January 2024, and panel members were asked to suggest any studies that may have been considered missed and fulfilled the inclusion criteria for the individual questions.

Under the direction of the University of Kansas Health System, researchers followed the general methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions (handbook.cochrane.org) for conducting updated or new systematic reviews of intervention effects. When existing reviews were used, judgments of the original authors about risk of bias were either randomly checked for accuracy and accepted, or conducted de novo if they were not available or not reproducible. For new reviews, risk of bias was assessed at the health outcome level using the Cochrane Collaboration's risk of bias tool for randomized trials or nonrandomized studies. In addition to conducting systematic reviews of intervention effects, the researchers searched for evidence related to baseline risks, values, preferences, and costs, and summarized findings within the EtD frameworks.[4,5,10] Subsequently, the certainty of the body of evidence (also known as quality of the evidence or confidence in the estimated effects) was assessed for each effect estimate of the outcomes of interest following the GRADE approach based on the following domains: risk of bias, precision, consistency and magnitude of the estimates of effects, directness of the evidence, risk of publication bias, presence of large effects, dose-response relationship, and an assessment of the effect of residual opposing confounding. The certainty was categorized into 4 levels ranging from very low to high.[7,8,31] Within this report, these categories are represented by the symbols, as shown in Figure 1.

Interested readers may find more explanation about the GRADE approach to assessing and rating certainty in a body of evidence in other publications.[7,8,31]

During a 1-day in-person meeting followed by online communication and a series of 31 conference calls, the panel developed clinical recommendations based on the evidence summarized in the EtD tables. For each recommendation, the panel took a population perspective and came to consensus on the following: the certainty in the evidence, the balance of benefits and harms of the compared management options, and the assumptions about the values and preferences associated with the decision. The guideline panel also explicitly considered the extent of resource use associated with alternative management options. The panel agreed on the recommendations (including direction and strength); remarks; and qualifications by consensus; or, in rare instances, by voting (an 80% majority was required for a strong recommendation), based on the balance of all desirable and undesirable consequences. The final guidelines, including recommendations, were reviewed and approved by all members of the panel. In the previous iteration, because of the sparsity of evidence, the panel used the expert evidence approach.[39] In this update, and because of the new evidence, there was no need to use that approach.

## Interpretation of strong and conditional recommendations

The recommendations are labeled as either "strong" or "conditional" according to the GRADE approach. The words "the guideline panel recommends" are used for strong recommendations, and "the guideline panel suggests" for conditional recommendations. Table 3 provides the GRADE's interpretation of strong and conditional recommendations by patients, clinicians, health care policymakers, and researchers.

## Document review

Draft recommendations were reviewed by all members of the panel, revised, and then made available online from 8 April through 8 May 2024 for external review by stakeholders including allied organizations, other medical professionals, patients, and the public. Six individuals and 1 organization submitted comments. The document was revised to address pertinent comments, but no changes were made to recommendations. On 15 October 2024, the ASH

**Table 1. PICO questions, subgroups, and outcomes of interest**

| PICO question | Subgroups | Outcomes |
|---|---|---|
| For pediatric patients with symptomatic DVT or PE, should anticoagulation vs no anticoagulation be used? | Neonates<br>Children<br>Adolescents<br>CVAD<br>Cancer<br>APLA | Mortality<br>Resolution<br>Recurrence of VTE<br>Extension of thrombus/PE<br>Major bleeding/CRNMB<br>PTS<br>HITT |
| For pediatric patients with clinically unsuspected (previously asymptomatic) DVT or PE, should anticoagulation vs no anticoagulation be used? | Neonates<br>Children<br>Adolescents<br>CVAD<br>Cancer<br>APLA<br>Presence of thrombophilia | Mortality<br>Resolution<br>Recurrence of VTE<br>Extension of thrombus/PE<br>Major bleeding/CRNMB<br>PTS<br>HITT |
| For pediatric patients with provoked VTE, should anticoagulation for 6 wk vs 3 mo be used? | Neonates<br>Children<br>Adolescents<br>CVAD<br>Cancer<br>APLA<br>CSVT<br>Provoked with persistent risk factors<br>Provoked with resolved risk factors | Mortality<br>Resolution<br>Recurrence of VTE<br>Extension of thrombus/PE<br>Major bleeding/CRNMB<br>PTS<br>HITT |
| For pediatric patients with unprovoked DVT or PE, should anticoagulation for 6 to 12 mo vs indefinite anticoagulation be used? | Neonates<br>Children<br>Adolescents<br>APLA | Mortality<br>Resolution<br>Recurrence of VTE<br>Extension of thrombus/PE<br>Major bleeding/CRNMB<br>PTS<br>HITT |
| For pediatric patients with CSVT, should anticoagulation vs no anticoagulation be used?<br>For pediatric patients with CSVT, should thrombolysis followed by anticoagulation vs anticoagulation alone be used? | Neonates<br>Children<br>Adolescents<br>ICH<br>Infection<br>Asparaginase<br>Trauma | Mortality<br>Recurrence of VTE<br>Resolution<br>Cerebral infarction<br>Neurologic outcome<br>Major bleeding/CRNMB<br>HITT |
| For neonates and pediatric patients with RAT, should anticoagulation vs no anticoagulation be used?<br>For neonates and pediatric patients with RAT, should thrombolysis followed by anticoagulation vs anticoagulation alone be used? | Neonates<br>Children | Mortality<br>Recurrence of VTE<br>Resolution<br>Cerebral infarction<br>Neurologic outcome<br>Major bleeding/CRNMB<br>PTS<br>HITT |
| For neonates with RVT, should anticoagulation vs no anticoagulation be used?<br>For neonates with RVT, should thrombolysis followed by anticoagulation vs anticoagulation alone be used? | Neonates<br>Unilateral vs bilateral<br>IVC extension<br>AKI | Mortality<br>Recurrence of VTE<br>Resolution<br>Kidney function (eGFR, proteinuria)<br>Blood pressure<br>Kidney atrophy<br>Major bleeding/CRNMB |
| For neonates and pediatric patients with PVT, should anticoagulation vs no anticoagulation be used? | Neonates<br>Children<br>Catheter related<br>Occlusive<br>Spontaneous<br>After liver transplant | Mortality<br>Resolution<br>Recurrence of VTE<br>Extension of thrombus/PE<br>Major bleeding/CRNMB<br>PHTN<br>HITT |
| For pediatric patients with SVT, should anticoagulation vs no anticoagulation be used? | Neonates<br>Children<br>Adolescents<br>Provoked<br>Unprovoked | Mortality<br>Resolution<br>Recurrence of VTE<br>Extension of thrombus/PE<br>Major bleeding/CRNMB<br>PTS<br>HITT |

AKI, acute kidney injury; APLA, anti phospholipid antibody; eGFR, estimated GFR; HITT, heparin induced thrombocytopenia and thrombosis; ICH, intracranial hemorrhage; PICO, population, intervention, caomparison, outcome.

**Table 1 (continued)**

| PICO question | Subgroups | Outcomes |
|---|---|---|
| For pediatric patients with proximal DVT, should thrombolysis followed by anticoagulation vs anticoagulation alone be used?<br>For pediatric patients with submassive PE, should thrombolysis followed by anticoagulation vs anticoagulation alone be used?<br>For pediatric patients with PE with hemodynamic compromise, should thrombolysis followed by anticoagulation vs anticoagulation alone be used? | Neonates<br>Children<br>Adolescents | Mortality<br>Resolution<br>Recurrence of VTE<br>Major bleeding/CRNMB<br>PTS |
| For pediatric patients with symptomatic CVAD-related thrombosis, should immediate removal of a nonfunctioning or unneeded CVAD vs delayed removal be used? | Neonates<br>Children<br>Adolescents<br>PICC line<br>Central line | Mortality<br>PE<br>Paradoxical emboli<br>Major bleeding/CRNMB<br>PTS |
| For pediatric patients with VTE, should DOACs vs SOC anticoagulants be used?<br>For pediatric patients with VTE, should rivaroxaban vs SOC anticoagulants be used?<br>For pediatric patients with VTE, should dabigatran vs SOC anticoagulants be used?<br>For pediatric patients with VTE, should either rivaroxaban or dabigatran be preferentially used? | Neonates<br>Children<br>Adolescents<br>Presence of bleeding<br>Thrombocytopenia<br>Periprocedural<br>Renal insufficiency<br>Hepatic insufficiency | Mortality<br>Resolution<br>Recurrence of VTE<br>Extension of thrombus/PE<br>Major bleeding/CRNMB<br>PTS |

AKI, acute kidney injury; APLA, anti phospholipid antibody; eGFR, estimated GFR; HITT, heparin induced thrombocytopenia and thrombosis; ICH, intracranial hemorrhage; PICO, population, intervention, caomparison, outcome.

guideline oversight subcommittee and the ASH Committee on Quality approved that the defined guideline development process was followed; and on 23 October 2024, the officers of the ASH executive committee approved submission of the guidelines for publication under the imprimatur of ASH. On 6 November 2024, the ISTH guidelines and guidance committee and the ISTH council approved the submission of the guidelines for publication. The guidelines were then subjected to peer review by *Blood Advances.*

### How to use these guidelines

ASH/ISTH guidelines are primarily intended to help clinicians make decisions about diagnostic and treatment alternatives. Other purposes are to inform policy, education, and advocacy, and to state future research needs. They may also be used by patients. These guidelines are not intended to serve or be construed as an SOC. Clinicians must make decisions on the basis of the clinical presentation of each individual patient, ideally through a shared process that considers the patient's values and preferences with respect to the anticipated outcomes of the chosen option. Decisions may be constrained by the realities of a specific clinical setting and local resources, including, but not limited to, institutional policies, time limitations, or availability of treatments. These guidelines may not include all appropriate methods of care for the clinical scenarios described. As science advances and new evidence becomes available, recommendations may become outdated. Following these guidelines cannot guarantee successful outcomes. The ASH/ISTH does not warrant or guarantee any products described in these guidelines.

Statements about the underlying values and preferences, as well as qualifying remarks accompanying each recommendation, are integral parts and serve to facilitate a more accurate interpretation. They should never be omitted when quoting or translating recommendations from these guidelines. The use of these guidelines is also facilitated by the links to the EtD frameworks and interactive summary of findings tables in each section.

## Recommendations

### Good practice statement

The panel agreed that a pediatric hematologist or a pediatrician in consultation with a hematologist will be best suited to implement these recommendations given the complexity of the care involved in children with VTE.

*For pediatric patients with symptomatic DVT or PE, should anticoagulation vs no anticoagulation be used?*

**Recommendation 1**

For pediatric patients with symptomatic DVT or PE**,** the ASH/ISTH guideline panel *suggests* using anticoagulation rather than no anticoagulation (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

**Remarks:** Although there remains limited direct evidence in pediatric patients, there is strong indirect evidence in adults that symptomatic VTE requires treatment. However, based on recently published observational studies in pediatric patients, there may be specific clinical scenarios such as neonatal central venous catheter–associated VTE or trauma-associated VTE in which anticoagulation may result in either no significant benefit or potentially an increased risk of harm. Outside of these specific clinical scenarios, the panel agrees that in most pediatric patients with symptomatic DVT and PE, anticoagulation is warranted. Therefore, the panel made a conditional recommendation with very low certainty in the evidence.

**Table 2. Recommendations from the 2018 ASH pediatric VTE guidelines that were not addressed in this 2024 revision**

| | |
|---|---|
| **Thrombectomy and IVC filters** | |
| Recommendation 6: The ASH guideline panel *suggests* against using thrombectomy followed by anticoagulation, and rather use anticoagulation alone in pediatric patients with symptomatic DVT or PE (conditional recommendation based on very low certainty in the evidence about effects).<br>Recommendation 7: The ASH guideline panel *suggests* against using IVC filter, and rather use anticoagulation alone in pediatric patients with symptomatic DVT or PE (conditional recommendation based on very low certainty in the evidence about effects). | Remarks: The panel recognized that in certain cases, for example, with cardiovascular compromise secondary to the VTE, thrombectomy may be appropriate, but in the experience of the panel such cases were rare and not without risk. Anecdotal cases of catheter-directed thrombectomy could not be adequately assessed.<br>Remarks: The panel considered the benefits vs risks involved in IVC filter use and determined their use should be reserved for certain cases: for example, those patients with DVT and absolute contraindication to anticoagulation, or those children who failed adequate standard anticoagulation therapy in whom a filter might reduce embolic risk. IVC filters should be temporary and there should always be a clear plan for removal. When the absolute contraindication is resolved, restarting the anticoagulation and removal of the filter is appropriate. It is not feasible to place IVC filters in children with a weight of <10 kg. |
| **AT replacement therapy** | |
| Recommendation 8a: The ASH guideline panel *suggests* against using AT replacement therapy in addition to standard anticoagulation, and rather use standard anticoagulation alone in pediatric patients with DVT/CSVT/PE (conditional recommendation based on very low certainty in the evidence about effects).<br>Recommendation 8b: The ASH guideline panel *suggests* using AT replacement therapy in addition to standard anticoagulation rather than standard anticoagulation alone in pediatric patients with DVT/CSVT/PE who have failed to respond clinically to standard anticoagulation treatment and in whom subsequent measurement of AT concentrations reveals low AT levels based on age-appropriate reference ranges (conditional recommendation based on very low certainty in the evidence about effects). | Remarks: The use of AT replacement has increased dramatically in recent years in the management of VTE in children, although supportive published data are extremely limited. The most commonly used rationale is to facilitate attainment of therapeutic heparin activity. Most evidence is indirect, being in the prophylactic situation rather than treatment, and based on the prophylactic studies, there is little evidence of clinical benefit and perhaps evidence of clinical harm.<br>Remarks: Despite the overall recommendation against AT use, the panel considered several subgroups, and specific situations in which they agreed AT use might be justified. First, in children with documented inherited AT deficiency, in whom anticoagulation of VTE was not achieving clinical benefit. Other situations included children with low levels of AT compared with age-appropriate levels (as distinct from adult levels), acute lymphoblastic leukemia on induction using asparaginase, nephrotic syndrome, neonates, after liver transplant, and in children with disseminated intravascular coagulation and VTE. Usually, AT use would be commenced if there was continuous thrombus growth and/or failure of clinical response despite adequate anticoagulation. There was, however, no evidence to suggest improved outcomes in these patients. |
| **CVAD-related thrombosis** | |
| Recommendation 9: The ASH guideline panel *suggests* no removal rather than removal of a functioning CVAD, in pediatric patients with symptomatic CVAD-related thrombosis who continue to require venous access (conditional recommendation based on very low certainty in the evidence about effects).<br>Recommendation 10: The ASH guideline panel *recommends* removal rather than no removal of a nonfunctioning or unneeded CVAD, in pediatric patients with symptomatic CVAD-related thrombosis (strong recommendation based on very low certainty in the evidence about effects).<br>Recommendation 12: The ASH guideline panel *suggests* either removal or no removal of a functioning CVAD in pediatric patients who have symptomatic CVAD-related thrombosis with worsening signs or symptoms despite anticoagulation and who continue to require venous access (conditional recommendation based on very low certainty in the evidence about effects). | Remarks: The panel placed a high value on avoiding the insertion of another CVAD in children who may have limited availability of access sites and considered the thrombogenic effect of placing another line and new endothelial injury. The panel considered that treatment of symptomatic CVAD-related thrombus with anticoagulation likely leads to minimal complications.<br>Remarks: In situations in which ongoing care of the primary condition can be delivered adequately without central venous access, removal of the stimulus to the thrombosis is appropriate. An overriding principle is that any central access device should be removed as soon as feasible within the confines of the overall treatment of the child. The panel made a strong recommendation despite very low certainty in the evidence for benefits based on high evidence of harm or high cost.<br>Remarks: The panel considered the variability in value placed by families and clinicians on maintaining line access compared with potential risk of infection and further thrombus progression, which will vary for individual patients. If alternative venous access is readily available, then removal of CVAD in setting of worsening VTE symptoms despite anticoagulation is appropriate. However, in some children, venous access is paramount. |
| **LMWH vs VKAs** | |
| Recommendation 13: The ASH guideline panel *suggests* using either LMWH or VKAs in pediatric patients with symptomatic DVT or PE (conditional recommendation based on very low certainty in the evidence about effects). | Remarks: The decision should depend on (1) patient values and preferences; (2) health services resources; (3) infrastructure and support; and (4) underlying condition, comorbidities, and other medications. |
| **Purpura fulminans due to homozygous protein C deficiency** | |
| Recommendation 24: The ASH guideline panel *suggests* using protein C replacement rather than anticoagulation in pediatric patients with congenital purpura fulminans due to homozygous protein C deficiency (conditional recommendation based on very low certainty in the evidence about effects).<br>Recommendation 25: The ASH guideline panel *suggests* using anticoagulation plus protein C replacement rather than anticoagulation alone in pediatric patients with congenital purpura fulminans due to homozygote protein C deficiency (conditional recommendation based on very low certainty in the evidence about effects).<br>Recommendation 26: The ASH guideline panel *suggests* using either liver transplantation or no liver transplantation (anticoagulation or protein C replacement) in pediatric patients with congenital purpura fulminans due to homozygous protein C deficiency (conditional recommendation based on very low certainty in the evidence about effects). | Remarks: The panel determined that the long-term effectiveness of protein C replacement was superior to that offered by anticoagulation and also did not have the adverse bleeding risk of anticoagulation. However, protein C is expensive, and cost may be prohibitive.<br>Remarks: This recommendation applies in an acute setting (acute episode of purpura fulminans) in which the intervention of protein C replacement plus anticoagulation is considered a better option than anticoagulation alone. For long-term treatment, when recommendation to fully supplement with protein C cannot be followed for pragmatic or cost reasons, then the use of combined protein C replacement and anticoagulation rather than anticoagulation alone may reduce the required intensity of anticoagulation and hence reduce the bleeding risk.<br>Remarks: Liver transplantation is curative of protein C deficiency but has its own acute and chronic risks and burden of care. The panel agreed that long-term maintenance on protein C replacement becomes increasingly expensive and difficult as the child grows and that long-term anticoagulation at the intensity required has significant bleeding risks. Hence, the optimal therapy depends on the values and preferences of the family, as well as local health service factors. Given the historical outcomes for children with this severe condition, discussion of potential pathways of care should be determined early before progressive organ damage has been sustained. |

AT, antithrombin.

| Evidence Certainty | |
|---|---|
| **High Certainty** | |
| ⊕⊕⊕⊕ | We are very confident that the true effect lies close to that of the estimate of the effect. |
| **Moderate Certainty** | |
| ⊕⊕⊕◯ | We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. |
| **Low Certainty** | |
| ⊕⊕◯◯ | Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. |
| **Very Low Certainty** | |
| ⊕◯◯◯ | We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect. |

**Figure 1. Symbols used to designate certainty of evidence within these guidelines.**

## Summary of the evidence

Since the last published guidelines in 2018, the panel did not find any RCT that specifically addressed this question in pediatric patients. In addition to extrapolation from adult data, the panel reviewed 5 new studies in pediatric patients, 3 observational studies, and 2 RCTs. These studies include a retrospective, multicenter observational study (n = 346) investigating outcomes in neonates, infants, and children aged <2 years with VTE[40]; and a prospective, multicenter observational study investigating outcomes in neonates and infants aged ≤6 months with CVAD-associated VTE who were treated according to a national consensus guideline (the NEOCLOT study, n = 115).[41] Data from a retrospective, single-center study (n = 753) investigating outcomes in pediatric patients aged <18 years with trauma-associated VTE[42] were evaluated separately. In the 2 RCTs, namely the EINSTEIN-Junior (n = 500; from birth at >37 weeks gestational age to age 17 years, randomized)[43] and DIVERSITY trials (n = 267; from birth at >37 weeks gestational age to age <18 years, randomized).[44] DOACs were compared with SOC and helped inform potential risks and benefits of anticoagulation, although neither trial included a "no anticoagulation" arm.

The panel concluded that the desirable effects of anticoagulation in pediatric VTE outweigh the undesirable effects of anticoagulation for most pediatric patients with symptomatic VTE, particularly those with PE, proximal DVT, and occlusive thrombosis, and in pediatric patients with ongoing risk factors for thrombosis such as active malignancy, long-term CVAD requirement, or active infection. The panel was not confident that this recommendation applies to all pediatric patients with symptomatic or clinically apparent VTE, specifically neonates with CVAD-associated thrombosis and patients with trauma-associated thrombosis, for whom the risk of major bleeding may be greater than the benefits of anticoagulation, including decreased risk for thrombus recurrence/progression and PTS.

Overall, the balance of effects favors anticoagulation in symptomatic VTE. Based on the GRADE methodology framework, a conditional recommendation was given because of the very low certainty in the evidence because of risk of bias concerns and imprecision.

## Benefits

Based on 2 observational studies,[40,41] 7 of 223 (3.1%) patients receiving anticoagulation had recurrent VTE compared with 4 of 47 (8.5%) patients who did not receive anticoagulation (RR, 0.38; 95% confidence interval [CI]: 0.12-1.3). There were 52 fewer recurrent events per 1000 patients receiving anticoagulation (95% CI, 75 fewer to 23 more). In the EINSTEIN-Junior and DIVERSITY trials, 22 of 651 (3.4%) patients receiving anticoagulation had recurrent VTE. Across these studies, the risk of recurrence was similar despite different study designs and demographic characteristics of the study cohorts.

In the EINSTEIN-Junior and DIVERSITY trials,[43,44] 10 of 651 (1.5%) patients receiving anticoagulation had radiological thrombus extension, and no patient receiving anticoagulation had symptomatic PE. The relative effects for thrombus extension and PE were not estimable from the available data because of the absence of a "no anticoagulation" comparison arm in these trials. In the aforementioned NEOCLOT study, 8 of 25 (32.1%) infants who did not receive anticoagulation demonstrated radiological thrombus extension (after a median follow-up of 4 days), whereas no patient who received anticoagulation had thrombus extension.

In the NEOCLOT study, radiological thrombus resolution (after a median follow-up for 54 days) was noted in 21 of 24 (87.5%) neonates and infants receiving anticoagulation vs 11 of 13 (84.6%) patients who did not receive anticoagulation (RR, 1.02; 95% CI, 0.59-1.73). Of note, patients with upfront thrombus extension were excluded from this analysis. All-cause mortality in this study was 3 of 24 (12.5%) patients receiving anticoagulation vs 2 of 19 (10.5%) patients who did not receive anticoagulation (RR, 1.167; 95% CI, 0.21-6.36). One death (0.9%) was secondary to progressive thrombosis. In the EINSTEIN-Junior and DIVERSITY trials, all-cause mortality was reported in 3 of 651 (0.5%) patients receiving anticoagulation. One death in EINSTEIN-Junior was unrelated to bleeding or thrombosis.[43] In the DIVERSITY trial,[44]

**Table 3. Interpretation of strong and conditional recommendations**

| | Recommendation Strength | | | |
|---|---|---|---|---|
| | "Recommends…" | "Recommends against…" | "Suggests…" | "Suggests against…" |
| |  |  |  |  |
| | **Interpretation of Strong Recommendations** | | **Interpretation of Conditional Recommendations** | |
| **Patients** | Most individuals in this situation would want the recommended course of action, and only a small proportion would not. | | Most individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping patients to make decisions consistent with their individual risks, values, and preferences. | |
| **Clinicians** | Most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences. | | Different choices will be appropriate for individual patients; clinicians must help each patient arrive at a management decision consistent with the patient's values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values, and preferences. | |
| **Policymakers** | The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. | | Policymaking will require substantial debate and involvement of various stakeholders. Performance measures should assess if decision making is appropriate. | |
| **Researchers** | The recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty in the evidence. In such instances, further research may provide important information that alters the recommendations. | | The recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help identify possible research gaps. | |

1 death was attributed to bleeding, and 1 death was attributed to progressive thrombosis.

A retrospective, single-center observational study reported outcomes in pediatric patients with trauma-associated VTE.[42] Radiological thrombus resolution was noted in 13 of 31 (41.9%) patients receiving anticoagulation vs 6 of 10 (60.0%) patients who did not receive anticoagulation (RR, 0.69; 95% CI, 0.36-1.34). The rate of all-cause mortality was 1 of 31 (3.2%) patients who received anticoagulation vs 0 of 10 (0.0%) patients who did not receive anticoagulation.

In the aforementioned observational studies, overall outcomes may have been affected by the differing risk profiles for patients receiving anticoagulation compared with those not receiving anticoagulation. There were also insufficient data to assess the potential benefit of anticoagulation on the incidence or severity of extremity PTS. Altogether, the certainty in the evidence for these estimates was low to very low, given serious to very serious imprecision due to the low number of incident VTE and a serious risk of bias.

## Harms and burden

The relative effects for the risk of major bleeding and CRNMB with anticoagulation were not estimable from the available data because of the low number of events reported in the NEOCLOT study and the lack of a comparison arm in the EINSTEIN-Junior and DIVERSITY trials. In the NEOCLOT study, major bleeding and CRNMB were reported in 2 of 33 (6.1%) and 1 of 33 (3.0%) patients, respectively, receiving anticoagulation. In comparison, none of the patients who did not receive anticoagulation experienced a major or CRNMB. In the EINSTEIN-Junior and DIVERSITY trials, 8 of 767 (1.0%) and 14 of 767 (1.8%) patients receiving anticoagulation experienced major bleeding and CRNMB, respectively.[43,44]

Overall, the certainty of harms and benefits associated with anticoagulation vs no anticoagulation was very low, given a very serious imprecision because of the low number of events and a serious risk of bias. Particularly in the EINSTEIN-Junior and DIVERSITY trials, the eligibility criteria likely restricted enrollment of patients who were otherwise candidates for anticoagulation, and consequently limited generalizability of the data.

## Other EtD criteria and considerations

The guideline panel did not think that there were feasibility or acceptability considerations that would impair the implementation of this recommendation. Evidence profiles with the characteristics of all included studies and the complete EtD framework are online for recommendation 1.

## Conclusions and research needs for this recommendation

The guideline panel determined that there is a very low level of evidence for a net benefit/harm of anticoagulation in pediatric patients with symptomatic VTE. Despite the limitations of the published pediatric data, there is robust indirect evidence from adult studies that anticoagulation is warranted in patients with symptomatic DVT and PE. Additionally, data from recently published randomized trials of DOACs in pediatric patients underscore the safety and efficacy of anticoagulation in pediatric patients, including low rates of major bleeding, CRNMB, thrombus recurrence, and extension. The panel therefore agrees that most pediatric patients with symptomatic VTE

should receive anticoagulation. This is particularly true for patients with PE, proximal DVT, and occlusive thrombosis, and in pediatric patients with ongoing risk factors for thrombosis such as active malignancy, long-term CVAD requirement, or active infection. However, recently published observational data also highlight that in patients with an increased baseline risk of hemorrhage, such as neonates and pediatric patients with trauma-associated VTE, anticoagulation therapy may be associated with an increased risk of hemorrhage. In all patients, the decision to anticoagulate must be individualized after weighing the potential risk of thrombus progression and embolization against the risk of bleeding.

The panel identified the following additional research needs:

1. Study of pediatric patients with malignancy and thrombosis
2. Separate reporting of pediatric symptomatic vs clinically unsuspected VTE and therapies with extended follow-up
3. Risk stratification of pediatric subgroups who would benefit most and least from anticoagulation regardless of signs/symptoms, including defining benefit of anticoagulation in neonates
4. Real-life studies on benefits/harms of DOACs

*For pediatric patients with clinically unsuspected (previously termed asymptomatic) DVT or PE should anticoagulation vs no anticoagulation be used?*

**Recommendation 2**

For pediatric patients with clinically unsuspected (previously termed asymptomatic) DVT or PE, the ASH/ISTH guideline panel *suggests* either using anticoagulation or no anticoagulation (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

**Remarks:** The natural history of clinically unsuspected DVT or PE in pediatric patients appears to carry a lower risk (compared with symptomatic DVT or PE) of acute and long-term sequelae, especially in certain pediatric subpopulations. The recommendation is based on studies that report outcomes for pediatric patients with clinically unsuspected DVT or PE. Single-institution, observational, and retrospective studies in select subpopulations of pediatric patients suggest that not using anticoagulation for clinically unsuspected DVT or PE does not lead to severe outcomes. The benefits or harms of anticoagulation or no anticoagulation vary for different populations including neonates, pediatric patients who are critically ill, patients with cardiac disease, or patients who have experienced trauma. However, if clinically unsuspected DVT or PE is detected, the decision to treat or not treat should be individualized. Research to better understand the natural history of clinically unsuspected DVT or PE, benefits, and harms of treatment in a variety of subgroups and clinical settings in pediatrics is a high priority.

## Summary of the evidence

Clinically unsuspected VTE in children is defined as a VTE diagnosed via imaging test performed for surveillance (ie, with an intent to identify clinically silent VTEs) or incidentally found (most often via imaging performed for evaluation of regional pathology unrelated to VTE) in the absence of any VTE-associated signs or symptoms.[45] In previous literature, terms such as "asymptomatic" and "incidentally diagnosed" VTE were variably reported. We identified 3 studies that addressed this question in pediatric patients (1 single-arm, noncomparative study[46]; 1 observational nonrandomized study[41]; and 1 retrospective comparative study[42]). These studies included specific subpopulations including infants with cardiac disease,[46] neonates who are critically ill,[41] and pediatric patients who have experienced trauma.[42] The total number of pediatric patients with clinically unsuspected DVT or PE included in these 3 studies were <100. These studies provided data on the outcomes of interest that included VTE (DVT or PE) progression, resolution, recurrence, bleeding, mortality (all-cause and VTE related), and risk of PTS, including clinically relevant PTS.

Of the 3 included studies, 2 studies reported the effect of anticoagulation or no anticoagulation outcomes on VTE resolution,[41,42] 1 study reported thrombus progression and bleeding including CRNMB and major bleeding,[41] 2 studies assessed the risk of PTS,[42,46] and all 3 studies assessed mortality. These studies suggest that not using anticoagulation for clinically unsuspected DVT or PE does not result in negative outcomes. These studies included only specific pediatric subpopulations and a relatively small number of patients, and their results cannot necessarily be extrapolated to other pediatric subpopulations such as those with cancer or long-term central lines. Therefore, the panel made a conditional recommendation for either anticoagulation or no anticoagulation for clinically unsuspected DVT or PE. Clinicians will need to assess the benefits and harms of treatment vs no treatment, parental preference, and burden or costs of treatment on an individual basis until more evidence becomes available.

Two recent pediatric RCTs of DOACs compared with SOC were not included in this recommendation because the outcomes for symptomatic and clinically unsuspected DVT or PE were not reported separately.[43,44]

### Benefits

The relative effects were not estimable from the pediatric data because of the low number of patients in these studies and lack of direct comparison in one. The frequency of outcomes in pediatric patients who were treated with anticoagulation vs no anticoagulation were as follows: rate of thrombus extension 0 of 1 (0.0%) vs 2 of 5 (40.0%), thrombus resolution was 9 of 13 (69.2%) to 1 of 1 (100.0%) vs 5 of 9 (55.6%) to 3 of 3 (100.0%), and recurrence of 0 of 1 (0.0%) vs 0 of 3 (0%), respectively. The risk of PTS was 21.4% in patients who had experienced trauma, assessed at 13 months after VTE and 16.6% in pediatric patients with asymptomatic VTE related to short-term CVADs 2 years after VTE. Overall, the certainty in the evidence comparing anticoagulation over no anticoagulation for pediatric patients with clinically unsuspected VTE is very low due to the serious risk of bias and very serious imprecision in the included studies.

### Harms and burden

The risk of bleeding (major) was reported in 1 of 3 (33.3%) patients who had asymptomatic VTE and whom received

anticoagulation therapy.[46] Reported mortality (none was therapy related) was 1 of 13 (7.7%) vs 0 of 9 (0.0%) patients in the anticoagulation vs no-anticoagulation groups, respectively. Overall, the certainty of the harms and burdens associated with the intervention, or no intervention, is very low, owing to the serious risk of bias and very serious imprecision in the studies. The risk of major bleeding varies within the pediatric subpopulation, related to underlying age, disease process, and medical or surgical interventions, and should be taken into consideration. In particular, the 1 of 3 (33.3%) risk of bleeding reported in 1 of the studies is higher than that reported in recent multicenter randomized trials in which the reported rate of bleeding on anticoagulation was much lower at 2% to 3%. Because of the limited available evidence, the guideline panel considered the risk of adverse effects most likely to be small.

### Other EtD criteria and considerations

Currently, screening for clinically unsuspected VTE is not recommended and therefore the reported incidence and outcomes of clinically unsuspected clots are likely underreported. The guideline panel did not consider that there were feasibility or acceptability considerations that would impair implementation of this recommendation. Evidence profiles with the characteristics of all included studies and the complete EtD framework are online for recommendation 2.

### Conclusions and research needs for this recommendation

The guideline panel determined that there is a very low certainty in the evidence for a net health benefit or harm from using anticoagulation or no anticoagulation in clinically unsuspected VTE. New data are available to inform the recommendation presented in this guideline. However, the new data are from select subpopulations of pediatric patients with clinically unsuspected VTE that include infants and young children with congenital heart disease, neonates with short-term central venous catheters, and pediatric patients who have experienced trauma; and thus, the outcomes for other subpopulations of pediatric patients is unknown. Based on the body of available evidence, there appears to be a low risk of poor outcomes (thrombus extension, recurrence, mortality, and PTS) for these subpopulations despite no treatment. However, because of low certainty in the evidence, the fact that we did not find the evidence of an effect on these outcomes does not imply that such an effect does not exist.

The panel identified additional research questions and made the following recommendations:

1. Determining the outcomes of clinically unsuspected VTE in other subpopulations of pediatric patients such as those with cancer, children with short gut syndrome, and those with end-stage renal disease that need long-term central catheters
2. Designing future studies to present outcomes for patients with symptomatic and clinically unsuspected VTE separately so the true benefits and harms of treatment and nontreatment can be evaluated
3. Consistent use of international standard definitions of clinically unsuspected VTE across studies[45]

*For pediatric patients with provoked VTE, should anticoagulation for 6 weeks vs 3 months be used?*

**Recommendation 3**

For select pediatric patients with provoked VTE, the ASH/ISTH guideline panel *suggests* 6 weeks rather than 3 months of anticoagulation. Exclusions to this recommendation include: (1) PE, (2) recurrent VTE, (3) persistent occlusive thrombus at 6 weeks, (4) cancer-associated thrombosis, (5) patients with persistent APAs or major thrombophilia, and (6) ongoing VTE risk factors (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

**Remarks:** This recommendation is based mainly on the Kids-DOTT RCT that evaluated the duration of anticoagulation therapy in pediatric patients with provoked VTE. Importantly, the criteria for inclusion and randomization were stringent, and many pediatric patients with provoked VTE were excluded. The recommendation reflects the population that was studied and cannot be extrapolated to all patients with provoked VTE. For patients with provoked VTE not meeting these low-risk criteria, the panel suggests the use of anticoagulation therapy for 3 months, and for those with persistent provoking VTE risk factors, longer duration of anticoagulation may be considered.

### Summary of the evidence

We identified 1 new, multicenter international RCT,[47] as well as 2 retrospective cohort studies[48,49] comparing 6 weeks with 3 months treatment for pediatric VTE. The Kids-DOTT trial was the first RCT to evaluate duration of anticoagulation in pediatric patients with first episode–provoked VTE.[47] The trial excluded patients with active cancer, major thrombophilia traits, systemic lupus erythematosus, proximal PE, and those requiring thrombolysis. Additionally, patients who had persistent thrombus occlusion or positive APA at 6 weeks after VTE diagnosis were not eligible for randomization.

Among 417 randomized patients, 297 were included in the per-protocol analysis that demonstrated noninferiority of 6 weeks of anticoagulation compared with 3 months, based on an outcome of recurrent VTE and clinically relevant bleeding. The most common provoking factor in the trial was a CVAD (52%), followed by infection (34%) and trauma/surgery (20%).[47]

Additional evidence included a single-center retrospective cohort study[49] that compared 6 weeks of LMWH with 3 months in 74 pediatric patients with CVAD-related VTE and did not identify inferior outcomes in the 39 patients treated for a shorter duration. Lastly, a retrospective cohort study[48] reported outcomes of 23 pediatric patients with VTE treated with rivaroxaban for 6 weeks, 3 months, or 6 months of anticoagulation. None of the patients in this report had recurrent VTE or relevant bleeding.

### Benefits

The panel considered that a shortened duration of anticoagulation therapy may provide benefits including improved quality of life (QOL) for pediatric patients, particularly for those receiving subcutaneous (SQ) injections, increasing acceptability and feasibility

of the intervention, as well as the potential to provide moderate cost savings.

### Harms and burden

The relative effects were not estimable from the available data because of the low number of events reported in the studies. The Kids-DOTT trial[47] reported similar frequencies of symptomatic recurrent VTE at 1 year after VTE diagnosis between the 6-week and 3-month anticoagulant treatment groups (1/154 [0.6%] vs 2/143 [1.4%], respectively). There was also no difference in mortality between groups (4/206 [1.9%] vs 4/206 [1.9%]). Overall, the certainty of the harms and burdens associated with the different durations of anticoagulation therapy is low due to very serious imprecision. Furthermore, the panel acknowledged that the findings of the Kids-DOTT trial can only be extrapolated to a selected group of pediatric patients who meet the low-risk VTE criteria used in the trial. Whether the use of a shortened duration of anticoagulation therapy for patients who do not meet these criteria could potentially lead to an increased risk of adverse VTE outcomes including recurrent VTE is unknown.

### Other EtD criteria and considerations

Because the Kids-DOTT trial[47] did not report a reduction in bleeding or increase in recurrent VTE in patients treated for shorter duration, the evidence did not support a strong recommendation for a shorter duration.

The panel also noted that in the Kids-DOTT trial, all pediatric patients underwent thrombophilia testing, including APA. If elevated at VTE diagnosis, APA testing was repeated at 6 weeks, and if still elevated, these patients were excluded from randomization. The panel does not recommend that all pediatric patients with provoked VTE undergo thrombophilia testing to evaluate whether they are candidates for 6 weeks of anticoagulation. This is consistent with the ASH–American Society of Pediatric Hematology Oncology Choosing Wisely campaign, which does not recommend thrombophilia testing in pediatric patients with CVAD-related VTE.[50] Rather, the panel would recommend that such testing be driven based on factors including clinical presentation and family history. Lastly, most patients included in the per-protocol analysis had an extremity DVT (77%), with relatively low numbers of enrolled patients with VTE in other sites including CSVT (13%). Evidence profiles with the characteristics of all included studies and the complete EtD framework are online for recommendation 3.

### Conclusions and research needs for this recommendation

The guideline panel acknowledged that the Kids-DOTT trial[47] is a landmark pediatric thrombosis trial that will have a significant impact in the field, allowing many pediatric patients with provoked VTE to receive a shorter duration of anticoagulation. Nonetheless, there remain questions in this area, including whether there are other patients who may benefit from a shorter duration, including those with occlusive thrombus at 6 weeks but who otherwise meet low-risk criteria. Whether continuing anticoagulation beyond 6 weeks for an occlusive thrombus improves thrombus resolution is unknown, and this could be an area of future investigation.

Lastly, >85% of patients treated on the Kids-DOTT trial received LMWH.[47] Although there was no direct evidence of shorter duration of anticoagulation therapy using DOACs, studies in pediatric patients and adults would suggest that the efficacy of DOACs for treatment of VTE is noninferior to SOC (LMWH or VKAs). Therefore, the panel felt that it was reasonable to consider DOACs in this population but also to collect additional data from cooperative cohort studies and registries that focus on the systematic, prospective collection of real-world data.

*For pediatric patients with unprovoked DVT or PE, should anticoagulation for 6 to 12 months vs indefinite anticoagulation be used?*

**Recommendation 4**

For pediatric patients with unprovoked DVT or PE, the ASH/ISTH guideline panel *suggests* using anticoagulation for 6 to 12 months rather than indefinite anticoagulation (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

**Remarks:** Unprovoked VTE is rare in pediatrics. Although studies suggest that rates of recurrent VTE in children and adolescents aged >1 year with unprovoked VTE are relatively high (21%-36% at age 3.5 years), there are no pediatric studies evaluating duration of therapy in this cohort.[20,21] Although extrapolation of adult data might favor prolonged treatment in terms of VTE recurrence, in the absence of pediatric data, the panel felt that the impact of indefinite anticoagulation on bleeding risk and QOL would more negatively affect pediatric patients compared with adults. Patient values and preferences should be considered when making this decision.

### Summary of the evidence

There were no new studies since the 2018 guidelines evaluating treatment duration in pediatric unprovoked VTE. A meta-analysis conducted to inform the ASH 2020 adult VTE treatment guidelines led the adult panel to suggest indefinite anticoagulation for patients with unprovoked VTE with low bleeding risk.[23] Other important outcomes, such as impact on mental health, lifestyle, and QOL, which the panel judged to be of significant importance, particularly when considering indefinite therapy for a pediatric population, have not been evaluated.

### Benefits

The relative effects were not estimable from the pediatric data because of the lack of direct comparisons, and the frequency of major outcomes in pediatric patients treated for 6 to 12 months compared with indefinite anticoagulation cannot be determined accurately. There were no baseline data in pediatric patients to compare. The ASH adult meta-analysis showed a significant reduction in both PE (relative risk [RR], 0.29; 95% CI, 0.15-0.56) and DVT (RR, 0.20; 95% CI, 0.12-0.34) with indefinite anticoagulation compared with discontinuation of anticoagulation (high-certainty evidence).[23] Although there was a reduction in mortality with indefinite anticoagulation, there was less certainty in the estimate (RR, 075; 95% CI, 0.49-1.13).

## Harms and burden

The relative adverse events (AEs) were not estimable from the pediatric data, and the frequency of AEs in pediatric patients treated for 6 to 12 months compared with indefinite anticoagulation cannot be determined accurately. The ASH adult meta-analysis observed an increase in major bleeding in those treated with indefinite anticoagulation (RR, 2.17; 95% CI, 1.20-3.35; high-certainty evidence). The panel judged that acceptability of longer duration of therapy would vary based on patients' perceived burden of treatment, lifestyle, and impact on QOL. The panel judged that this was a complex cost-effectiveness question, and it would not be easy to make judgments without available studies. Evidence profiles with the characteristics of all included studies and the complete EtD framework are online for recommendation 4.

## Conclusions and research needs for this recommendation

The guideline panel determined that there is very low certainty in the evidence for a net health benefit from using indefinite anticoagulation compared with 6 to 12 months of anticoagulation for unprovoked VTE in pediatric patients. Although indirect evidence from adults suggests the opposite in terms of recurrent VTE, this comes at the expense of increased major bleeding. The panel considered that the impact of prolonged anticoagulation may also more negatively affect the QOL in younger patients, particularly those involved in sports. Thus, individual values and preferences of patients and their families should be explored when making this decision. Factors associated with higher rates of recurrence include age of >12 years at index VTE and inherited thrombophilia.[20,51] There is an urgent need to prospectively evaluate long-term outcomes in pediatric patients with unprovoked VTE, including the significance of persistent risk factors such as thrombophilia, or anatomic abnormalities. Studies should seek to evaluate the impact of anticoagulation adherence, intensity and duration on recurrence, bleeding, and QOL.

*For pediatric patients with CSVT, should anticoagulation vs no anticoagulation be used?*

**Recommendation 5**

For pediatric patients with CSVT with and without hemorrhage secondary to venous congestion, the ASH/ISTH guideline panel *suggests* using anticoagulation rather than no anticoagulation (conditional recommendation based on very low certainty in the evidence based on pediatric data ⊕◯◯◯).

**Remarks:** Observational studies suggest lower mortality and improved neurologic outcomes in patients with CSVT treated with anticoagulation. However, the panel recognized that different populations of patients with CSVT (eg, neonates, and those with infection-associated CSVT, who have experienced trauma, have had surgery, and have cancer) may have different risks for bleeding and neurologic outcomes that should be considered in the decision to use anticoagulation. Evidence of venous congestion secondary to thrombus obstruction with or without hemorrhage should be managed with anticoagulation. The panel notes that when anticoagulation is prescribed, it is important that appropriate therapy for additional associated conditions (eg, surgical interventions for infection-associated CSVT) be used.

*For pediatric patients with CSVT, should thrombolysis followed by anticoagulation vs anticoagulation alone be used?*

**Recommendation 6**

For pediatric patients with CSVT, the ASH/ISTH guideline panel *suggests* using anticoagulation alone rather than thrombolysis followed by anticoagulation (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

**Remarks:** The evidence is sparse for the balance of benefits and harms of thrombolysis compared with anticoagulation in pediatric patients with CSVT. Based on the experience of the panel members, the panel suggests use of anticoagulation rather than thrombolysis for children with CSVT who have no evidence of ischemia. However, thrombolysis may be considered when there is neurologic deterioration despite anticoagulation and, in such or similar instances, reperfusion therapies may be considered depending on local resources or experiences.

## Summary of the evidence

The updated systematic review identified 9 pediatric studies that assessed the use of anticoagulation in the management of CSVT encompassing >700 pediatric patients. These studies included neonates up to adolescents aged 18 years with CSVT, most of whom had identifiable risk factors. Most patients received anticoagulation. The outcomes considered were mortality, neurologic outcomes, thrombus resolution, thrombus recurrence, and bleeding. Mortality was assessed and reported in 3 studies.[52-54] Six studies reported neurologic outcome, 2 of which used the pediatric stroke outcome measure to assess neurologic outcome.[52-57] Thrombus resolution was reported in 5 studies.[52,54-57] Three studies assessed the risk of thrombus recurrence as an end point.[52,57,58] Bleeding was assessed in 6 studies.[52,54-56,59,60] A single case series of 10 pediatric patients with nephrotic syndrome was identified, addressing the use of thrombolysis followed by anticoagulation (6 patients) vs anticoagulation alone in children aged 3 to 10 years with CSVT.[61]

There is limited experience with systemic thrombolysis or reperfusion therapies such as catheter-directed thrombolysis (CDT) for pediatric patients with CSVT. The panel notes that adult guidelines for CSVT recommend reserving thrombolysis for patients with neurologic deterioration or thrombus progression despite anticoagulation.[62] A randomized trial in adults did not show a benefit from endovascular treatment vs anticoagulation alone with higher mortality in the endovascular treatment arm.[63] The panel noted that endovascular treatment options in pediatric patients would depend on patient size and institutional resources and experience.

## Benefits

Anticoagulation was associated with reduced mortality with an RR of 0.12 (95% CI, 0.04-0.36). Among nonneonates, mortality

with anticoagulation was 5 of 366 (1.4%), and 9 of 82 (11.0%) in those without anticoagulation. There were no studies that reported mortality in neonates. The description of neurologic deficits varied between studies and included a standardized assessment with a previously validated tool, (pediatric stroke outcome measure), presence of cranial nerve palsies, or a general description of neurologic deficits or symptoms. The risk of aggregate neurologic deficits was reduced (RR, 0.95; 95% CI, 0.69-1.30) in those who received anticoagulation. Pooled estimates were derived from studies that reported similar radiologic outcomes of CSVT. Of 79 pediatric patients who were treated with anticoagulation, 64 (78%) experienced partial or complete resolution compared with 38 of 71 (53.5%) of those not treated with anticoagulation (RR, 1.5; 95% CI, 1.2-1.9). The relative effects for the risk of recurrence were not estimable because there were no events reported in the included studies. Of 6 patients in the nephrotic syndrome case series who received thrombolysis followed by anticoagulation, all had resolution of the CSVT. Thrombus resolution was also observed in all 4 patients who were treated with anticoagulation alone. There were no deaths or recurrent events; thus, the RR was not estimable. Overall, the certainty of these estimated effects is very low owing to the high risk of bias and confounding in the studies and imprecision of the estimates.

## Harms and burden

The risk of developing bleeding was not significantly different in patients treated with anticoagulation (3 of 64 [4.7%]) compared with 1 of 31 (3.2%) patients not treated with anticoagulation. However, studies did not report major bleeding separately from CRNMB. The pooled RR of bleeding was higher with anticoagulation, but with large CIs because of small numbers of patients with bleeding events (RR, 1.90; 95% CI, 0.27-13.31). The EINSTEIN-Junior substudy on pediatric patients with CSVT reported 6 of 114 (5.4%) bleeding events overall, comprising 1 major bleed and 5 CRNMBs.[52] Several studies were not included in the pooled estimate because they reported 0 events. Of patients who received thrombolysis (with or without anticoagulation), no bleeding was reported in either group. There is low certainty in the estimate of the risk of bleeding because of significant confounding by indication and selection biases.

## Other EtD criteria and considerations

The panel recognized subpopulations of pediatric patients with CSVT that may carry different risks for bleeding, thrombus recurrence, and neurologic outcomes (eg, neonates, infection-associated, postsurgical, trauma, malignancy, and inflammatory conditions such as systemic lupus erythematous and inflammatory bowel disease). Pooled studies of these heterogenous groups show a reduction in mortality and suggest improvement in neurologic outcomes with anticoagulation. However, thrombus resolution has been demonstrated in observational studies of select populations of neonates and patients with postsurgical and infection-associated CSVT not treated with anticoagulation. These findings may be affected by selection bias of withholding anticoagulation in patients with a low risk of thrombus progression or high bleeding risk. The panel notes, however, that in observational studies, most patients across all subgroups were treated with anticoagulation.

Infections of the head and neck are commonly associated with CSVT. A high frequency of patients with infection associated with CSVT received surgical intervention to manage the underlying infection and are in the included studies. Although beyond the scope of this guideline, the panel notes that appropriate treatment of underlying comorbidities (eg, surgical intervention for infection) is important in the overall management of the patient and should be performed at the treating providers' discretion per local practice/guidelines. Additionally, some of the studies included pediatric patients with cavernous sinus thrombosis. The panel's practice is to recommend anticoagulation for these patients if there are no contraindications. However, the panel notes that there may be differences in the pathophysiology of these thrombi compared with thrombi affecting other sinuses in the brain, which should be taken into consideration when approaching management of affected pediatric patients.

Lastly, the panel noted that some pediatric patients have bleeding or a higher risk for bleeding in which treating providers must carefully balance the risk of anticoagulation vs no anticoagulation. This includes CSVT in premature neonates who may have a higher risk of intraventricular hemorrhage, patients who have experienced trauma, or postsurgical patients. Importantly, when deciding to anticoagulate in the presence of hemorrhage, the panel members agreed that it is important to distinguish bleeding due to venous congestion vs bleeding from another etiology. Patients with intracranial hemorrhage or other symptoms due to venous congestion or venous infarction should receive anticoagulation because of risk of complications from thrombus progression. Evidence profiles with the characteristics of all included studies and the complete EtD framework are online for recommendation 5 and recommendation 6.

## Conclusions and research needs for these recommendations

The guideline panel determined that there is very low certainty in the evidence for a net health benefit from using anticoagulation in pediatric patients with CSVT. Although randomized controlled trials in adults with CSVT have demonstrated a benefit of anticoagulation, there are no randomized trials in pediatric patients with CSVT. Observational studies, however, have suggested the safety of anticoagulation in the pediatric population. Based on these considerations, and the potential life-threatening complications of CSVT that warrant treatment with anticoagulation, the previous ASH 2018 guidelines made a strong recommendation for anticoagulation for CSVT without hemorrhage. However, the guideline panel reviewed new pediatric data that have emerged in the last 5 years and has recognized the heterogeneity of etiology, outcomes, and bleeding risk. These subpopulations may have different balances of harms and benefits with anticoagulation. Because of these considerations, and the very low certainty in the evidence, the panel chose to make a conditional recommendation rather than a strong recommendation.

Based on the body of available evidence, it is likely that anticoagulation reduces the risk of mortality and neurologic deficits without increasing the risk of bleeding. There is very low certainty that there is a benefit of anticoagulation on other outcomes such as thrombus resolution. The relationship between thrombus resolution and neurologic outcomes could not be assessed in the available published data. However, the fact that we did not find evidence of

an effect on these outcomes does not imply that such an effect does not exist.

The panel identified the following additional research needs:

1. Further studies evaluating the impact of the degree of CSVT resolution/recanalization on neurological outcomes in CSVT
2. Further studies assessing harms and benefits of anticoagulation in subgroups with CSVT
3. Further studies to evaluate the efficacy and safety profile of thrombolysis in the management of pediatric CSVT

*For neonatal and pediatric patients with RAT, should anticoagulation vs no anticoagulation be used?*

**Recommendation 7a**

For neonates and pediatric patients with RAT, the ASH/ISTH guideline panel *suggests* anticoagulation rather than no anticoagulation for patients with high-risk features and low perceived risk of bleeding (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

**Remarks:** Insufficient data are available for formal risk stratification of RAT and bleeding from anticoagulation. Based on available literature and experience of panel members, high-risk features of RAT to consider include large size, shape (snake-shaped or pedunculated), mobility, location (eg, involvement of tricuspid valve or restricting blood flow), presence of intracardiac right-to-left shunt, presence of a central venous catheter, or associated with symptoms (arrhythmias, hemodynamic compromise, etc).

The decision to start anticoagulation should be individualized based on the risk of thrombotic complications and the perceived risk of bleeding from anticoagulation.

**Recommendation 7b**

For neonates and pediatric patients with RAT and the absence of high-risk features or with unacceptable perceived risk of bleeding, the ASH/ISTH guideline panel *suggests* no anticoagulation over anticoagulation (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

**Remarks:** Studies in patients without high-risk features treated with anticoagulation do not demonstrate clinical benefits compared with patients not treated with anticoagulation. The studies are not randomized, are small, and are subject to significant bias. Study patients treated with anticoagulation had an increased risk of bleeding.

*For neonatal and pediatric patients with RAT, should thrombolysis followed by anticoagulation vs anticoagulation alone be used?*

**Recommendation 8**

For neonates and pediatric patients with RAT requiring antithrombotic treatment, the ASH/ISTH guideline panel *suggests* using anticoagulation alone over thrombolysis followed by anticoagulation (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

**Remarks:** In most cases, anticoagulation alone is adequate. However, there will be individual cases in which the hemodynamic status, size, and mobility of the thrombus might dictate more aggressive therapy. The choice to use thrombolysis will depend on feasibility or the intervention and patient and family acceptability of the anticipated risks and benefits of thrombolysis.

## Summary of the evidence

In this update, there were no new data for recommendation 7; however, for recommendation 8, we found 2 additional pediatric observational studies[41,64] to the 28 observational studies from the original guidelines that addressed this question. One study focused on neonates with RAT,[41] whereas the second reported RAT in pediatric patients receiving chronic hemodialysis.[64] We identified 1 additional study[65] published after the search for the systematic review was completed. Three studies reported the effect of anticoagulation on thrombosis resolution, whereas 2 studies reported rates of thrombosis resolution, mortality, and recurrence. One study reported thrombus extension. Additionally, 3 observational studies, with a total of 44 patients, informed recommendation 8.[41,66,67] No randomized trial addressed this question. Indirect adult data were not used.

## Benefits

No clear benefit following anticoagulation was observed in the available literature in terms of resolution rates and recurrence. Resolution rates were 32 of 42 (76.2%) and 23 of 25 (92.0%) patients in the anticoagulation and no-anticoagulation groups, respectively. Recurrence of RAT was observed in 1of 16 (6.3%) and 1 of 25 (4.0%) patients in the anticoagulation and no-anticoagulation groups, respectively. Extension occurred in 3 of 14 (21.4%) patients in the anticoagulation group and in 5 of 28 (17.9%) patients in the no-anticoagulation group.

Similarly, the studies showed no benefit of thrombolysis over anticoagulation alone. For recommendation 8, 2 of 11 (18.2%) patients treated with thrombolysis followed by anticoagulation died. Rates of complete and partial resolution combined were 16 of 17 (94.1%) patients in the thrombolysis group, and 25 of 27 (92.6%) patients in the anticoagulation alone group, respectively. No recurrence of RAT was reported in either group.

Overall, the certainty of these estimated effects is very low owing to the serious risk of bias in the studies included and the very serious imprecision of the estimates.

## Harms and burden

Three studies reported bleeding[41,64,65] for patients treated with and without anticoagulation, and 2 studies for thrombolysis followed by anticoagulation.[41,67] Of 31 patients (29%) in the anticoagulation group, 9 died; 2 deaths were deemed to be related to anticoagulation. None of the 4 patients (0%) in the no-anticoagulation group died. Major bleeding and bleeding of unspecified severity were reported in 3 of 41 (7.3%) and 7 of 46 (15.2%) patients, respectively, in the anticoagulation group, and in

0 of 25 (0.0%) and 0 of 27 (0.0%) patients, respectively, in the no-anticoagulation group. For patients treated with thrombolysis followed by anticoagulation, bleeding of unspecified severity and major bleeding were observed in 3 of 10 (30.0%) and in 1 of 6 (16.7%) patients, respectively. There is very low certainty in the estimate of the risk of adverse effects because of a serious risk of bias and very serious imprecision. Given the available evidence, the guideline panel considered the risk of adverse effects most likely to be small for anticoagulation alone and moderate for thrombolysis followed by anticoagulation.

## Other EtD criteria and considerations

The panel noted that the rates of adverse outcomes (including absence of thrombus resolution, thrombotic recurrence, death, and bleeding) were higher in the anticoagulation group than in the no-anticoagulation group. However, this finding may be affected by selection bias in these observational studies, in which anticoagulation is more likely to be given to high-risk patients who are also more likely to have worse outcomes.

Insufficient data are available for formal risk stratification of RAT. Garcia-Nicoletti et al[64] considered RAT to be at intermediate to high risk if at least 2 of 3 of the following features were present: size of >1 cm, mobile, or leading to hemodynamic flow issues. In the NEOCLOT study,[41] the following criteria were used to define high-risk RAT requiring antithrombotic treatment: (1) size of >50% of the right atrium; (2) restricting flow through the tricuspid valve; (3) extension through the tricuspid valve or patent foramen ovale; (4) causing hemodynamic instability; (5) pedunculated, mobile, or snake-shaped; or (6) increasing despite therapeutic anticoagulation. A review from Yang et al outlined the following at-risk elements: large size of >2 cm in any dimension, pedunculated, mobile, or snake-shaped and mobile.[68] Yang et al theorized in a subsequent letter to the editor that the critical size of the RAT is proportional to the expected size of the pulmonary valve.[69] There is no formal risk stratification for bleeding with anticoagulation in pediatric patients.

Additional considerations from expert members of the panel as high-risk features for RAT included the presence of intracardiac right-to-left shunt, concomitant cardiac anomalies (eg, decreased cardiac function, abnormal rhythm, presence of a pacemaker or implantable defibrillator, etc), ongoing presence of a CVAD and location of the thrombus in relation with the catheter, presence of symptoms (eg, arrhythmias, emboli, etc), assumed age of thrombus (fresh vs chronic), as well as patient age and underlying conditions.

Conversely, a wait-and-see approach, with no anticoagulation and close radiological reassessment (<3 days), was described for patients without high-risk features and was not associated with a higher risk of adverse outcomes. Withholding anticoagulation may be appropriate in neonates and pediatric patients with small, mural, asymptomatic thrombi.[41] Evidence profiles with the characteristics of all included studies and the complete EtD framework are online for recommendation 7 and recommendation 8.

## Conclusions and research needs for these recommendations

The guideline panel determined that there is very low certainty evidence for a net health benefit from using anticoagulation in RAT. The decision to start anticoagulation should be individualized based on the balance of the risk of thrombotic complications and the perceived risk of bleeding from anticoagulation.

The panel identified the following additional research priorities:

1. Description of the natural history of clinical outcomes for RAT in different patient subgroups; prospective evaluation of the prognostic impact of patient- and thrombosis-related factors, allowing more precise risk stratification in various patient subgroups
2. Risk stratification of bleeding from anticoagulation in various patient subgroups

*For neonates with RVT, should anticoagulation vs no anticoagulation be used?*

**Recommendation 9**

For neonates with RVT, the ASH/ISTH guideline panel *suggests* using anticoagulation rather than no anticoagulation (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

**Remarks:** The panel considers the intervention to have a potential beneficial effect if the long-term outcomes of avoiding hypertension, chronic kidney disease, and renal failure are considered. Anticoagulation is likely more important with bilateral renal vein involvement compared with unilateral involvement with or without extension to the IVC. Severity of disease, gestational age, presence of intraventricular hemorrhage, underlying comorbidities, and degree of thrombocytopenia may affect bleeding risk with treatment.

*For neonates with RVT, should thrombolysis followed by anticoagulation vs anticoagulation alone be used?*

**Recommendation 10a**

For neonates with non–life-threatening RVT, the ASH/ISTH guideline panel *recommends* anticoagulation alone vs thrombolysis followed by anticoagulation (strong recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

**Remarks:** Available evidence is derived from observational studies in which patients treated with thrombolysis were critically ill, and because the studies did not adjust for this bias, causation is difficult to ascertain. The panel placed a high value on avoiding the potential bleeding risks of thrombolysis, especially in neonates, and therefore made this recommendation for cases with low mortality risk (ie, unilateral RVT or unilateral RVT with IVC extension). The panel made a strong recommendation, considering high-quality evidence for harm and high costs, despite very low quality evidence for benefit.

**Recommendation 10b**

For neonates with life-threatening RVT, the ASH/ISTH guideline panel *suggests* using thrombolysis followed by

anticoagulation, rather than anticoagulation alone (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

**Remarks:** When RVT is life threatening (ie, bilateral thrombosis), the panel considered that the beneficial effects of thrombolysis may outweigh the undesirable consequences of the intervention. Gestational age, presence of intraventricular hemorrhage, underlying comorbidities, and degree of thrombocytopenia may affect bleeding risk with thrombolysis.

## Summary of the evidence

In this update, 2 additional observational studies were identified[21,70] that inform recommendation 9. One study was a retrospective case series of 27 neonates with RVT,[70] whereas the other was a retrospective cohort study of unprovoked VTE in 40 infants, 11 of whom had RVT.[21] We also identified a retrospective study of 19 neonates with RVT published as an abstract.[71] Two observational studies were also identified[70,72] with a total of 10 patients that inform recommendation 10. The Ndoudi Likoho study additionally assessed outcomes of thrombolysis for bilateral RVT[70], whereas the Niada study reported a retrospective case series of neonates with spontaneous unilateral RVT[72]. All studies had a serious risk of bias (confounding and selection of participants) and imprecision (very small number of events and total population). Indirect adult data were not used to inform this recommendation.

This recent evidence included outcome data on all-cause mortality; thrombus resolution; thrombus recurrence; bleeding; as well as short- and long-term outcomes of chronic kidney disease, proteinuria, hypertension, kidney atrophy, and glomerular filtration rate (GFR). RVT may present as unilateral disease limited to the renal vein (in which case renal function should be normal because the opposite kidney is unaffected); thus, the disease is not life threatening. RVT may present as unilateral disease with extension into the IVC, in which case the risk of embolic phenomenon is thought to be higher and the risk of loss of an entire kidney higher, but it is not necessarily considered life threatening. Finally, RVT may present as bilateral disease with deterioration of renal function; this is almost always life threatening or organ threatening in neonates. Because of the retrospective nature of the studies and the small number of reported patients, the treatment and outcomes were not risk stratified between different severities of RVT such as unilateral with/without IVC involvement or bilateral.

## Benefits

For recommendation 9, studies assessed anticoagulation vs no anticoagulation for treatment of RVT. Of 8 patients, 2 (25%) in the anticoagulation group had chronic kidney disease at a median follow-up of 5.7 years, compared with 4 of 5 patients (80%) in the group that did not receive anticoagulation. None of the patients in either group developed proteinuria or hypertension at a median follow-up of 5.7 years. Median estimated GFR at a median follow-up of 4.7 years was 111 mL/min per 1.73 $m^2$ in the anticoagulation group compared with 75 mL/min per 1.73 $m^2$ in the group that did not receive anticoagulation. There was complete or partial thrombus resolution in 18 of 20 patients (90%) in the anticoagulation group compared with 2 of 2 patients (100%) in the no-anticoagulation group.

For recommendation 10, studies assessed thrombolysis followed by anticoagulation vs anticoagulation alone for treatment of RVT. There was no thrombus recurrence in either group. Of 7 patients, 5 (71%) in the thrombolysis plus anticoagulation group had complete or partial thrombus resolution, whereas 3 of 3 patients (100%) in the anticoagulation alone group had complete or partial thrombus resolution.

Direct comparison of these outcomes is difficult given the likely significant bias in treatment selection. Overall, the certainty of these estimated effects is very low owing to critical risk of bias and very serious imprecision in the included studies.

## Harms and burden

Studies assessing recommendation 9 showed that 1 of 19 patients (5.3%) died in the anticoagulation group; the cause of death was unrelated to thrombotic or bleeding complications. There were no deaths in the group that did not receive anticoagulation (0/2). In patients who received anticoagulation (n = 13) compared with those who did not (n = 5), the rate of unilateral kidney atrophy was 11 of 13 (81%) vs 3 of 5 (66%); thrombus recurrence occurred in 1 of 26 patients (3.8%) vs 0 of 7 (0.0%), and bleeding was observed in 2 of 25 patients (8%) vs 0 of 7 (0.0%).

Studies assessing recommendation 10 showed that 3 of 4 patients (75%) in the thrombolysis plus anticoagulation group had bleeding, whereas 0 of 3 (0%) in the anticoagulation alone group had bleeding. The severity of bleeding was not reported. There was thrombus progression in 1 of 3 patients (33%) in the thrombolysis plus anticoagulation group. On follow-up, in the thrombolysis plus anticoagulation group, proteinuria (median, 5.7 years), chronic kidney disease (median, 6 months to 5.7 years), or hypertension (median, 6 months to 5.7 years) were present in 1 of 4 (25%), 1 of 7 (14%), and 1 of 7 (14%) patients, respectively; in the anticoagulation alone group (n = 6), there was no proteinuria, chronic kidney disease, or hypertension in any patient. Of 4 patients, 3 (75%) in the thrombolysis plus anticoagulation group and 2 of 3 patients (67%) in the anticoagulation alone group had long-term pathologic kidney features (defined as proteinuria, kidney atrophy, hypertension, or chronic kidney disease) at a median of 5.7 years. There was no mortality in the 4 patients (0%) in the thrombolysis plus anticoagulation group, whereas 1 of 3 patients (33%) in the anticoagulation alone group died (attributed to bilateral RVT, acute kidney injury, and complications from an underlying condition).

Overall, there was very low certainty in the estimate of the risk of adverse effects because of a critical risk of bias and very serious imprecision. The guideline panel also considered that bleeding rates will also depend on gestational age of the neonate, degree of thrombocytopenia, underlying comorbidities, and presence of adrenal gland hemorrhage.

## Other EtD criteria and considerations

The panel noted that the rates of adverse outcomes (including long-term kidney function, thrombus recurrence, and bleeding) were higher in the group who received anticoagulation or thrombolysis plus anticoagulation compared with the group of children who did not receive either. This could be attributable to the observational nature of the reported data, in which high-risk

patients are more likely to be prescribed anticoagulation and/or thrombolysis.

In this guideline revision, the panel changed the undesirable effects of anticoagulation vs no anticoagulation for RVT from "trivial" to "small" due to new observational data demonstrating an increase in bleeding in the anticoagulation vs no-anticoagulation group, while also acknowledging that the sample size was very small.

The panel recognized that there is marked variability in the presentation of RVT in the neonatal population and that the decision to treat should be made weighing the risks of loss of kidney, chronic kidney disease, or mortality with the risk of bleeding. The risk for bleeding will be higher with thrombolysis, by virtue of its mechanism of action, and this risk must be balanced with the risk of devastating outcomes without its use. Although the data presented had very small sample sizes, it showed minimal differences in long-term outcomes between the thrombolysis plus anticoagulation group and the anticoagulation alone group. However, the panel members recognized that, in certain instances, thrombolysis may be warranted to preserve life or organ function in the short term.

Insufficient data are available for formal risk stratification of the different presentations of RVT. Consensus from expert panel members include that neonates with RVT are high risk if they have bilateral thrombosis that could lead to anuria and death or severe long-term kidney disease. The panel also agreed that patients with unilateral RVT, even with extension to the IVC, are at lower risk of these complications. Important considerations for bleeding risk are gestational age, presence or absence of intraventricular or adrenal gland hemorrhage, underlying comorbidities, and degree of thrombocytopenia. Evidence profiles with the characteristics of all included studies and the complete EtD framework are online for recommendation 9 and recommendation 10.

## Conclusions and research needs for these recommendations

The guideline panel determined that there is a very low certainty in the evidence for a net health benefit from using anticoagulation and/or thrombolysis in neonates with RVT related to avoiding long-term kidney disease. The decision to start anticoagulation and/or thrombolysis should be individualized based on balancing the risk of thrombotic complications with the underlying bleeding risk.

The panel identified the following additional research needs:

1. Treatment and outcomes of unprovoked or provoked RVT in subpopulations of pediatric patients other than the neonatal age group, which include older pediatric patients, and patients with nephrotic syndrome, infection-related RVT, or RVT associated with CVADs
2. Prospective evaluation of the prognostic impact of patient- and thrombosis-related factors, allowing for more precise risk stratification in various patient subpopulations
3. Subgroups of neonates and pediatric patients who would benefit most from thrombolysis

*For neonates and children with PVT, should anticoagulation vs no anticoagulation be used?*

**Recommendation 11a**

For neonates and children with occlusive PVT and for children with nonocclusive PVT, post–liver transplant PVT, or unprovoked PVT, the ASH/ISTH guideline panel *suggests* using anticoagulation rather than no anticoagulation (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

**Recommendation 11b**

For neonates with nonocclusive PVT, and for children who have already developed PHTN secondary to PVT, the ASH/ISTH guideline panel *suggests* no anticoagulation rather than using anticoagulation (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

**Remarks for recommendations 11a and 11b:** Neonates and pediatric patients who did not receive anticoagulation warrant follow-up monitoring, because extension of thrombus or organ dysfunction may require reconsideration of treatment options. Evidence from the available observational studies describes (complete or partial) PVT resolution in patients who did receive anticoagulation, as well as those who did not receive anticoagulation. This does not allow for assessment of the degree of benefit from anticoagulation. However, the panel placed value on avoiding the potential increased risk of long-term complications associated with persistent occlusive thrombus, and therefore favored treatment in this setting. The panel also recognized the potential increased risk of bleeding in pediatric patients with PHTN and development of esophageal varices, and therefore did not recommend anticoagulation in that setting.

## Summary of the evidence

We identified 4 new observational studies that included data on PVT.[41,73-75] Three studies focused on neonates (including 23, 74, and 9 neonates with PVT)[41,73,75] and 1 included both neonates (n = 20) and older pediatric patients (n = 27) with PVT.[74] One study focused on neonates and infants with line-associated thrombi, of which 9 of 115 (8%) had PVT.[41] The proportion of neonates receiving anticoagulation in these studies ranged from 22% to 60%, whereas 85% of older pediatric patients received anticoagulation. The proportion of neonates with umbilical vein catheters ranged from 62% to 87%. The left portal vein was the most common site of PVT in neonates. Among the older pediatric patients included, 17 of 27 (63%) had a liver transplant.[74]

## Benefits

For studies that reported on PVT radiologic outcomes, some degree of resolution (either complete or partial) was reported in 40 of 56 (71.4%) patients who received anticoagulation compared with 44 of 72 (61.1%) who did not receive

anticoagulation. In 1 study, no patients were reported to have PHTN (0/19 [0.0%] vs 0/55 [0.0%]), which may be because of the small sample size or inadequate follow-up duration.[73] Additionally, no deaths were reported secondary to PVT (0/2 [0.0%] vs 0/5 [0.0%]). Overall, the certainty in these estimated effects is very low owing to inadequate numbers, very serious bias within the studies, and imprecision of the estimates.

### Harms and burden

The rate of major bleeding in all patients with PVT varies from 5% to 80% and is primarily related to esophageal varices in the setting of PHTN. Newly reviewed studies did not clearly define bleeding, and only 1 of 56 infants treated with anticoagulation was reported to have bleeding.[41] The panel noted that this may have been because of the small number of included patients, careful selection of those who received anticoagulation, duration of follow-up, or underreporting of events.

### Other EtD criteria and considerations

The panel noted the importance of distinguishing between clinical benefits (eg, decreased incidence of PHTN, esophageal varices, splenomegaly, and organ dysfunction) and radiologic outcomes (partial or complete thrombus resolution) with anticoagulation. There are insufficient data to determine an association between the degree of thrombus resolution and improved long-term prognosis. The panel noted that PVT may occur in several clinically distinct scenarios (such as in neonates secondary to umbilical vein catheterization or in patients after liver transplant) and that management of these subgroups needed to be considered differently. Evidence profiles with the characteristics of all included studies and the complete EtD framework are online for recommendation 11.

### Conclusions and research needs for this recommendation

The guideline panel determined that there is very low certainty in the evidence for a net health benefit/harm from using anticoagulation. The evidence favors anticoagulation for occlusive PVT in pediatric patients of any age, nonocclusive PVT in children (nonneonates), PVT present after liver transplant, or unprovoked PVT. The evidence favors no anticoagulation for nonocclusive PVT in neonates (who should be followed-up radiologically to monitor for thrombus progression), or in the presence of PHTN, which suggests chronic thrombosis, and is accompanied by an increased risk of bleeding from esophageal varices. In addition, the panel considered that the limited evidence may preclude the ability to identify those at greater risk of PVT sequelae who may have a variable profile in terms of intervention benefits. There is very low certainty that there is an effect of anticoagulation on other outcomes. However, because there is no published information about other outcomes, the fact that we did not find evidence of an effect on these outcomes does not imply that such an effect does not exist.

The panel identified the following additional considerations for future research:

1. Studies to determine the outcomes, with or without anticoagulation, in clinical subgroups of PVT
2. Use of clear definitions of clinical and radiologic outcomes for standardization between research studies
3. The association of radiologic outcomes with long-term clinical outcomes

*For pediatric patients with SVT, should anticoagulation vs no anticoagulation be used?*

**Recommendation 12a**

For pediatric patients with SVT secondary to IV cannulation in the upper limb, the ASH/ISTH guideline panel *suggests* no anticoagulation rather than using anticoagulation (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

**Recommendation 12b**

For pediatric patients with SVT in the upper limb, which is not cannula related, or in the lower limbs associated with cancer or varicose veins, the ASH/ISTH guideline panel *suggests* anticoagulation rather than no anticoagulation (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

**Remarks:** There were no direct and only limited, indirect data upon which to base this recommendation. The panel members' experience suggested that in most instances (eg, PIV- or CVAD-related events in the upper extremity), no anticoagulation may be required. However, anticoagulation could be considered in select patients with symptomatic SVT (eg, non–PIV-/PICC-related, cancer, varicose vein, or lower limb events) or select scenarios (eg, PIV/long-term PICC and/or symptom progression). The panel notes that when anticoagulation is prescribed, there is uncertainty about the optimal intensity (eg, prophylactic vs full dose) and duration of therapy.

### Summary of the evidence

The updated systematic review identified 1 pediatric study describing the prevalence of SVT in hospitalized pediatric patients. However, it was not included in the EtD framework because it did not include information on anticoagulation.[76] This single-center retrospective cohort study described 277 children and adolescents aged up to 21 years diagnosed with an objectively confirmed SVT. Almost one-third of the SVTs reported were concomitant with an adjacent DVT, and when occurred in isolation and before the DVT, progressed to the ipsilateral deep venous territory in ~6% of patients within the initial week from SVT onset. Notably, the study indicated a few critical distinctions from SVT in adults, because no events were located in the lower limbs, being mostly CVAD related. Moreover, the study highlighted an increasing prevalence of non–CVAD-related SVTs with aging, except in neonates, infants, and children, suggesting that age, SVT

location, or line presence may result in distinct clinical phenotypes. Because of the study design, this publication was assessed to have selection bias.

Given these limitations, the panel considered only indirect evidence from adult data as a basis for the recommendations. The adult literature included 3 randomized studies that together enrolled 3914 patients diagnosed with non–CVAD-related SVTs exclusively located in the lower limbs: the CALISTO study (fondaparinux [prophylactic dose] vs placebo for 6 weeks)[77]; the STENOX study (LMWH [prophylactic dose] vs LMWH [therapeutic dose] vs nonsteroidal anti-inflammatory drugs [NSAIDs] vs placebo for ~2 weeks)[78]; and the SURPRISE trial (rivaroxaban [prophylactic dose] vs fondaparinux [prophylactic dose] for 6 weeks).[79] Mortality, SVT complicated by PE, and SVT complicated by DVT were the study outcomes, all reported at 3 months.

Given the potential phenotypic SVT discrepancies between adults and pediatric patients (eg, asymptomatic or symptomatic event, provocation by PIV/CVAD or not, location within the upper vs lower limb), the panel was not confident that these recommendations apply to all pediatric patients with SVT, considering them more generalizable only to pediatric SVT subtypes whose course resembles the course described in the adult literature.

### Benefits

Anticoagulation as compared with no anticoagulation was not significantly associated with reduced mortality, with an RR of 1.87 (95% CI, 0.17-20.67). There was 1 more death per 1000 patients receiving anticoagulation (95% CI, 1 fewer to 12 more). The death rates reported in the respective intervention arms were 0.1% (CALISTO), none in the STENOX study, and 0.4% in the SURPRISE trial. Anticoagulation was not associated with a significant reduction of SVT complicated by PE with an RR of 0.31 (95% CI, 0.06-1.54), but there were 3 fewer PE complications per 1000 patients receiving anticoagulation (95% CI, 3 fewer to 2 more). Anticoagulation may favor a reduction of SVT complicated by DVT with an RR of 0.53 (95% CI, 0.26-1.04). There were 7 fewer DVT complications per 1000 patients receiving anticoagulation (95% CI, 10 fewer to 1 more). Of note, the effect estimates of the intervention arms grouped patients receiving prophylactic and therapeutic LMWH intensities together, whereas only ~6% of them received a therapeutic regimen. Overall, the certainty of these estimated effects is very low owing to the indirectness of the data and the imprecision of the effect estimates because of the small number of events encountered in the studies.

### Harms and burden

The risk of developing major bleeding was not significantly different in patients treated with anticoagulation (1/1715 [0.1%]) compared with patients not treated with anticoagulation (1/1600 [0.1%]), with an RR of 0.93 (95% CI, 0.05-14.90). There was no difference (0 more) in major bleeding events per 1000 patients receiving anticoagulation (95% CI, 1 fewer to 9 more). Again, there is very low certainty in the estimate of the risk of major bleeding because of indirectness and the imprecision resulting from the small number of patients with this treatment complication.

### Other EtD criteria and considerations

The panel recognized that the evidence extracted from adult studies perhaps favors anticoagulation based on reduced DVT, recognizing this recommendation relates to non–PIV- or CVAD-related SVTs located in the lower limbs. Furthermore, most SVTs in pediatric patients are PIV or CVAD related, located in the upper extremity, whose natural history may differ from the typical adult SVT described. Evidence profiles with the characteristics of all included studies and the complete EtD framework are online for recommendation 12.

## Conclusions and research needs for these recommendations

The guideline panel determined that there is very low certainty in the evidence for a net health benefit from using anticoagulation in pediatric patients with SVT. Although RCTs in adults with SVT may suggest benefit in selected patients, there are no randomized trials in pediatric patients with SVT. Scant observational pediatric studies have started to unravel the epidemiology and the natural history of SVT in pediatrics, but neither the efficacy nor the safety of anticoagulation in the pediatric population has been well characterized.[80] Based on these considerations, the previous ASH 2018 guidelines could not recommend anticoagulation or no anticoagulation for managing such cases in the pediatric population. However, more recent adult studies pointed toward an evolution favoring anticoagulation.[79,81,82] The guideline panel again reviewed the adult data, identifying a small desirable effect of anticoagulation in contrast to a small undesirable effect, recognizing these findings relate solely to non–catheter-associated events in the lower limb. Furthermore, although the adult literature favors prophylactic anticoagulation dosing for 45 days, the role of NSAIDs, shorter anticoagulation duration, and therapeutic intensity merits further investigation.[22]

Based on the body of available evidence, it is likely that anticoagulation reduces the complication rate of SVT in pediatric patients, but the panel recognized the need for improvement in the characterization of SVT phenotypes, differentiating cases with a likely more benign course in comparison with the typical adult non–line-associated lower limb SVT. The relationship between patient, SVT location/extension, and line-associated variables could not be assessed in the available pediatric published data.

The panel identified the following additional research needs:

1. Further studies evaluating the natural history of SVT resolution/progression, as well as DVT/PE complication according to patient (ie, age and underlying condition) and SVT characteristics (SVT location/extension and line dependence), as well as venous bed health (ie, varicosity/ectasia status, chronic venous hypertension)
2. Further studies assessing ideal diagnostic methods and imaging protocols in subgroups with SVT
3. Further studies to evaluate the efficacy and safety profile of anticoagulation of different intensities of pediatric SVT

4. Further studies to evaluate the role of antiplatelet/NSAID compared with anticoagulation in pediatric SVT

*For pediatric patients with proximal DVT, should thrombolysis followed by anticoagulation vs anticoagulation alone be used?*

**Recommendation 13**

For pediatric patients with proximal DVT, the ASH/ISTH guideline panel *suggests* using anticoagulation alone rather than thrombolysis followed by anticoagulation (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

**Remarks:** The panel considered characteristics, such as the extent and clinical impact of VTE, as important in determining the RR benefit ratio of thrombolysis. In most cases, the risks seem higher than the potential benefit; however, there may be individuals for whom the opposite is true. In this clinical scenario, extrapolation from adult data was difficult. There are insufficient data to address the RR benefit of local thrombolysis via interventional radiology compared with systemic thrombolysis, and the panel noted that the centers with access to pediatric interventional radiology were often stronger advocates of thrombolysis.

*For pediatric patients with submassive PE, should thrombolysis followed by anticoagulation vs anticoagulation alone be used?*

**Recommendation 14**

For pediatric patients with PE and echocardiographic or biochemical evidence of right ventricular dysfunction but without hemodynamic compromise, the ASH/ISTH guideline panel *suggests* using anticoagulation alone rather than thrombolysis followed by anticoagulation (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

**Remarks:** The panel considered submassive PE to represent pediatric patients with PE who do not have hemodynamic compromise (ie, systemic hypotension or other signs of shock) but who do have echocardiographic (eg, right ventricular dilation or intraventricular septal bowing into the left ventricle, etc) or biochemical (eg, elevated troponin or brain natriuretic peptide, etc) evidence of right ventricular dysfunction.[24] There were minimal pediatric data, and recent international adult guideline panels have recommended anticoagulation alone rather than thrombolysis followed by anticoagulation in this situation (based on low certainty in the evidence of effects).[23,25] These same adult guidelines, however, have suggested that thrombolysis may be reasonable to consider for younger patients with submassive PE at low risk of bleeding and those who have evidence of both echocardiographic and biochemical evidence of right ventricular dysfunction, which may be extrapolated to select pediatric patients. Patients with submassive PE should be monitored closely for the development of hemodynamic compromise.[23,24] The panel concluded that the risks of thrombolysis outweighed the benefits in most cases; hence, the conditional recommendation for anticoagulation alone.

*For pediatric patients with PE with hemodynamic compromise, should thrombolysis followed by anticoagulation vs anticoagulation alone be used?*

**Recommendation 15**

For pediatric patients with PE and hemodynamic compromise the ASH/ISTH guideline panel *suggests* using thrombolysis followed by anticoagulation rather than anticoagulation alone (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

**Remarks:** The panel considered massive PE to represent pediatric patients with PE who do have hemodynamic compromise that may be life threatening, with limited time to respond to standard anticoagulation, and therefore, conditionally recommended thrombolysis followed by anticoagulation, based predominantly on extrapolation from recent adult guidelines and 3 small pediatric studies that suggested a trend toward decreased mortality with thrombolysis.[23,25-27,83]

## Summary of the evidence

Despite observational and retrospective data, we did not identify any RCT that addressed these questions in pediatric patients and therefore considered extrapolation from adult data (contributing almost 90% of the evaluated data). For PE, the panel also considered a recently published management algorithm based upon a comprehensive literature review and expert opinion.[24] We identified 15 observational studies in pediatric patients, primarily single-arm studies with no comparison group, that provided data on the outcomes of interest. The total number of pediatric patients involved across all studies was <500, and the 10 new studies published since 2018 included <200 patients.

For DVT, mortality occurred in 11 of 126 (8.7%) patients managed with thrombolysis followed by anticoagulation compared with 2 of 21 (9.5%) managed with anticoagulation alone; recurrent/progressive DVT or failure of resolution was noted in 42 of 238 (17.6%) patients managed with thrombolysis followed by anticoagulation, compared with 11 of 50 (22%) managed with anticoagulation alone; major bleeding was reported in 2 of 20 (10%) patients managed with thrombolysis followed by anticoagulation compared with 5 of 55 (9.1%) with anticoagulation alone; and PTS occurred in 22 of 97 (22.7%) patients managed with thrombolysis followed by anticoagulation compared with 13 of 34 (38.2%) managed with anticoagulation alone.

During the creation of the original 2018 guidelines, adult data were used to support the evidence for submassive and massive PE because no comparative pediatric data were available in order to allow for pooling of outcome data to provide RR estimations. Incorporation of data from more recent studies, however, allowed

us to provide these estimates for this update. Regarding PE with hemodynamic compromise (massive PE), mortality occurred in 6 of 15 (40%) patients managed with thrombolysis followed by anticoagulation, compared with 8 of 16 (50%) patients managed with anticoagulation alone; recurrent/progressive PE or failure to respond was noted in 3 of 7 (42.9%) patients managed with thrombolysis followed by anticoagulation compared with 3 of 15 (20%) patients managed with anticoagulation alone; chronic thromboembolic pulmonary hypertension rates at 6 month follow-up were reported in 0 of 5 (0%) patients managed with thrombolysis followed by anticoagulation compared with 0 of 2 (0%) patients; and major bleeding was reported in 1 of 7 (14.3%) patients managed with thrombolysis followed by anticoagulation compared with 0 of 1 (0%) patients managed with anticoagulation alone. In the submassive PE category, mortality occurred in 0 of 14 (0%) patients managed with thrombolysis followed by anticoagulation compared with 1 of 9 (11.1%) patients managed with anticoagulation alone; recurrent/progressive PE or failure to respond was noted in 1 of 19 (5.3%) patients managed with thrombolysis followed by anticoagulation compared with 1 of 12 (8.3%) managed with anticoagulation alone; and major bleeding was reported in 0 of 19 (0%) patients managed with thrombolysis followed by anticoagulation compared with 0 of 9 (0%) patients managed with anticoagulation alone.

### Benefits

The relative effects were not estimable based on the pediatric data because of the lack of direct comparisons. Thrombolysis followed by anticoagulation was associated with a trend toward decreased RR for mortality in PE with hemodynamic compromise as compared with anticoagulation alone (RR, 0.88; 95% CI, 0.42-1.85) leading to our conditional recommendation with very low certainty in the evidence in the effects. Similarly, the adult guideline panels recommended thrombolysis based upon low certainty in the evidence in effects.[23,25] For submassive PE, there is no evidence suggesting that thrombolysis improves outcomes compared with anticoagulation alone, which is consistent with the adult guidelines. The frequency of major outcomes in pediatric patients treated with thrombolysis is based on very small numbers reported in the included studies. There were insufficient data to differentiate the outcomes for the use of systemic thrombolysis compared with CDT. There were no baseline data in pediatric patients to compare. Overall, the certainty in these estimated effects is very low owing to potential bias in the studies.

### Harms and burden

The relative effects were not estimable based on the pediatric data. Any difference in bleeding risk for CDT as distinct from systemic thrombolysis was not possible to establish from the available data. Although it is likely that thrombolysis may be better tolerated in young persons with low bleeding risk and may be considered for pediatric patients with submassive PE in some centers with experienced and well-equipped interventional radiology services to decrease the long-term risk of chronic thromboembolic pulmonary hypertension, there is very low certainty in the estimate of the risk of adverse effects as the result of serious risk of bias and indirectness. Given the available evidence, the guideline panel considered that the risk of adverse effects varied within the pediatric population, related to underlying age, disease process, and medical or surgical interventions. This, in part, led to the conditional nature of the thrombolysis recommendations.

### Other EtD criteria and considerations

The guideline panel did not think that there were feasibility or acceptability considerations that would impair implementation of these recommendations in terms of systemic thrombolysis, outside of the necessity of the treating institution having the requisite equipment and personnel with appropriate expertise to implement it. However, the panel noted that the use of CDT is more likely in centers in which there is strong interventional radiology input. Given the impact of interventionalist experience in pediatric patients on the benefit/harm ratio of such procedures, the panel concluded that it is very difficult to give a unified recommendation as to the appropriateness of catheter-directed procedures in a variety of circumstances. Evidence profiles with the characteristics of all included studies and the complete EtD framework are online for recommendation 13, recommendation 14, and recommendation 15.

### Conclusions and research needs for this recommendation

The guideline panel determined that there is very low certainty in the evidence for a net health benefit/harm from using thrombolysis. Based on the body of available evidence, it is unlikely that thrombolysis reduces the risk of developing recurrent VTE or PE, whereas it is likely that thrombolysis reduces the risk of PTS but increases the risk of bleeding. There is very low certainty that there is an effect of thrombolysis on other outcomes. However, because there is no published information about other outcomes, the fact that we did not find evidence of an effect on these outcomes does not imply that such an effect does not exist.

The panel identified the following additional research needs:

1. The role of thrombolysis in proximal VTE, submassive PE, and massive PE remains unknown in pediatrics, and further studies to identify the risk/benefit of thrombolysis compared with anticoagulation alone considering all outcomes of interest are required.
2. The role of CDT and the minimal infrastructure, experience, and annual caseload to offer this therapy in pediatric patients compared with systemic thrombolysis need to be determined.
3. The natural history of VTE or large PE in pediatric patients (including subgroup analyses [eg, intracardiac thrombi]) treated with anticoagulation alone needs to be understood to enable the aforementioned 2 research needs to be addressed properly.

*For pediatric patients with symptomatic CVAD-related thrombosis, should immediate removal of a nonfunctioning or unneeded CVAD vs delayed removal be used?*

**Recommendation 16**

For pediatric patients with symptomatic CVAD-related thrombosis who no longer require venous access or whose CVAD is nonfunctioning, the ASH/ISTH guideline panel *suggests* either immediate removal or delayed removal of the

CVAD (conditional recommendation based on low certainty in the evidence about effects ⊕⊕◯◯).

**Remarks:** Recent observational studies provided data that >48 hours of anticoagulation before CVAD removal vs immediate CVAD removal are comparable in terms of potential risk of emboli leading to PE or paradoxical stroke. The panel recognized that some clinical scenarios, such as children with a large thrombotic burden or those with right-to-left cardiac shunts, may benefit from a few days of anticoagulation before CVAD removal to decrease the risk of embolism.

### Summary of the evidence

We identified 2 multicenter, observational studies that addressed this question in pediatric patients.[41,84] The first study included 663 hospitalized children aged 0 to 21 years diagnosed with a hospital-acquired CVAD-related VTE.[84] A direct comparison of the development of PE was made between participants who had immediate removal of their CVAD (<48 hours of anticoagulation) compared with those who had delayed removal of their CVAD (≥48 hours of anticoagulation). The second study included 115 neonates and infants aged ≤6 months diagnosed with a CVAD-related VTE.[41] A direct comparison of the development of PE was made between participants who had immediate removal of their CVAD (without anticoagulation) and those who had delayed removal of their CVAD (median of 4 days of anticoagulation).

### Benefits

The outcome of interest for these recommendations included the development of a PE only. Combining results from both studies, the incidence of symptomatic PE was 0.2% (1/485) in pediatric patients who had immediate removal of their CVAD vs 0% (0/241) who had delayed removal of their CVAD after diagnosis of a CVAD-related thrombosis. Overall, the certainty of these estimated effects is low owing to a serious risk of selection bias (studies being observational without adjustment for known confounders) and serious imprecision of the estimates, with only 1 event in the immediate CVAD removal arm and no events in the delayed removal arm. Because of the lack of data, VTE progression or recurrence, CVAD-associated sepsis and mortality were not included as outcomes of interest.

### Harms and burden

The outcomes of interest included major bleeding. The panel was unable to assess the harm of bleeding from anticoagulation between the immediate vs delayed removal cohort because of some of the participants in the immediate removal group having received some (albeit minimal) anticoagulation. Given the scarcity of available evidence, the guideline panel considered the risk of adverse effects unknown.

### Other EtD criteria and considerations

In pediatric patients diagnosed with a symptomatic CVAD-related thrombosis whose CVAD is no longer needed or functional, determining the need for anticoagulation before removal of the line to potentially decrease the risk of PE or embolic stroke is an important factor. The panel did highlight that most patients do not routinely receive a screening ultrasound to identify asymptomatic thrombosis or bubble studies to look for right-to-left shunting before CVAD removal. The panel does acknowledge that some patients, such as those with a known right-to-left cardiac shunt or large clot burden, may benefit from >48 hours of anticoagulation before line removal. The panel recognizes that the immediate removal of an unnecessary or nonfunctioning CVAD may not be feasible because of the stability or the patient or the availability of a surgical team and operating suite. The guideline panel did not think that there were feasibility or acceptability considerations that would impair implementation of this recommendation. Evidence profiles with the characteristics of all included studies and the complete EtD framework are online for recommendation 16.

### Conclusions and research needs for this recommendation

The guideline panel determined that there is a low certainty in the evidence for a net health benefit or harm from either immediate or delayed removal of a CVAD in pediatric patients diagnosed with a CVAD-related VTE whose CVAD is no longer functioning or necessary. Based on the updated evidence, the panel determined the data do not conclusively demonstrate whether >48 hours of anticoagulation decrease the risk of a PE or embolic stroke in pediatric patients with a CVAD-related thrombosis. There is low certainty that there is an effect of delayed or immediate CVAD removal on other outcomes. However, because of low certainty in the evidence or no published information about other outcomes, the absence of evidence of an effect on these outcomes does not imply that such an effect does not exist.

The panel identified the following additional research needs:

1. The optimal duration of anticoagulation, if any, needed before CVAD removal in pediatric patients with CVAD-related VTE to decrease the risk of embolism
2. Subgroup studies of pediatric patients with a CVAD-related thrombosis at a potentially higher risk of embolism, such as those with a large thrombotic burden or with a right-to-left cardiac shunt in terms of management of CVAD removal
3. Cost-effectiveness analysis of immediate CVAD removal vs delayed removal and administration of anticoagulation with the potential for a prolonged hospital stay in pediatric patients

*For pediatric patients with VTE, should DOACs vs SOC anticoagulants be used?*

**Recommendation 17**

For pediatric patients with VTE, the ASH/ISTH guideline panel *suggests* using DOACs (rivaroxaban/dabigatran) over SOC anticoagulants (LMWH, UFH, VKAs, and fondaparinux; conditional recommendation based on low certainty in the evidence about effects ⊕◯◯◯).

**Remarks:** The panel concluded that there was a small benefit of DOACs over SOC, in relation to reduced

thrombus recurrence rate and increased rate of thrombus resolution. The undesirable effects of DOACs vs SOC were felt to be small, with a reduction in major bleeding albeit with an increase in CRNMB). The panel acknowledged the limitations of these data when evaluating the outcomes of mortality, recurrence, PTS, and major/CRNMB because of the small number of events reported. Given the natural history of PTS and thrombus recurrence, evaluation at 3 to 6 months was considered to be too soon to provide accurate representation of these outcomes. The monitoring of drug level and dose adjustment of dabigatran during the DIVERSITY trial raised concern about the potential effect on efficacy and safety of routine use according to current approvals, which do not require such monitoring. Although data on QOL, cost-effectiveness, and acceptability of an oral agent that does not require monitoring were lacking, the panel felt that these were important factors when making this recommendation.

*For pediatric patients with VTE, should rivaroxaban vs SOC anticoagulants be used?*

**Recommendation 18**

For pediatric patients with VTE, the ASH/ISTH guideline panel *suggests* using rivaroxaban over SOC anticoagulants (LMWH, UFH, VKA, and fondaparinux; conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

**Remarks:** The panel concluded that there was a small benefit of rivaroxaban over SOC, in relation to reduced thrombus recurrence and improved thrombus resolution. The undesirable effects of rivaroxaban vs SOC were felt to be small, with a reduction in major bleeding countered by an increase in CRNMB. These data were limited by the small number of important outcomes that were reported, that is mortality, recurrence, PTS, and major bleeding/CRNMB. The panel noted that some individuals were excluded from the EINSTEIN-Junior trial, including those aged <6 months with low birth weight and those with severe liver or renal impairment. The panel also noted reports of heavier menstrual bleeding while on rivaroxaban and felt that this was an important consideration when choosing an anticoagulant.

*For pediatric patients with VTE, should dabigatran vs SOC anticoagulants be used?*

**Recommendation 19**

For pediatric patients with VTE, the ASH/ISTH guideline panel *suggests* using dabigatran over SOC anticoagulants (LMWH, UFH, VKA, and ondaparinux; conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

**Remarks:** The panel concluded that there was a small benefit of dabigatran over SOC, in relation to reduced thrombus recurrence and improved thrombus resolution. The undesirable effects were felt to be trivial, with major bleeding reported in fewer patients treated with dabigatran and an equivalent frequency of CRNMB. The panel noted that some individuals were excluded from the DIVERSITY trial, including those aged <2 years with low body weight, and those with severe liver or renal impairment. The monitoring and dose adjustment of dabigatran during the DIVERSITY trial raised concern about the potential effect on efficacy and safety of routine use according to current approvals which do not require such monitoring. The panel also noted reports of gastrointestinal side effects while on dabigatran and felt that this was an important consideration when choosing an anticoagulant.

*For pediatric patients with VTE, should either rivaroxaban or dabigatran be used preferentially?*

**Recommendation 20**

For pediatric patients with VTE, the ASH/ISTH guideline panel *suggests* using either rivaroxaban or dabigatran although there may be individual populations or jurisdictional availability that would lead clinicians to choose 1 agent over the other (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

**Remarks:** The panel undertook an exercise to review the EtDs for rivaroxaban vs SOC and dabigatran vs SOC to examine if 1 of these agents (given the available data) would be a preferred agent to use in treatment of pediatric VTE. To accomplish this, the panel first assigned weights to the summary of judgments. Balance of effects, certainty in the evidence, and acceptability and feasibility of implementation were given the highest weighting; with resources required given moderate weighting; and cost-effectiveness and equity given the lowest weighting.

With RCT data limited to 523 pediatric patients globally receiving a DOAC, the certainty in the evidence was very low to low on beneficial effects and harms/burdens.[43,44,85] Given the fact that these agents are orally administered, thus avoiding daily injections of LMWH/UFH; have fewer drug interactions than VKAs; do not require monitoring; and, in the case of rivaroxaban, have dosage forms (oral suspension, granules) that are pediatric friendly; the panel felt that using these agents in treating pediatric VTE would be acceptable. For guidelines, ASH takes the perspective of high-income countries (HICs), and in this regard, the panel felt that it would be feasible to implement either of these agents in such settings, but the panel also acknowledges that access to these agents for pediatric patients in low- and middle-income countries (LMICs) needs to be addressed. Indeed, even in some HIC settings, rivaroxaban suspension or granules are not approved/marketed. The resources required to implement the use of either of these agents were deemed variable in HICs, driven by insurance coverage/copayments vs out-of-pocket costs for those without

insurance. This is compounded in the LMIC setting in which costs for these agents, although on average lower than in HICs, are generally higher than for SOC agents, and families having insurance to cover costs of these agents are much less prevalent. Given these latter considerations, the panel could make no judgment on the impact to equity in using either of these agents. Similarly, although there are some data from the adult setting on cost-effectiveness of using DOACs, there are (to date) no published cost-effectiveness/cost-utility studies of DOACs in the pediatric context, and the panel concurred that there are enough methodological considerations/differences in pediatric cost-effectiveness studies to not rely on indirect data from adults. At the present time, the panel could not identify any significantly different factors/drug characteristics/clinical benefits/harms that would lead to one recommending 1 of these agents being used over the other.

## Summary of the evidence

The updated systematic review identified 3 RCTs (2 of dabigatran, and 1 of rivaroxaban), 2 large multicenter trials,[43,44] and 1 smaller single-institution trial,[85] that compared anticoagulation with a DOAC with SOC in the treatment of acute VTE in pediatric patients. A total of 853 pediatric patients aged <18 years were recruited to these studies, 523 of whom received a DOAC. Acute VTE had been objectively confirmed by imaging in these studies. A minimum of 5 days of parenteral therapy was given before initiation of a DOAC. SOC treatment included UFH, LMWHs, VKAs (which no participants received), and fondaparinux. Rivaroxaban was dosed according to weight, and dabigatran was dosed according to both age and weight. Patients with severe liver or renal impairment, preterm neonates (<37 weeks gestational age), neonates and infants with weights below the third percentile, patients with active bleeding or at high risk of bleeding that would contraindicate anticoagulation, or who had a life expectancy shorter than the anticipated duration of the trial, were excluded. Participants were treated for a minimum of 3 months in the 2 large RCTs and 6 months in the single-institution study, apart from neonates, infants, and children aged <2 years with CVAD-related VTE in 1 large RCT who were treated for 1 month.[43] In the multicenter dabigatran study, ~10% of participants in the dabigatran arm were taken off study because of not reaching an a priori therapeutic level in the protocol.[44] The panel acknowledged the risk of bias that this attrition could introduce but, after deliberation and acknowledging that dabigatran is currently approved without a monitoring requirement, agreed to pool the rivaroxaban and dabigatran data. The data for the 2 drugs were then examined separately, a decision driven by the potential for differing side effect profiles, and the potential effect of monitoring and dose adjustment of dabigatran on efficacy and safety. The outcomes considered were mortality,[43,44,85] recurrence,[43,44,85] resolution,[43,44] PTS,[43,44,85] major bleeding,[43,44,85] and CRNMB.[43,44] The panel did not consider indirect evidence from adult data.

## Benefits

***DOAC vs SOC.*** The pooled data for the 3 RCTs[43,44,85] comparing DOAC (rivaroxaban, dabigatran) with SOC showed a mortality rate of 3 of 512 (0.6%) patients in the DOAC group vs 2 of 267 (0.7%) patients in the SOC group. Two of the deaths in the DOAC group were not reported in the published article but published on www.ClinicalTrials.gov.[44] Although the calculated RR of 0.71 favors DOAC, the CI is very wide (95% CI, 0.14-3.56), and with very few events, the certainty in the evidence is low. All 3 pooled studies reported recurrence rates, with the DOAC group having a recurrence rate of 11 of 523 (2.1%) vs 14 of 267 (5.2%) occurring in the SOC group for an RR of 0.41 favoring the DOAC group, with a 95% CI of 0.2 to 0.93 with moderate certainty in the evidence. Thrombus resolution (complete or partial) was reported in the 2 large RCTs.[43,44] In the DOAC group, thrombus resolution was observed in 395 of 512 (77.1%) whereas in the SOC group, it was 181 of 255 (71%) patients, with an RR of 1.09 and 95% CI of 0.99 to 1.19, favoring the DOAC group with moderate certainty in the evidence. The same 2 RCTs reported incidence of PTS with a total of 4 of 511 (0.8%) occurring in the DOAC group and no reported cases in the SOC group, making RR calculations impossible, and, with few events, very low certainty in the evidence. The panel concurred that the length of follow-up in both of these trials is too short to diagnose PTS accurately. Given these numbers, the panel gave more weighting to the outcomes of mortality, recurrence, and thrombus resolution, and judged the benefits of DOACs over SOC to be small (see the evidence profile at recommendation 17, recommendation 18, recommendation 19 and recommendation 20).

***Rivaroxaban vs SOC.*** One RCT compared anticoagulation with rivaroxaban with SOC.[43] Mortality rate was 1 of 335 (0.3%) patients in the rivaroxaban group vs 0 of 165 in the SOC group; the death was cancer-related and not due to VTE. Anticoagulation with rivaroxaban led to reduced recurrence rate, occurring in 4 of 335 patients (1.2%) vs 5 of 165 patients (3.0%) who received anticoagulation with SOC (RR, 0.39; 95% CI, 0.11-1.45) although this estimate is imprecise because of the small number of events and wide CI. Anticoagulation with rivaroxaban resulted in complete or partial resolution in a higher proportion of patients, 76.7% vs 71.5% with SOC, although the CI crosses 1 and does not rule out no effect (RR, 1.07; 95% CI, 0.96-1.20). PTS was reported in 2 (0.6%) patients treated with rivaroxaban vs no patients treated with SOC although the follow-up interval was short. Overall certainty of these estimated effects was low for the reasons stated, and the guideline panel considered the benefits of rivaroxaban over SOC to be small (see the evidence profile at https://guidelines.ash.gradepro.org/profile/g_mYG4kTaSM).

***Dabigatran vs SOC.*** Two RCTs compared anticoagulation with dabigatran with SOC.[44,85] Both studies reported mortality and recurrence. Dabigatran was associated with lower mortality than SOC, 2 of 187 (1.1%) vs 2 of 102 (2.0%) patients, respectively (RR, 0.51; 95% CI, 0.07-3.51) although deaths were judged as unrelated to anticoagulant therapy by the guideline panel. Anticoagulation with dabigatran was associated with reduced recurrence, occurring in 7 of 188 (3.7%) patients vs 9 of 102 (8.8%) patients treated with SOC (RR, 0.45; 95% CI, 0.17-1.17) although the estimate is imprecise because of the small number of events and with a risk of indirectness because of monitoring and dose adjustment of dabigtran.[44] One study reported resolution and PTS.[44] Anticoagulation with dabigatran resulted in complete or partial resolution in a higher proportion of patients, 138 of 177

(78.0%) patients vs 63 of 90 (70.0%) with SOC, although the CI does not rule out no effect (RR, 1.11; 95% CI, 0.95-1.30). PTS was reported in 1 of 176 (0.6%) patients treated with dabigatran and 0 of 90 (0%) patients treated with SOC. Overall certainty of these estimated effects was very low to low for the reasons stated, and the guideline panel considered the benefits of dabigatran over SOC to be small (see the evidence profile at https://guidelines.ash.gradepro.org/profile/clAG7b3MYuw).

### Harms and burden

***DOAC vs SOC.*** Major bleeding was reported in all of the RCTs that were pooled and occurred in 4 of 517 (0.8%) patients receiving DOAC and 5 of 264 patients (1.9%) receiving SOC with an RR of 0.48 and CI of 0.14 to 1.57, favoring DOAC but with low certainty in the evidence.[43,44,85] For CRNMB events, 12 of 506 patients (2.4%) experienced an event in the DOAC group and 2 of 252 patients (0.8%) in the SOC group, for an RR of 2.98 and CI of 0.67 to 13.27, in favor of SOC with low certainty in the evidence. The panel gave greater weight to major bleeding events being lower in the DOAC group than to CRNMB, and deemed the undesirable effects of DOAC vs SOC to be small (see the evidence profile at https://guidelines.ash.gradepro.org/profile/0xFZvTT2VUk).

***Rivaroxaban vs SOC.*** Major bleeding was not reported in patients treated with rivaroxaban and in 2 of 162 patients (1.2%) treated with SOC. The RR and CI were not estimable. CRNMB occurred in 10 of 329 patients (3.0%) treated with rivaroxaban and 1 of 162 (0.6%) of those treated with SOC (RR, 4.92; 95% CI, 0.64-38.13), although with serious imprecision because of the small number of events. The panel considered the risk of undesirable effects of rivaroxaban vs SOC to be small (see the evidence profile at https://guidelines.ash.gradepro.org/profile/g_mYG4kTaSM).

***Dabigatran vs SOC.*** Both studies reported major bleeding and 1 study[44] reported CRNMB. Major bleeding was reported in 4 of 188 patients (2.1%) treated with dabigatran and 3 of 102 patients (2.9%) treated with SOC (RR, 0.79; 95% CI, 0.19-3.32). CRNMB occurred in 2 of 177 patients (1.1%) treated with dabigatran and 1 of 90 (1.1%) of those treated with SOC (RR, 1.02; 95% CI, 0.09-11.07). Certainty of estimated effects was very low for major bleeding and low for CRNMB because of the small number of events, and the panel considered the risk of undesirable effects of dabigatran to be trivial (see the evidence profile at https://guidelines.ash.gradepro.org/profile/clAG7b3MYuw).

### Other EtD criteria and considerations

In reviewing the limited RCT data on rivaroxaban and dabigatran for treatment of pediatric VTE, the panel made a conditional recommendation for using either of these agents over SOC. The certainty of this evidence ranges from very low to at best moderate on the key reported outcomes.

The panel identified patient groups/factors in which a DOAC should not be used or used with great caution including in patients with known/potential gut absorption issues whether chronic or temporary, including short gut syndrome, recent surgery, liver disease (alanine transaminase >5× upper limit of normal, and/or bilirubin of >2× the upper limit of normal) or kidney disease (GFR of <30 mL/min) severe enough to cause a coagulopathy, patients with antiphospholipid syndrome, preterm neonates, and those with active cancer. Based on reported side effects of these agents from the RCTs, heavier menstrual bleeding was reported with rivaroxaban and could be a consideration in prescribing this agent in postmenarche girls. Similarly, gastrointestinal side effects were more commonly reported with dabigatran. In adults, there are 2 specific reversal agents: andexanant alfa for rivaroxaban, and idarucizumab for dabigatran, to manage uncontrollable/life-threatening bleeding. Additionally, prothrombin complex concentrates (PCCs) have also been used to achieve hemostasis in this context but, at the present time, there is no good pediatric dosing information for this specific indication for the panel to comment on.

As mentioned earlier, a significant barrier to implementing these recommendations on a global scale is access to the drugs themselves, which currently have regulatory approval for pediatric indications in a subset of HICs, and, in some cases, not all pediatric-friendly dosage forms (rivaroxaban suspension, dabigatran pellets) are approved/marketed in all HICs. The addition of rivaroxaban and/or dabigatran to the World Health Organization Essential Medicines List for children would be an important first step in making these agents accessible to pediatric patients in LMICs.

### Conclusions and research needs for these recommendations

***Conclusion.*** Based on available data to date, the panel makes a conditional recommendation to use a DOAC agent to treat pediatric patients with VTE.

***Research needs.*** The panel identified the following research priorities as being most important to address going forward:

1. Efficacy and safety data on use of DOACs in certain patient populations including neonates; preterm infants; infants; and those patients with mild to moderate liver/renal impairment, malabsorptive states, short gut syndrome, or active cancer
2. Can DOACs be started immediately vs after ≥5 days of alternative anticoagulation in pediatric VTE?
3. Cost-effectiveness and cost utility studies of DOACs in treatment of pediatric VTE in both HIC and LMIC settings
4. Specific reversal agents for DOACs
5. Long-term follow-up data on recurrence, mortality, and PTS in pediatric patients

## Implementation guidance

As previously discussed, there are many physiological differences between children and adults, and there are many pathophysiological differences in VTE between children and adults. In recent years, therapeutic options for the treatment of pediatric VTE have

increased and now include DOACs. These options are further expected to increase in the upcoming years, as ongoing clinical trials are completed.

Clinical factors that should be considered when choosing anticoagulants include the patient's clinical status (ie, critically ill or likely to need an intervention), renal function, comorbidities, oral intake, drug interactions, drug access/cost, need for monitoring, and patient/family preference. Special attention in children should be given to procedural pain,[86] and the impact of therapy on the global health of the child including their mental health.[87] Given the complexities of both the patients and the drugs, the panel considered the use of anticoagulants in children to be a specialist endeavor, best managed by a pediatric hematologist with experience in treating pediatric VTE. However, this is often not possible, and therefore the panel agreed that providing further guidance on the use of anticoagulants and fibrinolytics in pediatric patients would be of value to many readers. Guidance is provided for the following drugs: UFH, LMWH, fondaparinux, VKAs, rivaroxaban, dabigatran, and tissue plasminogen activator (t-PA). Although other anticoagulants may be used in children, there were limited published data to support their routine use for VTE treatment at the time of this guidance. For example, bivalirudin has become more frequently used in specific pediatric cardiac populations with some limited evidence available; however, at this time, the panel does not support its standard use in pediatric VTE because of a lack of research into its safety or efficacy. Table 4 compares the mechanism of action, routes of administration, pharmacokinetics (PKs), metabolism, drug interactions, and use in renal or hepatic impairment of these drugs; Table 5 highlights the major advantages and disadvantages of each antithrombotic; and Figure 2 provides a general overview to guide the selection of anticoagulant agents for the management of pediatric VTE. A general approach to dosing, monitoring, and management of procedures or bleeding with these drugs is provided hereafter, along with additional data on AEs.

## Good practice statement

For pediatric patients who are at high risk of bleeding (eg, CSVT and associated hemorrhage secondary to venous congestion, immediate after or anticipated invasive procedures), consider the use of a short half-life agent such as UFH rather than LMWH or DOACs if anticoagulation is required, to decrease the risk of worsening hemorrhage or bleeds.

## UFH

***Therapeutic range.*** A therapeutic range for heparin was derived from experimental animal studies in which the whole-blood clotting time was used.[88] A prospective study using aPTT for monitoring heparin therapy in adult patients with VTE showed that the risk of recurrent VTE was associated with failure to obtain an aPTT ratio of ~1.5 times the control value and that a heparin concentration of 0.2 to 0.4 IU/mL by protamine titration correlated with this aPTT range.[89] This aPTT ratio became the standard for the lower limit of the therapeutic range in adults.

A therapeutic range for UFH in children is largely extrapolated from adult studies and recommend targeting an aPTT range that reflects a heparin level by protamine titration of 0.2 to 0.4 IU/mL or an anti–factor Xa (anti-FXa) level of 0.35 to 0.7 IU/mL,[90] but this has yet to be confirmed by RCTs. The measured response to the aPTT and the anti-FXa varies between reagents and instruments used to measure these tests.[91] Additionally, there are multiple variations to the anti-FXa assay that change the response to UFH, and there are no data to confirm which test variation is clinically optimal.[92] Therefore, clinicians must understand the specifics/pitfalls of the tests run in their laboratories.[93]

The evidence for adjusting the dose of heparin to maintain a therapeutic range is weak and is based on a post hoc subgroup analysis of a descriptive study.[89] There is a paucity of data on the performance of the aPTT or anti-FXa for UFH monitoring in children,[94,95] and a therapeutic UFH dose targeting an aPTT of 60 to 85 seconds and anti-FXa activity of 0.35 to 0.7 IU/mL is most commonly used.

***Monitoring.*** In vitro and ex vivo data suggest that UFH monitoring using the aPTT titrated to an anti-FXa assay result of 0.35 to 0.7 IU/mL is associated with significant age-related variation.[96,97] The mechanism for the discrepancies between anti-FXa and aPTT is unclear but may be associated with the variable anti-FIIa–to–anti-FXa effect of UFH.[96] Infants and children can have significantly higher aPTT compared with adult reference ranges because of developmental hemostasis.[98-100] Most laboratories do not adjust aPTT therapeutic ranges based on age. Additionally, pediatric studies report a poor correlation between aPTT and anti-FXa activity,[95,101] and therefore some pediatric institutions use anti-FXa activity as the monitoring test for UFH therapy.

The use of anti-FXa instead of aPTT for monitoring UFH in pediatrics is supported by very few studies, which suggest that greater time is spent within the therapeutic range for children receiving UFH monitored with anti-FXa compared with aPTT.[101,102] The chromogenic anti-FXa assay is not influenced by elevated concentrations of FVIII or fibrinogen or by factor deficiencies.[94,103] In contrast, anti-FXa activity represents the amount of heparin in the blood and not necessarily its antithrombotic function, which may be more accurately measured with aPTT and thus not reflect UFH's true anticoagulant effect.[104]

***Dosing.*** There are no PK dose-finding studies reported for UFH in preterm or term neonates or children. A single-center case series (n = 25 neonates; gestational age range, 25-36 weeks) giving a bolus infusion of 100 U/kg and plasma heparin levels assayed at timed intervals to measure clearance showed that UFH clearance and volume of distribution was significantly higher in all neonatal groups (greater in preterm than term neonates) than in adults.[105] In another study, which included infants (n = 15) on continuous UFH for VTE treatment, plasma heparin levels in the therapeutic range (0.35-0.7 IU/mL) and clinical resolution of the thrombi were associated with doses of 16 to 35 IU/kg per hour (mean, 27 IU/kg per hour), which is higher than in adults.[106] Similarly, another single-institution prospective study of UFH therapy in 65 consecutive children with age-matched controls reported an average requirement of 28 IU/kg per hour for infants to maintain therapeutic aPTT.[107]

A weight-based nomogram for heparin doses in pediatric patients has been previously published.[107,108] Subsequently, the American College of Chest Physician guidelines suggested a higher bolus

**Table 4. Characteristics of anticoagulants/thrombolytics used for acute VTE in pediatrics**

| Agent | Class and mechanism of action | Route | Half-life | Metabolism and excretion | Drug interactions | Use in liver or renal impairment | Preparations |
|---|---|---|---|---|---|---|---|
| UFH | Binds to AT to increase AT inhibitory effect on FIIa and FXa | IV (preferred), SQ (lower bioavailability in children) | Nonlinear 60-90 min | Metabolized by the liver; renally cleared and excreted in urine | None | Careful monitoring | N/A |
| LMWH | Smaller than UFH; binds to AT increasing AT's inhibitory effect on FXa (less FIIa effect) | SQ (rarely IV) | Enoxaparin 3-7 h; dalteparin 3-5 h | Metabolized by the liver; renally cleared and excreted in urine | None | Dose adjustment required in patients with decreased CrCl | Enoxaparin:<br>prefilled syringes: 30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/1mL;<br>graduated prefilled syringes: 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/1 mL;<br>multipledose vial: 300 mg/3 mL<br>Dalteparin:<br>prefilled syringes: 2 500 IU/0.2 mL, 5 000 IU/0.2 mL, 7 500 IU/0.3 mL, 10 000 IU/1 mL, 12 500 IU/0.5 mL, 15 000 IU/0.6 mL, and 18 000 IU/0.72 mL;<br>multidose vials: 10 mL containing 10 000 IU/mL, 3.8 mL containing 25 000 IU/mL |
| Fondaparinux | Synthetic pentasaccharide; binds to AT and increases AT inhibitory effect on FXa | SQ | 17-21 h | Renally cleared and excreted unaltered in urine | None | Contraindicated in severe renal impairment (CrCl of <30 mL/min) | Prefilled syringes: 1.5 mg, 2.5 mg, 5 mg, and 10 mg doses |
| Warfarin, acenocoumarol, and phenprocoumon (VKAs) | VKAs; inhibit vitamin K epoxide reductase and interruption in the synthesis of activated vitamin K, preventing carboxylation of FII, FVII, FIX, and FX (proteins S and C) | po | 20-60 h | Metabolized in the liver by CYP2C9 with minor contributions from CYP2C18 and VYP2C19; excreted in urine and feces | Multiple drug and food interactions, including OTC drugs;<br>caution with concurrent use of antimicrobials, anti-arrhythmic drugs, and other anticoagulant agents<br>Food interactions: foods rich in vitamin K | No dose adjustment for renal impairment<br>Hepatic impairment requires close INR monitoring, response may be increased in obstructive jaundice, hepatitis, or cirrhosis | No liquid preparation<br>Warfarin sodium (Coumadin: 1 mg, 2 mg, 2.5 mg, 5 mg, and 10 mg; Marevan: 1 mg, 3 mg, and 5 mg)<br>Acenocoumarol (Sintrome: 1 mg)<br>Phenprocoumon (1.5 mg and 3 mg) |
| Rivaroxaban | FXa inhibitor; directly binds to free and prothrombinase-complex-bound FXa inhibiting its function (reversible inhibition) | po, NG, or GT | Mean half-life: adolescents, 4.2 h; age 2 to <12 y, 3 h; age 0.5 to <2 y, 1.9 h; age <0.5 y, 1.6 h | Metabolized by the liver; renally cleared and excreted in urine | Concurrent use of P-gp and strong CYP3A4 inducers and inhibitors | Avoid in moderate and severe hepatic impairment or with any hepatic disease associated with coagulopathy<br>Avoid in children with eGFR of <50 mL/min per 1.73 $m^2$ (serum Cr of >97.5th percentile in infants) | Oral suspension: 1 mg/mL<br>Tablets: 2.5 mg, 10 mg, 15 mg, and 20 mg; no pediatric data with 2.5 mg tablets<br>Tablets can be crushed and mixed with water or applesauce<br>Availability varies based on jurisdiction |
| Dabigatran | Direct thrombin inhibitor; directly binds to free and fibrin bound thrombin, blocking conversion of fibrinogen to fibrin (reversible inhibition) | po (all dosage forms) NG or GT (oral suspension only) | Elimination half-life: 9-11 h | Rapid and complete conversion into active form after intestinal absorption; renally cleared and excreted in urine | Concurrent use of P-gp inducers and inhibitors | Avoid in active liver disease, including active hepatitis, or elevated ALT, AST, or AP of >3× ULN<br>Contraindicated in renal dysfunction with eGFR of <50 mL/min per 1.73 $m^2$ (serum Cr of >97.5th percentile in infants) | Oral capsules: 75 mg, 110 mg, and 150 mg; cannot be crushed<br>Oral pellets: 20 mg, 30 mg, 40 mg, 50 mg, 110 mg, and 150 mg per packet.<br>Powder and solvent for oral solution (6.25 mg/mL).<br>Availability varies based on jurisdiction.<br>Cannot combine different preparations<br>The oral solution is compatible with nasal tubes made of PVC, polyurethane, and silicone |
| t-PA | Thrombolytic/fibrinolytic;<br>Cleaves plasminogen to plasmin, which can then degrade fibrin (and fibrinogen). Binds to fibrin in blood clot activating clot-bound plasminogen (clot-specific fibrinolysis) | IV | Alteplase: initial half-life of 5 min; terminal half-life of 72 min | Hepatic clearance | None | No contraindications in renal or liver disease, although risk of bleeding may be higher | N/A |

ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; AT, antithrombin; Cr, creatinine; CrCl, creatinine clearance; GT, gastric tube; N/A, not applicable; NG, nasogastric; OTC, over the counter; P-gp, P-glycoprotein; po, Per oral or by mouth; PVC, polyvinyl chloride; ULN, upper limit of normal.

**Table 5. Comparison of advantages and disadvantages of anticoagulants/thrombolytics for pediatric VTE**

| Agent | Advantages | Disadvantages | Impact on QOL |
|---|---|---|---|
| UFH | Short half-life<br>Available reversal agent (protamine)<br>No drug or food interactions<br>Extensive clinical experience<br>Can be used in renal failure<br>Modulatory effect on inflammation | Difficult to titrate in younger patients<br>Variable bioavailability because of binding to plasma proteins<br>Need for frequent dose monitoring<br>Poor correlation between dose and aPTT or anti-FXa levels<br>Need for IV access | No studies |
| LMWH | More predictable dosing (vs UFH and VKAs)<br>Few drug and food interactions<br>Extensive clinical experience | Unpredictable dose-effect response as measured by anti-FXa levels<br>SQ administration<br>Not fully reversible (protamine)<br>Needs careful monitoring in renal impairment | SQ injections are traumatic |
| Fondaparinux | Once daily dosing<br>Excellent bioavailability<br>Lower risk of HIT (vs UFH and LMWH) | SQ administration<br>Difficult to administer small doses (no multidose vial)<br>Long half-life; not fully reversible | No studies |
| Warfarin, acenocoumarol, and phenprocoumon (VKAs) | Oral administration (only after therapeutic anticoagulant with parenteral agent)<br>Once daily dosing<br>Can be used in renal failure<br>Available reversal agent (PCC, vitamin K) | No commercially available liquid formulation<br>Multiple food and drug interactions<br>Stability affected by developmental hemostasis and intercurrent illnesses<br>Need for frequent monitoring<br>Due to long and variable half-life, achieving target therapeutic range can take 5-7 d | At home point-of-care monitoring improves QOL |
| Rivaroxaban | Oral administration (only after ≥5 d of parenteral anticoagulant)<br>Rapid onset and offset of action<br>Stable pharmacological profile<br>Few drug and food interactions<br>No need for routine laboratory monitoring<br>No risk for HIT | Should not be used in children with mechanical valves and APS<br>Limited efficacy and safety data on neonates and infants<br>Rivaroxaban-specific anti-FXa assays not widely available<br>No pediatric data available for reversal agent (andexanet alfa)<br>Concern for increased menstrual bleeding (vs LMWH, fondaparinux, and VKAs) | No studies |
| Dabigatran | Oral administration (only after ≥5 d of parenteral anticoagulant)<br>Rapid onset and offset of action<br>Stable pharmacological profile<br>Wide therapeutic window<br>Few drug and food interactions<br>No need for routine laboratory monitoring<br>No risk for HIT | Should not be used in children with mechanical valves and APS<br>Limited efficacy and safety data on neonates and infants<br>No pediatric data available for reversal agent (idarucizumab)<br>Capsules cannot be crushed and dosage forms for children who cannot swallow capsules are not widely available<br>No administration via enteral tubes or syringes (except for oral solution) | No studies |
| t-PA | More rapid thrombus resolution than anticoagulation alone<br>Rapid onset and offset of action<br>Very short half-life | High risk of bleeding requiring administration in a critical care setting for close monitoring<br>IV administration only | N/A |

APS, antiphospholipid syndrome; N/A, not applicable.

dose of 75 to 100 IU/kg based on unpublished data that resulted in therapeutic aPTT values in the majority of children.[108] The maintenance dose required to prolong the aPTT to within the adult therapeutic range, corresponding to an anti-FXa level of 0.35 to 0.7 is higher in neonates compared with older children and is also gestational age dependent.[105,106]

Both aPTT and anti-FXa levels are used in clinical practice to monitor UFH therapy. Multiple preanalytic, analytic, and clinical factors affect both aPTT and anti-FXa results. Studies have demonstrated a poor correlation between these tests when used to monitor UFH therapy[95,101,102,109] and lack of superiority in predicting thrombosis or bleeding. Therefore, we suggest that clinicians consistently use 1 test to monitor patients on UFH anticoagulation. Table 6 shows the suggested loading and initial age-based doses for UFH and monitoring.

***AEs.*** The incidence of bleeding in children treated with UFH is reported to be between 2% and 24%.[107,110] These studies included infants with underlying congenital heart disease and children who were critically ill who are at higher risk of bleeding and thus may not reflect the bleeding risk in other pediatric populations. There are no studies reporting the incidence of bleeding specifically in the preterm or term infant population.

Heparin-induced thrombocytopenia (HIT) is rare in pediatrics.[111,112] The incidence of HIT has been reported to be between 0% and 2.3% in different subgroups of children and with the use of variable laboratory detection methods.[113-116] A recent review reported an incidence of 1.5%, and no cases of HIT identified in nearly 3000 newborns who underwent cardiac surgery.[117]

One of the major risks of UFH therapy reported is accidental overdoses due to stocking of UFH of different strengths (5000

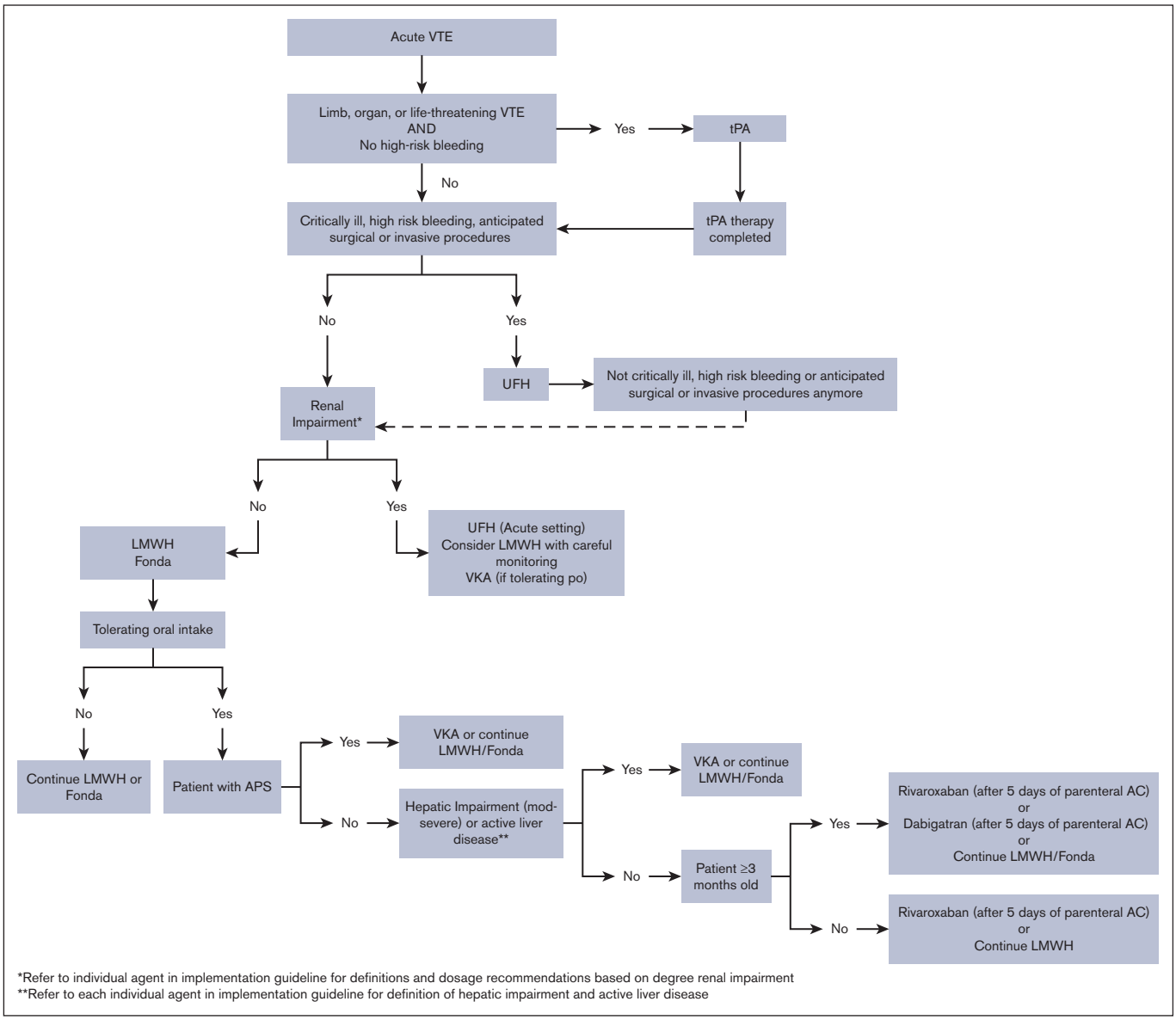


**Figure 2. Guide to the selection of anticoagulant agent for treatment of VTE in pediatric patients.** APS, antiphospholipid syndrome; Fonda, fondaparinux; po, by mouth.

IU/mL vs 50 IU/mL), and erroneous vial selection resulting in supratherapeutic doses being administered in neonates or children.[118]

UFH can adversely affect bone remodeling and development, and can cause osteoporosis.[119] Therefore, extended use in neonates and young children should be avoided. Additionally, UFH has been reported to have antiangiogenic properties and its impact in this regard on growth in young babies is unknown.[120] Lastly, heparin-related immediate-type hypersensitivity reactions are rare.[121]

***Periprocedural management and management of heparin-induced bleeding.*** Owing to its quick onset and offset of action, UFH infusion can be discontinued 4 to 6 hours before any anticipated surgeries or in the case of bleeding. For quick reversal, protamine can be administered to neutralize UFH based on the amount of UFH received (1 mg for every 100 IU, for a maximum dose of 50 mg).

## LMWH

***Therapeutic range.*** The "therapeutic range" of LMWH for treatment of VTE in children has been extrapolated from small studies in adults, which targeted a peak anti-FXa level of 0.5 to 1.0 IU/mL in a sample taken 4 hours (range, 3-5) after a dose.[122] Although most pediatric studies have used this range, a large cohort study of enoxaparin used a range of 0.5 to 0.8 IU/mL with similar outcomes.[123] Although monitoring LMWH in adults is not routine, monitoring and adjusting the dose to stay in the therapeutic anti-FXa range is the recommended approach in children, based on numerous studies that have identified significant interpatient dose variation across multiple age groups.[90]

**Table 6. Dosing nomogram for UFH for pediatric VTE**

| | | | |
|---|---|---|---|
| **Loading dose*** | | | |
| ≤ 1 y: 75 IU/kg over 10 min (maximum dose 5000 IU) | | | |
| ≥ 15 y: 80 IU/kg over 10 min (maximum dose 5000 IU) | | | |
| **Initial maintenance rate** | | | |
| <1 y: 28 IU/kg per h | | | |
| ≤1 to 15 y: 20 IU/kg per h (or an equivalent IU/kg per h to a maximum rate of 1250 IU/h) | | | |
| ≥15 y: 18 IU/kg per h (or an equivalent IU/kg per h to a maximum rate of 1250 IU/h) | | | |
| **aPTT† (s)** | **Anti-FXa (IU/mL)** | **Dose adjustment** | **Time to repeat anti-FXa/aPTT‡** |
| <50 | <0.1 | Bolus of 50 IU/kg and increase infusion rate by 20% | 4 h after rate change |
| 50-59 | 0.1-0.29 | Increase infusion rate by 10% | 4 h after rate change |
| 60-85 | 0.35-0.7 | No change | 4 h and when there are 2 consecutive levels in goal range then check next day |
| 86-95 | 0.71-0.9 | Decrease infusion rate by 10% | 4 h after rate change |
| 96-120 | 0.91-1 | Hold infusion for 30 min and decrease infusion rate by 10% | 4 h after rate change |
| >120 | >1 | Hold infusion for 60 min and decrease infusion rate by 20% | 4 h after rate change |

*Loading dose is not recommended in neonates and in patients at high risk of bleeding
†Assumes this reflects an anti-FXa level of 0.35-0.7 IU/mL or a protamine titration on 0.2-0.4 IU/mL.
‡Because of high intrapatient and interpatient variability in anticoagulant response to UFH, consider checking anti-FXa levels every 4 hours. Changes in renal function or with changes in various types of renal replacement therapies may require dose adjustment.

Whether this is the optimal therapeutic anti-FXa range for children remains unknown, and most retrospective studies have been unable to correlate anti-FXa levels with efficacy or safety outcomes, with some exception.[124-130] In addition, there is poor interlaboratory agreement and considerable variation among available anti-FXa assays, likely providing false reassurance regarding the importance of the therapeutic range.[131,132] Although some have proposed that fixed weight-based dosing in children without titrating to a "therapeutic range" may be safe, effective, and reduce venipuncture, this has not been demonstrated clinically.[131,133]

Despite these challenges, we have several decades of experience titrating LMWHs in children targeting this range. Recent phase 3 clinical trials in pediatric VTE have confirmed low rates of bleeding and recurrent VTE in children treated with LMWHs across a wide range of settings.[134-136]

***Monitoring.*** Anti-FXa levels can ensure the drug is within the target range, typically 0.5 to 1 U/mL. Nonadherence can be detected if anti-FXa levels are not measurable or well below the anticipated level. The optimal frequency of anti-FXa monitoring in children has not been investigated. Clinically stable older children likely require minimal monitoring. Younger children with more rapid changes in weight, as well as children who are critically ill and those with changing renal status or antithrombin levels are likely to benefit from closer monitoring.

***Dosing.*** Current recommended dosing of LMWHs is shown in Table 7. These are predominantly age dependent.[128,137-144]

A typical nomogram for adjusting LMWH dose according to anti-FXa level is provided in Table 8.[146] The first anti-FXa level is usually checked 4 hours (range, 3.5-6) after the second or third dose of LMWH and adjusted if not in the therapeutic range. Because of the difficulty of administering submilligram dosing of enoxaparin, rounding up to the nearest whole milligram is recommended.[147] This recommendation applies also to the other LMWHs, which are dosed in units. A pragmatic approach also applies to the use of

**Table 7. Recommended starting dose for LMWHs and fondaparinux**

| Drug | Weight | Age | Initial treatment dose* |
|---|---|---|---|
| Enoxaparin[19] | N/A | <3 mo<br>3 m to 1 y<br>1-5 y<br>>5 y | 1.5-1.7 mg/kg, q12h<br>1-1.5 mg/kg, q12h<br>1-1.2 mg/kg, q12h<br>1 mg/kg, q12h |
| Dalteparin[9,17] | N/A | 1-24 mo<br>2-8 y<br>8-16 y | 150 IU/kg, q12h†<br>125 IU/kg, q12h<br>100 IU/kg, q12h |
| Tinzaparin[10,18,19] | N/A | 0-2 mo<br>2-12 mo<br>1-5 y<br>5-10 y<br>10-16 y | 275 U/kg, q24h<br>250 U/kg, q24h<br>240 U/kg, q24h<br>200 U/kg, q24h<br>175 U/kg, q24h |
| Reviparin[90] | <5 kg<br>>5 kg | N/A<br>N/A | 150 U/kg, q12h<br>100 U/kg, q12h |
| Nadroparin[28] | N/A | 0-2 mo<br>2-24 mo<br>2-11 y<br>12-18 y | 224 U/kg, q12h<br>127 U/kg, q12h<br>107 U/kg, q12h<br>92 U/kg, q12h |
| Bemiparin[30] | N/A | 0-2 mo<br>2-12 mo<br>1-5 y<br>6-12 y | 197 U/kg, q24h<br>163 U/kg, q24h<br>150 U/kg, q24h<br>126 U/kg, q24h |
| Fondaparinux | N/A | 1-17 y | 0.1 mg/kg, q24h |

N/A, not applicable; q12h, every 12 hours.
*Dose should be subsequently titrated to achieve a peak heparin anti-FXa level of 0.5-1.0 IU/mL.
†Neonates may need higher doses.[145]

**Table 8. Nomogram for adjusting LMWH dose**

| Anti-FXa level | Dose change* |
|---|---|
| <0.35 IU/mL | Increase by 25% |
| 0.35-0.49 IU/mL | Increase by 10% |
| 0.5-1.0 IU/mL | None |
| 1.1-1.5 IU/mL | Decrease by 20% |
| 1.6-2.0 IU/mL | Decrease by 30% |

*If dose is changed, recheck after second dose.

prefilled syringes of LMWH (using the closest dose within reason [10%-15%], rather than exact weight-based dose). Administration from multidose vials may be preferred in smaller children because it allows the use of a smaller bore needle than the standard for the prefilled syringes.

ADDITIONAL POINTS ON DOSING ENOXAPARIN. Existing age-related dosing recommendations and dose adjustments for enoxaparin (<2 months of age: 1.5 mg/kg SQ injection 2 times a day; >2 months of age: 1 mg/kg SQ every 12 hours) are based on a small prospective dose-finding study of 23 children.[90,148] There have been numerous subsequent studies demonstrating that this dosing strategy results in subtherapeutic anti-FXa levels in many children aged <5 years who often require multiple dose adjustments, although the proportion varies across studies, partly because of variation in anti-FXa assays.[123,126,127,130,149-168] The proportion of neonates with subtherapeutic values is even higher, likely because of a higher volume of distribution, lower concentration of antithrombin, and more rapid clearance.[130,147,153,158,159,166] These findings have led many to call for higher starting doses for younger patients, particularly neonates. Two retrospective studies comparing the current dosing recommendations to higher starting doses have reported that fewer dose adjustments and venipunctures were needed in those with a higher starting dose, without an increase in bleeding.[147,155] In contrast, a large retrospective population PK study of enoxaparin in >800 children aged >1 year predicted that using 1 mg/kg, 2 times a day, had the highest probability of achieving a therapeutic anti-FXa level.[163]

Although higher dosing strategies have not been prospectively validated, existing studies suggest that if an anti-FXa range of 0.5 to 1.0 IU/mL is the target, higher starting doses in younger patients will achieve this target more rapidly than current recommendations.[132,149,157] Many centers have developed modified dosing strategies based on analysis of their own patient data, which has the benefit of center-specific anti-FXa assays, and, when possible, this approach is recommended. Although it remains uncertain whether higher dosing strategies will influence clinical outcomes, a reduction in dose adjustments and venipuncture has merit, and retrospective studies have not reported higher bleeding rates with higher starting doses. Therefore, we have included a higher enoxaparin starting dose strategy for children aged <5 years in Table 7. This strategy is informed by ~25 studies and >3000 children.[126,127,130,147-156,159,161-170] Prospective evaluation of this strategy is strongly encouraged. This range may also allow for more individualized dosing based on unique patient risks for bleeding or thrombotic complications.

ONCE-A-DAY ENOXAPARIN. Enoxaparin is approved for treatment of adult VTE at a dose of 1.5 mg/kg SQ once daily. Several studies have investigated once daily administration in children with variable results and conclusions, in part because they used different anti-FXa target ranges.[171]

A prospective PK and pharmacodynamic study investigated the use of once daily enoxaparin in 16 children aged >3 months with VTE who received >48 hours of twice daily enoxaparin dosing and then transitioned to 1.5 mg/kg once daily.[171] Peak anti-FXa was measured 4 hours after the second dose, with a therapeutic anti-FXa range of 1.0 to 2.0 IU/mL. The study found significant variation in the dose required to achieve this target range and low anti-FXa trough values, resulting in lower total drug exposure in children compared with adults. The conclusion from this small study was that once daily enoxaparin was probably not feasible in children.[171]

A second PK study compared 120 children with VTE who received either once or twice daily treatment after 10 to 14 days of twice daily treatment.[172] In this study the 2- to 4-hour peak anti-FXa target range was 0.5 to 0.8 IU/mL and the 24-hour trough anti-FXa target was >0.1 IU/mL. Patients aged >1 year received 1 mg/kg once daily, and those aged <1 year received 1.5 mg/kg once daily. There were no differences in recurrent VTE or bleeding in the groups. There was significant interpatient variability in PK parameters and among patients treated once daily, only 53% had adequate trough levels.[172]

A retrospective study comparing 39 children who received once daily enoxaparin "maintenance therapy," started after >2 weeks of twice daily therapy, with 32 children who continued to receive twice daily dosing, did not identify differences in outcomes between these 2 groups, although patients with less extensive thrombus were more likely to receive once daily therapy.[173] Patients treated once daily started at 1.5 mg/kg to target a peak therapeutic anti-FXa of 0.7 to 1.2 IU/mL.[173]

IV ENOXAPARIN. IV enoxaparin has been used in a small number of pediatric studies, including patients who are critically ill and those with significant soft tissue edema or burns.[174-177] When administered as an infusion over 30 minutes, peak anti-FXa levels were similar to those reported with SQ administration.[174,176] The clearance of the drug has not been carefully studied with IV administration.

LMWH DOSING CONSIDERATIONS IN OBESITY. Increasing data support concerns that patients who are overweight/obese and are receiving enoxaparin are more likely to have supratherapeutic anti-FXa values.[178-180] In a review that included 94 pediatric patients from 6 studies, the mean final enoxaparin dose had been reduced from 1 mg/kg twice daily to 0.84 mg/kg twice daily, and population models developed using fat-free mass have been proposed.[178,181] These studies highlight the importance of more closely monitoring for drug accumulation in this subgroup of patients. There is a lack of data to advise dosing of other LMWHs in children who are overweight/obese.[178]

***AEs.*** Increased bleeding risk, particularly in patients with other bleeding risk factors, concomitant use of antiplatelet or other anticoagulation medications, and in those undergoing an invasive

procedure. In the EINSTEIN-Junior trial, enoxaparin was used in 85% patients in the SOC arm, and major bleeding occurred in 2.4% patients (n = 1), and CRNMB occurred in 0%.[43] In the KIDS-DOTT trial, ~86% of all patients were on enoxaparin and there were 12 CRNMB events that occurred in 7 patients (3%).[47] Safety data on 50 children treated with dalteparin reported injection site bruising in 30%, with minor bleeding in 40% and major bleeding (intestinal hematoma) in 1 patient (2%).[129]

***Periprocedural management.*** The 2022 American College of Chest Physicians adult guidelines generally recommend hold on LMWH 24 hours before procedure and resuming 24 hours after the procedure in low-risk procedures. Resumption of LMWH should be 48 to 72 hours after a procedure with a high bleeding risk, although the use of low-dose LMWH or UFH can be used for patients with a high risk of thromboembolic complications.[182]

***Management of bleeding.*** Protamine can partially reverse the anti-FIIa activity of LMWH, but it only reverses 60% to 70% of the anti-FXa activity.[183] Dosing of protamine depends on the dose and timing of the most recent LMWH administration. If it has been <8 hours since the last dose, 1 mg of protamine per 100 U, or 1 mg of LMWH can be given; if it has been 8 to 12 hours, 0.5 mg of protamine per 100 U, or 1 mg of LMWH is recommended.[184] Repeated measurements of anti-FXa level may be required in cases of ongoing bleeding, with further doses of protamine being administered. The maximum recommended dose of protamine is 50 mg.[184]

## Fondaparinux

***Therapeutic range.*** Fondaparinux is not routinely monitored in adults but, if required, can be monitored using an anti-FXa activity assay, calibrated with fondaparinux. Target peak concentration for therapeutic anticoagulation in adults is 0.5 to 1.0 mg/L, and this range has been extrapolated to children treated with fondaparinux. Fondaparinux does not usually affect routine coagulation tests, prothrombin time, or aPTT, when used in therapeutic doses but can cause aPTT prolongation at higher doses.

***Dosing/dose frequency.*** A starting dose of 0.1 mg/kg once daily is recommended in children aged 1 to 17 years. This is based on an open-label prospective study (FondaKIDS) of 24 children treated for DVT or HIT.[185] Dosing was adjusted to achieve peak concentrations of 0.5 to 1.0 mg/L after 4 hours, tested initially after the first dose, with 88% of individuals achieving the target concentration without dose adjustment.[185]

***Periprocedural management.*** The anticoagulant effect of fondaparinux may persist for 2 to 4 days in patients with normal renal function because of its long elimination half-life.

***Management of bleeding.*** There is no antidote to fondaparinux. Bleeding should be managed as per protocols for managing bleeding due to other irreversible anticoagulants.

## Warfarin, acenocoumarol, and phenprocoumon

***Therapeutic range.*** Target therapeutic ranges for children are currently extrapolated from the therapeutic ranges used in adults for the different indications.[144,146,185-189] The most common target international normalized ratio (INR) for children for the treatment of VTE is 2.5 (range, 2.0-3.0). High-risk conditions may require a higher range of 2.5 to 3.5. As yet, there have been no clinical trials to assess appropriate INR ranges for children.

***Monitoring.*** VKAs have a very narrow therapeutic index, and patients require frequent blood monitoring to ensure therapeutic anticoagulation and to minimize the risk of bleeding.[190,191] The blood monitoring test for warfarin therapy is the INR. Decisions around frequency of INR monitoring are informed by the child's age, length of time on treatment, changes in medication and food, and the presence of infections or comorbidities.[11,187,192,193] The age group found to be most susceptible to fluctuations in INR are children aged <1 year.[190,191,193,194] This susceptibility has been attributed to low concentrations of vitamin K in breast milk and high concentrations of vitamin K in most formula.[146,186,187,192-195] Infants and small children require very regular INR tests (on average, 2 tests per week) compared with once-a-month testing in most adult patients.[191,194,196,197]

***Dosing.*** At VKA commencement, children will experience a prothrombotic state. The peak anticoagulation effect is not reached until 5 to 7 days after initiation and for this reason, bridging with other anticoagulants (UFH or LMWH) for patients with acute VTE is necessary until the target INR range is achieved.

Many factors, such as a patient age, weight, height, concurrent drug therapy, genetics, and vitamin K intake can affect the appropriate dose for VKAs in children to achieve the target INR value. Younger children require higher dosing per kilogram of body weight to achieve similar INR values compared with older children.[192,193,197,198] Warfarin is the most well-established VKA used in children. The initial loading dose is 0.2 mg/kg per day, with a maximum dose of 10 mg per dose in those whose INR goal is between 2.0 and 3.0[192,193,198,199] (Table 9). For children who require warfarin after undergoing a Fontan procedure or who have liver dysfunction, the initial loading dose should be 0.1 mg/kg per dose.

The starting dose for acenocoumarol ranges from 0.20 mg/kg to 0.06 mg/kg, dependent on age (Table 9).[199,200] Dosing guidelines for phenprocoumon for children are limited, with most based on adult studies. One multicenter study was able to provide guidance for initial and maintenance phenprocoumon dosing for children (Table 9).[201]

After initial per-kilogram dosing, the VKA dose should then be increased, held, or decreased dependent on INR values. VKA dose adjustment guidelines for children with a target INR range of 2.0 to 3.0 following a published nomogram are presented in Table 9.[90,202]

***Food interactions.*** The anticoagulant effects of VKA may be decreased if taken with food rich in vitamin K. All infant formulas are fortified with vitamin K, whereas breast milk has low concentration of vitamin K, making breast-fed infants more susceptible to warfarin. Vitamin E and cranberry juice may increase warfarin effect. Maintaining a consistent diet and taking warfarin at the same time every day will enhance INR stability; however, developmentally, children's diet will change with age.[90,202]

**Table 9. Starting dose for VKAs by age**

| VKA | Age | Starting dose (mg/kg)* | Frequency |
|---|---|---|---|
| **Warfarin** | | | |
| Standard | 0-18 y | 0.20 | Once daily |
| Fontan | 0-18 y | 0.10 | Once daily |
| Liver dysfunction | 0-18 y | 0.10 | Once daily |
| Acenocoumarol | | | |
| | 2 mo to 1 y | 0.20 | Once daily |
| | >1-5 y | 0.09 | Once daily |
| | 6-10 y | 0.07 | Once daily |
| | 11-18 y | 0.06 | Once daily |
| Phenprocoumon (median dose) | | | |
| | <1 y | 0.15 | Once daily |
| | >1-5 y | 0.09 | Once daily |
| | 6-10 y | 0.13 | Once daily |
| | 11-18 y | 0.08 | Once daily |
| Maintenance dosing for INR target range of 2.0-3.0 | | | |
| | INR | Adjustment | |
| | 1.1-1.4 | Increase dose by 20% | |
| | 1.5-1.9 | Increase dose by 10% | |
| | 2.0-3.0 | No change | |
| | 3.1-3.5 | Decrease dose by 10% | |
| | >3.5 | Hold until INR of <3.5, then restart at 20% of dose | |

*Maximum starting dose, 10 mg.

***AEs.*** The most common AE is bleeding, which can be severe because of the narrow therapeutic index.[202-204] Reported bleeding rates in pediatric studies are highly variable because of varying patient populations.[205-215] When reported, major bleeding occurred in 0% to 5.5% of patients, other bleeding events occurred in 0% to 35.5% of patients, and thrombosis occurred in 0% to 13.8% of patients.

Other less common but reported side effects noted in product labeling include skin necrosis (especially in patients with protein C or protein S deficiencies), vasculitis, dermatitis including livedo reticularis, gastrointestinal symptoms, transaminitis, and hypersensitivity reactions. Reports of postmarketing side effects include alopecia,[216] calcium uremic arteriolopathy,[216,217] tracheobronchial,[217-220] and decreased bone mineral density in children and adolescents receiving long-term (>1 year) VKA therapy.[221-225]

***Periprocedural management.*** Whether to discontinue VKAs in patients undergoing a procedure depends on the degree of invasiveness and expected bleeding. Minor dental or surgical procedures associated with minimal bleeding risk may allow for continuation of VKA; however, coordination with the proceduralist and the provider managing anticoagulation is needed.[225,226] For more invasive procedures, VKA doses should be held 4 to 5 days before the procedure to allow INR values to return to normal. Because of the initial prothrombotic state and delayed onset of anticoagulation with initiation of VKAs, a practice of bridging with a shorter-acting anticoagulant (usually UFH or LMWH) may be instituted. Adult studies have shown that perioperative bridging therapy may not be needed for most patients, especially in light of the fact that it has been shown to lead to a threefold increased risk of major bleeding.[227-230] Adult patients who may require bridging are those at high risk of thrombosis, including patients who have had a recent VTE within the previous month, who have a history of VTE during prior pauses in anticoagulation therapy, or in those who are undergoing a procedure with high inherent risk for VTE.[226] A single-center retrospective study in children reported no instances of major bleeding or thromboembolism in 61 instances of periprocedural interruption in warfarin, whether bridging was instituted or not, and, therefore, the authors suggest bridging only for pediatric patients at high risk for thrombosis.[230,231] Postoperatively, anticoagulation should be initiated as soon as the bleeding risk has declined and it is deemed safe by the proceduralist. For those who are bridging, the bridging agent should be continued until the INR has reached desired therapeutic range.[230,231]

***Management of bleeding.*** Management of bleeding in patients with VTE being treated with VKAs is mostly extrapolated from the adult data. The adult guidelines from the American College of Chest Physicians suggest that for INR between 4.5 and 10 without bleeding, VKAs should be held until the INR returns to the desired range.[232] For INRs of >10 without bleeding, VKAs should be reversed with oral vitamin K. For major bleeding at any INR level, VKAs should be reversed rapidly with IV vitamin K along with an activated prothrombin concentrate.[232] Limited pediatric data have shown that most children on VKAs with supratherapeutic INR values and no bleeding symptoms may be safely monitored with observation alone.[205]

## Rivaroxaban

***Dosing.*** As per license, rivaroxaban use is not recommended in children aged <6 months who were <37 weeks of gestation at birth, had <10 days of full oral feeding, or weigh <2.6 kg. Treatment with ≥5 days of parenteral anticoagulant therapy (UFH, LMWH, or fondaparinux) is recommended before starting rivaroxaban for acute treatment of VTE.[43] Rivaroxaban should be taken with meals, given improved bioavailability noted for higher doses.[233,234] The dosing and frequency of administration in children is based on body weight and is provided in Table 10.

***Monitoring.*** Routine monitoring is typically not required. Rivaroxaban-specific, chromogenic anti-FXa assays are available in some laboratories and can be useful in specific circumstances such as cases of overdose and to monitor compliance.

***AEs.*** In the EINSTEIN-Junior trial, no patient had major bleeding, whereas the rate of CRNMB was noted to be 3%.[43] A higher rate of CRNMB (~19%; 3/16) was reported in an observational study reporting rivaroxaban use for patients with cancer with thrombosis.[235] Of adolescent females enrolled in the EINSTEIN-Junior phase 2 and phase 3 trials, 15% and 19% reported heavy menstrual bleeding, respectively, although real-world data from an American Thrombosis and Hemostasis Network (ATHN) study reported heavy menstrual bleeding in 46% (26/54) of females (aged ≥12 years) receiving rivaroxaban.[43,136,236] Impact of rivaroxaban on bone density is not known.

**Table 10. Rivaroxaban pediatric dosing**

| Dosage form | Body weight | Dosage | | | Total daily dose |
|---|---|---|---|---|---|
| | | Once a day | Twice a day | Three times a day | |
| Oral suspension only | 2.6-2.9 kg | – | – | 0.8 mg | 2.4 mg |
| | 3-3.9 kg | – | – | 0.9 mg | 2.7 mg |
| | 4-4.9 kg | – | – | 1.4 mg | 4.2 mg |
| | 5-6.9 kg | – | – | 1.6 mg | 4.8 mg |
| | 7-7.9 mg | – | – | 1.8 mg | 5.4 mg |
| | 8-8.9 mg | – | – | 2.4 mg | 7.2 mg |
| | 9-9.9 kg | – | – | 2.8 mg | 8.4 mg |
| | 10-11.9 kg | – | – | 3 mg | 9 mg |
| | 12-29.9 mg | – | 5 mg | – | 10 mg |
| Oral suspension or tablets | 30-49.9 kg | 15 mg | – | – | 15 mg |
| | ≥50 kg | 20 mg | – | – | 20 mg |

***Periprocedural management.*** Periprocedural management of rivaroxaban in children has not been studied. The following recommendations have been extrapolated from the Perioperative Anticoagulation Use for Surgery Evaluation study.[237] For low-risk bleeding procedure, pause treatment 24 hours before procedure; for high-risk bleeding procedure, pause treatment 48 hours before procedure. This recommendation does not take into consideration the shorter half-life in younger patients.

***Management of bleeding.*** For major/life-threatening bleeding in younger children, rivaroxaban should be held, and use of a 3- or 4-factor PCC should be considered. Andexanet alfa can be considered in older adolescents with major bleeding on rivaroxaban. Andexanet alfa, an inactive recombinant FXa, sequesters FXa inhibitors including rivaroxaban and is approved for use in adults on rivaroxaban who experience life-threatening hemorrhage.[238] There are no pediatric studies of andexanet alfa. Lastly, activated charcoal should be considered if the last dose of rivaroxaban was administered within the previous 2 hours.

## DE

***Therapeutic range/monitoring.*** Dabigatran etexilate (DE) is licensed for use without the need for monitoring. Although the routine monitoring of dabigatran levels is not recommended, there are certain circumstances in which measuring dabigatran-related anticoagulation activity may be helpful or necessary, such as in cases of overdose or to monitor therapy compliance.[239] The dilute thrombin time is the recommended assay but not widely available. The aPTT, which has the advantage of being widely available, can provide an approximate estimate of the anticoagulant effect of dabigatran; however, the aPTT lacks sensitivity, particularly at higher dabigatran plasma concentrations; thus, results should be interpreted with caution.[240]

***Dosing.*** Dosing of DE depends on age, weight, and formulation, and is provided in Table 11. Oral pellets and capsules cannot be combined or substituted on a milligram-to-milligram basis.

***AEs.*** In the DIVERSITY trial, 77% of children receiving dabigatran reported an AE; most of these were mild to moderate in severity, whereas serious AEs occurred in 13% of children.[44] Headache, vomiting, dyspepsia, and abdominal pain were the most reported AEs in the trial.[44] Any bleeding events were reported in 22% of patients receiving dabigatran, of which major bleeding occurred in 2% and CRNMB in 1% of patients.

***Periprocedural management.*** Duration of DE discontinuing before a surgical procedure is dependent upon renal function. For patients with an estimated GFR of >80 mL/min per $m^2$, a 24-hour hold is recommended; for those with an estimated GFR of 50 to 80 mL/min per $m^2$, a 48-hour hold is recommended.

***Management of bleeding.*** For major/life-threatening bleeding in younger children, DE should be held, and use of 3- or 4-factor PCC should be considered. Idarucizumab can be considered in older adolescents with major bleeding on DE. Idarucizumab is a humanized monoclonal antibody fragment that binds to dabigatran with high affinity, resulting in an immediate, complete, and sustained reversal of its anticoagulant activity.[241] There are no pediatric studies of idarucizumab. Lastly, activated charcoal should be considered if last dose of dabigatran was within the previous 2 hours.

## t-PA

Thrombolysis with an antifibrinolytic agent such as t-PA can be considered when more rapid clot resolution is necessary, but its use comes at a cost of increased bleeding. The use of t-PA is contraindicated in patients with active bleeding, and potential benefits vs harms should be carefully evaluated in the following patients: those having undergone recent surgery (especially intracranial or spinal surgery), recent documented bleeding events, and known central nervous system lesions (eg, tumor, vascular malformation, stroke, or recent trauma). The recombinant products available include alteplase, reteplase, and tenecteplase. Most publications in pediatrics describing the use of thrombolytic therapy have used alteplase (which is most widely available globally) for the treatment of VTE, so we have focused on this agent.

***Dosing.*** Fibrinolytic therapy is administered IV systemically or via multiside, hole catheter directly into the thrombus (CDT). CDT can

**Table 11. Dabigatran pediatric dosing**

| Age of >3 mo to <2 y<br>Oral pellets | Age of 2 y to <12 y<br>Oral pellets | Age of 8 y to <18 y<br>Capsules |
|---|---|---|
| Body weight, 3 to <4 kg (age, 3 to <6 mo): 30 mg bid | Body weight, 7 to <9 kg: 70 mg bid | Body weight, 11 to <16 kg: 75 mg bid |
| Body weight, 4 to <5 kg (age, 3 to <10 mo): 40 mg bid | Body weight, 9 to <11 kg: 90 mg bid | Body weight, 16 to <26 kg: 110 mg bid |
| Body weight, 5 to <7 kg (age, 3 to <5 mo): 40 mg bid | Body weight, 11 to <13 kg: 110 mg bid | Body weight, 26 to <41 kg: 150 mg bid |
| Body weight, 5 to <7 kg (age, 5 to <24 mo): 50 mg bid | Body weight, 13 to <16 kg: 140 mg bid | Body weight, 41 to <61 kg: 185 mg bid |
| Body weight, 7 kg to <9 kg (age, 3 to <4 mo): 50 mg bid | Body weight, 16 to <21 kg: 170 mg bid | Body weight, 61 to <81 kg: 220 mg bid |
| Body weight, 7 kg to <9 kg (age, 4 to <9 mo): 60 mg bid | Body weight, 21 to <41 kg: 220 mg bid | Body weight, ≥81 kg: 260 mg bid |
| Body weight, 7 kg to <9 kg (age, 9 to <24 mo): 70 mg bid | Body weight, ≥41 kg: 260 mg bid | |
| Body weight, 9 kg to <11 kg (age, 5 to <6 mo): 60 mg bid | | |
| Body weight, 9 kg to <11 kg (age, 6 to <11 mo): 80 mg bid | | |
| Body weight, 9 kg to <11 kg (age, 11 to <24 mo): 90 mg bid | | |
| Body weight, 11 to <13 kg (age, 8 to <18 mo): 100 mg bid | | |
| Body weight, 11 to <13 kg (age, 18 to <24 mo): 110 mg bid | | |
| Body weight, 13 to <16 kg (age, 10 to <11 mo): 100 mg bid | | |
| Body weight, 13 to <16 kg (age, 11 to <24 mo): 140 mg bid | | |
| Body weight, 16 kg to <21 kg (age, 12 to <24 mo): 140 mg bid | | |
| Body weight, 21 kg to <26 kg (age, 18 to <24 mo): 180 mg bid | | |

bid, twice a day.

be used in conjunction with mechanical methods of thrombolysis. CDT requires available local resources and expertise. CDT may offer similar rates of thrombus resolution as systemic thrombolysis, with the proposed benefit of lower bleeding risk; however, there is limited evidence for this in both adults and pediatrics

SYSTEMIC THROMBOLYSIS. The US Food and Drug Administration approved adult dosing regimens for systemic thrombolysis using alteplase for the treatment of DVT and PE at a standard dose of 100 mg IV infused over 2 hours. In contrast, the published systemic thrombolysis dosing regimens in children use weight-based dosing at what has been termed "standard doses" or a "low dose" over a longer duration. A usual standard dosing regimen is 0.5 mg/kg per hour over 6 hours, with a range of 0.1 mg/kg per hour to 0.5 mg/kg per hour over 2 to 6 hours.[90,242] Various low-dose regimens have been published and range from 0.01 to 0.06 mg/kg per hour for 12 to 48 hours.[243-245] Wang et al[245] reported that an initial dose rate of 0.01 mg/kg per hour to 0.03 mg/kg per hour is effective for thrombus lysis in most patients; however, neonates required higher doses at 0.06 mg/kg per hour; infusions of FFP are considered in this population because of low levels of plasminogen.[246] A more recent study used a standardized regimen with an initial dose of 0.03 mg/kg per hour for 48 hours, with a maximum dose of 2 mg/kg per hour.[243]

CDT. Usual adult initial dosing of t-PA for DVT is in the range of 0.5 mg/h to 1 mg/h. For children, weight-based dosing of 0.01 to 0.03 mg/kg per hour has been reported with a maximum of 2 mg/h.[247-251] In case series of pediatric patients with PE treated with CDT, weight-based dosing of 0.03 to 0.06 mg/kg per hour up to a maximum dose of 2 mg/h was used.[83,252]

CONCOMITANT ANTICOAGULATION WITH THROMBOLYSIS. There is no consensus for the concomitant use of heparin with thrombolysis. With standard-dose infusions of t-PA, the bleeding risk may be increased with the use of anticoagulation and there is limited experience for its safety. However, in published regimens with low-dose systemic thrombolysis or CDT, UFH is commonly used. Both low-dose UFH (5-10 U/kg per hour) and therapeutic UFH have been reported. Less commonly, LMWH has also been used with thrombolysis but is not usually recommended because of safety concerns, given that LMWH has a longer half-life and is less readily reversible compared with UFH.

***Monitoring.*** There is no therapeutic range for thrombolytic agents; however, fibrinogen levels, aPTT, and prothrombin time are commonly monitored during thrombolytic infusions. t-PA binds to clot-bound fibrin; however, systemic depletion of fibrinogen may be observed. Fibrinogen values of <150 mg/dL have been associated with increased bleeding.

***AEs.*** Between 10% and 40% of patients treated with t-PA will experience major AEs.[253,254] The most common AE is bleeding, and bleeding is more likely in patients who weighed less, had a longer duration of therapy, a greater decrease in fibrinogen levels, and who failed to have resolution of their clot. Hypersensitivity reactions are among the less common AEs described with t-PA use. Allergic reactions have been reported and resolve with conventional treatment methods.

***Periprocedural management.*** Although it has a very short half-life (5 minutes), fibrinolytic effects of t-PA may continue for up to 1 hour after discontinuation. Thus, the infusion should be discontinued accordingly in preparation for any procedure(s).[255,256]

***Management of bleeding.*** If bleeding occurs, the infusion should be stopped immediately. Although there is no direct reversal agent for t-PA, antifibrinolytics such as tranexamic acid and aminocaproic acid have been shown to be effective treatments.

Additionally, in cases of hypofibrinogenemia, fresh frozen plasma or cryoprecipitate may be used. Transfusion of blood products may be administered as appropriate.[90,255,256]

## Limitations of these guidelines

The limitations of these guidelines are inherent in the low or very low certainty in the evidence that we have identified for many of the questions.

## Revision or adaptation of the guidelines

### Plans for updating these guidelines

After publication of these guidelines, ASH/ISTH will maintain them through surveillance for new evidence, ongoing review by experts, and regular revisions.

### Updating or adapting recommendations locally

Adaptation of these guidelines will be necessary in many circumstances. These adaptations should be based on the associated EtD frameworks.[257,258]

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## Authorship

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## References

1. Institute of Medicine. Clinical Practice Guidelines We Can Trust. National Academies Press; 2011.
2. Qaseem A, Forland F, Macbeth F, Ollenschläger G, Phillips S, van der Wees P; Board of Trustees of the Guidelines International Network. Guidelines International Network: toward international standards for clinical practice guidelines. *Ann Intern Med*. 2012;156(7):525-531.
3. Schünemann HJ, Al-Ansary LA, Forland F, et al. Guidelines International Network: principles for disclosure of interests and management of conflicts in guidelines. *Ann Intern Med*. 2015;163(7):548-553.
4. Alonso-Coello P, Oxman AD, Moberg J, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: clinical practice guidelines. *BMJ*. 2016;353:i2089.
5. Alonso-Coello P, Schünemann HJ, Moberg J, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: introduction. *BMJ*. 2016;353:i2016.
6. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. *Br Med J*. 2004;328(7454):1490.
7. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011;64(4):383-394.
8. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *Br Med J*. 2008;336(7650):924-926.
9. Schünemann HJ, Best D, Vist G, Oxman AD; GRADE Working Group. Letters, numbers, symbols and words: how to communicate grades of evidence and recommendations. *CMAJ*. 2003;169(7):677-680.
10. Schünemann HJ, Mustafa R, Brozek J, et al. GRADE guidelines: 16. GRADE evidence to decision frameworks for tests in clinical practice and public health. *J Clin Epidemiol*. 2016;76:89-98.

11. Andrew M, David M, Adams M, et al. Venous thromboembolic complications (VTE) in children: first analyses of the Canadian registry of VTE. *Blood*. 1994;83(5):1251-1257.
12. Gibson BES, Chalmers EA, Bolton-Maggs P, Henderson DJ, Lynn R. Thromboembolism in childhood: a prospective two year BPSU study in the United Kingdom. February 2001-February 2003. *Br J Haematol*. 2004;1:OC422.
13. van Ommen CH, Heijboer H, Büller HR, Hirasing RA, Heijmans HSA, Peters M. Venous thromboembolism in childhood: a prospective two-year registry in The Netherlands. *J Pediatr*. 2001;139(5):676-681.
14. Raffini L, Huang Y-S, Witmer C, Feudtner C. Dramatic increase in venous thromboembolism in children's hospitals in the United States from 2001 to 2007. *Pediatrics*. 2009;124(4):1001-1008.
15. O'Brien SH, Stanek JR, Witmer CM, Raffini L. The continued rise of venous thromboembolism across US children's hospitals. *Pediatrics*. 2022;149(3):24.
16. Jaffray J, Mahajerin A, Young G, et al. A multi-institutional registry of pediatric hospital-acquired thrombosis cases: the Children's Hospital-Acquired Thrombosis (CHAT) project. *Thromb Res*. 2018;161:67-72.
17. Vidal E, Sharathkumar A, Glover J, Faustino EVS. Central venous catheter-related thrombosis and thromboprophylaxis in children: a systematic review and meta-analysis. *J Thromb Haemost*. 2014;12(7):1096-1109.
18. Minford A, Brandão LR, Othman M, et al. Diagnosis and management of severe congenital protein C deficiency (SCPCD): communication from the SSC of the ISTH. *J Thromb Haemost*. 2022;20(7):1735-1743.
19. Minford A, Brandão LR, Othman M, et al. Corrigendum to diagnosis and management of severe congenital protein C deficiency (SCPCD): communication from the SSC of the ISTH [J Thromb Haemost. 2022 Jul;20(7):1735-1743]. *J Thromb Haemost*. 2023;21(4):1069.
20. Nowak-Gottl U, Junker R, Kreuz W, et al. Risk of recurrent venous thrombosis in children with combined prothrombotic risk factors. *Blood*. 2001;97(4):858-862.
21. Whitworth H, Beslow LA, Hubbard RA, et al. Outcomes in infants with unprovoked venous thromboembolism: a retrospective cohort study. *Res Pract Thromb Haemost*. 2023;7(4):100174.
22. Rathbun SW, Aston CE, Whitsett TL. A randomized trial of dalteparin compared with ibuprofen for the treatment of superficial thrombophlebitis. *J Thromb Haemost*. 2012;10(5):833-839.
23. Ortel TL, Neumann I, Ageno W, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. *Blood Adv*. 2020;4(19):4693-4738.
24. Ross C, Kumar R, Pelland-Marcotte MC, et al. Acute management of high-risk and intermediate-risk pulmonary embolism in children: a review. *Chest*. 2022;161(3):791-802.
25. Stevens SM, Woller SC, Kreuziger LB, et al. Antithrombotic therapy for VTE disease: second update of the CHEST guideline and expert panel report. *Chest*. 2021;160(6):e545-e608.
26. Morgan RW, Stinson HR, Wolfe H, et al. Pediatric in-hospital cardiac arrest secondary to acute pulmonary embolism. *Crit Care Med*. 2018;46(3):e229-e234.
27. Pelland-Marcotte M-C, Tucker C, Klaassen A, et al. Outcomes and risk factors of massive and submassive pulmonary embolism in children: a retrospective cohort study. *Lancet Haematol*. 2019;6(3):e144-e153.
28. Monagle P, Adams M, Mahoney M, et al. Outcome of pediatric thromboembolic disease: a report from the Canadian Childhood Thrombophilia Registry. *Pediatr Res*. 2000;47(6):763-766.
29. Polikoff LA, Faustino EV. Venous thromboembolism in critically ill children. *Curr Opin Pediatr*. 2014;26(3):286-291.
30. Witmer CM, Takemoto CM. Pediatric hospital acquired venous thromboembolism. *Front Pediatr*. 2017;5:198.
31. Atkins D, Eccles M, Flottorp S, et al. Systems for grading the quality of evidence and the strength of recommendations I: critical appraisal of existing approaches the GRADE Working Group. *BMC Health Serv Res*. 2004;4(1):38.
32. Schünemann HJ, Wiercioch W, Etxeandia I, et al. Guidelines 2.0: systematic development of a comprehensive checklist for a successful guideline enterprise. *CMAJ*. 2014;186(3):E123-E142.
33. Institute of Medicine. Committee on Conflict of Interest in Medical Research, Education, and Practice. National Academies Press; 2009.
34. Akl EA, El-Hachem P, Abou-Haidar H, Neumann I, Schünemann HJ, Guyatt GH. Considering intellectual, in addition to financial, conflicts of interest proved important in a clinical practice guideline: a descriptive study. *J Clin Epidemiol*. 2014;67(11):1222-1228.
35. Guyatt G, Akl EA, Hirsh J, et al. The vexing problem of guidelines and conflict of interest: a potential solution. *Ann Intern Med*. 2010;152(11):738-741.
36. Schünemann HJ, Osborne M, Moss J, et al. An official American Thoracic Society policy statement: managing conflict of interest in professional societies. *Am J Respir Crit Care Med*. 2009;180(6):564-580.
37. *GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University and Evidence Prime*. 2025. Accessed 30 April 2024. Available at https://gradepro.org
38. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. *J Clin Epidemiol*. 2011;64(4):395-400.
39. Mustafa RA, Garcia CAC, Bhatt M, et al. GRADE notes: how to use GRADE when there is "no" evidence? A case study of the expert evidence approach. *J Clin Epidemiol*. 2021;137:231-235.

40. Chan A, Lensing AWA, Kubitza D, et al. Clinical presentation and therapeutic management of venous thrombosis in young children: a retrospective analysis. *Thromb J*. 2018;16:29.

41. van Ommen H, Bergman K, Boerma M, 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*. 2023;21(4):963-974.

42. Leeper CM, Vissa M, Cooper JD, Malec LM, Gaines BA. Venous thromboembolism in pediatric trauma patients: ten-year experience and long-term follow-up in a tertiary care center. *Pediatr Blood Cancer*. 2017;64(8).

43. Male C, Lensing AWA, Palumbo JS, et al. Rivaroxaban compared with standard anticoagulants for the treatment of acute venous thromboembolism in children: a randomised, controlled, phase 3 trial. *Lancet Haematol*. 2020;7(1):e18-e27.

44. Halton J, Brandão LR, Luciani M, 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*. 2021;8(1):e22-e33.

45. Betensky M, Kulkarni K, Rizzi M, et al. Recommendations for standardized definitions, clinical assessment, and future research in pediatric clinically unsuspected venous thromboembolism: communication from the ISTH SSC Subcommittee on Pediatric and Neonatal Thrombosis and Hemostasis. *J Thromb Haemost*. 2022;20(7):1729-1734.

46. Jones S, Butt W, Monagle P, Cain T, Newall F. The natural history of asymptomatic central venous catheter–related thrombosis in critically ill children. *Blood*. 2019;133(8):857-866.

47. Goldenberg NA, Kittelson JM, Abshire TC, 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*. 2022;327(2):129-137.

48. Hassan E, Khakwani M, Motwani J. Single centre study on safety and efficacy of rivaroxaban in paediatric venous thromboembolism. *Br J Haematol*. 2023;201(S1):119-185.

49. Smith R, Jones S, Newall F. Six weeks versus 3 months of anticoagulant treatment for pediatric central venous catheter-related venous thromboembolism. *J Pediatr Hematol Oncol*. 2017;39(7):518-523.

50. O'Brien SH, Badawy SM, Rotz SJ, et al. The ASH-ASPHO choosing wisely campaign: 5 hematologic tests and treatments to question. *Blood Adv*. 2022;6(2):679-685.

51. Whitworth H, Clark HH, Hubbard RA, Witmer C, Leonard CE, Raffini L. High rate of recurrent venous thromboembolism in children and adolescents with unprovoked venous thromboembolism. *J Thromb Haemost*. 2023;21(1):47-56.

52. Connor P, Sánchez van Kammen M, Lensing AWA, et al. Safety and efficacy of rivaroxaban in pediatric cerebral venous thrombosis (EINSTEIN-Jr CVT). *Blood Adv*. 2020;4(24):6250-6258.

53. Felling RJ, Hassanein SMA, Armstrong J, et al. Treatment and outcome of childhood cerebral sinovenous thrombosis. *Neurol Clin Pract*. 2020;10(3):232-244.

54. Karakas C, Hajiyev Y, Skrehot HC, Kralik SF, Lambert EM, Pehlivan D. Clinical profile and long-term outcomes in pediatric cavernous sinus thrombosis. *Pediatr Neurol*. 2022;130:28-40.

55. Harrar DB, Goss M, Donofrio MT, et al. Cerebral sinus venous thrombosis in infants after aurgery for congenital heart disease. *J Pediatr*. 2022;248:59-65.e3.

56. Petrov D, Uohara MY, Ichord R, et al. Pediatric cerebral sinovenous thrombosis following cranial surgery. *Childs Nerv Syst*. 2017;33(3):491-497.

57. Schneider S, Kapelushnik J, Kraus M, El Saied S, Levi I, Kaplan DM. The association between otogenic lateral sinus thrombosis and thrombophilia – a long-term follow-up. *Am J Otolaryngol*. 2018;39(3):299-302.

58. Rodrigues SG, Vieira D, Bernardo F, et al. Pediatric cerebral sinus venous thrombosis: clinical characterization of a Portuguese cohort. *Acta Neurol Belg*. 2022;122(5):1211-1218.

59. Engelhardt MI, Phan N, Zavala H, Chinnadurai S, Roby BB. Head and neck venous thrombosis secondary to pediatric otolaryngologic infection. *Int J Pediatr Otorhinolaryngol*. 2023;168:111513.

60. Roth H, Ränsch R, Kossorotoff M, et al. Post traumatic cerebral sinovenous thrombosis in children: a retrospective and multicenter study. *Eur J Paediatr Neurol*. 2023;43:12-15.

61. Rong L, Chen L, Dong Z, et al. Analysis of 10 pediatric nephrotic syndrome cases with complications of cerebral sinovenous thrombosis. *Front Pediatr*. 2020;8:607776.

62. Saposnik G, Bushnell C, Coutinho JM, et al. Diagnosis and management of cerebral venous thrombosis: a scientific statement from the American Heart Association. *Stroke*. 2024;55(3):e77-e90.

63. Coutinho JM, Zuurbier SM, Bousser MG, et al. Effect of endovascular treatment with medical management vs standard care on severe cerebral venous thrombosis: the TO-ACT randomized clinical trial. *JAMA Neurol*. 2020;77(8):966-973.

64. Garcia-Nicoletti M, Sinha MD, Savis A, Adalat S, Karunanithy N, Calder F. Silent and dangerous: catheter-associated right atrial thrombus (CRAT) in children on chronic haemodialysis. *Pediatr Nephrol*. 2021;36(5):1245-1254.

65. Agarwal S, Abdelghani E, Stanek JR, et al. Intracardiac thrombi in pediatrics: anticoagulation approach and treatment outcomes. *Res Pract Thromb Haemost*. 2023;7(8):102266.

66. Kara M, Güler M, Keskin Yildirim Z, Tekgunduz K, Laloglu F, Ceviz N. Clinical features and treatment results in preterm infants with intracardiac thrombus. *J Matern Fetal Neonatal Med*. 2021;34(11):1763-1767.

67. Odaman Al I, Oymak Y, Erdem M, et al. Assessment of clinical characteristics and treatment outcomes of pediatric patients with intracardiac thrombosis: a single-center experience. *Blood Coagul Fibrinolysis*. 2022;33(1):34-41.

68. Yang JY, Williams S, Brandão LR, Chan AK. Neonatal and childhood right atrial thrombosis: recognition and a risk-stratified treatment approach. *Blood Coagul Fibrinolysis*. 2010;21(4):301-307.

69. Yang JY, Williams S, Brandão LR, Chan AK, Mondal T. Neonatal and childhood right atrial thrombosis: critical clot size. *Blood Coagul Fibrinolysis*. 2013;24(4):458.

70. Ndoudi Likoho B, Berthaud R, Dossier C, et al. Renal vein thrombosis in neonates: a case series of diagnosis, treatment and childhood kidney function follow-up. *Pediatr Nephrol*. 2023;38(9):3055-3063.

71. Lim C, Alamelu J, Roy S, melhem N, CJ B. Should we heparinise in neonatal renal vein thrombosis (RVT)? A single paediatric tertiary centre experience. IPNA 2022[abstract]. *Pediatr Nephrol*. 2023;38(7):2446.

72. Niada F, Tabin R, Kayemba-Kay's S. Spontaneous neonatal renal vein thromboses: should we treat them all? A report of five cases and a literature review. *Pediatr Neonatol*. 2018;59(3):281-287.

73. Bhatt MD, Patel V, Butt ML, Chan AKC, Paes B; Thrombosis and Hemostasis in Newborns THiN Group. Outcomes following neonatal portal vein thrombosis: a descriptive, single-center study and review of anticoagulant therapy. *Pediatr Blood Cancer*. 2019;66(4):e27572.

74. Cervio C, Hepner M, Bianco B, et al. Portal vein thrombosis (PVT) in neonates and children: a ten-year prospective registry of a tertiary care single-centre in Argentina. *Res Pract Thromb Haemost*. 2021;5(S2):e12591.

75. Solgun HA, Uysalol EP, Bayram C, et al. Neonatal portal vein thrombosis: risk factors, diagnosis, treatment recommendations and review of the literature. *Thromb J*. 2023;21(1):62.

76. Doan P, Cox A, Rao E, Branchford B. Temporal and anatomic relationship between superficial and deep vein thromboses in hospitalized children. *Thromb Res*. 2021;200:30-33.

77. Decousus H, Prandoni P, Mismetti P, et al. Fondaparinux for the treatment of superficial-vein thrombosis in the legs. *N Engl J Med*. 2010;363(13):1222-1232.

78. Superficial Thrombophlebitis Treated By Enoxaparin Study Group. A pilot randomized double-blind comparison of a low-molecular-weight heparin, a nonsteroidal anti-inflammatory agent, and placebo in the treatment of superficial vein thrombosis. *Arch Intern Med*. 2003;163(14):1657-1663.

79. Beyer-Westendorf J, Schellong SM, Gerlach H, et al. Prevention of thromboembolic complications in patients with superficial-vein thrombosis given rivaroxaban or fondaparinux: the open-label, randomised, non-inferiority SURPRISE phase 3b trial. *Lancet Haematol*. 2017;4(3):e105-e113.

80. Menéndez JJ, Verdú C, Calderón B, et al. Incidence and risk factors of superficial and deep vein thrombosis associated with peripherally inserted central catheters in children. *J Thromb Haemost*. 2016;14(11):2158-2168.

81. Di Nisio M, Middeldorp S. Treatment of lower extremity superficial thrombophlebitis. *JAMA*. 2014;311(7):729-730.

82. Wichers IM, Di Nisio M, Büller HR, Middeldorp S. Treatment of superficial vein thrombosis to prevent deep vein thrombosis and pulmonary embolism: a systematic review. *Haematologica*. 2005;90(5):672-677.

83. Ross CE, Shih JA, Kleinman ME, Donnino MW. Pediatric massive and submassive pulmonary embolism: a single-center experience. *Hosp Pediatr*. 2020;10(3):272-276.

84. Jaffray J, Baumann Kreuziger L, Branchford B, et al. Symptomatic pulmonary embolus after catheter removal in children with catheter related thrombosis: a report from the CHAT Consortium. *J Thromb Haemost*. 2022;20(1):133-137.

85. Eghbali A, Rahimi Afzal R, Sheikhbeygloo R, Eghbali A, Taherkhanchi B, Bagheri B. Dabigatran versus warfarin for the treatment of pediatric thromboembolism: a pilot randomized trial. *Pharm Sci*. 2020;26(3):338-342.

86. Gilmore H, Jones S, Monagle P, Monagle S, Newall F. Investigating the experience of parents who have given their infants enoxaparin at home. *Thromb Res*. 2022;214:16-20.

87. Jones S, Mertyn E, Alhucema P, Monagle P, Newall F. HEEADSSS assessment for adolescents requiring anticoagulation therapy. *Arch Dis Child*. 2012;97(5):430-433.

88. Zucker S, Cathey MH. Control of heparin therapy. Sensitivity of the activated partial thromboplastin time for monitoring the antithrombotic effects of heparin. *J Lab Clin Med*. 1969;73(2):320-326.

89. Basu D, Gallus A, Hirsh J, Cade J. A prospective study of the value of monitoring heparin treatment with the activated partial thromboplastin time. *N Engl J Med*. 1972;287(7):324-327.

90. Monagle P, Chan AKC, Goldenberg NA, 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*. 2012;141(suppl 2):e737S-e801S.

91. Toulon P, Smahi M, De Pooter N. APTT therapeutic range for monitoring unfractionated heparin therapy. Significant impact of the anti-Xa reagent used for correlation. *J Thromb Haemost*. 2021;19(8):2002-2006.

92. Ignjatovic V, Summerhayes R, Gan A, et al. Monitoring unfractionated heparin (UFH) therapy: which anti-factor Xa assay is appropriate? *Thromb Res*. 2007;120(3):347-351.

93. Teien AN, Lie M. Evaluation of an amidolytic heparin assay method: increased sensitivity by adding purified antithrombin III. *Thromb Res*. 1977;10(3):399-410.

94. Byun JH, Jang IS, Kim JW, Koh EH. Establishing the heparin therapeutic range using aPTT and anti-Xa measurements for monitoring unfractionated heparin therapy. *Blood Res*. 2016;51(3):171-174.

95. Woods GM, Stanek J, Harrison S, et al. Activated partial thromboplastin time versus anti-factor Xa levels for monitoring unfractionated heparin therapy in children: an institutional experience. *J Pediatr Hematol Oncol*. 2017;39(7):576-577.

96. Ignjatovic V, Furmedge J, Newall F, et al. Age-related differences in heparin response. *Thromb Res*. 2006;118(6):741-745.

97. Ignjatovic V, Summerhayes R, Than J, Gan A, Monagle P. Therapeutic range for unfractionated heparin therapy: age-related differences in response in children. *J Thromb Haemost*. 2006;4(10):2280-2282.

98. Andrew M, Paes B, Johnston M. Development of the hemostatic system in the neonate and young infant. *Am J Pediatr Hematol Oncol*. 1990;12(1):95-104.

99. Andrew M, Paes B, Milner R, et al. Development of the human coagulation system in the healthy premature infant. *Blood*. 1988;72(5):1651-1657.

100. Andrew M, Paes B, Milner R, et al. Development of the human coagulation system in the full-term infant. *Blood*. 1987;70(1):165-172.

101. Hanslik A, Kitzmüller E, Tran US, et al. Monitoring unfractionated heparin in children: a parallel-cohort randomized controlled trial comparing 2 dose protocols. *Blood*. 2015;126(18):2091-2097.

102. Trucco M, Lehmann CU, Mollenkopf N, Streiff MB, Takemoto CM. Retrospective cohort study comparing activated partial thromboplastin time versus anti-factor Xa activity nomograms for therapeutic unfractionated heparin monitoring in pediatrics. *J Thromb Haemost*. 2015;13(5):788-794.

103. McGlasson DL, Kaczor DA, Krasuski RA, Campbell CL, Kostur MR, Adinaro JT. Effects of pre-analytical variables on the anti-activated factor X chromogenic assay when monitoring unfractionated heparin and low molecular weight heparin anticoagulation. *Blood Coagul Fibrinolysis*. 2005;16(3):173-176.

104. Delavenne X, Ollier E, Chollet S, et al. Pharmacokinetic/pharmacodynamic model for unfractionated heparin dosing during cardiopulmonary bypass. *Br J Anaesth*. 2017;118(5):705-712.

105. McDonald MM, Jacobson LJ, Hay WW Jr, Hathaway WE. Heparin clearance in the newborn. *Pediatr Res*. 1981;15(7):1015-1018.

106. McDonald MM, Hathaway WE. Anticoagulant therapy by continuous heparinization in newborn and older infants. *J Pediatr*. 1982;101(3):451-457.

107. Andrew M, Marzinotto V, Massicotte P, et al. Heparin therapy in pediatric patients: a prospective cohort study. *Pediatr Res*. 1994;35(1):78-83.

108. Michelson AD, Bovill E, Andrew M. Antithrombotic therapy in children. *Chest*. 1995;108(suppl 4):506S-522S.

109. Vandiver JW, Vondracek TG. Antifactor Xa levels versus activated partial thromboplastin time for monitoring unfractionated heparin. *Pharmacotherapy*. 2012;32(6):546-558.

110. Kuhle S, Eulmesekian P, Kavanagh B, Massicotte P, Vegh P, Mitchell LG. A clinically significant incidence of bleeding in critically ill children receiving therapeutic doses of unfractionated heparin: a prospective cohort study. *Haematologica*. 2007;92(2):244-247.

111. Avila ML, Shah V, Brandão LR. Systematic review on heparin-induced thrombocytopenia in children: a call to action. *J Thromb Haemost*. 2013;11(4):660-669.

112. Obeng EA, Harney KM, Moniz T, Arnold A, Neufeld EJ, Trenor III CC. Pediatric heparin-induced thrombocytopenia: prevalence, thrombotic risk, and application of the 4Ts scoring system. *J Pediatr*. 2015;166(1):144-150.

113. Boning A, Morschheuser T, Blase U, et al. Incidence of heparin-induced thrombocytopenia and therapeutic strategies in pediatric cardiac surgery. *Ann Thorac Surg*. 2005;79(1):62-65.

114. Hanson SJ, Punzalan RC, Ghanayem N, Havens P. Prevalence of heparin-dependent platelet antibodies in children after cardiopulmonary bypass. *Pediatr Crit Care Med*. 2007;8(4):358-361.

115. Schmugge M, Risch L, Huber AR, Benn A, Fischer JE. Heparin-induced thrombocytopenia-associated thrombosis in pediatric intensive care patients. *Pediatrics*. 2002;109(1):E10.

116. Spadone D, Clark F, James E, Laster J, Hoch J, Silver D. Heparin-induced thrombocytopenia in the newborn. *J Vasc Surg*. 1992;15(2):306-312.

117. Gay J, Le Beller C, Asgari R, et al. Heparin-induced thrombocytopenia in newborns: experience at a pediatric hospital and a literature review. *Res Pract Thromb Haemost*. 2023;7(7):102214.

118. Roesler R, Ward D, Short M. Supporting staff recovery and reintegration after a critical incident resulting in infant death. *Adv Neonatal Care*. 2009;9(4):163-173.

119. Kock HJ, Handschin AE. Osteoblast growth inhibition by unfractionated heparin and by low molecular weight heparins: an in-vitro investigation. *Clin Appl Thromb Hemost*. 2002;8(3):251-255.

120. Khorana AA, Sahni A, Altland OD, Francis CW. Heparin inhibition of endothelial cell proliferation and organization is dependent on molecular weight. *Arterioscler Thromb Vasc Biol*. 2003;23(11):2110-2115.

121. Berkun Y, Haviv YS, Schwartz LB, Shalit M. Heparin-induced recurrent anaphylaxis. *Clin Exp Allergy*. 2004;34(12):1916-1918.

122. Holm HA, Ly B, Handeland GF, et al. Subcutaneous heparin treatment of deep venous thrombosis: a comparison of unfractionated and low molecular weight heparin. *Haemostasis*. 1986;16(suppl 2):30-37.

123. Trame MN, Mitchell L, Krumpel A, Male C, Hempel G, Nowak-Gottl U. Population pharmacokinetics of enoxaparin in infants, children and adolescents during secondary thromboembolic prophylaxis: a cohort study. *J Thromb Haemost*. 2010;8(9):1950-1958.

124. Estepp JH, Smeltzer M, Reiss UM. The impact of quality and duration of enoxaparin therapy on recurrent venous thrombosis in children. *Pediatr Blood Cancer*. 2012;59(1):105-109.

125. Fan JL, Roberts LE, Scheurer ME, Yee DL, Shah MD, Lee-Kim YJ. Association of outcomes and anti-Xa levels in the treatment of pediatric venous thromboembolism. *Pediatr Blood Cancer*. 2017;64(11):2330.

126. Ho SH, Wu JK, Hamilton DP, Dix DB, Wadsworth LD. An assessment of published pediatric dosage guidelines for enoxaparin: a retrospective review. *J Pediatr Hematol Oncol*. 2004;26(9):561-566.

127. Leung M, Ho SH, Hamilton DP, et al. Utility of anti-xa monitoring in children receiving enoxaparin for therapeutic anticoagulation. *J Pediatr Pharmacol Ther*. 2005;10(1):43-50.

128. Musgrave KM, Webber K, Murphy P, Avery P, Biss TT. Evaluation of the age-dependent dosing recommendations for the administration of daily tinzaparin in children with thrombosis. *J Thromb Haemost*. 2017;15(12):2361-2366.

129. O'Brien SH, Kulkarni R, Wallace A, Hamblin F, Burr S, Goldenberg NA. Multicenter dose-finding and efficacy and safety outcomes in neonates and children treated with dalteparin for acute venous thromboembolism. *J Thromb Haemost*. 2014;12(11):1822-1825.

130. Wiltrout K, Lissick J, Raschka M, Nickel A, Watson D. Evaluation of a pediatric enoxaparin dosing protocol and the impact on clinical outcomes. *J Pediatr Pharmacol Ther*. 2020;25(8):689-696.

131. Cuker A, Ptashkin B, Konkle BA, et al. Interlaboratory agreement in the monitoring of unfractionated heparin using the anti-factor Xa-correlated activated partial thromboplastin time. *J Thromb Haemost*. 2009;7(1):80-86.

132. Greene LA, Law C, Jung M, et al. Lack of anti-factor Xa assay standardization results in significant low molecular weight heparin (enoxaparin) dose variation in neonates and children. *J Thromb Haemost*. 2014;12(9):1554-1557.

133. Bhatt M, Hamilton K, Kulkarni K, et al. A pilot feasibility and safety multicenter trial of administering weight adjusted FiXED dose of low molecular weight heparin (ENOXAPARIN) to neonates and children with thrombosis. *Medicine*. 2021;2(2):e0053.

134. Brandao LR, Albisetti M, Halton J, et al. Safety of dabigatran etexilate for the secondary prevention of venous thromboembolism in children. *Blood*. 2020;135(7):491-504.

135. Goldenberg NA, Brandao LR, Male C; Kids-DOTT Trial Investigators. Anticoagulant therapy for 6 weeks vs 3 months and recurrence and bleeding in patients younger than 21 years with provoked venous thromboembolism-reply. *JAMA*. 2022;327(17):1709-1710.

136. Monagle P, Lensing AWA, Thelen K, et al. Bodyweight-adjusted rivaroxaban for children with venous thromboembolism (EINSTEIN-Jr): results from three multicentre, single-arm, phase 2 studies. *Lancet Haematol*. 2019;6(10):e500-e509.

137. Damle B, Jen F, Sherman N, Jani D, Sweeney K. Population pharmacokinetic analysis of dalteparin in pediatric patients with venous thromboembolism. *J Clin Pharmacol*. 2021;61(2):172-180.

138. Fontcuberta Boj J. New frontiers with bemiparin: use in special populations. *Drugs*. 2010;70(suppl 2):43-47.

139. García-Boyano M, Caballero-Caballero JM, Escosa García L, Gutiérrez Alvariño M, Blanco Bañares MJ, Climent Alcalá FJ. Optimal dosing of bemiparin for deep vein thrombosis treatment in children: a retrospective study. *Blood Coagul Fibrinolysis*. 2021;32(7):526-527.

140. Latalski M, Fatyga M, Misztal M, Gregosiewicz A, Danilewicz Bromberek A. Clinical experience with the use of low molecular weight heparin in orthopaedic treatment of paediatric patients. *Ortop Traumatol Rehabil*. 2012;14(4):329-333.

141. Noailly J, Sadozai L, Hurtaud-Roux MF, et al. [Enoxaparin and tinzaparin in pediatrics: impact of recommendation on prescription quality and anti-Xa levels]. *Ann Pharm Fr*. 2021;79(6):710-719.

142. Roeleveld PP, van der Hoeven A, de Wilde RB, Eikenboom J, Smiers FJ, Bunker-Wiersma HE. Higher tinzaparin dosing is needed to achieve target anti-Xa levels in pediatric cardiac intensive care patients. *Pediatr Crit Care Med*. 2016;17(3):203-209.

143. van Ommen CH, van den Dool EJ, Peters M. Nadroparin therapy in pediatric patients with venous thromboembolic disease. *J Pediatr Hematol Oncol*. 2008;30(3):230-234.

144. Iqbal Z, Sadaf S. Commercial low molecular weight heparins - patent ecosystem and technology paradigm for quality characterization. *J Pharm Innov*. 2022;18(2):803-835.

145. Steenman F, Vijlbrief DC, Huisman A, Bierings M. Dalteparin in newborn thrombosis, time for a new starting dose. *Neonatology*. 2021;118(3):345-347.

146. Monagle P, Michelson AD, Bovill E, Andrew M. Antithrombotic therapy in children. *Chest*. 2001;119(suppl 1):344S-370S.

147. Bauman ME, Belletrutti MJ, Bajzar L, et al. Evaluation of enoxaparin dosing requirements in infants and children. Better dosing to achieve therapeutic levels. *Thromb Haemost*. 2009;101(1):86-92.

148. Massicotte P, Adams M, Marzinotto V, Brooker LA, Andrew M. Low-molecular-weight heparin in pediatric patients with thrombotic disease: a dose finding study. *J Pediatr*. 1996;128(3):313-318.

149. Altuwayjiri A, AlDarwish A, Alshuraim R. An evaluation of the appropriateness of initial enoxaparin dosing among pediatric patients. *Cureus*. 2023;15(11):e48830.

150. Andrade-Campos MM, Montes-Limon AE, Fernandez-Mosteirin N, et al. Dosing and monitoring of enoxaparin therapy in children: experience in a tertiary care hospital. *Blood Coagul Fibrinolysis*. 2013;24(2):194-198.

151. Chander A, Nagel K, Wiernikowski J, Paes B, Chan AK; Thrombosis and Hemostasis in Newborns THiN Group. Evaluation of the use of low-molecular-weight heparin in neonates: a retrospective, single-center study. *Clin Appl Thromb Hemost*. 2013;19(5):488-493.

152. Dinh CN, Moffett BS, Galati M, Lee-Kim Y, Yee DL, Mahoney D. A critical evaluation of enoxaparin dose adjustment guidelines in children. *J Pediatr Pharmacol Ther*. 2019;24(2):128-133.

153. Dix D, Andrew M, Marzinotto V, et al. The use of low molecular weight heparin in pediatric patients: a prospective cohort study. *J Pediatr*. 2000;136(4):439-445.

154. Fung LS, Klockau C. Effects of age and weight-based dosing of enoxaparin on anti-factor xa levels in pediatric patients. *J Pediatr Pharmacol Ther*. 2010;15(2):119-125.

155. Ignjatovic V, Najid S, Newall F, Summerhayes R, Monagle P. Dosing and monitoring of enoxaparin (low molecular weight heparin) therapy in children. *Br J Haematol*. 2010;149(5):734-738.

156. Klaassen ILM, Sol JJ, Suijker MH, Fijnvandraat K, van de Wetering MD, Heleen van Ommen C. Are low-molecular-weight heparins safe and effective in children? A systematic review. *Blood Rev*. 2019;33:33-42.

157. Lulic-Botica M, Rajpurkar M, Sabo C, Tutag-Lehr V, Natarajan G. Fluctuations of anti-Xa concentrations during maintenance enoxaparin therapy for neonatal thrombosis. *Acta Paediatr*. 2012;101(4):e147-e150.

158. Malowany JI, Knoppert DC, Chan AK, Pepelassis D, Lee DS. Enoxaparin use in the neonatal intensive care unit: experience over 8 years. *Pharmacotherapy*. 2007;27(9):1263-1271.

159. Malowany JI, Monagle P, Knoppert DC, et al. Enoxaparin for neonatal thrombosis: a call for a higher dose for neonates. *Thromb Res*. 2008;122(6):826-830.

160. Bauman ME, Belletrutti MJ, Bajzar L, et al. Evaluation of enoxaparin dosing requirements in infants and children. *Thromb Haemost*. 2009;101(1):86-92.

161. Michaels LA, Gurian M, Hegyi T, Drachtman RA. Low molecular weight heparin in the treatment of venous and arterial thromboses in the premature infant. *Pediatrics*. 2004;114(3):703-707.

162. Moffett BS, Galati M, Mahoney D, et al. Enoxaparin population pharmacokinetics in the first year of life. *Ther Drug Monit*. 2017;39(6):632-639.

163. Moffett BS, Lee-Kim Y, Galati M, et al. Population pharmacokinetics of enoxaparin in pediatric patients. *Ann Pharmacother*. 2018;52(2):140-146.

164. Sanchez de Toledo J, Gunawardena S, Munoz R, et al. Do neonates, infants and young children need a higher dose of enoxaparin in the cardiac intensive care unit? *Cardiol Young*. 2010;20(2):138-143.

165. Schloemer NJ, Abu-Sultaneh S, Hanson SJ, et al. Higher doses of low-molecular-weight heparin (enoxaparin) are needed to achieve target anti-Xa concentrations in critically ill children. *Pediatr Crit Care Med*. 2014;15(7):e294-e299.

166. Streif W, Goebel G, Chan AK, Massicotte MP. Use of low molecular mass heparin (enoxaparin) in newborn infants: a prospective cohort study of 62 patients. *Arch Dis Child Fetal Neonatal Ed*. 2003;88(5):F365-F370.

167. Wolsey A, Wilcox RA, Olson JA, Boehme S, Anderson CR. Retrospective comparison of two enoxaparin dosing and monitoring protocols at a pediatric hospital. *Am J Health Syst Pharm*. 2019;76(11):815-819.

168. Wysocki EL, Kuhn A, Steinbrenner J, et al. Enoxaparin dose requirements to achieve therapeutic low-molecular-weight heparin anti-factor Xa levels in infants and young children. *J Pediatr Hematol Oncol*. 2021;43(7):e946-e950.

169. Bauman ME, Black KL, Bauman ML, Belletrutti M, Bajzar L, Massicotte MP. Novel uses of insulin syringes to reduce dosing errors: a retrospective chart review of enoxaparin whole milligram dosing. *Thromb Res*. 2009;123(6):845-847.

170. McCormick EW, Parbuoni KA, Huynh D, Morgan JA. Evaluation of enoxaparin dosing and monitoring in pediatric patients at Children's Teaching Hospital. *J Pediatr Pharmacol Ther*. 2015;20(1):33-36.

171. O'Brien SH, Lee H, Ritchey AK. Once-daily enoxaparin in pediatric thromboembolism: a dose finding and pharmacodynamics/pharmacokinetics study. *J Thromb Haemost*. 2007;5(9):1985-1987.

172. Schobess R, During C, Bidlingmaier C, Heinecke A, Merkel N, Nowak-Gottl U. Long-term safety and efficacy data on childhood venous thrombosis treated with a low molecular weight heparin: an open-label pilot study of once-daily versus twice-daily enoxaparin administration. *Haematologica*. 2006;91(12):1701-1704.

173. Gibson A, Montanez N, Addy K, et al. Once-daily compared with twice-daily enoxaparin maintenance therapy appears safe and efficacious in pediatric venous thromboembolism. *J Pediatr Hematol Oncol*. 2023;45(5):e655-e659.

174. Cies JJ, Santos L, Chopra A. IV enoxaparin in pediatric and cardiac ICU patients. *Pediatr Crit Care Med*. 2014;15(2):e95-e103.

175. Crary SE, Van Orden H, Journeycake JM. Experience with intravenous enoxaparin in critically ill infants and children. *Pediatr Crit Care Med*. 2008;9(6):647-649.

176. Diab YA, Ramakrishnan K, Ferrell B, et al. IV versus subcutaneous enoxaparin in critically ill infants and children: comparison of dosing, anticoagulation quality, efficacy, and safety outcomes. *Pediatr Crit Care Med*. 2017;18(5):e207-e214.

177. Streetz VN, Patatanian LK. Intravenous enoxaparin in pediatric burn patients: a case series. *J Pediatr Pharmacol Ther*. 2019;24(5):456-461.

178. Garner MP, Onuoha CP, Fenn NE 3rd. Low-molecular-weight heparin and fondaparinux use in pediatric patients with obesity. *Ann Pharmacother*. 2021;55(5):666-676.

179. Gerhart JG, Carreno FO, Loop MS, et al. Use of real-world data and physiologically-based pharmacokinetic modeling to characterize enoxaparin disposition in children with obesity. *Clin Pharmacol Ther*. 2022;112(2):391-403.

180. Richard AA, Kim S, Moffett BS, Bomgaars L, Mahoney D Jr, Yee DL. Comparison of anti-Xa levels in obese and non-obese pediatric patients receiving treatment doses of enoxaparin. *J Pediatr*. 2013;162(2):293-296.

181. Derbalah A, Duffull S, Sherwin CM, Job K, Al-Sallami H. Optimal dosing of enoxaparin in overweight and obese children. *Br J Clin Pharmacol*. 2022;88(12):5348-5358.

182. Douketis JD, Spyropoulos AC, Murad MH, et al. Perioperative management of antithrombotic therapy: an American College of Chest Physicians clinical practice guideline. *Chest*. 2022;162(5):e207-e243.

183. Crowther MA, Berry LR, Monagle PT, Chan AK. Mechanisms responsible for the failure of protamine to inactivate low-molecular-weight heparin. *Br J Haematol*. 2002;116(1):178-186.

184. Garcia DA, Baglin TP, Weitz JI, Samama MM. Parenteral anticoagulants: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(uppl 2):e24S-e43S.

185. Young G, Yee DL, O'Brien SH, Khanna R, Barbour A, Nugent DJ. FondaKIDS: a prospective pharmacokinetic and safety study of fondaparinux in children between 1 and 18 years of age. *Pediatr Blood Cancer*. 2011;57(6):1049-1054.

186. Monagle P, Chan A, deVeber G, Massicotte MP. *Andrew's Pediatric Thromboembolism and Stroke*. 3rd ed. BC Decker Inc; 2006.

187. Andrew M, Marzinotto V, Brooker LA, et al. Oral anticoagulation therpay in pediatric patients: a prospective study. *Thromb Haemost*. 1994;71(3):265-269.

188. Massicotte MP. Editorial. *Prog Pediatr Cardiol*. 2005;21(1):1.

189. Patricia Massicotte M, Olley Chair P. Evidence based recommendation for anticoagulation in children with congenital heart disease (primary prophylaxis: cardiac catheterization, mechanical heart valves, cardiac shunts, central lines and secondary prophylaxis: systemic thrombosis and stroke). *Prog Pediatr Cardiol*. 2005;21(1):123-127.

190. Ansell J. Out-of-hospital coagulation monitoring and management. *J Thromb Thrombolysis*. 1999;7(2):191-194.

191. Marzinotto V, Monagle P, Chan A, et al. Capillary whole blood monitoring of oral anticoagulants in children in outpatient clinics and the home setting. *Pediatr Cardiol*. 2000;21(4):347-352.

192. Christensen TD, Attermann J, Hjortdal VE, Maegaard M, Hasenkam JM. Self-management of oral anticoagulation in children with congenital heart disease. *Cardiol Young*. 2001;11(3):269-276.

193. Streif W, Andrew M, Marzinotto V, et al. Analysis of warfarin therapy in pediatric patients: a prospective cohort study of 319 patients. *Blood*. 1999;94(9):3007-3014.

194. Newall F, Savoia H, Campbell J, Monagle P. Anticoagulation clinics for children achieve improved warfarin management. *Thromb Res*. 2004;114(1):5-9.

195. Desai H, Farrington E. Anticoagulation with warfarin in pediatrics. *Pediatr Nurs*. 2000;26(2):199-203.

196. Bradbury MJ, Taylor G, Short P, Williams MD. A comparative study of anticoagulant control in patients on long-term warfarin using home and hospital monitoring of the international normalised ratio. *Arch Dis Child*. 2008;93(4):303-306.

197. Mahonen S, Riikonen P, Vaatainen RL, Tikanoja T. Oral anticoagulant treatment in children based on monitoring at home. *Acta Paediatr*. 2004;93(5):687-691.

198. Nowak-Göttl U, Dietrich K, Schaffranek D, et al. In pediatric patients, age has more impact on dosing of vitamin K antagonists than VKORC1 or CYP2C9 genotypes. *Blood*. 2010;116(26):6101-6105.

199. Marek E, Momper JD, Hines RN, et al. Prediction of warfarin dose in pediatric patients: an evaluation of the predictive performance of several models. *J Pediatr Pharmacol Ther*. 2016;21(3):224-232.

200. Bonduel M, Sciuccati G, Hepner M, et al. Acenocoumarol therapy in pediatric patients. *J Thromb Haemost*. 2003;1(8):1740-1743.

201. Spoor N, Smiers FJ, van der Meer FJ, Hutten BA, van Ommen CH. Phenprocoumon and acenocoumarol treatment in paediatric patients. *Thromb Haemost*. 2012;108(6):1238-1241.

202. Monagle P, Chan AKC, Goldenberg NA, et al. Antithrombotic therapy in neonates and children. *Chest*. 2012;141(suppl 2):e737S-e801S.

203. Moffett BS, Kim S, Bomgaars LR. Readmissions for warfarin-related bleeding in pediatric patients after hospital discharge. *Pediatr Blood Cancer*. 2013;60(9):1503-1506.

204. Young G. Anticoagulation therapies in children. *Pediatr Clin North Am*. 2017;64(6):1257-1269.

205. Cohen CT, Zobeck M, Han H, et al. Bleeding outcomes and management of supratherapeutic episodes secondary to warfarin in children: a single center 10-year experience. *Thromb Res*. 2023;228:148-150.

206. Faircloth JM, Miner KM, Alsaied T, et al. Time in therapeutic range as a marker for thrombotic and bleeding outcomes in Fontan patients. *J Thromb Thrombolysis*. 2017;44(1):38-47.

207. Hardin J, Michelson AD, McCrindle BW, et al. Real-world anticoagulant use and incidence of venous thromboembolism and major bleeding in children. *Clin Ther*. 2021;43(12):2074-2087.

208. Harkin M, Shaddix BP, Neely SB, et al. Evaluation of dosing and safety outcomes of low-dose prophylactic warfarin in children after cardiothoracic surgery. *Am J Health Syst Pharm*. 2020;77(13):1018-1025.

209. Ino N, Masutani S, Tanikawa S, et al. Effects of home prothrombin international ratio (PT-INR) management in children with mechanical prosthetic valves – importance of individual correlations between laboratory and CoaguChek device PT-INRs. *J Cardiol*. 2018;71:187-191.

210. Jeremiasen I, Hanséus K, Naumann P, et al. Establishing a regional paediatric registry improved the overview and detection of side effects in children on anticoagulants. *Acta Paediatr*. 2018;107(1):166-167.

211. Jones S, Hislop J, Allan A, et al. Guiding warfarin self-management in children: development of a warfarin nomogram. *Res Pract Thromb Haemost*. 2023;7(8):102255.

212. Jones S, Hislop JL, Gilmore H, et al. Using an electronic medical record patient portal for warfarin self-management: empowering children and parents. *Res Pract Thromb Haemost*. 2023;7(2):100066.

213. Maagdenberg H, Bierings MB, van Ommen CH, et al. Characteristics and quality of oral anticoagulation treatment in pediatric patients in the Netherlands based on the CAPS cohort. *J Thromb Haemost*. 2018;16(1):116-124.

214. Miwa K, Iwai S, Nagashima T. Anticoagulation therapy after the Fontan procedure. *Pediatr Cardiol*. 2022;43(6):1271-1276.

215. Rodriguez V, Stanek J, Cua CL, et al. A regional anticoagulation program improves safety and outcomes for both children and adults. *J Thromb Thrombolysis*. 2023;56(1):27-36.

216. Watras MM, Patel JP, Arya R. Traditional anticoagulants and hair loss: a role for direct oral anticoagulants? A review of the literature. *Drugs Real World Outcomes*. 2016;3(1):1-6.

217. Yu WY, Bhutani T, Kornik R, et al. Warfarin-associated nonuremic calciphylaxis. *JAMA Dermatol*. 2017;153(3):309-314.

218. Eckersley L, Stirling J, Occleshaw C, Wilson N. Two cases of Warfarin-induced tracheobronchial calcification after Fontan surgery. *Pediatr Cardiol*. 2014;35(6):954-958.

219. Golding LP, Walsh MJ, Sumner TE, Nakagawa TA. Tracheobronchial calcifications in children. *Pediatr Radiol*. 2013;43(8):937-940.

220. Kansara T, Tornay J, Agarwal S. Warfarin-associated tracheobronchial calcification. *Am J Ther*. 2019;26(6):e787-e788.

221. Attard C, Monagle PT, d'Udekem Y, et al. Long-term outcomes of warfarin versus aspirin after Fontan surgery. *J Thorac Cardiovasc Surg*. 2021;162(4):1218-1228.e1213.

222. Barnes C, Newall F, Ignjatovic V, et al. Reduced bone density in children on long-term warfarin. *Pediatr Res*. 2005;57(4):578-581.

223. Bendaly EA, DiMeglio LA, Fadel WF, Hurwitz RA. Bone density in children with single ventricle physiology. *Pediatr Cardiol*. 2015;36(4):779-785.

224. Hepponstall M, Chan A, Monagle P. Anticoagulation therapy in neonates, children and adolescents. *Blood Cells Mol Dis*. 2017;67:41-47.

225. Signorelli SS, Scuto S, Marino E, Giusti M, Xourafa A, Gaudio A. Anticoagulants and osteoporosis. *Int J Mol Sci*. 2019;20(21):5275.

226. Witt DM, Clark NP, Kaatz S, Schnurr T, Ansell JE. Guidance for the practical management of warfarin therapy in the treatment of venous thromboembolism. *J Thromb Thrombolysis*. 2016;41(1):187-205.

227. Clark NP, Witt DM, Davies LE, et al. Bleeding, recurrent venous thromboembolism, and mortality risks during warfarin interruption for invasive procedures. *JAMA Intern Med*. 2015;175(7):1163-1168.

228. Douketis JD, Spyropoulos AC, Kaatz S, et al. Perioperative bridging anticoagulation in patients with atrial fibrillation. *N Engl J Med*. 2015;373(9):823-833.

229. Siegal D, Yudin J, Kaatz S, Douketis JD, Lim W, Spyropoulos AC. Periprocedural heparin bridging in patients receiving vitamin K antagonists: systematic review and meta-analysis of bleeding and thromboembolic rates. *Circulation*. 2012;126(13):1630-1639.

230. Steinberg BA, Peterson ED, Kim S, et al. Use and outcomes associated with bridging during anticoagulation interruptions in patients with atrial fibrillation: findings from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *Circulation*. 2015;131(5):488-494.

231. Campbell S, Monagle P, Newall F. Oral anticoagulant therapy interruption in children: a single centre experience. *Thromb Res*. 2016;140:89-93.

232. Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(suppl 2):e152S-e184S.

233. Bratsos S. Pharmacokinetic properties of rivaroxaban in healthy human subjects. *Cureus*. 2019;11(8):e5484.

234. Kreutz R. Pharmacokinetics and pharmacodynamics of rivaroxaban–an oral, direct factor Xa inhibitor. *Curr Clin Pharmacol*. 2014;9(1):75-83.

235. Barg AA, Levy-Mendelovich S, Gilad O, et al. Rivaroxaban treatment among children with cancer-associated thromboembolism: real-world data. *Pediatr Blood Cancer*. 2022;69(10):e29888.

236. Corrales-Medina FF, Raffini L, Recht M, Santos J, Thornburg CD, Davila J. Direct oral anticoagulants in pediatric venous thromboembolism: experience in specialized pediatric hemostasis centers in the United States. *Res Pract Thromb Haemost*. 2023;7(1):100001.

237. Douketis JD, Spyropoulos AC, Duncan J, et al. Perioperative management of patients with atrial fibrillation receiving a direct oral anticoagulant. *JAMA Intern Med*. 2019;179(11):1469-1478.

238. Connolly SJ, Crowther M, Eikelboom JW, et al. Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors. *N Engl J Med*. 2019;380(14):1326-1335.

239. Mitchell LG, Röshammar D, Huang F, et al. Anticoagulant effects of dabigatran on coagulation laboratory parameters in pediatric patients: combined data from five pediatric clinical trials. *Thromb Haemost*. 2022;122(9):1573-1583.

240. Pradaxa, international non-proprietary name: dabigatran etexilate. European Medicines Agency, 12 November 2020. Accessed 30 April 2024. https://www.ema.europa.eu/en/documents/variation-report/pradaxa-h-c-829-x-0122-g-epar-assessment-report-extension_en.pdf

241. Glund S, Moschetti V, Norris S, et al. A randomised study in healthy volunteers to investigate the safety, tolerability and pharmacokinetics of idarucizumab, a specific antidote to dabigatran. *Thromb Haemost*. 2015;113(5):943-951.

242. Giglia TM, Massicotte MP, Tweddell JS, et al. Prevention and treatment of thrombosis in pediatric and congenital heart disease: a scientific statement from the American Heart Association. *Circulation*. 2013;128(24):2622-2703.

243. Goldenberg NA, Durham JD, Knapp-Clevenger R, Manco-Johnson MJ. A thrombolytic regimen for high-risk deep venous thrombosis may substantially reduce the risk of postthrombotic syndrome in children. *Blood*. 2007;110(1):45-53.

244. Leary SE, Harrod VL, de Alarcon PA, Reiss UM. Low-dose systemic thrombolytic therapy for deep vein thrombosis in pediatric patients. *J Pediatr Hematol Oncol*. 2010;32(2):97-102.

245. Wang M, Hays T, Balasa V, et al. Low-dose tissue plasminogen activator thrombolysis in children. *J Pediatr Hematol Oncol*. 2003;25(5):379-386.

246. Pennica D, Holmes WE, Kohr WJ, et al. Cloning and expression of human tissue-type plasminogen activator cDNA in E. coli. *Nature*. 1983;301(5897):214-221.

247. Cohen CT, Sartain SE, Sangi-Haghpeykar H, Kukreja KU, Desai SB. Clinical characteristics and outcomes of combined thrombolysis and anticoagulation for pediatric and young adult lower extremity and inferior vena cava thrombosis. *Pediatr Hematol Oncol*. 2021;38(6):528-542.

248. Dandoy CE, Kukreja KU, Gruppo RA, Patel MN, Tarango C. Outcomes in children with deep vein thrombosis managed with percutaneous endovascular thrombolysis. *Pediatr Radiol*. 2015;45(5):719-726.

249. Gaballah M, Shi J, Kukreja K, et al. Endovascular thrombolysis in the management of iliofemoral thrombosis in children: a multi-institutional experience. *J Vasc Interv Radiol*. 2016;27(4):524-530.

250. Kukreja KU, Lungren MP, Patel MN, et al. Endovascular venous thrombolysis in children younger than 24 months. *J Vasc Interv Radiol*. 2014;25(8):1158-1164.

251. Lungren MP, Ward TJ, Patel MN, Racadio JM, Kukreja K. Endovascular thrombolysis to salvage central venous access in children with catheter-associated upper extremity deep vein thrombosis: technique and initial results. *J Thromb Thrombolysis*. 2015;40(3):274-279.

252. Belsky J, Warren P, Stanek J, Kumar R. Catheter-directed thrombolysis for submassive pulmonary embolism in children: a case series. *Pediatr Blood Cancer*. 2020;67(4):e28144.

253. Gupta AA, Leaker M, Andrew M, et al. Safety and outcomes of thrombolysis with tissue plasminogen activator for treatment of intravascular thrombosis in children. *J Pediatr*. 2001;139(5):682-688.

254. Newall F, Browne M, Savoia H, Campbell J, Barnes C, Monagle P. Assessing the outcome of systemic tissue plasminogen activator for the management of venous and arterial thrombosis in pediatrics. *J Pediatr Hematol Oncol*. 2007;29(4):269-273.

255. Hughes R, Tadi P, Bollu P. TPA Therapy. In: *StatPearls*. StatPearls Publishing; 2023.

256. Semba CP, Bakal CW, Calis KA, et al. Alteplase as an alternative to urokinase. Advisory panel on catheter-directed thrombolytic therapy. *J Vasc Interv Radiol*. 2000;11(3):279-287.

257. Schünemann HJ, Wiercioch W, Brozek J, et al. GRADE Evidence to Decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations: GRADE-ADOLOPMENT. *J Clin Epidemiol*. 2017;81:101-110.

258. Monagle P, Male C, Raffini L. The value of the old and the new. *Blood Adv*. 2023;7(14):3683-3685.