CLINICAL GUIDELINES

blood advances

# American Society of Hematology 2018 Guidelines for management of venous thromboembolism: treatment of pediatric venous thromboembolism

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**Background:** Despite an increasing incidence of venous thromboembolism (VTE) in pediatric patients in tertiary care settings, relatively few pediatric physicians have experience with antithrombotic interventions.

**Objective:** These guidelines of the American Society of Hematology (ASH), based on the best available evidence, are intended to support patients, clinicians, and other health care professionals in their decisions about management of pediatric VTE.

**Methods:** ASH formed a multidisciplinary guideline panel that included 2 patient representatives and was balanced to minimize potential bias from conflicts of interest. The McMaster University GRADE Centre supported the guideline-development process, including updating or performing systematic evidence reviews (up to April of 2017). The panel prioritized clinical questions and outcomes according to their importance for clinicians and patients. The panel used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach, including GRADE Evidence-to-Decision frameworks, to assess evidence and make recommendations, which were subject to public comment.

**Results:** The panel agreed on 30 recommendations, covering symptomatic and asymptomatic deep vein thrombosis, with specific focus on management of central venous access device–associated VTE. The panel also addressed renal and portal vein thrombosis, cerebral sino venous thrombosis, and homozygous protein C deficiency.

**Conclusions:** Although the panel offered many recommendations, additional research is required. Priorities include understanding the natural history of asymptomatic thrombosis, determining subgroup boundaries that enable risk stratification of children for escalation of treatment, and appropriate study of newer anticoagulant agents in children.

## Summary of recommendations

These guidelines are based on updated and original systematic reviews of evidence conducted by researchers and developed under the direction of the McMaster University GRADE Centre with

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Resources for implementing these guidelines, including apps, patient decision aids, and teaching slide sets, may be accessed at the ASH Web page hematology.org/vte

The full-text version of this article contains a data supplement.

international collaborators. The panel followed best practice for guideline development recommended by the Institute of Medicine and the Guidelines International Network.[1-4] The panel used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach[5,6] to assess quality of evidence and formulate recommendations. There are many aspects to the diagnosis, treatment, and management of thromboembolic disease in children; however, the panel focused on the treatment of venous thromboembolism (VTE).

The incidence of VTE in children at a population level is very low, reported to be 0.07 to 0.14 per 10 000 children.[7-10] However, in hospitalized children the rate is increased 100 to 1000 times, to ≥58 per 10 000 admissions.[11] Thus, despite some exceptions, venous thrombosis should be considered a disease of sick children. The commonest age groups for VTE are neonates and teenagers, and this reflects the pattern of associated underlying diseases and interventions. The most common precipitating factor is the presence of a central venous access device (CVAD), which is related to almost 90% of VTE in neonates and >60% in older children.[7] Although rare, spontaneous thrombosis in previously well children can often present the most challenging treatment dilemmas. The natural history of many types of VTE in children remains unclear. There are no anticoagulant drugs approved for use in children, with very little specific research in children. Much of the evidence for treatment is extrapolated from adult practice, despite the major differences between adults and children in the epidemiology and pathophysiology of thrombosis, the physiology of the coagulation system, and the impact of this on the pharmacology of antithrombotic agents. The recommendations within these guidelines address questions predominantly of whether to treat and which type of treatment is optimal for given clinical situations. They do not address the optimal use of particular therapeutic agents in terms of dose, intensity, or duration (with a couple of exceptions) or monitoring strategies. When referring to anticoagulation treatment, the panel is referring to unfractionated heparin, low-molecular-weight heparin, fondaparinux, or vitamin K antagonists, because these drugs are currently used in children, and there are published safety data for each. An a priori decision was made that the direct oral anticoagulants (eg, dabigatran, rivaroxaban, apixaban) were out of scope for these recommendations, because these remain investigational in children, given no published pharmacokinetics, safety, or efficacy studies, although the panel noted that many such trials are ongoing. In that context, the panel believed that direct oral anticoagulants should only be used within the context of formal clinical trials.

In general, the panel preferred to word recommendations as "against" an intervention rather than "for" the comparator, primarily for ease of understanding about the intention of the recommendation.

### Interpretation of strong and conditional recommendations

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

***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 policy makers: 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 recommendation.

***Conditional recommendation***

- For patients: the majority of 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 individuals risks, values, and preferences.
- For clinicians: different choices will be appropriate for individual patients, and clinicians 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 policy makers: policy making 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 to identify possible research gaps.

## Recommendations

### Anticoagulation in symptomatic and asymptomatic deep vein thrombosis or pulmonary embolism

***Recommendation 1.*** The American Society of Hematology (ASH) guideline panel *recommends* using anticoagulation rather than no anticoagulation in pediatric patients with symptomatic deep vein thrombosis (DVT) or pulmonary embolism (PE) (strong recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remarks:** Although there remains limited direct evidence in children, there is very strong indirect evidence from adults that symptomatic VTE requires treatment. Further, given that the majority of VTEs occur in sick hospitalized children, in whom VTE is often life-threatening, low-quality evidence suggesting benefit justifies a strong recommendation. Hence, the panel made a strong recommendation based on extrapolation from adults, as well as potential consequences of symptomatic VTE in children, despite low certainty of evidence.

***Recommendation 2.*** The ASH guideline panel *suggests* either using anticoagulation or no anticoagulation in pediatric patients with asymptomatic DVT or PE (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remarks:** The adult data would suggest that treatment of most asymptomatic VTE is not required. However, there are major epidemiological, anatomical, and pathophysiological differences between VTE in adults and children that make extrapolation in this regard very difficult. The unknown benefits of anticoagulation therapy relative to the known potential risks associated with therapy do not support routine radiological screening for asymptomatic VTE. However, if detected, the decision to treat or not treat should be individualized. Research to understand the natural history of asymptomatic VTE in a variety of subgroups is a high priority.

## Thrombolysis, thrombectomy, and inferior vena cava filters

***Recommendation 3.*** The ASH guideline panel *suggests against* using thrombolysis followed by anticoagulation; rather, anticoagulation alone should be used in pediatric patients with DVT (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remarks:** The panel considered issues such as the size and clinical impact of VTE as important in deciding the relative risk benefit ratio of thrombolysis. In most cases, the risks seem too high for the potential benefit; however, there may be individuals in whom the opposite is true. Extrapolation of adult data was difficult. There are insufficient data to address the relative risk 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.

***Recommendation 4.*** The ASH guideline panel *suggests against* using thrombolysis followed by anticoagulation; rather, anticoagulation alone should be used in pediatric patients with submassive PE (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remarks:** The panel considered submassive PE to represent children with PE who did not have hemodynamic instability. There were minimal pediatric data, and review of adult data revealed considerable uncertainty that was complicated by limitations in ability to extrapolate. The panel concluded the risks outweighed the benefits in most cases; hence, a conditional recommendation against thrombolysis.

***Recommendation 5.*** The ASH guideline panel *suggests* using thrombolysis followed by anticoagulation, rather than anticoagulation alone, in pediatric patients with PE with hemodynamic compromise (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remarks:** The panel considered PE with hemodynamic compromise to be life-threatening with limited time to respond to standard anticoagulation and so conditionally recommended thrombolysis in addition to anticoagulation based predominantly on extrapolation of adult data.

***Recommendation 6.*** The ASH guideline panel *suggests against* using thrombectomy followed by anticoagulation; rather, anticoagulation alone should be used in pediatric patients with symptomatic DVT or PE (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remarks:** The panel recognized that, in certain cases (eg, with cardiovascular compromise secondary to the VTE), thrombectomy may be appropriate; however, 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.

***Recommendation 7.*** The ASH guideline panel *suggests against* using inferior vena cava (IVC) filter; rather anticoagulation alone should be used in pediatric patients with symptomatic DVT or PE (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remarks:** The panel considered the benefits vs risks involved in IVC filter use and determined that their use should be reserved for certain cases (eg, patients with DVT and absolute contraindication to anticoagulation or 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 are appropriate. It is not feasible to place IVC filters in children who weigh <10 kg.

## Antithrombin replacement therapy

***Recommendation 8a.*** The ASH guideline panel *suggests against* using antithrombin (AT)-replacement therapy in addition to standard anticoagulation; rather, standard anticoagulation alone should be used in pediatric patients with DVT/cerebral sino venous thrombosis (CSVT)/PE (conditional recommendation based on very low certainty in the evidence of 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; based on the prophylactic studies, there is little evidence of clinical benefit and perhaps evidence of clinical harm. This recommendation is independent of the plasma AT level in the patient, which should not be routinely measured.

***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 of effects ⊕◯◯◯). **Remarks:** Despite the overall recommendation against AT use, the panel considered several subgroups and specific situations in which they agreed that AT use might be justified. The first is 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 (ALL) on induction using asparaginase, children with nephrotic syndrome, neonates, postliver transplant patients, and children with disseminated intravascular coagulation and VTE. Usually, AT use would be commenced if there were continuous thrombus growth and/or failure of clinical response, despite adequate anticoagulation. However, there was 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 of 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.

***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 of effects ⊕◯◯◯). **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 of evidence for benefits based on high evidence of harm or high cost.

***Recommendation 11.*** The ASH guideline panel *suggests* delayed removal of a CVAD until after initiation of anticoagulation (days), rather than immediate removal in pediatric patients with symptomatic central venous line–related thrombosis who no longer require venous access or in whom the CVAD is nonfunctioning (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remarks:** The panel placed high value on avoiding potential risk of emboli leading to PE or paradoxical stroke, and this was thought to be achieved by a few days of anticoagulation. The risk of infection and bleeding with anticoagulation before removing the CVAD was considered to be small. The panel recognized that surgical availability was often a pragmatic determinant of timing of CVAD removal.

***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 of effects ⊕◯◯◯). **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 the setting of worsening VTE symptoms, despite anticoagulation, is appropriate. However, in some children, venous access is paramount.

## Low-molecular-weight heparin vs vitamin K antagonists

***Recommendation 13.*** The ASH guideline panel *suggests* using either low-molecular-weight heparin or vitamin K antagonists in pediatric patients with symptomatic DVT or PE (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remarks:** The decision should depend on patient values and preferences, health services resources, infrastructure and support, and underlying condition, comorbidities, and other medications.

## Provoked DVT or PE

***Recommendation 14.*** The ASH guideline panel *suggests* using anticoagulation for ≤3 months rather than anticoagulation for >3 months in pediatric patients with provoked DVT or PE (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remarks:** The panel noted that the exact duration for optimal anticoagulation was unknown, and there are ongoing studies comparing durations within this time frame. In cases in which the provoking factor is resolved, treatment for >3 months is unjustified. However, for patients who have persistence of the causative risk factor for provoked DVT/PE, longer anticoagulation could be considered.

## Unprovoked DVT or PE

***Recommendation 15.*** The ASH guideline panel *suggests* using anticoagulation for 6 to 12 months rather than anticoagulation for >6 to 12 months in pediatric patients with unprovoked DVT or PE (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remarks:** There were little pediatric data. Extrapolation of adult data might favor prolonged treatment periods in terms of VTE recurrence. However, the bleeding risk and impact on quality of life of prolonged therapy were judged to be significantly higher in children compared with adults. Patient values and preferences should be considered.

## CVAD-related superficial vein thrombosis

***Recommendation 16.*** The ASH guideline panel *suggests* using either anticoagulation or no anticoagulation in pediatric patients with CVAD-related superficial vein thrombosis (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remarks:** There were very little direct or indirect data on which to base this recommendation. The collective experience of the panel suggested that, in most patients, no anticoagulation will be appropriate. However, anticoagulation seems appropriate for patients who have a CVAD line that is still functioning and who continue to need venous access, as well as in patients whose symptoms progress.

## Right atrial thrombosis

***Recommendation 17.*** The ASH guideline panel *suggests* using anticoagulation, rather than no anticoagulation, in pediatric patients with right atrial thrombosis (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remarks:** The panel was unable to distinguish between symptomatic and asymptomatic VTE in this instance, because many right atrial thromboses are discovered during routine imaging, especially in cardiac surgical patients. Factors, such as size and mobility of the thrombus, patient's hemodynamic status, and bleeding risk, are important considerations, but there are insufficient data to define specific subgroup effects.

***Recommendation 18.*** The ASH guideline panel *suggests against* using thrombolysis or surgical thrombectomy followed by standard anticoagulation; rather, anticoagulation alone should be used in pediatric patients with right atrial thrombosis (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 of thrombectomy vs

thrombolysis will depend on patient and family acceptability and feasibility of the interventions.

## Renal vein thrombosis

***Recommendation 19.*** The ASH guideline panel *suggests* using anticoagulation, rather than no anticoagulation, in neonates with renal vein thrombosis (RVT) (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remarks:** The panel considers the intervention to have a potential beneficial effect if the long-term benefits of avoiding hypertension and/or renal damage are considered. Anticoagulation is likely more important with bilateral compared with unilateral involvement or with progression to the inferior vena cava. Severity of disease, age, gestational age, and degree of thrombocytopenia will impact bleeding risk with treatment.

***Recommendation 20a.*** The ASH guideline panel *recommends against* using thrombolysis followed by standard anticoagulation; rather, anticoagulation alone should be used in neonates with non–life-threatening RVT (strong recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remarks:** All evidence comes from observational studies in which patients who are treated with thrombolytics are typically more unwell and have bilateral RVT, as well as inferior vena cava involvement; studies did not adjust for these factors, and causation is difficult to ascertain. However, the panel placed a high value on avoiding the potential bleeding risks of thrombolysis, especially in neonates, and so made this recommendation for cases with very low mortality risk (ie, unilateral RVT). Therefore, the panel made a strong recommendation due to high-quality evidence for harm or high costs, despite very low–quality evidence for benefit.

***Recommendation 20b.*** The ASH guideline panel *suggests* using thrombolysis followed by standard anticoagulation rather than anticoagulation alone in neonates with life-threatening RVT (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remarks:** When the condition is life-threatening (ie, bilateral thrombosis), the panel considered that the beneficial effects of thrombolysis would outweigh the undesirable consequences of the intervention.

## Portal vein thrombosis

***Recommendation 21a.*** The ASH guideline panel *suggests* using anticoagulation, rather than no anticoagulation, in pediatric patients with portal vein thrombosis (PVT) with occlusive thrombus, postliver transplant, and idiopathic PVT (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

***Recommendation 21b.*** The ASH guideline panel *suggests* using no anticoagulation, rather than anticoagulation, in pediatric patients with PVT with nonocclusive thrombus or portal hypertension (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remarks for recommendations 21a and 21b:** In children who will not be anticoagulated, follow-up monitoring is important, because extension of thrombus or organ dysfunction may require reconsideration of treatment options.

## CSVT

***Recommendation 22a.*** The ASH guideline panel *recommends* using anticoagulation, rather than no anticoagulation, in pediatric patients with CSVT without hemorrhage (strong recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remarks:** The panel determined that, even in the presence of very low certainty in the evidence, the magnitude and direction of effect, in addition to indirect evidence from adult patients with the same direction of effect, support a strong recommendation because this is a life-threatening situation.

***Recommendation 22b.*** The ASH guideline panel *suggests* using anticoagulation, rather than no anticoagulation, in pediatric patients with CSVT with hemorrhage (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remarks:** Patients with intracerebral hemorrhage were included in the identified studies with lack of specific evidence; the panel's collective expertise suggests that patients with hemorrhagic CSVT have worse outcomes, leading to this recommendation as conditional.

***Recommendation 23.*** The ASH guideline panel *suggests against* using thrombolysis followed by standard anticoagulation; rather, anticoagulation alone should be used in pediatric patients with CSVT (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remarks:** The evidence does not clearly separate systemic vs catheter-directed thrombolysis. Patients who receive thrombolytics are likely to be sicker with worse outcomes, which leads to very low certainty in the evidence. However, there were insufficient data to support specific subgroups who would benefit from the intervention. Based on the panel's collective experience, for children with CSVT without evidence of ischemia, there is no rationale for using thrombolysis.

## 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 of 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.

***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 homozygous protein C deficiency (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **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, 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.

***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 of effects ⊕◯◯◯). **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.

### 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.

## Introduction

### Aims of these guidelines and specific objectives

The purpose of these guidelines is to provide evidence-based recommendations about the management of VTE in neonates and children. Subsequent guidelines will provide evidence-based recommendations about the optimization of antithrombotic therapy in neonates and children, as well as diagnosis of and prophylaxis for VTE in neonates and children. The target audience includes patients, hematologists, neonatologists and pediatricians, other clinicians, and decision-makers. Policy makers interested in these guidelines include those involved in developing local, national, or international plans with the goal to reduce the incidence of and manage VTE and evaluate direct and indirect harms and costs related to VTE. This document 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 severe problem because of the potential for associated mortality and significant complications, including PE, cerebrovascular events, and postthrombotic syndrome (PTS).[12,13] VTE occurs when ≥1 component of Virchow's triad is activated: stasis of blood flow, injury to the endothelial lining, or hypercoagulability of blood components. This is the most useful pathophysiological construct for thinking about thromboembolism in children.[14]

Over recent years, there has been a dramatic increase in available information, knowledge, and expertise in relation to appropriate diagnosis, prevention, and clinical management of VTE in neonates and children. However, there remain many unknowns, and large data registries and ongoing studies will hopefully continue to improve our knowledge.

Patient registries from Canada, the United States, and The Netherlands have reported anywhere from 0.07 to 0.49 VTE per 10 000 children aged between 1 month and 18 years, with a peak in children younger than 1 year of age and a second peak in the adolescent group.[7-10] If one considers hospitalized children, the rate is 100 to 1000 times the population rate: ≥58 per 10 000 admissions.[11] Thus, despite some exceptions, venous thrombosis should be considered a disease of hospitalized children.[14] More than 90% of cases of pediatric VTE have >1 risk factor, with venous access devices being the most common single risk factor and accounting for >90% of neonatal VTE and >50% of pediatric VTE.[15]

The natural history of VTE in children remains unclear in many circumstances. The reported VTE mortality from registry data is ~3%, in the context of ~16% of children dying from their underlying illness.[7] The recurrence risk is reported to be up to 10% to 15%. Reports of PTS vary from 10% to 60%, depending on the tools used to assess for it, and there remains great controversy as to the clinical implications of PTS in many children.[16]

## Methods

The guideline panel developed and graded the recommendations and assessed the certainty in the supporting evidence following the GRADE approach.[5,6] 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 Guidelines International Network–McMaster Guideline Development Checklist (http://cebgrade.mcmaster.ca/guidecheck.html) and intended to meet recommendations for trustworthy guidelines by the Institute of Medicine and the Guidelines International Network.[1-4] An article detailing the methods used to develop these guidelines is forthcoming.

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

The work of this panel was coordinated with that of 9 other guideline panels (addressing other aspects of VTE) by ASH and the McMaster University GRADE Centre (funded by ASH under a paid agreement). Project oversight was provided initially by a coordination panel, which reported to the ASH Committee on Quality, and then by the coordination panel chair (Adam Cuker) and vice-chair (Holger Schünemann). ASH vetted and appointed individuals to the guideline panel. The McMaster University GRADE Centre 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 panel and the GRADE center team is described in Supplement 1.

The panel included 9 pediatric hematologists, a pediatric intensivist, a pediatric cardiologist, a pediatric hematology pharmacist, and an anticoagulation nurse practitioner, all of whom had clinical and research expertise on the guideline topic. The panel also included 2 methodologists with expertise in evidence appraisal and guideline development and 2 patient representatives. The panel chair was an ASH member and content expert. The vice-chair was an ASH member and methodologist with experience in guideline development processes. Panel members represented North and South America, Europe, and Australasia.

In addition to synthesizing evidence systematically, the McMaster University GRADE Centre supported the guideline-development process, including determining methods, preparing agendas and

meeting materials, and facilitating panel discussions. The panel's work was done using Web-based tools (https://www.surveymonkey.com and https://gradepro.org) and face-to-face and online meetings.

## Guideline funding and management of conflicts of interest

Development of these guidelines was wholly funded by ASH, a nonprofit medical specialty society that represents hematologists. Most members of the guideline panel were members of ASH. 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. One patient representative received an honorarium of $200; the other declined this. The panelists received no other payments. Some researchers who contributed to the systematic evidence reviews received salary or grant support through the McMaster University GRADE Centre. 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[17] and the Guidelines International Network.[4] At the time of appointment, a majority of the guideline panel, including the chair and the vice-chair, had no conflicts of interest as defined and judged by ASH (ie, no current material interest in any commercial entity with a product that could be affected by the guidelines). Some panelists disclosed new interests or relationships during the development process, but the balance of the majority was maintained.

Before appointment to the panel, individuals disclosed financial and nonfinancial interests. Members of the VTE Guideline Coordination Panel reviewed the disclosures and judged which interests were conflicts and should be managed. Supplement 2 provides the complete "Disclosure of Interests" forms of all panel members. In part A of the forms, individuals disclosed material interests for 2 years prior to appointment. In part B, they disclosed interests that were not mainly financial. Part C summarizes ASH decisions about which interests were judged to be conflicts. Part D describes new interests disclosed by individuals after appointment.

Recusal was also used to manage conflicts of interest. During all deliberations, panel members with a current and direct financial interest in a commercial entity with any product that could be affected by the guidelines were recused from making judgments about relevant recommendations.[4,18-20] The Evidence-to-Decision (EtD) framework for each recommendation describes which individuals were recused from making judgments about each recommendation.

None of the McMaster University–affiliated researchers who contributed to the systematic evidence reviews or who supported the guideline-development process had any current and material interest in a commercial entity with any product that could be affected by the guidelines. 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

The panel used the GRADEpro Guideline Development Tool (https://gradepro.org)[21] and SurveyMonkey (https://surveymonkey.com) to brainstorm and then prioritize the following questions addressed by these guidelines:

1. Should anticoagulation vs no anticoagulation be used in pediatric patients with symptomatic DVT or PE?
2. Should anticoagulation vs no anticoagulation be used in pediatric patients with asymptomatic DVT or PE?
3. Should thrombolysis followed by anticoagulation vs anticoagulation alone be used in pediatric patients with DVT?
4. Should thrombolysis followed by anticoagulation vs anticoagulation alone be used in pediatric patients with submassive PE?
5. Should thrombolysis followed by anticoagulation vs anticoagulation alone be used in pediatric patients with PE with hemodynamic compromise?
6. Should thrombectomy followed by anticoagulation vs anticoagulation alone be used in pediatric patients with symptomatic DVT or PE?
7. Should IVC filter vs anticoagulation be used in pediatric patients with symptomatic DVT or PE?
8. Should AT replacement in addition to standard anticoagulation vs standard anticoagulation alone be used in pediatric patients with DVT or CSVT or PE?
9. Should removal of a functioning CVAD vs no removal be used in pediatric patients with symptomatic CVAD-related thrombosis who continue to require access?
10. Should removal of a nonfunctioning or unneeded CVAD vs no removal be used in pediatric patients with symptomatic CVAD-related thrombosis?
11. Should immediate removal of a nonfunctioning or unneeded CVAD vs delayed removal be used in pediatric patients with symptomatic CVAD-related thrombosis?
12. Should removal of a functioning CVAD vs no removal be used in pediatric patients with symptomatic CVAD-related thrombosis with worsening signs or symptoms, despite anticoagulation, who continue to require access?
13. Should low-molecular-weight heparin vs vitamin K antagonist be used in pediatric patients with symptomatic DVT or PE as maintenance therapy after the first few days?
14. Should anticoagulation for >3 months vs anticoagulation for up to 3 months be used in pediatric patients with provoked DVT or PE?
15. Should anticoagulation for >6 to 12 months vs anticoagulation for 6 to 12 months be used in pediatric patients with unprovoked DVT or PE?
16. Should anticoagulation vs no anticoagulation be used in pediatric patients with CVAD-related superficial vein thrombosis?
17. Should anticoagulation vs no anticoagulation be used in neonates and pediatric patients with right atrial thrombosis?
18. Should thrombolysis or surgical thrombectomy followed by standard anticoagulation vs anticoagulation alone be used in neonates and pediatric patients with right atrial thrombosis?
19. Should anticoagulation vs no therapy be used in neonates with RVT?

20. Should thrombolysis followed by standard anticoagulation vs anticoagulation alone be used in neonates with RVT? (life-threatening or nonlife-threatening)
21. Should anticoagulation vs no anticoagulation be used in pediatric patients with PVT?
22. Should anticoagulation vs no anticoagulation be used in pediatric patients with CSVT? (with or without hemorrhage)
23. Should thrombolysis followed by standard anticoagulation vs anticoagulation alone be used in pediatric patients with CSVT?
24. Should protein C replacement vs anticoagulation be used in pediatric patients with congenital purpura fulminans due to homozygous protein C deficiency?
25. Should anticoagulation plus protein C replacement vs anticoagulation alone be used in pediatric patients with congenital purpura fulminans due to homozygous protein C deficiency?
26. Should liver transplantation vs no liver transplantation (anticoagulation or protein C replacement) be used in pediatric patients with congenital purpura fulminans due to homozygous protein C deficiency?

The panel selected outcomes of interest for each question a priori, following the approach described in detail elsewhere.[22] First, the panel brainstormed all possible outcomes and then rated their relative importance for decision making. During this rating process, the panel used definitions of the outcomes ("marker states") that were developed for these guidelines by the McMaster University GRADE Centre. Rating outcomes by their relative importance can help to focus attention on those outcomes that are considered most important and help to resolve or clarify potential disagreements. The highly rated outcomes and those identified as important based on the literature reviews were further refined through a rating of their utility using a visual analog rating scale.[22]

## Evidence review and development of recommendations

For each guideline question, the McMaster University GRADE Centre prepared a GRADE EtD table, using the GRADEpro Guideline Development Tool (https://gradepro.org). The EtD table summarized the results of systematic reviews of the literature that were updated or performed specifically for these guidelines.[23,24] The EtD table addressed effects of interventions, resource utilization, values and preferences (relative importance of outcomes), feasibility, and acceptability. The guideline panel reviewed draft EtD tables, made suggestions for corrections, and identified missing evidence. To ensure that recent studies were not missed, searches (presented in Supplement 4) were updated in April of 2017; this did provide some additional references.

Under the direction of the McMaster University GRADE Centre, researchers followed the methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions (https://handbook.cochrane.org) for conducting updated or new systematic reviews of intervention effects. When existing reviews were used, judgments of the original investigators about risk of bias were accepted. For new reviews, risk of bias was assessed at the 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 and preferences and costs and summarized findings within the EtD tables. Subsequently, the certainty in the body of evidence (also known as quality of the evidence or confidence in the estimated effects) was assessed for each of the effect estimate of the outcomes of interest, the importance of outcomes, and the baseline risk 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 dose–effect relationship, and an assessment of the effect of residual, opposing confounding. The certainty was categorized into 4 levels ranging from very low to high.[6,25,26]

During a 2-day in-person meeting preceded and followed by online discussion, the panel developed clinical recommendations based on the evidence summarized in the EtD tables. For each recommendation, the panel took a population perspective and agreed on the following: the certainty in the evidence, the balance of benefits and harms of the compared management options, and inferences regarding the values and preferences associated with the decision. The guideline panel explicitly considered the extent of resource use associated with alternative management options. The guideline panel agreed on the recommendations (including direction and strength), remarks, and qualifications on the basis of consensus or, in rare instances, by voting, based on the balance of all desirable and undesirable consequences. All panel members reviewed and approved the final recommendations.

Of note, the 26 questions addressed by the panel generated 30 recommendations. Questions 8, 20, 21, and 22 each generated 2 recommendations based on specific subpopulations for whom the panel agreed that different recommendations should be made. These recommendations are numbered as recommendations 8a and 8b, 20a and 20b, 21a and 21b, and 22a and 22b, respectively.

## Interpretation of strong and conditional recommendations

The recommendations are labeled as either "strong" or "conditional" according to the GRADE approach.[6] The words "the guideline panel recommends" are used for strong recommendations, and the phrase "the guideline panel suggests" for conditional recommendations. Table 1 provides the suggested interpretation of strong and conditional recommendations by patients, clinicians, and health care policy makers.

## Document review

Draft recommendations were reviewed by all members of the panel, revised, and then made available online on 24 July 2017 for external review by stakeholders, including allied organizations, other medical professionals, patients, and the public. Thirty-four individuals or organizations submitted comments. The document was revised to address pertinent comments, but no changes were made to recommendations. On 30 July 2018, the ASH Guideline Oversight Subcommittee and the ASH Committee on Quality approved that the defined guideline-development process was followed, and on 3 August 2018, the officers of the ASH Executive Committee approved submission of the guidelines for publication under the imprimatur of ASH. The guidelines were then subjected to peer review by *Blood Advances*.

**Table 1. Interpretation of strong and conditional recommendations**

| Implications for: | Strong recommendation | Conditional recommendation |
|---|---|---|
| Patients | Most individuals in this situation would want the recommended course of action, and only a small proportion would not. | The majority of 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 receive the intervention. 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, and 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 values and preferences. |
| Policy makers | 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. |
| 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 consideration) that determined the conditional (rather than strong) recommendation will help to identify possible research gaps. |

## How to use these guidelines

ASH 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 a standard of care. 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, and 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. ASH 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 more accurate interpretation. They should never be omitted when recommendations from these guidelines are quoted or translated. Implementation of the guidelines will be facilitated by the related interactive forthcoming decision aids. 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

## Anticoagulation in symptomatic and asymptomatic DVT or PE

*Question: Should anticoagulation vs no anticoagulation be used in pediatric patients with symptomatic DVT or PE?*

### Recommendation 1

The ASH guideline panel *recommends* using anticoagulation rather than no anticoagulation in pediatric patients with symptomatic DVT or PE (strong recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remarks:** Although there remains limited direct evidence in children, there is very strong indirect evidence from adults that symptomatic VTE requires treatment. Further, given that the majority of VTE occurs in sick hospitalized children, in whom VTE is often life-threatening, low-quality evidence suggesting benefit justifies a strong recommendation. Hence, the panel made a strong recommendation based on extrapolation from adults and potential consequences of symptomatic VTE in children, despite low certainty of evidence.

*Question: Should anticoagulation vs no anticoagulation be used in pediatric patients with asymptomatic DVT or PE?*

### Recommendation 2

The ASH guideline panel suggests either using anticoagulation or no anticoagulation in pediatric patients with asymptomatic DVT or PE (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remarks:** The adult data would suggest that treatment of most asymptomatic VTE is not required. However, there are major epidemiological, anatomical, and pathophysiological differences between VTE in adults and children that make extrapolation in this regard very difficult. The unknown benefits of anticoagulation therapy relative to the known potential risks associated with therapy do not support routine radiological screening for asymptomatic VTE. However, if detected, the decision to treat or not treat should be individualized. Research to understand the natural history of asymptomatic VTE in a variety of subgroups is a high priority.

***Summary of the evidence.*** We did not find any randomized controlled trial (RCT) that addressed these questions in children and

had to consider extrapolation from adult data for symptomatic thrombosis (~40% of the considered evidence). We identified a number of observational studies in children, primarily single-arm studies with no comparison, that provided data on the outcomes of interest (mortality, recurrent VTE, PE, major bleeding); however, the total number of children involved across all studies was <1000. Most studies did not separate symptomatic from asymptomatic thrombosis, limiting the ability to differentiate the effects between the 2 groups. The GRADE methodology framework states that a strong recommendation may be warranted despite low or very low certainty in effect estimates under 5 specific circumstances.[27] The first such instance is when low-quality evidence suggests benefit in a life-threatening situation. The panel agreed that symptomatic thrombosis was life-threatening, based on adult data and given that the majority of VTE occurs in sick hospitalized children. Although the evidence for the benefits of treatment was of low certainty in children, the available evidence and the extrapolation from higher-certainty evidence in adults supported a strong recommendation.

For asymptomatic VTE, the panel did not consider adult data because the pathophysiology of asymptomatic VTE in children is vastly different from adults.[7] Most published pediatric studies report treating asymptomatic thrombosis without any data to demonstrate improved outcomes (ie, usually case series with no comparison groups). The heterogeneity of VTE in children (obstructive CVAD related, non-obstructive CVAD related, upper limb venous system, lower limb venous system, intracardiac, cerebral sino venous) and the heterogeneity of the underlying physiology (age, comorbidities, need for vascular access for life-saving treatment, presence or absence of right-to-left shunt making paradoxical emboli possible) led the panel to make a conditional recommendation for either anticoagulation or no anticoagulation based on individual patient factors. Clinicians will need to assess the perceived risk of local and embolic complications, the overall state of the child, the risks of therapy, and the parental preferences until better evidence becomes available. Evidence profiles with the characteristics of all included studies are online for Recommendation 1 and Recommendation 2. The complete EtD frameworks for these recommendations are also online.

***Benefits.*** The relative effects were not estimable from the pediatric data because of the lack of direct comparisons. The frequency of major outcomes in children treated with anticoagulation were as follows: mortality, 3.6%; pulmonary embolus, 1.3 to 3.3%; and recurrent VTE, 2.7 to 2.8%. There were no baseline data in children to compare. Overall, the certainty in these estimated effects is very low, primarily as a result of imprecision and high risk of bias in the included studies.

***Harms and burden.*** The relative effects were not estimable from the pediatric data, and the frequency of major bleeding in children treated with anticoagulation was from 0% to 21.8%. There is very low certainty in the estimate of the risk of adverse effects due to serious risk of bias and some 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.

***Other EtD criteria and considerations.*** The guideline panel did not think that there were feasibility or acceptability considerations that would impair implementation of this recommendation. The full EtD framework is available online for Recommendation 1 and Recommendation 2.

***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. Based on the body of available evidence, it is likely that anticoagulation reduces the risk of developing recurrent VTE and pulmonary embolus and death in symptomatic VTE, but this is less certain in asymptomatic patients (VTE found incidentally or VTE identified because of screening radiology). 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 research topics:

- Determining the natural history of asymptomatic VTE in children and, hence, the benefits of treatment vs no treatment remains a high research priority;
- Determining the role of radiological screening for asymptomatic VTE is a related, but separate, important question; and
- Understanding subgroups in whom the approach to the first 2 questions might be different.

## Thrombolysis, thrombectomy, and IVC filters

*Question: Should thrombolysis followed by anticoagulation vs anticoagulation alone be used in pediatric patients with DVT?*

**Recommendation 3**

The ASH guideline panel *suggests against* using thrombolysis followed by anticoagulation; rather, anticoagulation alone should be used in pediatric patients with DVT (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remarks:** The panel considered issues, such as the size and clinical impact of VTE, as important in deciding the relative risk benefit ratio of thrombolysis. In most cases, the risks seem too high for the potential benefit; however, there may be individuals in whom the opposite is true. Extrapolation of adult data was difficult. There are insufficient data to address the relative risk 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.

*Question: Should thrombolysis followed by anticoagulation vs anticoagulation alone be used in pediatric patients with submassive PE?*

**Recommendation 4**

The ASH guideline panel *suggests against* using thrombolysis followed by anticoagulation; rather, anticoagulation alone should be used in pediatric patients with submassive PE (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remarks:** The panel considered submassive PE to represent children with PE who did not have hemodynamic instability. There were minimal pediatric data, and review of adult data revealed considerable uncertainty that was complicated by limitations in the ability to extrapolate. The panel concluded the risks outweighed the benefits in most cases, hence the conditional recommendation against thrombolysis.

*Question: Should thrombolysis followed by anticoagulation vs anticoagulation alone be used in pediatric patients with PE with hemodynamic compromise?*

**Recommendation 5**

The ASH guideline panel *suggests* using thrombolysis followed by anticoagulation rather than anticoagulation alone in pediatric patients with PE with hemodynamic compromise (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remarks:** The panel considered PE with hemodynamic compromise to be life-threatening, with limited time to respond to standard anticoagulation, and so conditionally recommended thrombolysis, in addition to anticoagulation, based predominantly on extrapolation of adult data.

***Summary of the evidence.*** We did not find any RCT that addressed these questions in children and had to consider extrapolation from adult data (contributing almost 90% of the evaluated data). We identified up to 15 observational studies in children, primarily single-arm studies with no comparison, that provided data on the outcomes of interest (mortality, 3.6% with thrombolysis compared with 0% with anticoagulation alone; progressive VTE or failure of VTE resolution, 22.2% for thrombolysis vs 50% for anticoagulation alone; PE [adult data only], 1.9% with thrombolysis vs 4% with anticoagulation alone; major bleeding, 5.7% with thrombolysis vs 0% with anticoagulation alone; and PTS, 9.5% with thrombolysis vs 28.6% with anticoagulation alone). The total number of children involved across all studies was <500. Evidence profiles and characteristics of all included studies are online for Recommendation 3, Recommendation 4, and Recommendation 5.

***Benefits.*** The relative effects were not estimable based on the pediatric data because of the lack of direct comparisons. The frequency of major outcomes in children treated with thrombolysis is based on very small numbers reported in the included studies. In particular, there were insufficient data to differentiate the outcomes for the use of systemic thrombolysis compared with catheter-directed thrombolysis. There were no baseline data in children to compare. Overall, the certainty in these estimated effects is very low owing to potential bias in the studies (see evidence profiles online for Recommendation 3, Recommendation 4, and Recommendation 5).

***Harms and burden.*** The relative effects were not estimable based on the pediatric data. Any difference in bleeding risk for catheter-directed thrombolysis as distinct from systemic thrombolysis was not possible to establish from the available data. 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.

***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. However, the panel noted that the use of catheter-directed thrombolysis is much more likely in centers in which there is strong interventional radiology input. Given the impact of interventionalist experience in children 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. The full EtD framework is available online for Recommendation 3, Recommendation 4, and Recommendation 5.

***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/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, and it is likely that thrombolysis reduces the risk of PTS but increases the risk of bleeding. Thus, thrombolysis use should be restricted to limb- or life-threatening cases in which anticoagulation alone is unlikely to be successful and, hence, the bleeding risk of thrombolysis becomes more acceptable. 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 questions:

- The role of thrombolysis in large VTE, submassive PE, and massive PE remains unknown in children, and further studies to identify the risk/benefit of thrombolysis compared with anticoagulation alone considering all outcomes of interest are required.
- The role of catheter-directed thrombolysis and the minimal infrastructure, experience, and annual case load to offer this therapy in children compared with systemic thrombolysis need to be determined.
- The natural history of VTE or large PE in children (including subgroup analysis [eg, intracardiac thrombi]) treated with anticoagulation alone needs to be understood to enable the first 2 questions to be properly addressed.

*Question: Should thrombectomy followed by anticoagulation vs anticoagulation alone be used in pediatric patients with symptomatic DVT or PE?*

**Recommendation 6**

The ASH guideline panel *suggests against* using thrombectomy followed by anticoagulation; rather, anticoagulation alone should be used in pediatric patients with symptomatic DVT or PE (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remarks:** The panel recognized that, in certain cases (eg, cardiovascular compromise secondary to the VTE), thrombectomy may be appropriate; however, 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.

*Question: Should IVC filter vs anticoagulation be used in pediatric patients with symptomatic DVT or PE?*

**Recommendation 7**

The ASH guideline panel *suggests against* using IVC filter; rather, anticoagulation alone should be used in pediatric patients with symptomatic DVT or PE (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remarks:** The panel considered the benefits vs risks involved in IVC filter use and determined their use should be reserved for certain cases (eg, 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 are appropriate. It is not feasible to place IVC filters in children who weigh <10 kg.

***Summary of the evidence.*** We did not find any RCT that addressed these questions in children and had to consider extrapolation from adult data. With respect to thrombectomy, we identified 5 observational studies in children, primarily single-arm studies with no comparison, that provided data on the outcomes of interest (mortality, failure resolution VTE, major bleeding, PTS). However, the total number of children receiving thrombectomy across all studies was <60. Extrapolation of indirect data from adults (approximately one third of the evaluable data) supported a conditional recommendation against thrombectomy; however, there may be specific subgroups in whom thrombectomy might be relevant (eg, cardiac surgical patients with hemodynamically significant thrombosis within the surgical field/shunt/intracardiac). The panel predominantly considered adult data (two thirds of evaluable data) with respect to the use of IVC filters. Observational studies in children included 429 subjects across 8 studies and reported mortality of 1.9%, PE due to VTE/filter of 3.4%, and no major bleeding. Panel experience was obtained through a survey of their current practices and contributed to the available evidence. The panel considered the risks involved in IVC filter use and determined that only temporary filters should be used and reserved for certain cases with a clear plan for removal. Important subgroups to consider for an IVC filter include those patients with DVT and absolute contraindication to anticoagulation and those children failing an appropriate anticoagulation treatment (new PE while on adequate anticoagulation) in whom an IVC filter could be considered.

When the absolute contraindication is resolved, restarting the anticoagulation and removal of the filter are appropriate. The panel noted that it is not feasible to place IVC filters in children who weigh <10 kg. Online evidence profiles for Recommendation 6 and Recommendation 7 present the characteristics of all included studies.

***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 children treated with thrombectomy or IVC filters cannot be determined accurately. A survey of panel members' unpublished experience revealed that, in an average of 800 patients managed in the last 5 years, 1% to 8% of patients with symptomatic VTE were treated with mechanical thrombectomy, of which ~10% had a recurrent VTE, and ~10% were managed with an IVC filter, of which 2 or 3 (8%) had a recurrent or new VTE compared with 2% to 8% of those managed without a filter. Of note, the use of either intervention is also operator dependent and so operator experience and institutional infrastructure will impact on the availability and feasibility of these procedures, especially in younger children. There were no baseline data in children to compare. Overall, the certainty in these estimated effects is very low owing to potential risk of bias in the included studies (see online evidence profiles for Recommendation 6 and Recommendation 7).

***Harms and burden.*** The relative effects were not estimable from the pediatric data. From the panel survey, of children treated with thrombectomy, ~5% to 20% had major bleeding, but <2% died. Approximately 2% of patients with an IVC filter had a complication related to the filter, and <1% died.

There is very low certainty in the estimate of the risk of adverse effects due to serious risk of bias and some 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, as well as operator experience and institutional infrastructure.

***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 thrombectomy, because the few children who would likely have a potential indication for thrombectomy were likely to be patients in whom the infrastructure and operator experience existed to adequately manage the patient (eg, pediatric cardiac surgical services). However, the panel did note that the use of IVC filters requires experienced interventional radiology services, and the availability of such services would influence the risk benefit ratio of inserting an IVC filter. The EtD framework is available online for Recommendation 6 and Recommendation 7.

***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/harm from using either thrombectomy or IVC filter. Based on the body of available evidence, it is likely that either intervention increases the risk of developing recurrent VTE and possibly also the development of bleeding or other procedural-related complications. As such, these interventions should only be used in specific limited circumstances. There is very low certainty that there is an effect of thrombectomy or IVC filter 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 questions:

- Further studies to identify subgroups who might benefit from thrombectomy or IVC filter;
- Further studies to identify the optimal methods of performing thrombectomy (eg, open surgical vs catheter thrombus retrieval) in appropriate cases; and
- Further studies to determine the minimal infrastructure and operator experience required for safe placement of IVC filters especially in smaller children.

## AT-replacement therapy

*Question: Should AT replacement in addition to standard anticoagulation vs standard anticoagulation alone be used in pediatric patients with DVT or CSVT or PE?*

### Recommendation 8a

The ASH guideline panel *suggests against* using AT-replacement therapy in addition to standard anticoagulation; rather, standard anticoagulation alone should be used in pediatric patients with DVT/CSVT/PE (conditional recommendation based on very low certainty in the evidence of 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; based on the prophylactic studies, there is little evidence of clinical benefit and perhaps evidence of clinical harm. This recommendation is independent of the plasma AT level in the patient, which should not be routinely measured.

### 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 of effects⊕◯◯◯). **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. The first is in children with documented inherited antithrombin 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, postliver transplant, and in children with disseminated intravascular coagulation and VTE. Usually, AT use would be commenced if there were continuous thrombus growth and/or failure of clinical response, despite adequate anticoagulation. However, there was no evidence to suggest improved outcomes in these patients.

***Summary of the evidence.*** We found only 1 direct observational study (retrospective cohort of infants <1 year old given AT or no AT plus enoxaparin for treatment of VTE), which showed that AT increased time to therapeutic anti-Xa, increased cost, and increased bleeding (14.3% vs 3.9%; $P = 0.55$). However, the study had significant risk of bias. Indirect data included 2 RCTs of prophylactic AT replacement for other indications and 6 observational studies of AT replacement as primary prophylaxis, with or without anticoagulation, in a variety of specific pediatric patient populations (cardiopulmonary bypass, extracorporeal membrane oxygenation, ALL); the balance of data from these studies suggested increased harm without clinical benefit. Adult data did not contribute to these recommendations. The evidence profile and EtD framework are available online for Recommendations 8a and 8b.

***Benefits.*** The relative effects were not estimable from direct pediatric data as a result of the lack of direct comparisons. From indirect data, there were wide 95% confidence intervals (CIs) that included no effect, plausible benefit, and harm when considering outcomes of mortality or VTE occurrence. Overall, the certainty in these estimated effects is very low owing to indirectness of the patient populations studied, risks of bias within the study designs, and imprecision of the estimates (see online evidence profile for Recommendations 8a and 8b).

***Harms and burden.*** The direct study suggested increased bleeding with AT, and this was supported by the indirect data in which the lower limit of the CI of the absolute effect (≥33 more deaths per 1000 treated) surpasses the appreciable harm and excludes the null. There is very low certainty in the estimate of the risk of adverse effects as the result of indirectness and risk of bias. However, given the available evidence, the guideline panel considered the risk of adverse effects to outweigh the likelihood of benefit.

***Other EtD criteria and considerations.*** The panel noted that the cost of AT therapy (plasma derived and recombinant) was substantial compared with the alternative of anticoagulation alone.

***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 AT replacement. The evidence considered was inherently indirect. The panel agreed that, for any child with any VTE, the first line of treatment is anticoagulation, independent of the AT level (hence, no plasma AT measurements would be required). However, the panel considered the following subgroups: children with age-appropriate low level of AT, children with ALL on induction, children with nephrotic syndrome, neonates, liver transplant patients, and patients with disseminated intravascular coagulation and VTE.

The panel accepted that, in the scenario of progressive clinical thrombosis that was failing to respond to anticoagulation alone, it might be reasonable to measure plasma AT levels and consider the use of AT-replacement therapy to supplement anticoagulation in the aforementioned subgroups. In such cases in which progressive worsening clinical thrombosis was apparent, the increased risk of bleeding with AT therapy may be acceptable. However, there was no evidence to suggest improved outcomes in these patients.

Similarly, in children with known inherited AT deficiency and VTE who did not respond to anticoagulation alone, the use of AT therapy in addition to anticoagulation seems appropriate.

Based on the body of available evidence, it is likely that AT does not alter the risk of developing progressive VTE and increases the risk of bleeding, in the setting of being a relatively expensive therapy. There is very low certainty that there is an effect of AT 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 issue: use of AT-replacement therapy in pediatric patients, in addition to anticoagulation (heparinoid), in the treatment of VTE in a variety of subgroups.

## CVAD-related thrombosis

*Question: Should removal of a functioning CVAD vs no removal be used in pediatric patients with symptomatic CVAD-related thrombosis who continue to require access?*

**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 of 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.

*Question: Should removal of a nonfunctioning or unneeded CVADs vs no removal be used in pediatric patients with symptomatic CVAD-related thrombosis?*

**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 of effects ⊕◯◯◯). **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.

*Question: Should immediate removal of a nonfunctioning or unneeded CVAD vs delayed removal be used in pediatric patients with symptomatic CVAD-related thrombosis?*

**Recommendation 11**

The ASH guideline panel *suggests* delayed removal of a CVAD until after initiation of anticoagulation (days), rather than immediate removal in pediatric patients with symptomatic central venous line–related thrombosis who no longer require venous access or in whom the CVAD is nonfunctioning (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remarks:** The panel placed high value on avoiding potential risk of emboli leading to PE or paradoxical stroke, and this was thought to be achieved by a few days of anticoagulation. The risk of infection and bleeding with anticoagulation before removing the CVAD was considered to be small. The panel recognized that surgical availability was often a pragmatic determinant of CVAD removal.

*Question: Should removal of a functioning CVAD vs no removal be used in pediatric patients with symptomatic CVAD-related thrombosis with worsening signs or symptoms, despite anticoagulation, who continue to require access?*

**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 of effects ⊕◯◯◯). **Remarks:** The panel considered the variability in value placed by families and clinicians on maintaining line access compared with the 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 the setting of worsening VTE symptoms, despite anticoagulation, is appropriate. However, in some children, venous access is paramount.

***Summary of the evidence.*** We found 1 observational study (17 children total) from 1996, and 2 indirect observational studies from adults with cancer. In terms of available data, the adult data constituted almost 90%. The recommendations were further informed by surveying the panel to understand unpublished outcomes in their practice. The panel placed high value on avoiding the insertion of another CVAD in children who may have limited availability of access sites. The panel also agreed that treatment of symptomatic CVAD-related thrombus with anticoagulation likely leads to minimal complications, and the benefits outweigh the potential harm associated with placing another line. The evidence profiles and EtD frameworks are available online for Recommendation 9, Recommendation 10, Recommendation 11, and Recommendation 12.

***Benefits.*** The relative effects were not estimable from the data as the result of the lack of direct comparisons. The outcomes of interest included VTE progression or recurrence, PE, CVAD-associated sepsis, and mortality; however, the frequency of these outcomes cannot be determined.

***Harms and burden.*** The relative effects were not estimable from the data. The outcomes of interest included major bleeding and complications from further CVAD insertion; however, the frequency of these outcomes cannot be determined.

***Other EtD criteria and considerations.*** The panel acknowledged that availability of another access site, surgeon/operating suite availability to place a new CVAD, and how long a CVAD will be needed are important considerations. The thrombogenic effect of placing another CVAD and new endothelial injury must also be considered. The panel also acknowledged that, although they placed a high value on avoiding the insertion of another CVAD in children who may have limited availability of access sites, maintaining access and avoiding having to find another access site for CVAD placement may be viewed differently by different patients and families; hence, patient values and preferences are important considerations.

***Conclusions and research needs for these recommendations.*** The guideline panel determined that there is very low certainty in the evidence for a net health harm from CVAD removal in cases of

CVAD-associated VTE in the situation in which the CVAD was still functional, and ongoing access is required for the treatment of the underlying primary condition (for which the CVAD was inserted in the first place). Conversely, if the CVAD is not functional, or no longer required, then there is low certainty in the evidence of benefit for CVAD removal but high-quality indirect evidence of harm; therefore, the panel agreed to make a strong recommendation for removal of the CVAD. The GRADE methodology framework states that a strong recommendation may be warranted, despite low or very low confidence in effect estimates under 5 specific circumstances.[21] In this instance, the panel agreed that the circumstance when low-quality evidence suggests benefit and high-quality evidence suggests harm or a very high cost was applicable. However, the optimal timing of removal was deemed uncertain. Previous publications have recommended delaying removal until after 3 to 5 days of anticoagulation to reduce the risk of embolic phenomenon on CVAD removal (especially in children with known or potential right-to-left shunts).[28] There are no outcome data to support an optimal timing of CVAD removal, and this recommendation is based on anecdotal experience and first principles. The panel noted that pragmatic decisions (surgeon/operating suite availability) often determine timing of CVAD removal. In cases in which the thrombosis clinically extends/embolizes, despite adequate anticoagulation, the decision to remove or not remove a functioning CVAD must be made on an individual basis considering the factors outlined in this discussion: availability of further vascular access, requirement for vascular access to treat the underlying condition successfully, balance of perceived risk from underlying condition, and surgical removal of CVAD vs progressive thrombosis. There is very low certainty that there is an effect of CVAD removal 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 questions:

- The optimal timing of CVAD removal (delayed by what duration vs immediate) once CVAD-associated VTE is diagnosed needs to be established.
- Subgroup studies are needed to identify specific patient populations in whom the approach might vary, including consideration of risk of CVAD-associated sepsis.

## Low-molecular-weight heparin vs vitamin K antagonists

*Question: Should low-molecular-weight heparin vs vitamin K antagonists be used in pediatric patients with symptomatic DVT or PE as maintenance therapy after the first few days?*

**Recommendation 13**

The ASH guideline panel *suggests* using either low-molecular-weight heparin or vitamin K antagonists in pediatric patients with symptomatic DVT or PE (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remarks:** The decision should depend on patient values and preferences, health services resources, infrastructure and support, and underlying condition, comorbidities, and other medications.

***Summary of the evidence.*** We found 1 RCT (the REVIVE trial, which was stopped early because of difficulties in participant recruitment and was underpowered to detect differences between the 2 interventions) and 18 observational studies with <1000 total patients involved (see evidence profile online for Recommendation 13 for study description and references). Most of the observational studies were single-arm cohorts, with no comparison arm to detect an effect. Adult data were not considered. The evidence profile and EtD framework are online for Recommendation 13.

***Benefits.*** For the outcomes of mortality, PE, severe VTE, or recurrent VTE, the RCT results had wide CIs that did not exclude thresholds for plausible benefit or harm. Risk estimates cannot be calculated from the observational data because of the lack of direct comparisons. Overall, the certainty in these estimated effects is very low owing to bias in the observational studies and imprecision of the estimates from the RCT.

***Harms and burden.*** For the adverse event of major bleeding, the RCT effect estimates had wide CIs that did not exclude thresholds for plausible benefit or harm. Risk estimates could not be calculated from the observational data. Overall, the certainty in these estimated effects is very low owing to important risk of bias in the observational studies and imprecision of the estimates from the RCT.

***Other EtD criteria and considerations.*** The panel considered that the decision to use either option should depend on patient values and preferences, health services resources, infrastructure and support, and underlying condition, comorbidities, and other medications. The panel recognized that the burden of care was an important consideration for each treatment (regular subcutaneous injections vs frequent blood tests, whether point of care or laboratory based), and there were insufficient data on this important outcome. The panel agreed that appropriate infrastructure support is required for either option, and the costs of such infrastructure likely vary in different health care systems.

***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 or harm from using low-molecular-weight heparin compared with vitamin K antagonists. There is very low certainty as to the effect of low-molecular-weight heparin on other outcomes (eg, bone density, likely related to duration of treatment). 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 questions:

- Further studies are required to elucidate the minimal infrastructure requirements for services to support parents and families to optimize therapy with either low-molecular-weight heparin or vitamin K antagonists.
- Further studies are required to determine the impact of vitamin K antagonists vs low-molecular-weight heparin on bone density, especially for longer durations of therapy.
- Further studies are required to understand the factors influencing patient preferences for either therapy and the optimal ways to mitigate negative factors.

## Provoked DVT or PE

*Question: Should anticoagulation for >3 months vs anticoagulation for up to 3 months be used in pediatric patients with provoked DVT or PE?*

**Recommendation 14**

The ASH guideline panel *suggests* using anticoagulation for ≤3 months rather than anticoagulation for >3 months in pediatric patients with provoked DVT or PE (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remarks:** The panel noted that the exact duration for optimal anticoagulation was unknown, and there are ongoing studies comparing durations within this time frame. In cases in which the provoking factor is resolved, treatment for >3 months is unjustified. However, for patients who have persistence of the causative risk factor for provoked DVT/PE, longer anticoagulation could be considered.

***Summary of the evidence.*** We found 1 observational study of <90 children that included variable durations of therapy and included some children with unprovoked VTE. There was 1 RCT that did not specifically address duration of therapy. Two thirds of the data considered by the panel were indirect data from adult studies. The characteristics of all included studies are presented in the evidence profile online for Recommendation 14.

The panel noted that the definition of provoked VTE was not uniformly accepted and that, although CVAD-associated VTE or postsurgical VTE was usually considered provoked, VTE in the setting of specific medications, such as oral contraceptives, or of physiological disturbances, such as severe dehydration, could be considered as provoked or unprovoked. The panel noted that the ability to remove/reverse the provoking factor would be a major determinant. The panel also noted that there is an ongoing multicenter RCT[29] comparing 3 months of anticoagulation with 6 weeks of anticoagulation in a subgroup of provoked VTE in children; the results of this trial will be most helpful to answer this question.

***Benefits.*** The relative effects were not estimable from the pediatric data, and the frequency of major outcomes in children treated for >3 months compared with ≤3 months cannot be determined accurately. There were no baseline data in children to compare. Extrapolation from adult data would suggest there is little advantage in outcomes from treating for >3 months in provoked VTE.

Overall, the certainty in these estimated effects is very low owing to the indirectness of studies and imprecision in the indirect studies (see evidence profile online for Recommendation 14).

***Harms and burden.*** The relative effects on adverse events were not estimable from the pediatric data, and the frequency of major outcomes in children treated for >3 months compared with ≤3 months cannot be determined accurately. There were no baseline data in children to compare. Extrapolation from adult data would suggest there are increased adverse events with increasing durations of anticoagulation.

***Other EtD criteria and considerations.*** Cost and burden of care are incrementally increased with increasing duration of therapy. The panel judged that there may be important uncertainty or variability in how much people value the main outcomes. The panel also noted that the age of the child may be a substantial subgroup consideration with respect to optimal duration of therapy. The panel considered that the aim should be to treat for the minimal duration of time to achieve optimal VTE-resolution rates. The panel noted that the current RCT addressing duration of therapy would suggest that most clinicians believe that shorter duration of therapy rather than longer is potentially appropriate for provoked VTE in children. The EtD framework is available online for Recommendation 14.

***Conclusions and research needs for this recommendation.*** The guideline panel determined that there is very low certainty in the evidence for a net health harm from using anticoagulation for >3 months compared with 3 months for provoked VTE. However, for patients who have persistence of the causative risk factor for the provoked DVT/PE, longer anticoagulation could be considered. There is very low certainty that there is an effect of prolonged therapy 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 questions:

- Studies to determine of the impact of differing provoking factors to optimal duration of therapy;
- Studies to determine the impact of age on optimal duration of therapy for provoked VTE; and
- Studies to determine the required improvement in outcomes for patients and families compared with the perceived increased burden of care from prolonged therapy.

## Unprovoked DVT or PE

*Question: Should anticoagulation for >6 to 12 months vs anticoagulation for 6 to 12 months be used in pediatric patients with unprovoked DVT or PE?*

**Recommendation 15**

The ASH guideline panel *suggests* using anticoagulation for 6 to 12 months rather than anticoagulation for >6 to 12 months in pediatric patients with unprovoked DVT or PE (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remarks:** There were little pediatric data. Extrapolation of adult data might favor prolonged treatment periods in terms of VTE recurrence. However, the bleeding risk and impact of prolonged therapy on quality of life were judged to be significantly higher in children compared with adults. Patient values and preferences should be considered.

***Summary of the evidence.*** We found 1 study of <90 children; only 7% of VTEs were unprovoked, and the duration of therapy was not standard. In this context, all of the data that contributed to the panel decision were extrapolated from indirect data from adult

studies. The panel noted that the definition of unprovoked VTE was not uniformly accepted and that, although CVAD-associated VTE or postsurgical VTE was usually considered provoked, VTE in the setting of specific medications, such as oral contraceptives, or of physiological disturbances, such as severe dehydration, could be considered as provoked or unprovoked. Furthermore, although adult studies considered major outcomes, such as recurrent VTE and mortality, there was no consideration of burden of care (including impact on mental health), lifestyle, and quality of life, which the panel judged to be of significant importance in the pediatric population. The characteristics of all included studies are presented in the online evidence profile for Recommendation 15.

***Benefits.*** The relative effects were not estimable from the pediatric data as a result of the lack of direct comparisons, and the frequency of major outcomes in children treated for 6 to 12 months compared with >6 to 12 months cannot be determined accurately. There were no baseline data in children to compare. Extrapolation from adult data would suggest an advantage in terms of the major outcome of recurrent VTE, although in many studies the 95% CI contains both an effect and no effect.

Overall, the certainty in these estimated effects is very low owing to insufficient studies addressing the question and potential bias in the available studies (see online evidence profile for Recommendation 15).

***Harms and burden.*** The relative adverse events were not estimable from the pediatric data, and the frequency of adverse events in children treated for >6 to 12 months compared with 6 to 12 months cannot be determined accurately. There were no baseline data in children to compare. Extrapolation from adult data would suggest no difference in bleeding risk, although the 95% CI contains both an effect and no effect.

Overall, the certainty in these estimated effects is very low owing to indirectness of studied populations and imprecision in the indirect studies (see online evidence profile for Recommendation 15).

***Other EtD criteria and considerations.*** The panel judged that acceptability of longer duration of therapy would vary based on patients' perceived burden of treatment, lifestyle, and impact on quality of life. The panel judged that this was a complex cost-effectiveness question, and it would not be easy to make judgments without available studies. The evidence profile and EtD framework are available online for 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 from using anticoagulation for 6 to 12 months compared with >6 to 12 months for unprovoked VTE in children. Although indirect evidence from adults suggests the opposite in terms of recurrent VTE, the panel strongly considered the impact of prolonged burden of care on quality of life. Thus, individual values and preferences of patients and their families should be explored when making this decision. There is very low certainty that there is an effect of the duration of anticoagulation on other outcomes, such as mental health. 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 question: the mortality, recurrence risk, major bleeding risk, and quality of life outcomes for differing durations of treatment in children with unprovoked VTE need to be determined. The potential role of serial D-dimers to predict recurrence also needs to be determined.

## CVAD-related superficial vein thrombosis

*Question: Should anticoagulation vs no anticoagulation be used in pediatric patients with CVAD-related superficial vein thrombosis?*

**Recommendation 16**

The ASH guideline panel *suggests* using either anticoagulation or no anticoagulation in pediatric patients with CVAD-related superficial vein thrombosis (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remarks:** There was very little direct or indirect data on which to base this recommendation. The collective experience of the panel suggested that, in most patients, no anticoagulation will be appropriate. However, anticoagulation seems appropriate for patients who have a CVAD line that is still functioning and who continue to need venous access, as well as in those whose symptoms progress.

***Summary of the evidence.*** We did not find any study in children. The panel considered only indirect data from 1 adult study, which was marked by wide CIs that included null hypothesis and thresholds for plausible benefit or harm. Based on survey results from the panel's collective experience, progression when untreated is very low (recurrence) and 0 to few bleeds and 0 to low mortality with no anticoagulation. The panel judged that, in most patients, no anticoagulation will be appropriate. However, for patients who have a CVAD line that is still functioning and who continue to need access, as well as in those whose symptoms progress, anticoagulation seems appropriate. The evidence profile and EtD framework are available online for Recommendation 16).

***Benefits.*** There were no pediatric data to assess major outcomes of VTE progression, recurrence, or mortality. The indirect data had significant imprecision. The panel survey suggested no difference in major outcomes with treatment compared with no treatment.

***Harms and burden.*** There were no pediatric data to assess adverse events, including major bleeding. The indirect data had significant imprecision. The panel survey suggested there was no major bleeding if no anticoagulation was given.

***Other EtD criteria and considerations.*** The panel judged that variation in the perceived importance of superficial vein thrombosis will exist among patients and clinicians. Although, in general, the panel judged that no anticoagulation was appropriate, there will be specific patients with progressive symptoms, particularly difficult vascular access, or with strong preferences in whom anticoagulation is appropriate (see online EtD framework for Recommendation 16).

***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 or harm from using anticoagulation or not and, therefore, could not suggest either choice, because individual patient factors will alter the decision. 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 research question: with the increasing use of peripherally inserted central catheters in a wide range of pediatric care scenarios, the frequency of superficial vein CVAD VTE will increase, and studies of the natural history and role of anticoagulation treatment are required.

## Right atrial thrombosis

*Question: Should anticoagulation vs no anticoagulation be used in neonates and pediatric patients with right atrial thrombosis?*

**Recommendation 17**

The ASH guideline panel *suggests* using anticoagulation, rather than no anticoagulation, in pediatric patients with right atrial thrombosis (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remarks:** The panel was unable to distinguish between symptomatic and asymptomatic VTE in this instance, because many right atrial thromboses are discovered during routine imaging, especially in cardiac surgical patients. Factors, such as size and mobility of the thrombus, patient's hemodynamic status, and bleeding risk, are important considerations, but there are insufficient data to define specific subgroup effects.

*Question: Should thrombolysis or surgical thrombectomy followed by standard anticoagulation vs anticoagulation alone be used in neonates and pediatric patients with right atrial thrombosis?*

**Recommendation 18**

The ASH guideline panel *suggests against* using thrombolysis or surgical thrombectomy, followed by standard anticoagulation; rather, anticoagulation alone should be used in pediatric patients with right atrial thrombosis (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 of thrombectomy vs thrombolysis will depend on patient and family acceptability and feasibility of the interventions.

***Summary of the evidence.*** We found 28 observational studies (case series or case reports) in children, including a total of 41 patients exposed to no anticoagulation, 30 patients exposed to anticoagulation alone, and 65 patients exposed to thrombolysis or thrombectomy. Indirect adult data were not used. The evidence profiles and EtD frameworks are available online for Recommendation 17 and Recommendation 18.

***Benefits.*** Ten of 65 (15.4%) patients died in the thrombolysis (4 patients) and thrombectomy (6 patients) groups, whereas 2 of 30 (6.7%; none said to be VTE related) died among those exposed to anticoagulation alone vs 4 of 41 (9.8%; all VTE related) in the nonanticoagulated group. There were 13 of 69 (18.8%) reported cases of PE in the thrombolysis group vs 0 of 25 (0%) in the anticoagulation group and 4 of 41 (9.7%) in the observation group. Overall, the certainty in these estimated effects is very low owing to very serious risks of bias and imprecision in the studies.

***Harms and burden.*** There were 8 of 69 (11.6%) reported events of major bleeding in the thrombolysis group, and no reported major bleeding event in the anticoagulation group or untreated group. Overall, the certainty in these estimated effects is very low owing to very serious risks of bias and imprecision in the studies.

***Other EtD criteria and considerations.*** The panel noted that, although more patients in the thrombolysis/thrombectomy group had undesirable consequences (death, PE, bleeding), this could be due to higher-risk patients being assigned to these interventions, given the uncontrolled nature of the available data. Factors, such as size and mobility of the thrombus, patient's hemodynamic status, patient age, and bleeding risks, are important considerations, but there are insufficient data to define specific subgroup effects. In cases in which more aggressive therapy was thought appropriate, the choice of thrombectomy vs thrombolysis will depend on patient and family acceptability and feasibility of the interventions (see online EtD frameworks for Recommendation 17 and Recommendation 18).

***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 children with right atrial thrombosis. Factors, such as size and mobility of the thrombus, patient's hemodynamic status, patient age, and bleeding risks, are important considerations in deciding for no treatment, anticoagulation, thrombolysis, or thrombectomy. Given the available data, the panel judged that anticoagulation alone was appropriate in most cases. 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 research questions:

- The natural history of right atrial thrombosis in different patient subgroups needs to be determined.
- The impact of thrombosis size and mobility on natural history needs to be determined.

## RVT

*Question: Should anticoagulation vs no therapy be used in neonates with RVT?*

**Recommendation 19**

The ASH guideline panel *suggests* using anticoagulation rather than no anticoagulation in neonates with RVT (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remarks:** The panel considers the intervention to have a potential beneficial effect if the long-term benefits of avoiding hypertension and/or renal damage are considered. Anticoagulation is likely more important with bilateral involvement compared with unilateral involvement or with progression to the inferior vena cava. Severity of disease, age, gestational age, and degree of thrombocytopenia will impact bleeding risk with treatment.

*Question: Should thrombolysis followed by standard anticoagulation vs anticoagulation alone be used in neonates with RVT (life-threatening or nonlife-threatening)?*

**Recommendation 20a**

The ASH guideline panel *recommends against* using thrombolysis, followed by standard anticoagulation; rather, anticoagulation alone should be used in neonates with nonlife-threatening RVT (strong recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remarks:** All evidence comes from observational studies in which patients who are treated with thrombolytics are typically more unwell, have bilateral RVT, and have inferior vena cava involvement; studies did not adjust for these factors, and causation is difficult to ascertain. However, the panel placed a high value on avoiding the potential bleeding risks of thrombolysis, especially in neonates, and so made this recommendation for cases with very low mortality risk (ie, unilateral RVT). Therefore, the panel made a strong recommendation as a result of high-quality evidence for harm or high costs, despite very low–quality evidence for benefit.

**Recommendation 20b**

The ASH guideline panel *suggests* using thrombolysis followed by standard anticoagulation rather than anticoagulation alone in neonates with life-threatening RVT (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remarks:** When the condition is life-threatening (ie, bilateral thrombosis), the panel considered that the beneficial effects of thrombolysis would outweigh the undesirable consequences of the intervention.

***Summary of the evidence.*** We found 9 observational studies in children with a total of 175 patients. All were studies with serious risk of bias as a result of confounding, selection of participants, and measurement. Indirect adult data were not used. 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 inferior vena cava, 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 in neonates because of the practical difficulties of adequately dialyzing small infants. The treatment and outcomes, as described in the observational studies, were not able to be clearly sorted by these different disease severities. The evidence profiles and EtD frameworks are available online for Recommendation 19 and Recommendations 20a and 20b.

***Benefits.*** In the patients (n = 66) who did not receive anticoagulation, mortality was 3%, no resolution of RVT was found in 6.1%, long-term renal impairment was noted in 73%, and hypertension (measured in 3 studies, n = 20 patients) occurred in 15%. In the group who received anticoagulation alone (n = 85), the outcomes were 0%, 0%, 75%, and 10% (measured in 3 studies, n = 20 patients), respectively. For patients who received thrombolysis and anticoagulation (n = 24), the outcomes were 0%, 8%, 75%, and 22% (measured in 3 studies, n = 9), respectively. Direct comparison of these outcomes is very difficult given the likely significant selection bias as to which patients were offered which therapy.

***Harms and burden.*** In the patients (n = 66) who did not receive anticoagulation, the major bleeding rate was 6%. In the group who received anticoagulation alone (n = 85), the major bleeding rate was 5%, and for patients who received thrombolysis and anticoagulation (n = 24), the major bleeding rate was 21%. Direct comparison of these outcomes is very difficult given the likely significant selection bias as to which patients were offered which therapy. The panel noted that bleeding may occur in RVT, in the absence of anticoagulation, depending on gestation, severity of accompanying thrombocytopenia, and the involvement of the adrenal glands in the renal/peri-renal infarction. The panel also noted that bleeding risks with the use of heparinoids will increase substantially in the presence of renal failure.

***Other EtD criteria and considerations.*** The panel noted that babies with RVT are often in neonatal units where the risk benefit ratio of anticoagulation or thrombolysis is considered differently compared with hematologists (see online EtD frameworks for Recommendation 19 and Recommendations 20a and 20b).

***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 in terms of long-term renal damage and hypertension, in particular from using anticoagulation in all children with RVT. In children with unilateral disease, the panel placed a high value on the risk of bleeding from thrombolysis and recommends anticoagulation alone. The GRADE methodology framework states that a strong recommendation may be warranted despite low or very low confidence in effect estimates under 5 specific circumstances.[21] In this instance, the panel agreed that the circumstance when low-quality evidence suggests benefit and high-quality evidence suggests harm or a very high cost was applicable. In children with IVC extension, the decision may be more difficult, and individual factors need consideration; however, it likely that the potential benefits of thrombolysis outweigh the bleeding risk in children with bilateral disease and renal impairment. There is very low certainty that there is an effect of anticoagulation or 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 questions:

- More high-quality evidence for baseline risks, duration of treatment, and agents used, as well as better data to assess anticoagulation vs no anticoagulation in RVT and
- Better subgroup data to identify the children who would benefit most from thrombolysis.

## PVT

*Question: Should anticoagulation vs no anticoagulation be used in pediatric patients with PVT?*

**Recommendation 21a**

The ASH guideline panel *suggests* using anticoagulation rather than no anticoagulation in pediatric patients with PVT with occlusive thrombus, postliver transplant, and idiopathic PVT (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

**Recommendation 21b**

The ASH guideline panel *suggests* using no anticoagulation rather than anticoagulation in pediatric patients with PVT with nonocclusive thrombus or portal hypertension (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

**Remarks for recommendations 21a and 21b:** In children who will not be anticoagulated, follow-up monitoring is important, because extension of thrombus or organ dysfunction may require reconsideration of treatment options.

***Summary of the evidence.*** We found 3 observational studies. Two were follow-up studies of umbilical vein catheterization that reported PVT in 43 of 100 and 1 of 100 neonates. The third reported a retrospective cohort of 133 children with PVT. There were insufficient data about subgroups. The panel was surveyed and reported that they have managed ~800 patients during their years of practice. Indirect data from adults were not used. The evidence profile and EtD framework are available online for Recommendations 21a and 21b.

***Benefits.*** Studies reported 16% overall risk of death, with no information for each group separately. In patients with no anticoagulation, spontaneous resolution of PVT is reported in 70% to 77% of patients with nonocclusive thrombus and in 31% to 48% of patients with occlusive thrombus. The panel survey reported that ~50% of affected children are not treated with anticoagulation; of these, <5% have a progression of the thrombosis, and <1% die. 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 bleedings in all patients with PVT varies from 5% to 80% and is primarily related to esophageal varices and portal hypertension. Studies did not report bleeding events separately in those receiving or not receiving anticoagulation. The rate of bleeding (from other pediatric populations) ranges from 3% to 5% with low-molecular-weight heparin, unfractionated heparin, or vitamin K antagonists.

***Other EtD criteria and considerations.*** The panel noted that PVT may occur in a number of clinically distinct scenarios (eg, neonates secondary to umbilical vein catheterization, postliver transplant patients, or idiopathic in older children) and that these subgroups needed to be considered differently.

***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. Based on the body of available evidence, the balance probably favors anticoagulation for occlusive PVT, present in a liver transplant patient, or idiopathic PVT. The balance probably favors no anticoagulation for nonocclusive PVT or in the presence of portal hypertension, suggesting the thrombosis is old. 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 research question: studies to determine the outcomes, with or without anticoagulation, in clinical subgroups of PVT are required.

## CSVT

*Question: Should anticoagulation vs no anticoagulation be used in pediatric patients with CSVT?*

**Recommendation 22a**

The ASH guideline panel *recommends* using anticoagulation rather than no anticoagulation in pediatric patients with CSVT without hemorrhage (strong recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remarks:** The panel determined that, even in the presence of very low certainty in the evidence, the magnitude and direction of effect, in addition to indirect evidence from adult patients with the same direction of effect, support a strong recommendation because this is a life-threatening situation.

**Recommendation 22b**

The ASH guideline panel *suggests* using anticoagulation rather than no anticoagulation in pediatric patients with CSVT with hemorrhage (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remarks:** Patients with intracerebral hemorrhage were included in the identified studies with lack of specific evidence, and the panel's collective expertise suggests that patients with hemorrhagic CSVT have worse outcomes, leading to this recommendation as conditional.

*Question: Should thrombolysis followed by standard anticoagulation vs anticoagulation alone be used in pediatric patients with CSVT?*

**Recommendation 23**

The ASH guideline panel *suggests against* using thrombolysis followed by standard anticoagulation; rather, anticoagulation alone should be used in pediatric patients with CSVT (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remarks:** The evidence does not clearly separate systemic vs catheter-directed thrombolysis. Patients who receive thrombolytics are likely to be more unwell with worse outcomes, which leads to very low certainty in the evidence. However, there were insufficient data to support specific subgroups who would benefit from the intervention. Based on the panel's collective experience, for children with CSVT without evidence of ischemia, there is no rationale for using thrombolysis.

***Summary of the evidence.*** We found 17 observational studies in children, with >1200 total overall patients, that assessed mortality related to anticoagulation in CSVT. Eleven observational studies that included just over 800 children considered severe CSVT (children and neonates), assessed as progression or no recanalization on follow-up (range, 1 week to 6 months). Five observational studies (57 patients) assessed neurological outcome with a median follow-up of 2 years. Ten observational studies (726 patients) assessed major bleeding as an adverse outcome. There were 7 case reports or case studies that included patients who received thrombolysis, although the total number of patients receiving this therapy was 17. The panel noted that it would be important to consider the following CSVT subgroups of interest: hemorrhagic vs nonhemorrhagic, infarct vs no infarct present, and age (neonates vs older children). However, the evidence obtained makes no clear distinction among these subgroups in the intervention and control arms. The outcomes considered included mortality, progression and nonresolution of CSVT, major bleeding, and long-term neurological outcome. All studies were case control, cohorts, case series, or case reports, and some had comparative arms. There is a high risk of bias as the result of confounding and selection. Indirect evidence from adult data were not considered. The evidence profiles and EtD frameworks are available online for Recommendations 22a and 22b and Recommendation 23.

***Benefits.*** Anticoagulation reduced mortality (risk ratio [RR], 0.36; 95% CI, 0.16-0.81) in neonates and children combined. The baseline mortality was 75 per 1000 children, and it was 48 fewer per 1000 with anticoagulation (95% CI, 63 fewer to 14 fewer). However, when neonates and children were considered separately, the CI crossed the null and, hence, the threshold for plausible benefit or harm. In the 17 children who received thrombolysis, 3 patients (18%) died. Anticoagulation also reduced severe CSVT in children and neonates (RR, 0.33; 95% CI, 0.18-0.58), assessed as either progression or no recanalization on follow-up (range, 1 week to 6 months). The baseline rate was 176 per 1000; with anticoagulation, it was 118 fewer per 1000 (95% CI, 74 to 145 fewer). This effect remained when neonates and children were considered separately. Of the 17 patients who received thrombolysis, 1 patient (6%) had no resolution of the thrombosis. Neurological sequelae assessed with a median follow-up of 2 years was reduced by anticoagulation, with an odds ratio of 0.46 (95% CI, 0.23-0.94). The baseline risk obtained from 3 studies was 762 per 1000; with anticoagulation, it was 166 fewer per 1000 (95% CI, 11-338 fewer). Of 17 patients with CSVT who underwent thrombolysis, 4 (24%) had neurological sequelae. Overall, the certainty in these estimated effects is very low owing to the high risk of bias in the studies and imprecision of the estimates.

***Harms and burden.*** There was no difference in the risk of major bleeding between those who received anticoagulation and those who did not (RR, 1.03; 95% CI, 0.14-7.49). Of the 17 patients who received thrombolysis, 8 patients (47%) had major bleeding. There is very low certainty in the estimate of the risk of adverse effects due to significant selection bias and confounding.

***Other EtD criteria and considerations.*** The panel noted that a variety of comorbidities can be associated with CSVT in children. Some children may have local infection, such as mastoiditis, and others have acute leukemia and are receiving asparaginase. The appropriate management of these comorbidities is important in the overall management of the child.

***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 children with CSVT. The GRADE methodology framework states that a strong recommendation may be warranted, despite low or very low confidence in effect estimates under 5 specific circumstances.[21] In this instance, the panel agreed that the circumstance when low-quality evidence suggests benefit in a life-threatening situation (evidence regarding harms can be low or high) was applicable. The panel noted, even in the presence of very low certainty in the evidence, the magnitude and direction of effect and agreed to a strong recommendation in children without overt hemorrhage. Patients with intracerebral hemorrhage were included in the identified studies with lack of specific evidence, and the panel's collective expertise suggests that patients with hemorrhagic CSVT have worse outcomes, leading to the second recommendation as conditional.

The evidence does not clearly separate systemic vs catheter-directed thrombolysis. Patients who receive thrombolytics are likely to be more unwell with worse outcomes, which leads to very low certainty in the evidence. Based on the panel's collective experience, there is no rationale for using thrombolysis for children with CSVT without evidence of ischemia. There are insufficient data to support specific subgroups who would benefit from thrombolysis.

There is very low certainty that there is an effect of anticoagulation or 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 questions:

- Further studies focusing on specific subgroups (hemorrhagic vs nonhemorrhagic, infarct vs no infarct, neonatal vs older child) to determine whether different treatment strategies are required for different subgroups and
- Further studies to determine whether catheter-directed thrombolysis has a different risk benefit ratio from systemic thrombolysis

## Purpura fulminans due to homozygous protein C deficiency

*Question: Should protein C replacement vs anticoagulation be used in pediatric patients with congenital 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 of effects ⊕◯◯◯). **Remarks:** The panel determined that the long-term effectiveness of protein C replacement was superior to that offered by anticoagulation and did not have the adverse bleeding risk of anticoagulation. However, protein C is expensive, and cost may be prohibitive.

*Question: Should anticoagulation plus protein C replacement vs anticoagulation alone be used in pediatric patients with congenital purpura fulminans due to homozygous protein C deficiency?*

**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 homozygous protein C deficiency (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remarks:** This recommendation applies in an acute setting (acute episode of purpura fulminans) in which protein C replacement plus anticoagulation is considered a better option than anticoagulation alone. For long-term treatment, when the recommendation to fully supplement with protein C cannot be followed for pragmatic or cost reasons, 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.

*Question: Should liver transplantation vs no liver transplantation (anticoagulation or protein C replacement) be used in pediatric patients with congenital purpura fulminans due to homozygous protein C deficiency?*

**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 of effects ⊕◯◯◯). **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.

***Summary of the evidence.*** We found 1 case series and 4 case reports that described anticoagulation (n = 21) or protein C replacement (n = 11) for congenital purpura fulminans. There were also 13 case reports that described a combination of anticoagulation and protein C replacement therapy (n = 11) and 5 case reports of liver transplant for homozygous protein C deficiency. The panel considered that treatment consists of long-term maintenance therapy, as well as therapy required for acute exacerbations. Most case reports included the use of protein C replacement in the form of protein C concentrate or fresh-frozen plasma for management of acute exacerbations, independent of the long-term maintenance therapy being used. There were no relevant indirect data from adults. The evidence profiles and EtD frameworks are available online for Recommendation 24, Recommendation 25, and Recommendation 26.

***Benefits.*** The cases that received protein C replacement or protein C replacement and anticoagulation had no mortality, pulmonary embolus, bleeding, or skin necrosis compared with rates of 5%, 38%, 14%, and 14%, respectively, in children who received anticoagulation alone. In the 5 transplanted children, transplant took place at 6 months to 8 years of age. All patients survived with normal levels of protein C. None had major bleeding. Overall, the certainty in these estimated effects is very low owing to the risk of bias, including selection bias, and important imprecision of the estimates.

***Harms and burden.*** Anticoagulation is associated with a major bleeding rate of 14%; no major bleeding was reported in patients treated with protein C alone or with protein C and anticoagulation.

***Other EtD criteria and considerations.*** Protein C replacement is very expensive, especially as the child increases in age (and size), and may not be feasible in many health systems. In addition, protein C replacement must be given either IV or subcutaneously daily or at least multiple times per week. If anticoagulation is used, vitamin K antagonists at high intensity are usually required. The use of combination protein C and anticoagulation reduces the cost of replacement therapy and reduces the intensity of anticoagulation required, hence reducing the bleeding risk. In addition, if anticoagulation is used as maintenance therapy, protein C replacement may be required in acute exacerbations. Thus, Recommendation 24 acknowledges the long-term superiority of protein C replacement over anticoagulation alone. Recommendation 25 acknowledges that, in the acute setting, both therapies may be required, as well as that combination therapy is preferable to anticoagulation alone in situations in which complete protein C replacement is not possible for cost or pragmatic reasons. The use of CVADs in this patient population is associated with a high incidence of CVAD-associated VTE. Liver transplantation is curative but has the upfront risk of morbidity and mortality (varies with donor and institution) and confers a separate set of long-term risks (long-term immunosuppression).

***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 protein C replacement therapy. Although protein C replacement is likely optimal therapy, the cost is frequently prohibitive; hence, clinicians often need to use anticoagulation as an alternative. The panel agreed that, if cost is the rationale for using anticoagulation rather than protein C replacement, using a combination of anticoagulation and whatever protein C replacement is feasible may be preferable to using anticoagulation alone. However, the second recommendation applies in an acute setting (acute episode of purpura fulminans) in which protein C replacement plus anticoagulation is considered a better option than anticoagulation alone, whereas in the scenario of long-term usage, the benefits and cost-effectiveness of the intervention (protein C replacement plus anticoagulation) are less certain. The role of liver transplant will vary, depending on patient and family preferences and their willingness to undertake the separate risks of transplant. Although, in the panel's experience, liver transplant is often used to avoid the long-term costs of protein C therapy, the optimal timing of this therapy is unknown. Clearly, transplant prior to the child sustaining irreversible organ damage is optimal. Protein C replacement therapy is usually required rather than anticoagulation in the lead-up to transplantation. There is very low certainty that there is an effect of protein C replacement, anticoagulation, or liver transplant 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 question: more information about the long-term outcomes and the comparative success of management options, as well as the optimal age for introducing those options, is required. Given the rarity of the disease, further information is more likely to come from observational studies and registries, which are of paramount importance in this disease.

## 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.

## Limitations of these guidelines

The recommendations in these guidelines were limited in every case by very low or low certainty in the evidence. The contribution of indirect adult VTE data is specified with each group of recommendations. In addition, indirect evidence from non-VTE treatment scenarios in children was used. For some recommendations, which related to relatively common clinical questions, there was very little or no published direct or relevant indirect evidence, and the panel was surveyed to provide unpublished collective data on which decisions could then be based. This process is explicitly identified for relevant recommendations, and there was agreement among the panel members.

## Revision or adaptation of the guidelines

### Plans for updating these guidelines

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

This document will be best used in conjunction with future guidelines assessing optimization of anticoagulation therapy in children.

### 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.[30]

### Priorities for research

Specific suggestions for research are detailed with each recommendation. However, the panel noted that, although the need for randomized trials of antithrombotic therapies in children is not debated, completing RCTs in neonates and children, especially related to anticoagulation, is very difficult. This is evidenced by the small number of trials completed and the fact that almost all trials of anticoagulation in children failed to meet their recruitment targets, despite continuing over longer time periods than originally planned. In developing these guidelines, there was a paucity of data about baseline risks and natural history for most VTE in children. Outcome measures remain unclear. Treatment effect and safety were also frequently unclear. The panel recommends that collaborative cohort studies (retrospective and prospective), registries, and other observational studies addressing these issues could contribute much to improve the current levels of evidence and are likely much more feasible than RCTs. The small numbers of patients contributing to the data supporting individual recommendations seriously limited the confidence in most recommendations.

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## Authorship

Contribution: P.M. wrote the first draft of this manuscript and revised the manuscript based on the authors' suggestions. S.K.V. contributed to drafting and critical revisions of the manuscript and contributed to further drafts; guideline panel members (P.M., C.A., M. Bonduel, L.R.B., T.C., A.K.C.C., S.H., C.M., J.M., F.N., S.H.O., H.v.O., J.W., S.K.V.) critically reviewed the manuscript and provided suggestions for improvement; members of the knowledge synthesis team (M. Bhatt, C.A.C., R.A.M., J.J.R., Y.R., N.S.) contributed evidence summaries to the guidelines; and C.A.C. and R.A.M. also checked the manuscript accuracy and coordinated the systematic review team with S.K.V. All authors approved the content. P.M. and S.K.V. were the chair and vice-chair of the panel and led the panel meeting.

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