ASH® CLINICAL PRACTICE GUIDELINES

Treatment of Pediatric Venous Thromboembolism

An Educational Slide Set

American Society of Hematology/International Society of Thrombosis and Hemostasis
2025 updated guidelines for treatment of venous thromboembolism in pediatric patients

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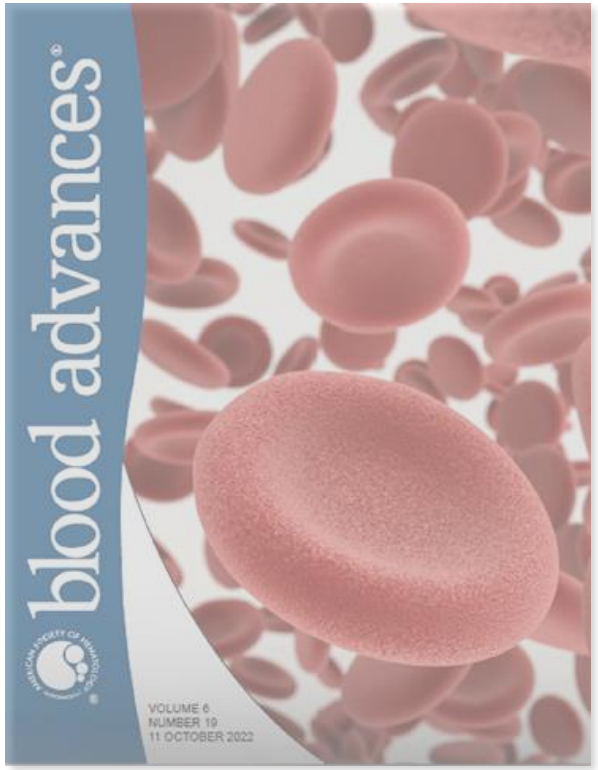
American Society of Hematology International Society on Thrombosis and Haemostasis 2025 updated guidelines for treatment of venous thromboembolism in pediatric patients



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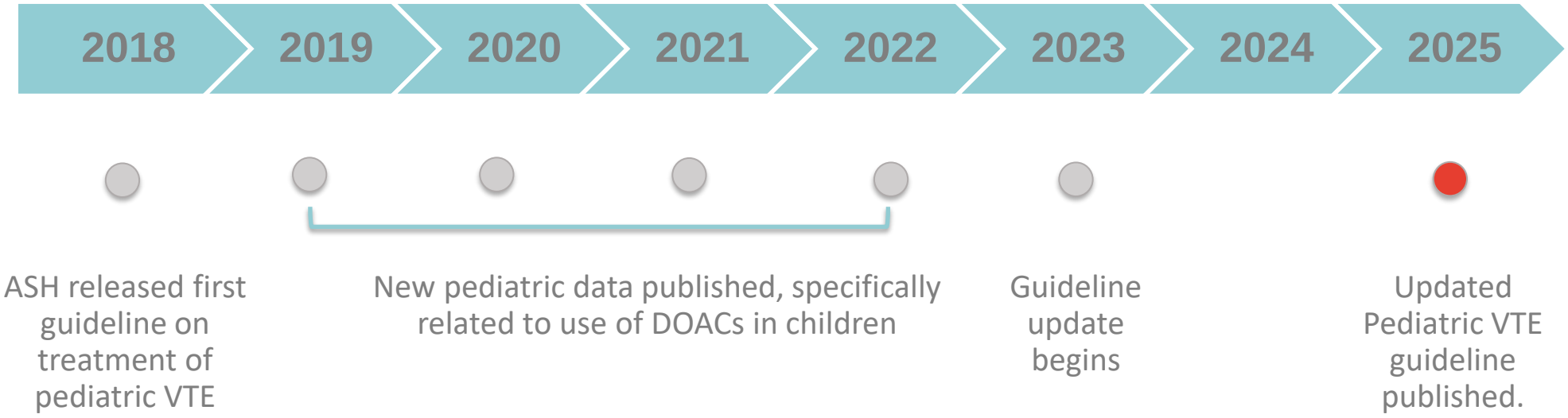
ASH Clinical Practice Guidelines on VTE

1. Prevention of VTE in Surgical Hospitalized Patients
2. Prevention of VTE in Medical Hospitalized Patients
3. Treatment of Acute VTE (DVT and PE)
4. Optimal Management of Anticoagulation Therapy
5. Prevention and Treatment of VTE in Patients with Cancer
6. Heparin-Induced Thrombocytopenia (HIT)
7. Thrombophilia
8. **Pediatric VTE**
9. VTE in the Context of Pregnancy
10. Diagnosis of VTE

History of VTE Pediatrics Guideline

ASH originally published guidelines for treatment of pediatric VTE in 2018. These guidelines were updated in 2025 in response to new pediatric data published over the preceding 4 years.



How were these guidelines updated?

PANEL FORMATION

Guideline panel was formed following these key criteria:

- Balance of expertise (including disciplines beyond hematology)
- Close attention to minimization and management of conflicts of interest

CLINICAL QUESTIONS

20 **clinically-relevant questions** generated in **PICO format** (population, intervention, comparison, outcome)

Example: PICO question
"Should anticoagulation versus no therapy be used in neonates with renal vein thrombosis?"

EVIDENCE SYNTHESIS

Evidence summary generated for each PICO question via systematic review of health effects plus:

- Resource use
- Feasibility
- Acceptability
- Equity
- Patient values and preferences

MAKING RECOMMENDATIONS

Recommendations made by guideline panel members based on evidence for all factors.

ASH guidelines are reviewed annually by expert work groups convened by ASH. Resources, such as this slide set, derived from guidelines that require updating are removed from the ASH website.

How patients and clinicians should use these recommendations

	STRONG Recommendation		CONDITIONAL Recommendation	
	"The panel recommends…"	"The panel recommends against…"	"The panel suggests…"	"The panel suggests against…"
				
For patients	Most individuals would want the intervention.		A majority would want the intervention, but many would not.	
For clinicians	Most individuals should receive the intervention.		Different choices will be appropriate for different patients, depending on their values and preferences. Use **shared decision making**.	

Objectives

By the end of this session, you should be able to

1. Describe recommendations for the duration of anticoagulant treatment of provoked VTE in children
2. Describe recommendations for the use of DOACs in children
3. Describe recommendations for the management of symptomatic and asymptomatic VTE in children

Pediatric venous thrombosis is a disease primarily of sick children

VTE in the general pediatric population is **rare** (0.07 to 0.14 per 10,000 children)

The rate of VTE in children is increased by **100 to 1,000 times** in hospitalized children

The most common precipitating factor is the presence of **CVAD*** which are related to 80-85% of pediatric VTE

There are now **3** anticoagulant drugs approved for use in children

**CVAD = central venous access device*

What is different in this updated guideline

- ***Whether to treat*** and ***what type of treatment*** in different scenarios
  - Includes discussion on duration and type of anticoagulation
- ***Anticoagulation*** **(AC)** refers to unfractionated heparin (UFH), low molecular weight heparin (LMWH), fondaparinux, vitamin K antagonists (VKA), and direct oral anticoagulants (DOACs) - rivaroxaban and dabigatran

Case 1: Provoked VTE in a child

- A 20-month-old toddler is admitted to the pediatric ICU with RSV and respiratory failure
- There is no personal or family history of thrombosis
- The patient is intubated, and a left femoral CVAD is placed
- 2 days after admission he develops left lower extremity swelling

Case 1: Provoked VTE in a child

Doppler ultrasound (US): occlusive thrombus is seen around the catheter in the common femoral vein - ***Provoked VTE***

Anticoagulation is started

Since the line is working and still necessary, it is left in place until just prior to discharge

Anticoagulation continues after hospital discharge

On follow-up at 6 weeks - swelling has resolved on physical exam, and an US with doppler shows a small segment of residual non-occlusive thrombus

This child has a provoked VTE.

His risk factors for the thrombus are resolved, and the clot has partially resolved and there is no longer occlusive thrombus.

How would you manage his VTE at this point?

A. Continue anticoagulation for a total of 3 months and then discontinue
B. Discontinue anticoagulation now that 6 weeks of treatment are completed
C. Continue treatment until thrombus resolves completely on US
D. Surgical thrombectomy

Recommendation

The ASH/ISTH guideline panel ***suggests*** 6 weeks rather than 3 months of anticoagulation **in select pediatric patients with provoked VTE**

Notes:

- This recommendation is based largely on the KIDS-DOTT* study evaluating treatment duration for provoked-VTE
- There were stringent inclusion/exclusion criteria and many children with provoked VTE were excluded

Patients are **excluded** from this recommendation if they have:

- **Pulmonary embolism**
- **Cancer associated VTE**
- **Recurrent VTE**
- **Persistent provoking risk factors**
- **Major thrombophilia**

Children with **persistent occlusive thrombus** at 6 weeks were not randomized in the KIDS-DOTT study and are **excluded** from this recommendation

Children with **persistent positive antiphospholipid antibodies** (APA) at 6 weeks were not randomized in the KIDS-DOTT study and are **excluded** from this recommendation

*Goldenberg N, et al; *JAMA*, 2022

Recommendation

The Kids-DOTT study demonstrated non-inferiority of 6 weeks of anticoagulation vs 3 months, based on outcomes of:

- Recurrent thrombosis
- Clinically relevant bleeding

Due to low numbers of events, relative effects were not estimable for:

- Risk of clinically relevant bleeding (6 weeks = 0.65% **vs** 3 months = 0.70%)
- Symptomatic recurrent VTE (6 weeks = 0.6% **vs** 3 months = 1.4%)
- Mortality (6 weeks = 1.9% **vs** 3 months = 1.9%)

Recommendation

The certainty of evidence for benefits, harms, and burden was considered low due to serious imprecision → ***Conditional recommendation***

The panel recognized that there may be benefits related to

- Quality of life with a shortened duration of therapy (especially for those receiving subcutaneous injections)
- Increasing acceptability and feasibility of the intervention
- Potential for moderate cost benefits

A note about thrombophilia testing…

- In the KIDS-DOTT study, all subjects had thrombophilia testing including APA
- Subjects with persistently positive APAs at 6 weeks were excluded from randomization
- The panel **DOES NOT** recommend thrombophilia testing in all pediatric patients with provoked VTE
  - **This is consistent with the ASH-ASPHO choosing wisely campaign** which does not recommend testing in pediatric patients with CVAD-associated VTE
  - Thrombophilia testing should be based on features such as clinical presentation and family history

Case 1: Conclusion

- The patient with provoked VTE had resolution of occlusive thrombus
- Given the resolution of provoking factors and symptoms, discontinuation of anticoagulation at this time is appropriate
- He continues to do well clinically and a follow-up ultrasound at 1 year shows no residual thrombosis

Case 1: Summary

It is now suggested that for many pediatric patients with provoked VTE, 6 weeks of anticoagulation treatment is an appropriate treatment course

Children with PE, recurrent VTE, persistent occlusive thrombus, cancer-associated VTE, persistent APAs or major thrombophilia, or ongoing provoking risk factors for VTE **are excluded** from this new recommendation

Future areas of study should include identifying additional patient groups who may benefit from 6 weeks of anticoagulation, and real-world data on DOACs for shortened duration of therapy

- *While DOACs are not excluded from this recommendation, the majority of children in KIDS-DOTT were treated with LMWH*

Case 2: Choice of anticoagulant

- A 14 year old, previously healthy female presents to the Emergency Department with acute onset dyspnea, cough and chest pain
- Vitals are notable for tachycardia, tachypnea with normal blood pressure
- **Past medical history**: dysmenorrhea for which she was started on a combined oral contraceptive pill 3-months ago
- **Family history**: negative for venous thrombo-embolism

Case 2: Choice of anticoagulant

- **CT Pulmonary Angiogram**: B/L segmental and subsegmental pulmonary embolism
- **Echocardiogram**: No evidence of right-sided heart strain
- **Troponin and pro-BNP levels**: Normal

Patient was admitted to the hospital and anticoagulation with LMWH was started. Gynecology referral was made to discuss appropriate alternative long-term menstrual management.

Chest pain and dyspnea improve over the next 3 days

Patient has provoked standard-risk PE (i.e. no echocardiographic or biochemical evidence of right ventricular dysfunction, and no evidence of hemodynamic compromise).

She has now completed 5-days of anticoagulation with LMWH

Which anticoagulant would you recommend for the ongoing management of this patient?

A. Continue LMWH for a total duration of 3-6 months

B. Transition the patient to rivaroxaban to complete 3-6 months

C. Transition the patient to dabigatran to complete 3-6 months

D. Transition the patient to VKA to complete 3-6 months

Both are reasonable options

Recommendation 17

- The ASH/ISTH guideline panel **suggests** using DOACs (Rivaroxaban/Dabigatran) over standard of care anticoagulants (LMWH, UFH, VKA, Fondaparinux) in pediatric patients with VTE

Remarks:

- Systematic review included 3 RCTs, 2 large multi-center trials and 1 small single-institution study
- 853 patients were recruited to these studies, of whom 523 received a DOAC (Rivaroxaban/Dabigatran)
- Rivaroxaban was dosed according to weight; Dabigatran dosed according to both age and weight

The following patients were **excluded** from the RCTs -

- Severe liver and renal impairment
- Pre-term neonates (<37 weeks GA)
- Neonates/infants <3rd percentile for weight
- Active bleeding/high risk of bleeding

In all the studies, **patients received a minimum of 5-days of parenteral anticoagulation with SOC** (i.e. unfractionated heparin, low molecular weight heparin or fondaparinux) before starting a DOAC (Rivaroxaban/Dabigatran).

Recommendation 17

Outcomes	Number of patients		Effect	
	DOAC	SOC	Relative (95% CI)	Absolute (95% CI)
Mortality	3/522	2/267	**RR: 0.71** (0.14 to 3.56)	**2 fewer per 1000** (6 fewer to 19 more)
Thrombus recurrence	11/523	14/267	**RR: 0.43** (0.2 to 0.93)	**30 fewer per 1000** (42 fewer to 4 fewer)
Thrombus resolution	395/512	181/255	**RR: 1.09** (0.99 to 1.19)	**64 more per 1000** (7 fewer to 135 more)
Major Bleeding	4/517	5/264	**RR: 0.48** (0.14 – 1.57)	**10 fewer per** 1000 (16 fewer to 11 more)
Clinically Relevant Non-Major Bleeding	12/506	2/252	**RR: 2.98** (0.67 – 13.27)	**16 more per 1000** (3 fewer to 97 more)

Certainty of evidence about benefits and adverse events ranged from very low to low to moderate

Length of follow up in the RCTs (3-6 months) was too short to accurately predict risk of post thrombotic syndrome

Recommendation 18

- The ASH/ISTH guideline panel **suggests** using rivaroxaban over standard of care anticoagulants (LMWH, UFH, VKA, Fondaparinux) in pediatric patients with venous thromboembolism (VTE).

Recommendation 19

- The ASH/ISTH guideline panel **suggests** using dabigatran over standard of care anticoagulants (LMWH, UFH, VKA, Fondaparinux) in pediatric patients with venous thromboembolism (VTE).

Recommendation 18 and 19

- Small **benefit** of rivaroxaban over SOC with regards to reduced thrombus recurrence and improved thrombus resolution.
- **Undesirable effects** of rivaroxaban namely an increase in clinically relevant non-major bleeding (CRNMB) was small.

- Small **benefit** of dabigatran over SOC with regards to reduced thrombus recurrence and improved thrombus resolution.
- **Undesirable effects** of dabigtran were trivial.

Remarks:

- Estimates were imprecise due to the small number of events and wide CI.
- Increased menstrual bleeding with rivaroxaban – important consideration in adolescent females.
- 10% of patients in the Dabigatran arm of DIVERSITY trial – taken off study since they failed to achieve an a-priori therapeutic levels.

Recommendation 20

- The ASH/ISTH guideline panel **suggests** using either rivaroxaban or dabigatran in pediatric patients with venous thromboembolism (VTE) although there may be individual populations or jurisdictional availability that would lead clinicians to choose one agent over the other

Remarks:

- DOACs orally administered – avoiding the need for daily injections of LMWH
- Fewer drug interactions compared to VKA
- Do not require routine monitoring labs
- Access to these agents in low and middle-income countries needs to be addressed

Patient cohorts where DOACs should not be used/ used with great caution -

- Patients with anti-phospholipid antibody syndrome and mechanical valves
- Patients with known/potential gut absorption issues including short gut syndrome
- Recent surgery
- Liver disease (ALT >5x ULN and/or bilirubin >2x ULN)/ liver disease causing coagulopathy
- Renal disease (GFR <30 mL/min)
- Pre-term neonates
- Patients with active cancer

Case 2

- Patient and her parents decide to transition to rivaroxaban
- Rivaroxaban 20 mg QHS is started after completing 5-days of LMWH
- Rivaroxaban is well tolerated with the exception of slightly heavy menstrual bleeding
- Follow up CTPA after 3-months of anticoagulation shows radiological thrombus resolution – rivaroxaban is discontinued

Case 2 Summary

Children with venous thromboembolism can be treated with direct oral anticoagulants (rivaroxaban/dabigatran) after ≥ 5days of initial parenteral treatment (UFH, LMWH or Fondaparinux)

Either rivaroxaban or dabigatran may be used to treat pediatric venous thromboembolism

In certain pediatric cohorts including anti-phospholipid antibody syndrome, active cancer, gut absorption issues, preterm neonates, severe liver and kidney disease, SOC may be preferred over DOACs till more evidence is available

Case 3: Anticoagulation for symptomatic DVT

- A 28-year-old female is admitted at 36 weeks of gestation and delivered fraternal twins
- Patient 1: Twin A
- Patient 2: Twin B

Case 3: Anticoagulation for symptomatic DVT

Patient 1 : Twin A

- Twin A has respiratory distress and venous access was required
- Attempted umbilical venous line was not successful; a PICC was inserted
- He developed swelling of the right arm, and thus doppler US was done
- Ultrasound showed occlusive thrombi in axillary vein and subclavian vein
- PICC was functional and the patient still required vascular access

Case 3: Anticoagulation for symptomatic DVT

Patient 1 : Twin A

Question 1: Does the patient need to receive an anticoagulant, and can the PICC be removed?

- ❑ Patient treated with LMWH, PICC removed
- ❑ Patient treated with LMWH, PICC not removed
- ❑ Patient not treated with anticoagulant , PICC removed

Case 3: Anticoagulation for symptomatic DVT

Patient 1 : Twin A

Question 1: Does the patient need to receive an anticoagulant, and can the PICC be removed?

- ❑ Patient treated with LMWH, PICC removed
- ✓ Patient treated with LMWH, PICC not removed
- ❑ Patient not treated with anticoagulant , PICC removed

- **The risk factor is not removed, and the patient is symptomatic, thus the patient is anticoagulated with LMWH**
- **Vascular access is necessary and PICC is functional, thus PICC is not removed**

Case 3: Anticoagulation for symptomatic DVT

Patient 1 : Twin A

- Patient received 5 days of LMWH and PICC is still required

Question 2: should the patient be switched to a DOAC or continue to use LMWH?

- ❑ Continue LMWH
- ❑ Switch to DOAC

Case 3: Anticoagulation for symptomatic DVT

Patient 1 : Twin A

- Patient received 5 days of LMWH and PICC is required

Question 2: should the patient be switched to a DOAC or continue to use LMWH?

✓ Continue LMWH

❑ Switch to DOAC

- **Neonates < 37 weeks gestation were excluded from phase 3 trials for the approved DOACs for children (rivaroxaban, dabigatran) and thus the patient stayed on LMWH**

Case 3: Anticoagulation for symptomatic DVT

Patient 1: Twin A

- PICC was not required at 2 weeks of age and PICC was removed
- Repeat US showed non-occlusive thrombus
- Swelling of arm improved

Question 3: how long shall the patient stay on LMWH

- ❑ 4 weeks of LMWH
- ❑ 6 weeks of LMWH
- ❑ 3 months of LMWH

Case 3: Anticoagulation for symptomatic DVT

Patient 1 : Twin A

- PICC was not required at 2 weeks of age and removed
- Repeat US showed no progress of thrombus
- Swelling of arm improved

Question 3: how long shall the patient stay on LMWH

- ✓ 4 weeks of LMWH
- ✓ 6 weeks of LMWH
- ❑ 3 months of LMWH

- According to the Kids-DOTT trial, non occlusive thrombus with risk factors removed can be treated for 6 weeks
- However, in real-world experience and the Einstein Jr. trial, the treatment period is only 1 month for CVC related thrombus in < 2 years of age

Case 3: Anticoagulation for symptomatic DVT

Patient 2 : Twin B

- Attempted umbilical venous line was not successful; a PICC was inserted
- Policy of the NICU was to do screening ultrasound for PICC before removal
- Ultrasound showed a non-occlusive thrombus in the subclavian vein with no symptoms

Case 3: Anticoagulation for symptomatic DVT

Patient 2 : Twin B

Question 4: Does the patient need to be treated, and can the PICC be removed?

- ❑ Patient treated with LMWH; PICC removed
- ❑ Patient treated with LMWH; PICC not removed
- ❑ Patient not treated with anticoagulant; PICC removed

Case 3: Anticoagulation for symptomatic DVT

Patient 2: Twin B

Question 4: Does the patient need to be treated, and can the PICC be removed?

- ❑ Patient treated with LMWH; PICC removed
- ❑ Patient treated with LMWH; PICC not removed
- ✓ Patient not treated with anticoagulant; PICC removed

- **The PICC was removed since vascular access was NOT required**
- **The baby was NOT anticoagulated since the thrombus did not cause any symptoms, and the risk factor was removed**
- **Repeat US done after three days showing no thrombus; the patient remained asymptomatic**

Recommendation #1

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

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

Recommendation #2

- The ASH/ISTH Guideline Panel **suggests** either using anticoagulation or no anticoagulation in pediatric patients with clinically unsuspected (previously termed asymptomatic) deep vein thrombosis (DVT) or pulmonary embolism (PE) (conditional recommendation based on very low certainty in the evidence about effects)

Remarks: The natural history of clinically unsuspected DVT or PE in pediatric patients appears to carry a lower risk of acute and long-term sequelae, especially in certain pediatric sub-populations. The recommendation is based on studies that report outcomes for pediatric patients with clinically unsuspected DVT or PE. If clinically unsuspected DVT or PE is detected, the decision to treat or not treat should be individualized.

Case 3: Summary

Anticoagulation is suggested for most pediatric patients with symptomatic DVT or PE, over no anticoagulation

For clinically unsuspected DVT or PE, the benefits and harms of anticoagulation vary among populations and either anticoagulation or no anticoagulation may be appropriate.

Future research should help to better understand the natural history of clinically unsuspected DVT or PE, benefits, and harms of treatment in a variety of subgroups and clinical settings in pediatrics.

Other guideline recommendations that were not covered in this session

For these topics, conditional recommendations were made based on low or very low certainty of evidence

- Management of unprovoked DVT or PE
- Management of superficial vein thrombosis
- Management of VTE in specific locations (cerebral sinus venous thrombosis, right atrial thrombosis, portal vein thrombosis)
- Use of thrombolysis
- When to remove a central line in setting of line-associated VTE

Future Priorities for Research

- Risk stratification of pediatric subgroups who would benefit most and least from treatment
- Further studies on specific VTE types
- Further studies on thrombolysis
- Studies on DOACs in special populations (such as neonates and children with cancer)
- Studies on reversal agents for DOACs
- Studies on the need for 5+ days of parenteral therapy prior to starting DOACs

In Summary: Back to our Objectives

1. Describe recommendations for the duration of anticoagulant treatment of provoked VTE in children
   - ✓ Anticoagulation for 6 weeks is suggested for many pediatric patients with provoked VTE
2. Describe recommendations for the use of DOACs in children
   - ✓ Anticoagulation with DOACs (rivaroxaban/dabigatran) is suggested for pediatric patients with VTE after at least 5 days of heparin therapy
3. Describe recommendations for the management of symptomatic and asymptomatic VTE in children
   - Anticoagulation is suggested for treatment of symptomatic VTE, but either anticoagulation or no anticoagulation may be appropriate in a child with asymptomatic VTE

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See more about the **ASH VTE guidelines** at *hematology.org/VTEguidelines*