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American Society of Hematology
2021 L Street NW, Suite 900,
Washington, DC 20036
Phone: 202-776-0544 | Fax 202-776-0545
bloodadvances@hematology.org

ASH ISTH 2026 guidelines for Anticoagulant Prophylaxis of Pediatric Patients at Risk of Venous Thromboembolism

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Marisol Betensky (Johns Hopkins All Children's Hospital, United States) Muayad Azzam (University of Kansas Medical Center, United States) Rachel Bercovitz (Northwestern University Feinberg School of Medicine, United States) Rukhmi Bhat (Ann and Robert H. Lurie Childrens Hospital of Chicago, United States) Tina Biss (The Newcastle upon Tyne Hospitals NHS Foundation Trust, United Kingdom) Brian Branchford (Versiti Blood Center Wisconsin, United States) Leonardo Brandão (The Hospital for Sick Children, Canada) Anthony Chan (McMaster University, Canada) E. Vincent Faustino (Yale School of Medicine, United States) Qais Hamarsha (The University of Kansas Medical Center, United States) Julie Jaffray (Rady Children's Hospital, University of California, San Diego, United States) Sophie Jones (The University of Melbourne, Australia) Hassan Kawtharany (University of Kansas Medical Center, United States) Bryce Kerlin (Abigail Wexner Research Institute at Nationwide Children's Hospital, United States) Jana Khawandi (The University of Kansas Medical Center, United States) Grace Krider (Ascension St. Vincent Indianapolis, United States) Nicole Kucine (Weill Cornell Medicine, United States) Riten Kumar (Harvard Medical School, United States) Christoph Male (Medical University of Vienna, Austria) Paul Monagle (department of Paediatrics, University of Melbourne , Australia , Australia, Australia) Marie-Claude Pelland-Marcotte (Centre Hospitalier Universitaire de Québec, Canada) Leslie Raffini (Children's Hospital of Philadelphia, United States) Chittalsinh Raulji (University of Nebraska Medical Center / Children's Nebraska, United States) Sarah Sartain (Department of Pediatrics, Division of Hematology/Oncology, Baylor College of Medicine, Texas Children's Hospital, United States) Clifford Takemoto (St. Jude Children's Hospital, United States) Cristina Tarango (Cincinnati Children's Hospital Medical Center Cancer and Blood Diseases Institute and the University of Cincinnati College of Medicine, United States) C. van Ommen (Erasmus MC/Sophia Children's Hospital, Netherlands) Maria Velez (LSU Health Sciences Center/Manning Family Children's, United States) Sara Vesely (University of Oklahoma Health Sciences Center, United States) John Wiernikowski (McMaster University, Canada) Suzan Williams (Hospital for Sick Children, Canada) Hope Wilson (University of Alabama at Birmingham Heersink School of Medicine, Children's of Alabama, United States) Gary Woods (Children's Healthcare of Atlanta, United States) Reem Mustafa (University of Kansas Medical Center, United States)

Abstract:
Background: Venous thromboembolism (VTE) is a significant cause of morbidity in children, particularly among hospitalized patients and those with chronic medical conditions. There is a lack of consensus on anticoagulant prophylaxis strategies. Objective: These evidence-based guidelines from the American Society of Hematology (ASH) and the International Society on Thrombosis and Haemostasis (ISTH) are intended to support patients and health care professionals in decisions about anticoagulant prophylaxis for pediatric VTE prevention. Methods: ASH formed a multidisciplinary guideline panel that included one patient representative. The University of Kansas Health System supported the guideline development process, including systematic evidence reviews up to April 2025. Clinical questions and outcomes were prioritized according to their importance for clinicians and patients. The panel used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to assess certainty in the evidence and make recommendations. Results: The panel agreed on 12 recommendations. For pediatric patients with solid cancer, trauma or critically ill, the panel issued conditional recommendations suggesting no anticoagulant prophylaxis. For pediatric patients with antiphospholipid antibody syndrome, or those on long-term total parenteral nutrition, the panel issued conditional recommendations suggesting the use of anticoagulant prophylaxis. Other pediatric subgroups addressed included patients with acute lymphoblastic leukemia or lymphoma, surgical and hospitalized patients, and those with a central venous access device. Conclusions: High-quality data on anticoagulant prophylaxis for pediatric VTE prevention are scarce. Key research priorities include the development and validation of subgroups-specific VTE risk assessment models, and evaluation of the safety and efficacy of risk-stratified anticoagulant prophylaxis strategies across different pediatric subgroups.

Conflict of interest: COI declared - see note

COI notes: All authors were members of the guideline panel or members of the systematic review team or both. As such, they completed a disclosure of interest form, which was reviewed by ASH/ISTH and is available as supplements 2 and 3 ("Participant Information Forms of Guideline Panel")

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Marisol Betensky[1], Muayad Azzam[2], Rachel Bercovitz[3], Rukhmi V Bhat[4], Tina Biss[5], Brian Branchford[6], Leonardo R. Brandão[7], Anthony KC Chan[8], E Vincent S Faustino[9], Qais Hamarsha[10], Julie Jaffray[11], Sophie Jones[12], Hassan Kawtharany[13], Bryce A. Kerlin[14], Jana Khawandi[15], Grace Krider[16], Nicole Kucine[17] , Riten Kumar[18], Christoph Male[19], Paul Monagle[20], Marie-Claude Pelland-Marcotte[21], Leslie Raffini [22], Chittalsinh Raulji [23], Sarah E Sartain[24], Clifford M. Takemoto[25], Cristina Tarango[26], C. Heleen van Ommen[27], Maria C. Velez[28], Sara K. Vesely[29], John Wiernikowski[30] , Suzan Williams[31], Hope P. Wilson[32], Gary Woods[33], Reem A. Mustafa[34]

Corresponding Author:

Marisol Betensky MD, MPH
Johns Hopkins All Children's Hospital
501 6th Avenue South
St. Petersburg, FL 33701, USA
P: 727-767-2381
F: 727-767-6949
Email: marisol.betensky@jhmi.edu

1. Department of Pediatrics, Division of Haematology, Johns Hopkins School of Medicine, Baltimore MD; Cancer and Blood Disorders Institute, Johns Hopkins All Children's Hospital, St. Petersburg, FL, marisol.betensky@jhmi.edu, ORCID 0001-6725-3035
2. Evidence-Based Practice and Impact Center, Department of Internal Medicine, University of Kansas Medical Center, Kansas City, KS, USA, mazzam@kumc.edu, ORCHID ID: 0000-0002-2046-8343
3. Northwestern University Feinberg School of Medicine, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA, rbercovitz@luriechildrens.org ORCID ID: 0000-0001-6653-5946
4. Northwestern University Feinberg School of Medicine, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA, rbhat@luriechildrens.org, ORCHID ID: 0000-0002-1700-4804
5. The Newcastle upon Tyne Hospitals NHS Foundation Trust, Department of Haematology, Newcastle upon Tyne, UK, t.biss@nhs.net, ORCHID ID 0000-0001-9986-4973
6. Versiti Medical Science Institute, Wauwatosa, WI, USA. bbranchford@versiti.org. ORCID 0000-0002-4076-270X

7. Dalla Lana School of Public Health, University of Toronto. The Hospital for Sick Children, Toronto, Ontario, Canada. Leonardo.brandao@sickkids.ca; ORCID ID 000-0001-7711-4530
8. McMaster Children's Hospital, McMaster University, Hamilton, Canada ORCID 0000-0003-1551-3995 akchan@mcmaster.ca
9. Yale School of Medicine, Department of Pediatrics, Section of Critical Care, New Haven, CT, USA, vince.faustino@yale.edu ORCHID ID 0000-0001-6155-2691
10. Evidence-Based Practice and Impact Center, Department of Internal Medicine, University of Kansas Medical Center, Kansas City, KS, USA, qhamarsha@kumc.edu, ORCHID 0000-0001-9711-4650
11. University of California, San Diego, Rady Children's Hospital, San Diego, CA, jjaffray@rchsd.org ORCHID ID 0000-0002-1175-7266
12. University of Melbourne, Royal Children's Hospital, Murdoch Children's Research Institute Melbourne, Victoria, Australia. sophie.jones@unimelb.edu.au. ORCID 0000-0002-9272-6540
13. Evidence-Based Practice and Impact Center, Department of Internal Medicine, University of Kansas Medical Center, Kansas City, KS, USA, hkawtharany@kumc.edu. ORCHID ID: 0009-0007-3725-8485
14. Nationwide Children's Hospital and The Ohio State University, Department of Pediatrics, Columbus, OH, USA, bryce.kerlin@nationwidechildrens.org, ORCID 0000-0002-1756-8271
15. Evidence-Based Practice and Impact Center, Department of Internal Medicine, University of Kansas Medical Center, Kansas City, KS, USA, jkhawandi@kumc.edu. ORCHID ID: 0000-0001-7581-4787
16. Ascension St. Vincent Indianapolis; Grace Krider BSN, RN; gnkrider@yahoo.com
17. Department of Pediatrics, Weill Cornell Medicine, New York, NY, USA; nik9015@med.cornell.edu; ORCID 0000-0002-4865-4033
18. Harvard Medical School, Department of Pediatrics, Dana Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA, riten.kumar@childrens.harvard.edu, ORCID 0000-0001-8004-4190
19. Department of Paediatrics, Medical University of Vienna, Vienna, Austria, Christoph.male@meduniwien.ac.at, ORCID 0000-0002-4989-6421
20. University of Melbourne, Royal Children's Hospital, Murdoch Children's Research Institute Melbourne, Victoria, Sydney Children's Hospital, Randwick NSW, Australia, paul.monagle@unimelb.edu.au, ORCHID ID 0000-0002-3970-8984
21. Department of Pediatrics, Centre Hospitalier Universitaire de Québec – Centre Mère-Enfant, Québec City, QC, marie-claude.pelland-marcotte.med@ssss.gouv.qc.ca, ORCID 0000-0003-2364-7205
22. University of Pennsylvania, Children's Hospital of Philadelphia, Department of Pediatrics, Philadelphia, PA, raffini@chop.edu, ORCHID ID 0000-0001-8152-1040
23. University of Nebraska Medical Center, Children's Hospital Nebraska, Department of Pediatrics, Omaha, NE. Chittalsinh.raulji@unmc.edu, ORCID 0009-0008-7610-7214
24. Baylor College of Medicine, Texas Children's Hospital, Department of Pediatrics, Section of Hematology, Houston, TX, USA, sartain@bcm.edu, ORCID ID 0000-003-2204-4568
25. St. Jude Children's Research Hospital, Department of Hematology, Memphis, TN clifford.takemoto@stjude.org, ORCID 0000-0002-2832-6884
26. University of Cincinnati College of Medicine, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH cristina.tarango@cchmc.org ORCID iD 0000-0002-0283-9972

27. Erasmus Medical Center Sophia Children's Hospital, Department of Pediatric Hematology, Rotterdam, the Netherlands c.vanommen@erasmusmc.nl ORCID 0000-0001-9036-039X
28. Louisiana State University Health Sciences Center/Children's Hospital New Orleans, Department of Pediatrics, New Orleans, Louisiana, mvelez@lsuhsc.edu ORCID ID 0009-0006-9426-4075
29. University of Oklahoma Health Sciences, Hudson College of Public Health, Department of Biostatistics and Epidemiology, Oklahoma City, OK, USA, sara-vesely@ouhsc.edu, ORCID 0000-0003-3448-0156
30. McMaster University, Department of Pediatrics, Division of Hematology/Oncology, Hamilton, ON, CANADA. John.wiernikowski@gmail.com ORCID ID 0000-0002-5058-3596
31. Hospital for Sick Children, Division of Haematology/Oncology, Department or Paediatrics, University of Toronto, Toronto, ON, Canada, suzan.williams@sickkids.ca, ORCID 0000-0002-9321-4301
32. University of Alabama at Birmingham Heersink School of Medicine, Department of Pediatrics, Children's of Alabama, Birmingham, AL, hopewilson@uabmc.edu ORCID ID 0000-0001-8904-3338
33. Emory University School of Medicine, Department of Pediatrics, Children's Healthcare of Atlanta, Atlanta, GA, gary.woods@choa.org, ORCID ID 0000-0002-0921-0974
34. Evidence-based Practice and Impact Center, Department of Internal Medicine/Division of Nephrology, University of Kansas Health System, Kansas City, Kansas, USA. Email: rmustafa@kumc.edu. ORCID ID 0000-0002-2091-0875

Abstract

Background: Venous thromboembolism (VTE) is a significant cause of morbidity in children, particularly among hospitalized patients and those with chronic medical conditions. There is a lack of consensus on anticoagulant prophylaxis strategies.

Objective: These evidence-based guidelines from the American Society of Hematology (ASH) and the International Society on Thrombosis and Haemostasis (ISTH) are intended to support patients and health care professionals in decisions about anticoagulant prophylaxis for pediatric VTE prevention.

Methods: ASH formed a multidisciplinary guideline panel that included one patient representative. The University of Kansas Health System supported the guideline development process, including systematic evidence reviews up to April 2025. Clinical questions and outcomes were prioritized according to their importance for clinicians and patients. The panel used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to assess certainty in the evidence and make recommendations.

Results: The panel agreed on 12 recommendations. For pediatric patients with solid cancer, trauma or critically ill, the panel issued conditional recommendations suggesting no anticoagulant prophylaxis. For pediatric patients with antiphospholipid antibody syndrome, or those on long-term total parenteral nutrition, the panel issued conditional recommendations suggesting the use of anticoagulant prophylaxis. Other pediatric subgroups addressed included patients with acute lymphoblastic leukemia or lymphoma, surgical and hospitalized patients, and those with a central venous access device.

Conclusions: High-quality data on anticoagulant prophylaxis for pediatric VTE prevention are scarce. Key research priorities include the development and validation of subgroups-specific VTE risk assessment models, and evaluation of the safety and efficacy of risk-stratified anticoagulant prophylaxis strategies across different pediatric subgroups.

Keywords

Pediatrics; neonates; infants; children; thrombosis; embolism; prophylaxis; hematology; practice guidelines; GRADE.

Summary of recommendations

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

Over the last few decades, venous thromboembolism (VTE) has increasingly been recognized as a significant complication in pediatric patients, particularly among hospitalized children and those with chronic medical conditions. Recent epidemiological data have shown a dramatic increase in the incidence of hospital-acquired (HA) VTE in children, which is now the second most common cause of preventable harm in this population.[11] In addition to the risk of mortality, estimated to be between 1.5-2.2%[12], VTE can result in significant short-term and long-term complications including the development of recurrent VTE, pulmonary embolism (PE), anticoagulant-associated bleeding, and the post-thrombotic syndrome (PTS).[13] The high physical and psychological burden associated with pediatric VTE underscores the need for the implementation of risk-stratified interventions aimed at preventing this complication in children.[14]

While the American Society of Hematology (ASH) 2018 Guidelines for VTE prophylaxis advocate for some method of routine thromboprophylaxis in all hospitalized adults, the use of anticoagulant prophylaxis for VTE prevention in children may not be as universally applicable as it is for the adult population.[14,15] Incidence rates of pediatric VTE are lower compared to adults, suggesting that the same level of prophylaxis may not be necessary or effective.[11] Furthermore, age-related differences in the hemostatic system influence the pathophysiology of pediatric VTE and the safety profiles of anticoagulant agents, leading to differences in thrombosis and bleeding risk profiles between age-groups and pediatric subgroups.[16] These factors limit the extrapolation of adult anticoagulant prophylaxis data to children, and highlight the need for risk-stratified, and in some cases subgroup-specific (e.g.; patients with cancer, critically ill patients), approaches for the prevention of pediatric VTE.

In response to this critical unmet need, there has been a growing interest in the development of risk assessment models aimed at the early identification of children at increased risk of VTE and who may benefit from anticoagulant prophylaxis.[17,18] However, these efforts have been hindered by a variety of factors unique to the development of VTE in children including the heterogeneity of the pediatric

population, the complexity of VTE risk-profiles which often include multiple acquired, environmental and genetic risk factors, and the paucity of high-quality clinical data on the safety and efficacy of anticoagulant prophylaxis in pediatrics. These challenges have led to significant variability in clinical practice.[19] This variability emphasizes the need for evidence-based guidelines regarding appropriate anticoagulant prophylactic practices for pediatric VTE prevention.

The questions addressed in these guidelines were judged by the panel to be the most relevant to clinical practice. The panel recognized the importance of prophylaxis for pediatric cardiac patients but decided this was beyond the scope of these guidelines. A dedicated guideline effort for antithrombotic management of cardiac and post-operative cardiac pediatric patients is necessary. The recommendations within the guidelines address questions predominantly of whether to provide anticoagulant (pharmacological) prophylaxis or not provide anticoagulant (pharmacological) prophylaxis for a given clinical situation. The guidelines do not address the use of mechanical thromboprophylaxis, including intermittent pneumatic compression devices. Most evidence supporting mechanical thromboprophylaxis for VTE prevention comes from adult trials focused on surgical and trauma populations.[20,21] Limited data on its application in pediatric patients indicate that mechanical thromboprophylaxis may often be insufficient as a preventive strategy for children at high risk of VTE.[22,23] Additionally, its use is constrained by size and weight specifications of the devices, and therefore it cannot be universally applied to all children, particularly smaller patients. The panel defined primary VTE prevention as being prophylaxis in patients without previous VTE, and secondary VTE prevention as being in patients with previous VTE who have now completed their treatment period. The guidelines are predominantly focused on primary VTE prevention; however, on occasion the evidence used to inform a recommendation did not differentiate between primary or secondary VTE prevention, thus the evidence may include patients receiving secondary VTE prophylaxis. In general, if the panel recommends primary prophylaxis for a specific patient population, then secondary prophylaxis would also be warranted for the same group, even if not explicitly stated in the recommendations. Apart from patients with antiphospholipid antibody syndrome, these guidelines did not specifically address secondary prophylaxis. In scenarios where primary prophylaxis is not recommended, that does not preclude that secondary prophylaxis would be appropriate in a similar patient population, and clinicians need to consider each individual patient's clinical situation. An *a priori* decision was made that antiplatelet therapy (e.g.; aspirin, clopidogrel) was out of scope for these recommendations.

For the majority of the recommendations, there was insufficient evidence for definitive risk stratification of the pediatric subgroups addressed in these guidelines. The risk factors for VTE and bleeding identified for each recommendation are those explicitly discussed in the evidence that informed the guidelines. While the panel acknowledges the existence of other known VTE risk factors, such as sickle cell disease and nephrotic syndrome, these were not included unless specifically addressed in the supporting evidence for each recommendation. The panel delineated high and low-risk scenarios based solely on the risk factors explicitly listed in the literature supporting the specific PICO question, ensuring that the recommendations are grounded in the available evidence.

Interpretation of strong and conditional recommendations

The strength of a recommendation is expressed as either strong ("the guideline panel recommends..."), or conditional ("the guideline panel suggests…") and has the following interpretation (Figure 1).

Interpretation of good practice statements

As described by the GRADE Guidance Group, good practice statements endorse interventions or practices that the panel agreed have unequivocal net benefit yet may not be widely recognized or used.[24] Good practice statements in these guidelines are not based on a systematic review of available evidence. Nevertheless, they may be interpreted as strong recommendations.

Recommendations

Pediatric Patients with Cancer

Recommendation 1: In pediatric patients with leukemia/lymphoblastic lymphoma, the ASH ISTH Guideline Panel ***suggests*** either anticoagulant prophylaxis or no anticoagulant prophylaxis, based on the individual assessment for risk of thrombosis and bleeding and patients' values and preferences (conditional recommendation based on low certainty in the evidence about effects ⊕⊕◯◯).

Remarks:

- The evidence suggested a benefit of reduced thrombosis with anticoagulant prophylaxis; however, prophylactic anticoagulation did not offer benefits for all subgroups of pediatric patients with leukemia/lymphoblastic lymphoma based on their differing risks. Subgroups that may benefit from anticoagulant prophylaxis include those ≥10 years of age or with obesity, T-cell immunophenotype, high-risk acute lymphoblastic leukemia, or personal or family history of thrombosis. Factors that may increase the risk of bleeding with anticoagulant prophylaxis include younger age, prior bleeding, severe thrombocytopenia, and renal dysfunction.

- The available evidence implicates asparaginase as an important pro thrombotic agent. If initiated, the panel suggests anticoagulant prophylaxis be given during asparaginase containing cycles only and discontinued after the prothrombotic effects of asparaginase are anticipated to have resolved.
- Anticoagulant prophylaxis should be paused peri-procedurally (e.g., lumbar punctures) and dose modified or held during periods of moderate to severe thrombocytopenia to reduce the risk of bleeding.

Recommendation 2: In pediatric patients with leukemia/lymphoblastic lymphoma, the ASH ISTH Guideline Panel ***suggests*** no antithrombin supplementation rather than antithrombin supplementation (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

- The evidence suggested a clinically significant benefit of antithrombin supplementation to prevent VTE with a small to negligible bleeding risk. However, the event free survival was reduced in patients receiving antithrombin supplementation compared to patients receiving unfractionated heparin (UFH) or low molecular weight heparin (LMWH).
- The panel placed a high value on preventing cancer recurrence, therefore suggested no antithrombin supplementation.

- The panel acknowledged that there is important uncertainty regarding the association between antithrombin and reduced event free survival.

Recommendation 3: In pediatric patients with solid tumors, including Hodgkin lymphoma, the ASH ISTH Guideline Panel ***suggests*** no anticoagulant prophylaxis rather than anticoagulant prophylaxis (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

- The panel noted that a significant proportion of reported thrombotic events were present at diagnosis and therefore not preventable with prophylactic anticoagulation.
- The panel considered that there are subgroups in whom the benefit:risk profile may be in favor of prophylactic anticoagulation, and might include pediatric patients meeting one or more of the following criteria: adolescent cancer patients, oral contraceptive pill (OCP) use, vessel compression or invasion by tumor, major cancer surgery, CVAD utilization, reduced mobility, known thrombophilia, and/or past history of thromboembolic disease, and without a significant risk of bleeding.

Total Parenteral Nutrition Prophylaxis

Recommendation 4: In infants, children, and adolescents considered for total parenteral nutrition (TPN) for more than 60 days (i.e., intestinal failure on home TPN), the ASH ISTH Guideline Panel ***suggests*** using anticoagulant prophylaxis rather than no anticoagulant prophylaxis (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

- This recommendation excludes neonates and patients requiring short-term (<60 days) TPN support.
- Based on the two comparative studies, primary pharmacological prophylaxis seemed to reduce the risk of developing catheter-related VTE.

- The anticoagulant prophylaxis administered included daily LMWH and vitamin K antagonists (VKAs).
- Patients receiving primary and secondary anticoagulant prophylaxis could not be separated in the included studies and thus the evidence includes pediatric patients receiving secondary prophylaxis.

Central Venous Access Device

Recommendation 5: In pediatric patients with a short-term (≤7 days) CVAD, the ASH ISTH Guideline Panel ***suggests*** no anticoagulant prophylaxis rather than anticoagulant prophylaxis (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

- The current evidence does not support the universal use of prophylactic anticoagulation for all pediatric patients with a short-term (≤7 days) CVAD. However, the panel acknowledges that there may be subgroups of patients at high-risk of VTE and low risk of bleeding, in whom anticoagulant prophylaxis may be of benefit. This high-risk VTE subgroup includes children ≥1 year old with a short-term CVAD who are critically ill, on invasive mechanical ventilation and have a low risk of bleeding, as well as patients expected to have prolonged immobility and/or hospitalization, those with autoimmune/inflammatory conditions, and those with active serious infections.

Recommendation 6: In children and adolescents who require medium/long term (≥8 days) CVAD in the absence of cancer or TPN, the ASH ISTH Guideline Panel ***suggests*** no anticoagulant prophylaxis rather than anticoagulant prophylaxis (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

- This recommendation pertains to the use of primary anticoagulant prophylaxis.

- The panel acknowledged that there may be pediatric patients who may benefit from prophylaxis. A thorough assessment of individual risks and careful consideration of benefits and harms when considering prophylactic anticoagulation is appropriate.

Antiphospholipid Antibodies

Recommendation 7: In pediatric patients with antiphospholipid antibody syndrome (APS), the ASH ISTH Guideline Panel ***suggests*** using secondary anticoagulant prophylaxis rather than no secondary anticoagulant prophylaxis (conditional recommendation based on low certainty in the evidence about effects ⨁◯◯◯

Remarks:

- An a-priori decision was made to exclude pediatric patients receiving only antiplatelet therapy from this evidence profile.
- The included evidence showed moderate benefit of secondary anticoagulation prophylaxis (with or without antiplatelet therapy) in reducing recurrent thromboembolism.

Recommendation 8: In pediatric patients with persistently positive antiphospholipid antibodies (APLA) without a history of thrombosis, the ASH ISTH Guideline Panel ***suggests*** no primary anticoagulant prophylaxis rather than primary anticoagulant prophylaxis (conditional recommendation based on very low certainty in the evidence about effects ⨁◯◯◯

Remarks:

- An a-priori decision was made to exclude pediatric patients receiving antiplatelet therapy, and therefore the panel cannot comment on the benefits and risk of using antiplatelet agents in this cohort.
- The panel acknowledges that evolving definitions of APS may influence clinical decision making and emphasizes that individual patient characteristics—such as the presence of an underlying autoimmune disorder, double or triple antibody positivity, the strength of

antibody titers, and microvascular manifestations should be considered when evaluating the need for primary anticoagulant prophylaxis.

Trauma Patients

Recommendation 9: In pediatric patients with trauma, the ASH ISTH Guideline Panel ***suggests*** no anticoagulant prophylaxis rather than anticoagulant prophylaxis (conditional recommendation based on very low certainty in the evidence about effects ⨁◯◯◯

Remarks:

- The evidence does not support the universal use of anticoagulant prophylaxis in pediatric trauma patients who comprise a heterogenous population in whom the overall prevalence of VTE is low.
- There are, however, subgroups in the included studies (patients deemed "high risk") that had higher reported rates of VTE who may benefit from prophylactic anticoagulation. These specific "high-risk" criteria included presence of shock, age > 12 years (or younger ages with multiple risk factors), immobility, intubation, and presence of a CVAD.

While the risk for bleeding from anticoagulant prophylaxis in pediatric trauma patients is overall low, it was noted to be higher in patients receiving prophylactic anticoagulation in one study.

Hospitalized Patients

Recommendation 10: In hospitalized pediatric patients, the ASH ISTH Guideline Panel ***suggests*** no anticoagulant prophylaxis rather than anticoagulant prophylaxis (conditional recommendation based on low certainty in the evidence about effects ⨁⨁◯◯

Remarks:

- Hospitalized pediatric patients encompass an extremely heterogeneous population with respect to age, underlying medical conditions and baseline risk of thrombosis.

- The panel acknowledged that there may be certain pediatric patients that may benefit from anticoagulant prophylaxis (e.g., immobility, use of estrogen, infection, obesity, inflammation), though additional studies are needed.
- Several subgroups (cancer, CVAD, surgery, trauma) are addressed in separate recommendations.

Critically Ill Patients

Recommendation 11: In pediatric patients who are critically ill with or without a CVAD, the ASH ISTH Guideline Panel ***suggests*** no anticoagulant prophylaxis rather than anticoagulant prophylaxis (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯

Remarks:

- The current evidence does not support the universal use of prophylactic anticoagulation in critically ill children for which there is insufficient data for formal stratification of the risks of VTE and the risk of bleeding.
- However, the panel acknowledged that there may be subgroups of critically ill children (children ≥1 year old with an untunneled CVAD and low risk of bleeding and children receiving invasive mechanical ventilation), in whom the risk of VTE may outweigh the risk of bleeding, who could potentially benefit from prophylactic anticoagulation.

Surgery Patients

Recommendation 12: In children undergoing noncardiac surgery, the ASH ISTH Guideline Panel ***suggests*** no anticoagulant prophylaxis rather than anticoagulant prophylaxis (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯

Remarks:

- The panel did not assess VTE risk by specific type of surgical procedure (e.g., orthopedic, bariatric, laparoscopic, etc.). Rather, the panel grouped available pediatric surgical data to assess the risk for postoperative VTE and found a low incidence in this heterogeneous group.
- Procedure-related and patient-related factors that increase the risk for VTE include longer operative time, prolonged immobilization, greater than seven days of central venous access, obesity, congenital thrombophilia, and the use of combined OCP.

Good practice statement 1.

In pediatric patients at increased risk for VTE, the decision regarding the use of anticoagulant prophylaxis requires careful consideration of not just the patient's individual risk for thrombosis but, importantly, their risk of bleeding. Using the principle of "first do no harm", anticoagulant prophylaxis should not be initiated in pediatric patients considered to be at high risk of major or clinically relevant non-major bleeding (CRNMB) even if the perceived risk of VTE is high. The benefit:risk ratio for the use of anticoagulant prophylaxis for VTE prevention in each patient should be reassessed regularly.

Good practice statement 2.

In pediatric patients receiving anticoagulant prophylaxis, decisions regarding the peri-procedural interruption of anticoagulation, including timing and duration, should be made by carefully balancing the individual patient's risk of bleeding and thrombosis complications, as well as the specific risks associated with the procedure. Institutions are encouraged to develop guidelines for the optimal management of peri-procedural anticoagulant prophylaxis, especially around lumbar puncture or spinal anaesthetic procedures for which the potential complications of bleeding are significant.

Values and preferences

The panel emphasized the importance of avoiding harm with the evaluated interventions, and considered the outcomes of major bleeding, CRNMB, and mortality as critical for decision making. Overall, the panel placed a high value on the outcomes of major bleeding, CRNMB, mortality, PE and proximal DVT.

Explanations and other considerations

Based on the different clinical scenarios addressed, the panel used the terms neonates (age, birth to day 28), infants (age, day 29 to 1 year), children (age, 1-11 years), and adolescents (age, 12-18 years) to differentiate between age-groups in certain recommendations, and the terms pediatric patients (encompassing all age groups) or neonates and pediatric patients (separating neonates from all other age groups) in other recommendations.

Throughout the guideline, the panel used the International Society on Thrombosis and Haemostasis (ISTH) Scientific and Standardization Subcommittee on Pediatric and Neonatal Thrombosis and Hemostasis' recommended definitions for the outcomes of major bleeding and CRNMB.[25]

Introduction

Aims of these guidelines and specific objectives

The purpose of these guidelines is to provide evidence-based recommendations on the prevention of VTE in pediatric patients at risk of VTE. The primary goals of these guidelines are to review and critically appraise published evidence and implement evidence-based recommendations that will assist clinicians in deciding which pediatric patients at risk of VTE require anticoagulant prophylaxis for VTE prevention. Through improved provider and patient education of the available evidence and evidence-based recommendations, these guidelines aim to provide clinical decision support for shared decision making that will lead to a decrease in practice variation surrounding the use of anticoagulant prophylaxis for the prevention of pediatric VTE and will foster the implementation of appropriate anticoagulant prophylaxis strategies in children at risk of VTE. These guidelines relate to the prevention of VTE and do not relate to

administration of anticoagulation for other purposes for example to promote central venous access device (CVAD) patency.

The target audience includes patients, hematologists, general practitioners, internists, 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 improve the care of pediatric patients. This document may also serve as the basis for adaptation by local, regional or national guideline panels.

Description of the health problem

The incidence of pediatric VTE has shown a dramatic increase in the last few decades, particularly among hospitalized children in whom it has emerged as the second leading cause of preventable harm.[11] VTE in children is associated with significant acute and chronic complications including the development of pain, recurrent VTE, compartment syndrome, chronic thromboembolic pulmonary hypertension, organ-specific damage (e.g.; renal atrophy, portal hypertension), among others. Despite the growing awareness and increased physical, psychosocial and economic burdens, there remains a paucity of high-quality data to guide the use of anticoagulant prophylaxis for VTE prevention in children, leading to significantly variability in practice.[19]

The pathophysiology of pediatric VTE is complex with different pediatric subgroups (e.g., cancer, patients with a CVAD, critically ill patients) exhibiting distinct thrombosis and bleeding risk profiles. The intricate balance of varying VTE and bleeding risks across the heterogenous pediatric population underscores the critical need for a risk-stratified and subgroup specific approach to the development of anticoagulant prophylaxis recommendations for VTE prevention in children. However, for many subgroups, such risk stratification is currently not possible, and this aspect is a high priority area for future research.

Methods

The panel developed and graded the recommendations and assessed the certainty of the supporting evidence following the GRADE approach.[4-10] 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 and ISTH policies and procedures derived from the

Guidelines International Network-McMaster Guideline Development Checklist (http://cebgrade.mcmaster.ca/guidecheck.html)[26], and was intended to meet recommendations for trustworthy guidelines by the Institute of Medicine and the Guidelines International Network.[1-3]

Organization, panel composition, planning and coordination

The work of this panel was coordinated by ASH, ISTH, and the University of Kansas Health System (funded by ASH and ISTH under a partner agreement). Project oversight was provided by the ASH Guideline Oversight Subcommittee, which reported to the ASH Committee on Quality, and the ISTH Guidelines and Guidance committee which reported to the ISTH Council. ASH vetted and appointed individuals to the guideline panel. The University of Kansas Health System vetted and retained researchers to conduct systematic reviews of evidence and coordinate the guideline development process including the use of the GRADE approach. The membership of the panel and the systematic review team is described in supplement 1.

The panel included 22 adult and pediatric hematologists, a pediatric cardiologist, a pediatric critical care expert, a pharmacist, a pediatric hematology and cardiology nurse, and a biostatistician, all of whom had clinical and research expertise on the guideline topic. The panel also included 3 methodologists (M.A., H.K. and J.K.) and one patient representative, a young adult with history of VTE as a child (G.K.). The panel was led by two senior co-chairs, one a content expert (P.M.) and the other one an expert in evidence appraisal and guideline development methodology (R.A.M.); and a “co-chair in-training” with expertise in the guideline topic (M.B.).

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

Guideline funding and management of conflicts of interest

Development of these guidelines was jointly funded by ASH, a nonprofit medical specialty society that represents hematologists, and ISTH, a nonprofit international medical specialty society committed to the understanding and treatment of all conditions related to thrombosis and hemostasis. Direct funding by for-profit companies was not received for the development of these guidelines. Most members of the

guideline panel were members of ASH and/or ISTH. ASH/ISTH staff supported panel appointments and coordinated meetings but had no role in choosing the guideline questions or determining the recommendations.

Through the University of Kansas Health System, some researchers who contributed to the systematic evidence reviews received salary or grant support. Other researchers participated to fulfill requirements of an academic degree or program.

Conflicts of interest of all participants were managed according to ASH policies based on recommendations of the Institute of Medicine and the Guidelines International Network[2]. Participants disclosed all financial and nonfinancial interests relevant to the guideline topic. ASH staff and the ASH Guideline Oversight Subcommittee reviewed the disclosures and composed the guideline panel to include a diversity of expertise and perspectives and avoid a majority of the panel having the same or similar conflicts. Greatest attention was given to direct financial conflicts with for-profit companies that could be directly affected by the guidelines. A majority of the guideline panel, including the co-chairs, had no such conflicts. None of the University of Kansas Health System researchers who contributed to the systematic evidence reviews or who supported the guideline development process had any such conflicts.

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

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

Formulating specific clinical questions and determining outcomes of interest

The panel used the GRADEpro Guideline Development Tool (www.gradepro.org)[27] and SurveyMonkey (surveymonkey.com) to brainstorm and then prioritized the questions described in Table 1.

The panel selected outcomes of interest for each question *a priori*, following the approach described in detail elsewhere.[28] In brief, the panel first brainstormed all possible outcomes before rating their relative importance for decision-making following the GRADE approach.[28] While acknowledging considerable variation in the impact on patient outcomes, the panel considered the outcomes listed in Table 1 as critical for clinical decision-making across questions:

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

PICO Question	Subgroups	Outcomes
For pediatric patients with leukemia/lymphoblastic lymphoma, should anticoagulant prophylaxis vs no anticoagulant prophylaxis be used?	• Age groups: Children, Adolescents • Mediastinal Mass • CVAD • Induction vs. Consolidation/Intensification/Maintenance • Hospitalized vs. Outpatient • Obesity • Known Congenital Thrombophilia or Family history of VTE	• CVAD-related VTE • Non-CVAD-related VTE • Symptomatic VTE • Asymptomatic VTE • PE • CSVT • Major bleeding/CRNMB • All-Cause Mortality • Event Free Survival
In pediatric patients with leukemia/lymphoblastic lymphoma, should antithrombin supplementation vs no antithrombin supplementation be used?		
In pediatric patients with solid tumors, including Hodgkin lymphoma, should anticoagulant prophylaxis vs no anticoagulant prophylaxis be used?	• Age groups: Children, Adolescents • Vascular Invasion • Renal/Caval Tumors • CNS Tumors • Mass lesion (with or w/o vessel compression) • CVAD • Tumor Thrombus • Hospitalized vs. Outpatient	• CVAD-related VTE • Non-CVAD-related VTE • Symptomatic VTE • Asymptomatic VTE • Major bleeding/CRNMB • All-Cause Mortality
In infants, children and adolescents considered for total parenteral nutrition (TPN) for more than 60 days (i.e., intestinal failure on home TPN), should anticoagulant prophylaxis vs. no anticoagulant prophylaxis be used?	• Age groups: Neonates, Children, Adolescents • Hospitalized vs. Outpatient	• CVAD-related VTE • Non-CVAD-related VTE • Symptomatic VTE • Asymptomatic VTE • Major bleeding/CRNMB • Mortality
In pediatric patients with a short-term (<7 days) CVAD, should anticoagulant prophylaxis vs. no anticoagulant prophylaxis be used?	• Age groups: Neonates, Children, Adolescents	• CVAD-related Symptomatic VTE • CVAD-related Asymptomatic VTE • Unspecified Bleeding • Major bleeding/CRNMB • All-Cause Mortality • VTE-related Mortality

In children and adolescents who require medium/long term (≥8 days) CVAD in the absence of cancer or total parental nutrition (TPN), should anticoagulant prophylaxis vs. no anticoagulant prophylaxis be used?		• CVAD-related Symptomatic VTE • CVAD-related Asymptomatic VTE • VTE-related Mortality
In pediatric patients with antiphospholipid antibody syndrome, should secondary anticoagulant (± antiplatelet) prophylaxis vs. no secondary anticoagulant prophylaxis be used?	• Age groups: Children, Adolescents • Primary (Idiopathic) vs. Secondary (autoimmune disease associated)	• Non-CVAD-related VTE • CVAD-related VTE • Symptomatic VTE • Asymptomatic VTE • Arterial Ischaemic Stroke • Myocardial Infarction/ arterial thrombosis • Major bleeding/CRNMB
In pediatric patients with persistent antiphospholipid antibodies and without history of thrombosis, should primary anticoagulant prophylaxis vs. no primary anticoagulant prophylaxis be used?	• Age groups: Children, Adolescents • Primary (Idiopathic) vs. Secondary (autoimmune disease associated) • Single vs. double vs. triple positivity	
In pediatric patients with trauma, should anticoagulant prophylaxis vs. no anticoagulant prophylaxis be used?	• Age groups: Children, Adolescents • Traumatic Brain Injury • Lower Extremity or Pelvic trauma • Spinal Cord, TBI • VTE risk subgroups: High vs. Low Risk	• VTE • Symptomatic VTE • DVT • PE • Major bleeding/CRNMB • All-Cause Mortality
In hospitalized pediatric patients, should anticoagulant prophylaxis vs. no anticoagulant prophylaxis be used?	• Age groups: Neonates, Children, Adolescents • Inflammatory Bowel Disease • Inflammatory Conditions • Thrombophilia • Nephrotic Syndrome • Hormonal Therapy • Obesity • Sickle Cell Disease • Immobilization	• VTE • Symptomatic VTE • Asymptomatic VTE • Major Bleeding • All-Cause Mortality
In pediatric patients who are critically ill with or without a CVAD, should primary anticoagulant prophylaxis over no prophylaxis be used?	• Age groups: Neonates, Children, Adolescents • Mechanical Ventilation • Non-invasive Ventilation • CVAD • Vasoactive Pressor Support • Immobilization • Severity of Illness	• CVAD-related VTE • Non-CVAD-related VTE • Symptomatic VTE • Asymptomatic VTE • Major bleeding/CRNMB • Mortality
In pediatric patients undergoing noncardiac surgery, should anticoagulant prophylaxis vs. no anticoagulant prophylaxis be used?	• Age groups: Neonates, Children, Adolescents • Lower Limb/Pelvic Orthopedic • Spinal Surgery	• VTE • Symptomatic VTE • CVAD-related VTE • DVT

	• Neurosurgery • Thoracoabdominal/Pelvic • Plastic Surgery • Obesity • Known Congenital Thrombophilia or Family history of VTE • Immobilization	• PE • Unspecified Bleeding • Major bleeding/CRNMB

Evidence review and development of recommendations

For each guideline question, the University of Kansas Health System prepared a GRADE EtD framework, using the GRADEpro Guideline Development Tool (www.gradepro.org).[4,5,10] The EtD table summarized the results of systematic reviews of the literature that were performed for this guideline. The EtD table addressed effects of interventions, resource utilization (cost-effectiveness), values and preferences (relative importance of outcomes), equity, acceptability and feasibility. The panel reviewed draft EtD tables before, during or after the guideline panel meeting and made suggestions for corrections and identified missing evidence. To ensure that recent studies were not missed, the original searches performed in June 4th, 2024 (presented in supplement 4) were updated in January 31st, 2025, and April 1st, 2025, and panel members were asked to suggest any studies that may have fulfilled the inclusion criteria for the individual questions and been considered missed. The studies informing these guidelines included randomized control trials and non-randomized studies of intervention.

Under the direction of the University of Kansas Health System, researchers followed the general methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions (handbook.cochrane.org) for conducting updated or new systematic reviews of intervention effects. When existing reviews were used, judgments of the original authors about risk of bias were either randomly checked for accuracy and accepted or conducted *de novo* if they were not available or not reproducible. For new reviews, risk of bias was assessed at the health outcome level using the Cochrane Collaboration's risk of bias tool for randomized trials or non-randomized studies. In addition to conducting systematic reviews of intervention effects, the researchers searched for evidence related to baseline risks, values, preferences and costs, and summarized findings within the EtD frameworks.[4,5,10] Subsequently, the certainty of the body of evidence (also known as quality of the evidence or confidence in the estimated effects) was assessed for each effect estimate of the outcomes of interest following the GRADE approach based on the following domains: risk of bias, precision, consistency and magnitude of the estimates of effects, directness of the evidence, risk of publication bias, presence of

large effects, dose-response relationship, and an assessment of the effect of residual, opposing confounding. The certainty was categorized into four levels ranging from very low to high.[6-8] Within this report, these categories are represented by the symbols, as shown in Figure 2.

Interested readers may find more explanation about the GRADE approach to assessing and rating certainty in a body of evidence in other publications.[6-8]

During online communication and a series of 28 conference calls the panel developed clinical recommendations based on the evidence summarized in the EtD tables. For each recommendation, the panel took a population perspective and came to consensus on the following: the certainty of the evidence, the balance of benefits and harms of the compared management options and the assumptions about the values and preferences associated with the decision. The panel also explicitly took into account the extent of resource use associated with alternative management options. The panel agreed on the recommendations (including direction and strength), remarks, and qualifications by consensus or, in rare instances, by anonymous voting (an 80% majority was required for consensus), based on the balance of all desirable and undesirable consequences. The final guidelines, including recommendations, were reviewed and approved by all members of the panel. Due to the sparsity of evidence for the recommendations addressing children with antiphospholipid syndrome and persistent antiphospholipid antibodies, the panel utilized an expert evidence approach by systematically gathering clinical experience through an anonymous electronic survey created specifically for these PICO questions.[29] The survey was distributed via a link emailed to panel members.

Document review

Draft recommendations were reviewed by all members of the panel, revised, and then made available online from May 13, 2025, through June 12, 2025, for external review by stakeholders including allied organizations, other medical professionals, patients, and the public. Twelve individuals or organizations submitted comments. The document was revised to address pertinent comments, but no changes were made to recommendations. On October 29, 2025 the ASH Guideline Oversight Subcommittee and the ASH Committee on Quality approved that the defined guideline development process was followed, and on November 12, 2025 the officers of the ASH Executive Committee approved submission of the guidelines for publication under the imprimatur of ASH. On December 10, 2025 the ISTH Guidelines and

Guidance Committee and ISTH Council approved the submission of the guidelines for publication. The guidelines were then subjected to peer review by *Blood Advances.*

How to use these guidelines

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

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

Recommendations

Pediatric Patients with Cancer

Question: For pediatric patients with leukemia/lymphoblastic lymphoma, should anticoagulant prophylaxis vs no anticoagulant prophylaxis be used?

Recommendation 1. In pediatric patients with leukemia/lymphoblastic lymphoma, the ASH ISTH Guideline Panel ***suggests*** either anticoagulant prophylaxis or no anticoagulant prophylaxis, based on the individual assessment for risk of thrombosis and bleeding and patients' values and preferences (conditional recommendation based on low certainty in the evidence about effects ⊕⊕◯◯).

Remarks:

- The evidence suggested a benefit of reduced thrombosis with anticoagulant prophylaxis; however, prophylactic anticoagulation did not offer benefits for all subgroups of pediatric patients with leukemia/lymphoblastic lymphoma based on their differing risks. Subgroups that may benefit from anticoagulant prophylaxis include those ≥10 years of age or with obesity, T-cell immunophenotype, high-risk acute lymphoblastic leukemia, or personal or family history of thrombosis. Factors that may increase the risk of bleeding with anticoagulant prophylaxis include younger age, prior bleeding, severe thrombocytopenia, and renal dysfunction.
- The available evidence implicates asparaginase as an important pro thrombotic agent. If initiated, the panel suggests anticoagulant prophylaxis be given during asparaginase containing cycles only and discontinued after the prothrombotic effects of asparaginase are anticipated to have resolved.
- Anticoagulant prophylaxis should be paused peri-procedurally (e.g., lumbar punctures) and dose modified or held during periods of moderate to severe thrombocytopenia to reduce the risk of bleeding.

Summary of the evidence

We found two randomized controlled trials (RCT)[30,31] and three non-randomized studies[32-34] that evaluated anticoagulant prophylaxis; all studies included children and adolescents with ALL. The two RCTs reported the effect of anticoagulant prophylaxis with enoxaparin or apixaban on the development of VTE (all events[30,31] and separated between symptomatic[30,31] and clinically unsuspected VTEs[31]) and bleeding (divided between major and CRNMB).[30,31] Overall survival (OS)[31] and event-free survival (EFS)[30] were evaluated in one study each. Among non-randomized studies, three reported the effect of

anticoagulant prophylaxis on the development of VTE (all events[32,33] and symptomatic VTE alone[34]). Only one of these studies described the risk of bleeding.[34]

Benefits

Among RCTs, anticoagulant prophylaxis appeared to reduce the risk for all VTE, but the estimate was imprecise, and the confidence interval (CI) did not exclude that there was no effect (relative risk [RR]: 0.73, 95% CI: 0.44 to 1.24, with low certainty of evidence due to risk of bias and imprecision). Anticoagulant prophylaxis reduced the risk of developing symptomatic VTE (RR: 0.48, 95% CI: 0.26 to 0.87, with moderate certainty of evidence due to serious risk of bias). Non-randomized studies found similar results for both symptomatic and asymptomatic events (all VTEs: RR: 0.16, 95% CI: 0.02 to 1.22; symptomatic VTEs: RR: 0.17, 95% CI: 0.03 to 1.11). No difference in OS was found between those receiving anticoagulant prophylaxis and their respective control groups (RR: 0.25, 95% CI: 0.03 to 22.22, low certainty of evidence due to risk of bias and imprecision).

Harms and burden

Regarding anticoagulant prophylaxis, two RCTs reported bleeding[30,31] with a median risk of 1% of major bleeding in the control groups. The risk of bleeding was not different among those receiving anticoagulant prophylaxis or SoC (major bleeding: RR: 0.66, 95% CI: 0.16 to 2.76; CRNMB Risk Difference: 0.02, 95% CI: 0.00 to 0.03). There was very low certainty in the estimate of the risk of adverse effects due to serious risk of bias and imprecision. Given the available evidence and in accordance with the risk of bleeding reported in other pediatric subgroups, the panel considered the risk of adverse effects of anticoagulant prophylaxis most likely to be small.

Other EtD criteria and considerations

Panel members felt that there was likely important variability in how patients, families, and practitioners valued the critical outcomes of VTE prevention and avoidance of bleeding. The weight placed on these values should be incorporated in the decision to use anticoagulant prophylaxis, as the balance of benefits and harms will vary based on the individual patient's thrombotic and bleeding risk. In addition, the potential impact of anticoagulant prophylaxis on leukemia treatment, relapse and survival would be important priorities for all stakeholders.

Overall, the panel judged the balance of effect following anticoagulant prophylaxis to favor neither the intervention nor the comparison. The certainty of evidence was very low to support the benefit of anticoagulant prophylaxis with its known small, though undesirable risks of bleeding. The panel assessed the patient population to be too heterogenous with regard to both VTE and bleeding risk to make a general recommendation for or against anticoagulant prophylaxis. The decision to implement anticoagulant prophylaxis should be individualized taking into account the balance of these risks. Insufficient data are available for formal stratification of thrombosis and bleeding risk to guide the use of anticoagulant prophylaxis in pediatric patients with leukemia and lymphoblastic lymphoma. However, based on the published literature from randomized and non-randomized studies, several patient subgroups, including those with obesity, ≥10 years old, T-Cell immunophenotype, high or very high risk acute lymphoblastic leukemia, prior thrombosis or a family history of thrombosis appear to benefit from anticoagulant prophylaxis. This is likely due to these patients having an increased baseline risk for thrombosis and as such, have more to gain from the use of anticoagulant prophylaxis.

Common factors that increase the risk of thrombosis in patients with hematological malignancies include asparaginase therapy and the presence of a CVAD. If initiated, anticoagulant prophylaxis should be given exclusively during asparaginase-containing cycles of chemotherapy which are typically Induction and consolidation phases of treatment. The evaluated studies employed differing durations of anticoagulant prophylaxis around asparaginase exposures so a clear duration of prophylaxis post final asparaginase dose could not be elucidated. However, in the panel's opinion, anticoagulant prophylaxis should be continued until the prothrombotic effects of asparaginase are anticipated to have resolved as per institutional norms, with consideration of the various long-acting formulations of asparaginase available. In the Apixaban versus no anticoagulation for the prevention of venous thromboembolism in children with newly diagnosed acute lymphoblastic leukaemia or lymphoma (PREVAPIX-ALL)[31] and the THROMBOTECT trial[30], anticoagulant prophylaxis was received between days two to four and day 29 of induction chemotherapy (before first exposure to asparaginase) and between days eight and 33 of induction chemotherapy, respectively.

Moreover, anticoagulant prophylaxis should be paused peri-procedurally (e.g., lumbar punctures) and during periods of moderate to severe thrombocytopenia to reduce the risk of bleeding. While specific platelet thresholds have not been prospectively evaluated, in PREVAPIX-ALL trial[31], apixaban was held for platelet counts below 20×10^9 per µl. For lumbar punctures, apixaban was interrupted at least 24 hours before the procedure and resumed no sooner than 18–24 hours after. In the event of a traumatic

lumbar puncture, apixaban was held for at least 48 hours after the procedure. In the THROMBOTECT trial[30], enoxaparin was postponed until at least 4 hours after the procedure on days with lumbar puncture or other invasive procedures. In the case of thrombocytopenia <30 x 10^9/L, platelet transfusion was required, or enoxaparin was withheld.

The Evidence Profile (EP) and Evidence to Decision (EtD) Framework are available online for Recommendation 1.

Conclusions and research needs for this recommendation

The panel identified the following additional research questions and priorities:

1. Need for an evidence-based risk stratification rubric for thrombotic and bleeding risk in children with leukemia/lymphoblastic lymphoma.

2. Determination of the variability of efficacy and safety of anticoagulant prophylaxis (including specific anticoagulant and dose) in various chemotherapy protocol backbones and phases of treatment.

3. Generating data on the long-term effects of pharmacological thromboprophylaxis including impact on EFS and OS overall survival in children with leukemia/lymphoblastic lymphoma.

4. Determining the optimal duration of anticoagulant prophylaxis post completion of treatment with asparaginase.

5. Determining the risk: benefit of prophylaxis for CVAD-associated thrombosis in later phases of leukemia/lymphoblastic lymphoma treatment.

Question: In pediatric patients with leukemia/lymphoblastic lymphoma, should antithrombin supplementation vs no antithrombin supplementation be used?

Recommendation 2. In pediatric patients with leukemia/lymphoblastic lymphoma, the ASH ISTH Guideline Panel ***suggests*** no antithrombin supplementation rather than antithrombin supplementation (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

- The evidence suggested a clinically significant benefit of antithrombin supplementation to prevent VTE with a small to negligible bleeding risk. However, the event free survival was reduced in patients receiving antithrombin supplementation compared to patients receiving unfractionated heparin (UFH) or low molecular weight heparin (LMWH).
- The panel placed a high value on preventing cancer recurrence, therefore suggested no antithrombin supplementation.
- The panel acknowledged that there is important uncertainty regarding the association between antithrombin and reduced event free survival.

Summary of the evidence

Two RCTs evaluated the effect of antithrombin supplementation on VTE development (all events[30,35] and symptomatic VTEs alone[35]) in children with leukemia/lymphoblastic lymphoma[30,35], while the risk of bleeding following antithrombin supplementation was reported in two RCTs[30,35] and one non-randomized study.[36]

Benefits

Antithrombin supplementation reduced the risk of all VTEs (RR: 0.41, 95% CI: 0.24 to 0.71) and symptomatic VTEs (RR: 0.23, 95% CI: 0.10-0.56), although the certainty of the evidence was low due to risk of bias and imprecision.

Harms and burden

The risk of bleeding appeared to be similar in patients with and without antithrombin supplementation. In pooled data from two RCTs[30,35], the risk of major bleeding was 0.8% in patients receiving antithrombin supplementation and 0.9% in patients receiving SoC (RR: 0.81, 95% CI: 0.21-3.12), and the risk of CRNM bleeding was 0% in both groups. A non-randomized study also reported a bleeding risk of 0% in patients with and without antithrombin supplementation.

However, Greiner and colleagues[30] reported a reduced event-free survival at five years in children receiving antithrombin supplementation versus children receiving anticoagulant prophylaxis or standard of care (SoC) with low dose unfractionated heparin (UFH; antithrombin supplementation: 65 events/320 patients, 80.9±2.2% vs. SoC: 45 events/312 patients, 85.9±2.0%). While this difference could be

attributed to chance alone and is not explained by a clear causative mechanism, the panel noted that reduced survival following antithrombin supplementation was described in other pediatric populations, warranting caution. For example, increased inpatient mortality was described in children with congenital heart disease receiving antithrombin while on extracorporeal membrane oxygenation, albeit in a non-randomized study with a potentially increased likelihood of antithrombin administration in patients with more severe clinical conditions.[37] Overall, the risk of undesirable effects with antithrombin supplementation was considered moderate.

Other EtD criteria and considerations

The panel noted a clinically significant benefit of antithrombin supplementation to prevent VTE and symptomatic VTE, and the risk of bleeding appeared small following antithrombin supplementation. However, the panel put a higher value on preventing cancer recurrence. Thus, considering the possible reduced EFS in children receiving antithrombin supplementation, the panel considered the balance of effects probably favored avoiding the use of antithrombin supplementation in children with leukemia/lymphoblastic lymphoma. The certainty of evidence was very low due to serious imprecision, indirectness, and risk of bias in the included studies. Additional considerations for the recommendation related to accessibility to antithrombin as an intervention globally, uncertainty in the timing and duration of antithrombin replacement, and optimal target levels to achieve the desired outcomes. The EP and EtD Framework are available online for Recommendation 2.

Conclusions and research needs for this recommendation

The panel identified the following additional research questions and priorities:

1. Generating data on the long-term effects of antithrombin replacement, including impact on EFS and OS overall survival in children with leukemia/lymphoblastic lymphoma.

2. Examination of the effects of antithrombin on immune regulation and inflammation related to leukemia/lymphoblastic lymphoma.

Question: In pediatric patients with solid tumors, including Hodgkin lymphoma, should anticoagulant prophylaxis vs no anticoagulant prophylaxis be used?

> **Recommendation 3.** In pediatric patients with solid tumors, including Hodgkin lymphoma, the ASH ISTH Guideline Panel ***suggests*** no anticoagulant prophylaxis rather than

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

Remarks:

- The panel noted that a significant proportion of reported thrombotic events were present at diagnosis and therefore not preventable with prophylactic anticoagulation.
- The panel considered that there are subgroups in whom the benefit:risk profile may be in favor of prophylactic anticoagulation, and might include pediatric patients meeting one or more of the following criteria: adolescent cancer patients, oral contraceptive pill (OCP) use, vessel compression or invasion by tumor, major cancer surgery, CVAD utilization, reduced mobility, known thrombophilia, and/or past history of thromboembolic disease, and without a significant risk of bleeding.

Summary of the evidence

The panel considered the data from four non-randomized comparative studies, each reported the incidence of VTE in pediatric patients with solid tumors and compared anticoagulant prophylaxis with LMWH to no anticoagulant prophylaxis.[38-41] All studies reported the overall incidence of VTE. Symptomatic VTE was reported by two studies[38,39], asymptomatic VTE by one study[39], and CVAD-related VTE by one study.[38] All thrombotic events were confirmed by imaging studies. Three studies commented on bleeding.[38,39,41]

An RCT reported by Ruud et al.[42] was considered by the panel but a decision was made not to include these data in the analysis for this recommendation because the study outcomes were not reported by cancer sub-type so the outcomes occurring in those with a solid tumor could not be quantified.

Benefits

Based on the pooled data from the four non-randomized comparative studies[38-41], VTE occurred in 68/883 (7.7%) of all individuals. This included 8/127 (6.3%) of those receiving anticoagulant prophylaxis vs 60/756 (7.9%) of those not receiving prophylaxis, with a risk difference of 0.03 (95% CI -0.03 to 0.09). Symptomatic VTE[38,39] occurred in 1/90 (1.1%) of those receiving anticoagulant prophylaxis vs 3/228 (1.3%) not receiving prophylaxis, risk difference 0.01 (95% CI -0.03 to 0.05). Asymptomatic VTE[39]

occurred in 1/5 (20.0%) of those receiving anticoagulant prophylaxis vs 7/158 (4.4%) not receiving prophylaxis, risk difference 0.16 (95% CI -0.20 to 0.51). CVAD-related VTE[38] occurred in 1/85 (1.2%) of those receiving anticoagulant prophylaxis vs 0/70 (0.0%) not receiving prophylaxis, risk difference 0.01 (95% CI -0.02 to 0.05).

Abate et al.[38] analysed incidence and risk factors for CVAD -related complications in 155 pediatric patients aged 0-17 years with bone sarcoma (osteosarcoma or Ewing sarcoma) in a non-randomized comparative prospective study. CVAD was an inserted Broviac (n=153) or Port-A-Cath (n=2) and anticoagulant prophylaxis was with enoxaparin. One out of 85 (1.2%) of those receiving anticoagulant prophylaxis developed a CVAD-related symptomatic DVT vs 0/70 (0%) not receiving anticoagulant prophylaxis.

Schonning et al.[39] compared the incidence of VTE in those treated with anticoagulant prophylaxis vs no anticoagulant prophylaxis in a retrospective cohort study in 163 pediatric patients aged 0-18 years with Hodgkin Lymphoma. One hundred and sixty had a CVAD (Port-A-Cath, 134; External line, 26). Anticoagulant prophylaxis was physician-led using LMWH. Symptomatic VTE occurred in 1.8%, including 0/50 (0%) of those receiving anticoagulant prophylaxis vs 1/5 (20%) not receiving prophylaxis. Asymptomatic VTE occurred in 4.9%, including 3/158 (1.9%) of those receiving anticoagulant prophylaxis vs 7/158 (4.4%) not receiving prophylaxis.

Sarangi et al.[40] compared the incidence of VTE in those treated with anticoagulant prophylaxis vs no anticoagulant prophylaxis in a non-randomized retrospective cohort study of 76 individuals aged 0-21 years with a malignant mediastinal mass between the years of 2000 and 2017. Anticoagulant prophylaxis was physician led using enoxaparin. VTE occurred in 13/76 (17.2%), including 4/19 (21%) of those receiving anticoagulant prophylaxis vs 9/57 (15.7%) not receiving prophylaxis. Mediastinal compression-related VTE was also reported, occurring in 1/19 (5.2%) of those receiving anticoagulant prophylaxis vs 6/57 (10.5%) not receiving prophylaxis.

Giertz et al.[41] compared the incidence of VTE in a retrospective cohort of 489 children (<18 years old) diagnosed with Hodgkin lymphoma between 2005 and 2019. LMWH prophylaxis was administered to 18/489 (3.7%) of perceived higher risk patients. VTE occurred in 42/489 (8.6%), including 2/18 (11.1%) who received anticoagulant prophylaxis vs 40/471 (8.4%) not receiving prophylaxis.

There was no significant difference in the incidence of VTE between those receiving anticoagulant prophylaxis and those not receiving prophylaxis in any of these studies or on analysis of the pooled data. A major limitation of these data is the non-randomized study design resulting in a serious risk of bias in

terms of patient selection for anticoagulant prophylaxis. The low event rate results in serious imprecision and a low certainty of the effects of anticoagulant prophylaxis.

Harms and burden

Abate et al.[38] reported no bleeding in the 85 pediatric patients who received anticoagulant prophylaxis with LMWH for a median duration of 177 days (range: 4-478 days). Schonning et al. [39] reported no bleeding in the 5 pediatric patients who received prophylaxis with LMWH. Sarangi et al.[40] did not comment on bleeding complications in their study. Giertz et al.[41] reported no bleeding in the 18 patients who received LMWH prophylaxis.

These data support the safety of anticoagulant prophylaxis in pediatric patients with solid tumors although the total number treated was low. There were also no data reported on the impact of LMWH prophylaxis on quality of life (QoL).

Other EtD criteria and considerations

The panel did not identify any specific issues affecting feasibility or acceptability of administering anticoagulant prophylaxis in pediatric patients with solid tumors. The resources required were considered to be moderate. Evidence profiles (EP) and Evidence to Decision (EtD) Frameworks are available online for Recommendation 3.

Conclusions and research needs for this recommendation

There are no RCTs for this recommendation. The recommendation was based on pooled analysis of 4 non-randomized comparative studies. The rate of VTE was significant (6.6%) although many events were present at diagnosis and therefore not preventable by anticoagulant prophylaxis. Event rates in this cohort were lower than those reported in adults with similar malignant conditions. The evidence presented does not support the efficacy of anticoagulant prophylaxis as a means of reducing thrombotic risk in this clinical setting, with the desirable effects of anticoagulant prophylaxis being judged by the panel as trivial. There is some evidence to support the safety of anticoagulant prophylaxis although not all studies reported on the occurrence of bleeding and bleeding is a recognised complication of solid tumors and their surgical and/or medical treatment. Burden of treatment was not reported in any study although the panel considered that this was likely to be significant, particularly given the use of injectable drugs and the potential for a prolonged period of anticoagulant prophylaxis to be required

due to ongoing thrombotic risk factors such as CVAD, surgery, chemotherapy and residual malignant disease. The panel judged the undesirable effects to be small but not trivial. The panel therefore *suggest* no anticoagulant prophylaxis in pediatric patients with solid tumors, including Hodgkin Lymphoma. This is a conditional recommendation based on very low certainty in the evidence of effects, due to the low rate of VTE and serious concerns about risk of bias as physician-led decisions were made about the need for anticoagulant prophylaxis.

The panel however recognises the potential for serious consequences of VTE when it occurs in this clinical setting. There are likely to be subgroups in whom the risk of a thrombotic event may outweigh the bleeding risk and potential adverse impact on QoL of receiving anticoagulant prophylaxis and in whom prophylaxis could be considered. Physicians should therefore assess the thrombotic risk of individual pediatric patients with solid tumors and consider this alongside the risk of bleeding. Important thrombotic risk factors to be considered include: 1) tumor-related factors such as vessel compression (e.g. mediastinal mass) or invasion by tumor, and locally advanced or metastatic disease; 2) treatment-related factors such as major cancer surgery, pelvic/abdominal/lower limb cancer surgery, or CVAD use; and/or, 3) patient-related factors such as adolescence, OCP use, known thrombophilia, past history of thromboembolic disease, obesity, or reduced mobility. Bleeding risk can be influenced by tumor site, recent surgery, and thrombocytopenia/coagulopathy.

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

1. Studies to better risk stratify pediatric patients with solid tissue cancers enabling subsequent trials comparing anticoagulant prophylaxis vs no prophylaxis in high-risk patients. Such studies should consider the safety/undesirable effects (bleeding, QoL, cost) and efficacy of different anticoagulant regimens.

2. More specific reporting by trials including separating data on CVAD-related and non CVAD-related VTE, and identifying VTE secondary to vessel compression in pediatric patients with solid tumors.

Total Parenteral Nutrition Prophylaxis

Question: In infants, children and adolescents considered for total parenteral nutrition (TPN) for more than 60 days (i.e., intestinal failure on home TPN), should anticoagulant prophylaxis vs. no anticoagulant prophylaxis be used?

Recommendation 4.: In infants, children, and adolescents considered for total parenteral nutrition (TPN) for more than 60 days (i.e., intestinal failure on home TPN), the ASH ISTH Guideline Panel ***suggests*** using anticoagulant prophylaxis rather than no anticoagulant prophylaxis (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

- This recommendation excludes neonates and patients requiring short-term (<60 days) TPN support.
- Based on the two comparative studies, primary pharmacological prophylaxis seemed to reduce the risk of developing catheter-related VTE.
- The anticoagulant prophylaxis administered included daily LMWH and vitamin K antagonists (VKAs).
- Patients receiving primary and secondary anticoagulant prophylaxis could not be separated in the included studies and thus the evidence includes pediatric patients receiving secondary prophylaxis.

Summary of the evidence

We found two non-randomized comparative studies and two non-comparative studies that addressed this question. All studies included children receiving long-term, TPN administered at home (TPN duration ranged from 2 months to 11 years). The anticoagulant prophylaxis administered included daily LMWH and VKAs.

The comparative studies[43,44] reported the effect of anticoagulant prophylaxis on the development of CVAD-related VTE among 147 children. Both studies compared the use of anticoagulant prophylaxis to no prophylaxis and included patients receiving either primary or secondary VTE prophylaxis. The low certainty of the evidence to inform this recommendation is in part due to the inclusion of children receiving secondary anticoagulant prophylaxis in both comparative studies. Three children transitioned from no anticoagulant prophylaxis to anticoagulant prophylaxis because of recurrent thrombosis in the Vegting[44] study and 47% of the patients in the anticoagulant prophylaxis group of the Demirok[43] study were receiving secondary prophylaxis. The rate of previous thrombosis in children who did not receive anticoagulant prophylaxis in the Demirok study was unknown.

Outcomes for patients receiving primary or secondary prophylaxis were not reported separately and thus there is very low certainty in the evidence informing this recommendation. One non-comparative cross-sectional study reported the incidence of VTE in a cohort of 12 children on long-term home TPN who did not receive prophylaxis.[45] A second non-comparative retrospective study[46] assessed the incidence of CVAD-related VTE among 55 children on home TPN, all of whom received primary anticoagulant prophylaxis.

The anticoagulant prophylaxis administered to patients in three studies[43,44,46] included once daily LMWH for 108 (83%) and VKAs for 22 (17%) patients. Across the three studies, the target anti-factor Xa peak level for LMWH prophylaxis was 0.1-0.4 IU/ml and the target International Normalized Ratio (INR) range for children on VKAs was 2.0-3.0.[43,44,46]

Benefits

Based on the two comparative studies, primary anticoagulant prophylaxis seemed to reduce the risk of developing CVAD-related VTE (RR: 0.83, 95% CI: 0.23 to 2.98). In the comparative study by Demirok et al.[43], propensity score stratification was used to balance the effects of covariates that were significantly different between the anticoagulant prophylaxis and non-prophylaxis groups. The risk of CVAD-related VTE seemed to be reduced in children receiving primary anticoagulant prophylaxis (odds ratio [OR]: 0.64, 95% CI: 0.12 to 3.40), however the wide CI indicates the result should be interpreted with caution. [43] CVAD-related VTE was identified in one child (6%) in the anticoagulant prophylaxis group and in nine (33%) children in the non-prophylaxis group in the comparative study by Vegting et al.[44]

In the non-comparative study by Nagelkerke[46], the rate of CVAD-related VTE in a cohort of children with intestinal failure on home TPN who received anticoagulant prophylaxis was 14.5% (8 out of 55, 0.2 per

1,000 catheter days).[46] Screening ultrasounds were performed every 12-24 months or if there was clinical suspicion of thrombosis. The median age at start of TPN was 8.4 months and the median duration of TPN at the end of the study was 31 months.

In the non-comparative study by Andrew et al.[45] of 12 children on home TPN who did not receive anticoagulant prophylaxis, the median age at the time of the study was five years. Eight out of 12 (66.7%) children were identified to have VTE via screening venography.[45] The median number of catheters per child was 3.5 (range 2-8), suggesting this small cohort had been receiving TPN for several years at the time of imaging.

Based on the reduced rate of CVAD-related VTE observed in patients receiving anticoagulant prophylaxis in the comparative studies, the beneficial effects from the included studies were considered moderate. Overall, the certainty of these estimated effects is very low owing to a serious risk of bias, serious indirectness and very serious imprecision. The inclusion of patients receiving secondary prophylaxis, potential selection bias, the small number of events, and the limited number of patients in the studies contribute to imprecise estimates and reduce the overall certainty of the evidence.

Harms and burden

Two studies collected data on adverse effects.[44,46] No bleeding events occurred in the Vegting et al.[44] study, although there were 5 deaths reportedly due to their underlying disease. Nagelkerke et al.[44] reported 16 bleeding events in 10 subjects receiving primary anticoagulant prophylaxis with LMWH. Major bleeding was noted in 3.6% (2 out of 55); CRNMB was reported in 9.1% (5 out of 55) and non-specified bleeding was reported in 18.2% (10 out of 55). Nagelkerke et al.[46] reported mortality; one patient died during follow up, but the cause of death was not specified. There were no incidences of major or CRNMB in the non-prophylaxis groups in either study. Consequently, the risk of adverse effects was not estimable.

There is low certainty in the estimate of the risk of adverse effects due to a very serious risk of bias and serious imprecision. However, given the available evidence, the panel considered the undesirable effects from the included studies to be small.

Other EtD criteria and considerations

The panel did not identify any specific issues affecting feasibility or acceptability of administering LMWH or VKA prophylaxis in pediatric patients receiving TPN. The resources required were considered to be

moderate. This decision was based on the costs associated with the requirement for long-term or lifelong anticoagulant prophylaxis for children receiving TPN. Evidence profiles (EP) and Evidence to Decision (EtD) Frameworks are available online for Recommendation 4.

Conclusions and research needs for this recommendation

Given the need for lifelong vascular access for most of these children, and the life-threatening consequences of loss of vascular access, the panel placed a high value on potential benefits of anticoagulant prophylaxis. The recommendation for primary anticoagulant prophylaxis cannot be extrapolated to children receiving time-limited TPN; but pertains specifically to infants and children with intestinal failure on home TPN for the foreseeable future. The patients in these studies were generally infants and older children on home TPN, with median ages from 4 months up to 6.9 years, and so the panel did not include neonates in this recommendation.

Children requiring long-term TPN for intestinal failure often require repeated catheter replacement due to catheter occlusion, catheter-related blood stream infection (CRBSI) or dislodgement.[47] The influence of the number of catheters per patient, CRBSI and of TPN duration on the risk of VTE has not been fully considered.[47] The role of prophylactic anticoagulation in reducing the risk of CRBSI is not addressed via this guideline.

Based on the body of available evidence, anticoagulant prophylaxis likely reduces the risk of developing CVAD-related VTE, and the consequences of CVAD-related VTE in this specific population are eventually life threatening. There is very low certainty that there is an effect of anticoagulant prophylaxis on other outcomes. Long-term use of anticoagulation is associated with reduced bone mineral density in other populations.[48-50] For this cohort reduced bone density is a likely sequela as they require lifelong central access and anticoagulant prophylaxis.[44] This is in addition to the risk of developing metabolic bone disease associated with long-term TPN, their underlying disease and malabsorption.[51]

The panel identified the following research priorities:

1. Studies of anticoagulant prophylaxis for neonates receiving long term TPN.
2. Studies determining the acceptability of various anticoagulant options including direct oral anticoagulants (DOACs) for long term use and their impact on QoL.
3. Ideally, studies should present the incidence of CVAD-related VTE per catheter days to account for variations in the number of catheters per patient and the duration of TPN.

CENTRAL VENOUS ACCESS DEVICE

Question: In pediatric patients with a short-term (≤7 days) CVAD, should anticoagulant prophylaxis vs. no anticoagulant prophylaxis be used?

Recommendation 5. In pediatric patients with a short-term (≤7 days) CVAD, the ASH ISTH Guideline Panel ***suggests*** no anticoagulant prophylaxis rather than anticoagulant prophylaxis (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

- The current evidence does not support the universal use of prophylactic anticoagulation for all pediatric patients with a short-term (≤7 days) CVAD. However, the panel acknowledges that there may be subgroups of patients at high-risk of VTE and low risk of bleeding, in whom anticoagulant prophylaxis may be of benefit. This high-risk VTE subgroup includes children ≥1 year old with a short-term CVAD who are critically ill, on invasive mechanical ventilation and have a low risk of bleeding, as well as patients expected to have prolonged immobility and/or hospitalization, those with autoimmune/inflammatory conditions, and those with active serious infections.

Summary of the evidence

The review team identified one multicenter RCT (n=51) that compared LMWH to SoC (no pharmacological prophylaxis) for the prevention of CVAD-related VTE in children with a short-term CVAD (Catheter-Related Early Thromboprophylaxis with Enoxaparin [CRETE] Trial).[52] This trial enrolled children admitted to the pediatric intensive care unit (PICU) who were <24 hours post-insertion of an untunneled CVAD and performed screening doppler ultrasounds within 24 hours of study termination. LMWH was started within 24 hours from CVAD insertion, given every 12 hours and titrated to achieve an anti-Xa level of 0.2-0.5 IU/mL. Of note, the trial had very stringent inclusion and exclusion criteria and as a result, only a very small subset of patients assessed for eligibility were enrolled (2.5%, 51/2058) raising concerns about the generalizability of its findings. Importantly, patients with coagulopathy, those with active- or <60 days from a clinically relevant bleed, and those <7 days after trauma or surgery were

excluded from the study. Further, the study was terminated prematurely before reaching full enrollment due to an incorrect estimation of the risk of CVAD-related VTE in the pre-approved analysis plan that affected the validity of the study's design and outcomes.

The review team also identified 4 non-randomized observational studies that compared rates of CVAD-related VTE in pediatric patients with and without anticoagulant prophylaxis.[53-56] These studies included pediatric patients with a short-term CVAD who were admitted to the PICU or surgical inpatient unit at their respective institutions. Anticoagulant agents used in these studies included UFH, LMWH and VKAs. Additionally, we included data derived from the subgroup of children with a short-term CVAD enrolled in the Prophylaxis for Thromboembolism in Critical Care (PROTEKT) trial, a multicenter RCT assessing the efficacy and safety of LMWH prophylaxis vs. SoC (no prophylaxis) for the prevention of CVAD-related VTE.[57]

Benefits

The beneficial effects of anticoagulant prophylaxis in the included studies were considered small. There seemed to be a small reduction in the rates of VTE in patients who received anticoagulant prophylaxis compared to those without prophylaxis, but this reduction was not observed consistently across all studies and VTE types. In the CRETE Trial[52], pediatric patients receiving anticoagulant prophylaxis had lower rates of CVAD-related DVT (30.4% (7/23) vs. 54.2% (13/24)), and symptomatic CVAD-related VTE (3.7% (1/27) vs 29.2% (7/24)) compared to those receiving SoC (no prophylaxis) (RR 0.13 95% CI 0.2-0.96). However, the panel noted the very small proportion of patients screened for eligibility that were enrolled in the trial (2.5%) raising concerns regarding the generalizability of its findings, the overall small number of patients assessed in each arm of the trial (prophylaxis arm n=27; SoC arm n=24), and the early termination of the study when considering this evidence. In the non-randomized studies, reductions in the rates of VTE in the anticoagulant prophylaxis arm were inconsistent across studies. While the combined rate of CVAD-related VTE was lower in children who received anticoagulant prophylaxis compared to those without (20.6% (30/189) vs. 35.7%(35/98)) (RR 0.66 95% CI 0.37-1.19)[53-55,57]; rates of symptomatic CVAD-related VTE and rates of all DVT were higher in patients with anticoagulant prophylaxis compared to those without (symptomatic CVAD-related VTE: 8% (2/25) vs. 5% (1/20) (RR 1.6 95% CI 0.16-16.4); all DVT: 8.9% vs. 5.3%, (RR 1.75 95% CI 0.58-5.26), respectively[56,57]) and rates of asymptomatic CVAD-related VTE did not differ substantially between patients with and without anticoagulant prophylaxis (4% [1/25] vs. 10% [2/20], respectively) (RR 0.4 95% CI 0.04-4.1).[57]

The overall difference in number of events between groups (anticoagulant prophylaxis vs. no prophylaxis) was considered small. In the RCT, the risk of bias was judged to be very serious and due to the overall low number of events, imprecision ranged from serious to very serious. For the non-randomized studies, the risk of bias was assessed as serious and imprecision as very serious. Overall, the certainty of these estimated effects was judged to be very low.

Harms and burden

The undesirable effects of anticoagulant prophylaxis in the included studies were considered small. Compared to those not receiving prophylaxis, patients who received anticoagulant prophylaxis had a slight increase in the rates of bleeding. In the CRETE Trial, there was one CRNMB in the anticoagulant prophylaxis arm, and zero events in the SoC arm.[52] In the non-randomized studies, the rate of clinically relevant bleeding was slightly higher among critically ill patients at high risk of bleeding without anticoagulant prophylaxis compared to those with prophylaxis (39% (30/77) vs. 33.3% (1/3) (RR 1.43 95% CI 0.18-11.43)); however, major bleeding, CRNMB occurred in 6.8% (8/118), 0.8% (1/118) respectively of patients receiving anticoagulant prophylaxis, and in none of the patients without prophylaxis (0/27).[54,56] Unspecified bleeding was reported in 3.2% (1/31) of patients with anticoagulant prophylaxis and in none of those without prophylaxis (0/167). In CRETE study, all-cause mortality was 18.5% with anticoagulant prophylaxis vs 8.3% with SoC, (RR 2.2 95% CI 0.47-10.42). Similarly, in the non randomised data, all-cause mortality was slightly higher in patients with anticoagulant prophylaxis compared to those without (4.8% vs. 3.3% respectively), while no VTE-related mortality events were reported in any of the groups.[54,57]

Overall, the difference in the number of events between groups was considered small. There was very serious risk of bias and serious imprecision in the RCT, and serious risk of bias and very serious imprecision in the non-randomized studies. The overall certainty of the estimated effects was judged to be very low. In considering the potential burdens associated with anticoagulant prophylaxis, while the intervention (anticoagulant prophylaxis) was considered to be probably acceptable, the panel took into consideration that oral medications are rarely used for prophylactic anticoagulation in hospitalized patients, particularly those with short-term CVADs who tend to be critically ill, thus the need for a parenteral medication was a consideration in this recommendation.

Other EtD criteria and considerations

The panel did not identify any specific issues affecting feasibility or acceptability of administering LMWH in pediatric patients with short term CVAD. The resources required were considered to be moderate. Evidence profiles (EP) and Evidence to Decision (EtD) Frameworks are available online for Recommendation 5.

Conclusions and research needs for this recommendation

The panel concluded that the current available evidence does not support a net benefit from using universal primary anticoagulant prophylaxis in pediatric patients with a short-term (≤7 days) CVAD. Overall, the slightly higher rates of bleeding and all-cause mortality reported in patients with anticoagulant prophylaxis compared to those without, in the setting of small and inconsistent reductions in the rates of CVAD-related VTE in those receiving anticoagulant prophylaxis, influenced the decision to suggest against prophylactic anticoagulation in pediatric patients with a short-term CVAD. While the balance of effects was judged to probably favor the comparison (no anticoagulant prophylaxis), it must be noted that the included data had significant bias and imprecision.

However, the panel acknowledges that there may be subgroups of pediatric patients with short-term CVADs who have a high-risk of VTE and low risk of bleeding, and who may benefit from anticoagulant prophylaxis. This high-risk VTE subgroup includes patients with a short-term CVAD who are critically ill, on invasive mechanical ventilation, expected to have prolonged immobility and/or hospitalization, those with autoimmune/inflammatory conditions, and those with active serious infections. The only RCT informing this recommendation excluded children at high risk of bleeding, defined as patients with coagulopathy, those with active- or <60 days from a clinically relevant bleed, and those <7 days after trauma or surgery.[52] Thus, the panel recommends careful consideration of the patient's individual risks for VTE and bleeding as there may be patients in whom the benefit of prophylactic anticoagulation outweighs its risks.

The panel identified the following research priorities:

1. Prospective multicenter cohort studies investigating the baseline risk of bleeding in select patients with a short-term CVAD and high risk of VTE to inform the design of risk-stratified anticoagulant prophylaxis trials.

2. Multicenter risk-stratified trials investigating the safety and efficacy of anticoagulant prophylaxis for short-term CVAD-related VTE in select pediatric patients identified to be at high risk of VTE. Such trials may consider the use of DOACs.

Question: In children and adolescents who require medium/long term (≥8 days) CVAD in the absence of cancer or TPN, should anticoagulant prophylaxis vs. no anticoagulant prophylaxis be used?

Recommendation 6. In children and adolescents who require medium/long term (≥8 days) CVAD in the absence of cancer or TPN, the ASH ISTH Guideline Panel ***suggests*** no anticoagulant prophylaxis rather than anticoagulant prophylaxis (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

- This recommendation pertains to the use of primary anticoagulant prophylaxis.
- The panel acknowledged that there may be pediatric patients who may benefit from prophylaxis. A thorough assessment of individual risks and careful consideration of benefits and harms when considering prophylactic anticoagulation is appropriate.

Summary of the evidence

There was a single RCT that addressed this question which reported the effect of primary anticoagulant prophylaxis on the development of asymptomatic CVAD-related VTE, symptomatic CVAD-related VTE and VTE-related mortality among 186 children.[57] The panel reviewed the data from a subgroup of 31 patients who did not have cancer or TPN use.[57] Patients were randomly assigned to receive twice daily reviparin sodium as anticoagulant prophylaxis or SoC. The primary efficacy outcome was a CVAD-related VTE detected by venogram at day 30 or at the time of CVAD removal, a confirmed symptomatic VTE within 30 days of CVAD placement, or death due to VTE during the study period. Anticoagulant prophylaxis did not prevent VTE events.

Benefits

Based on the single RCT, anticoagulant prophylaxis did not reduce the risk of developing CVAD-related VTE. There were asymptomatic CVAD-related VTEs in 3/12 (25.0%) patients in the anticoagulant prophylaxis group compared to 3/19 (15.8%) in the SoC group (RR 1.58, 95% CI 0.38 to 6.60). There were no reported symptomatic CVAD-related VTE or VTE-related deaths. The certainty of evidence was judged to be very low due to the risk of bias and imprecision.

Based on the trivial difference in the number of events between the anticoagulant prophylaxis and the no prophylaxis groups, there was no beneficial effect from the included study.

Harms and burden

There was one major bleeding event (1/94; 1.1%) in the non-prophylaxis group and none in the anticoagulant prophylaxis group in the overall study. There was no significant difference in the rate of minor bleeding between the non-prophylaxis group and the anticoagulant prophylaxis group (P=0.24). Undesirable effects were judged to be trivial because of the low number of events in both the anticoagulant prophylaxis and no prophylaxis groups, as well as the trivial difference in number of events in the included study. There was low certainty in the risk of adverse events due to serious bias and very serious imprecision.

Other EtD criteria and considerations

The panel identified that there may be differences in the acceptability and feasibility of administering a LMWH vs an oral anticoagulant in pediatric patients with medium and long term CVAD. The resources required were moderate. Evidence profiles (EP) and Evidence to Decision (EtD) Frameworks are available online for Recommendation 6.

Conclusions and research needs for this recommendation

Conclusions are based on a subgroup analysis from a single RCT which provided evidence on the benefits and risk of anticoagulant prophylaxis in children with medium and long term CVAD in the absence of cancer or TPN use. The evidence showed no benefit of anticoagulant prophylaxis. The panel discussed that the use of anticoagulant prophylaxis may increase the risk of bleeding; a 1.3% major bleeding rate has been reported with prophylactic or full dose anticoagulation for secondary prophylaxis for CVAD-

related VTE.[58] Based on their clinical expertise, the panel discussed that patients may have different perspectives even in the same situation, trying to balance the undesirable effect of increased bleeding with anticoagulation and the beneficial effect of preventing a VTE. Therefore, there was possibly important uncertainty or variability in how patients value the outcomes.

Given the low number of VTE events in both the anticoagulant prophylaxis and no prophylaxis arms, the trivial difference in number of VTE events, trivial undesirable effects, low certainty of evidence, and the variability in how patients value the outcomes, the balance of effects would not favor either anticoagulant prophylaxis or no prophylaxis. Therefore, a conditional recommendation was made to suggest no anticoagulant thromboprophylaxis.

The panel would like to highlight that while neonates were included in the study population, the mean age of included patients was 6 years. Given the even smaller evidence of benefit or harm of anticoagulant prophylaxis and potential different benefit:risk ratio, this recommendation may not be appropriate for extrapolation to neonates.

The following research priorities were identified by the panel:

1. Studies exploring risk stratification based on patient, treatment, and catheter-related risk factors for CVAD related VTE.
2. Subsequent studies exploring the safety and efficacy of different anticoagulant agents (LMWH, VKAs, DOACs) for primary prophylaxis for children who require medium and long term CVAD in the absence of cancer or TPN use. Such studies should include assessment of treatment acceptability and impact on QoL.
3. Specific studies of anticoagulant prophylaxis in neonates with CVADs.

ANTIPHOSPHOLIPID ANTIBODIES

Question: In pediatric patients with antiphospholipid antibody syndrome (APS), should secondary anticoagulant (± antiplatelet) prophylaxis vs. no secondary anticoagulant prophylaxis be used?

> **Recommendation 7.** In pediatric patients with antiphospholipid antibody syndrome (APS), the ASH ISTH Guideline Panel ***suggests*** using secondary anticoagulant prophylaxis rather

than no secondary anticoagulant prophylaxis (conditional recommendation based on low certainty in the evidence about effects ⊕⊕◯◯).

Remarks:

- An a-priori decision was made to exclude pediatric patients receiving only antiplatelet therapy from this evidence profile.
- The included evidence showed moderate benefit of secondary anticoagulation prophylaxis (with or without antiplatelet therapy) in reducing recurrent thromboembolism.

Summary of the evidence

The panel reviewed data from two single-center observational studies[59,60], a cross-sectional international database study[61], and subgroup analysis of the phase 2B/3 DIVERSITY trial.[62] These studies estimated the rate of recurrent thrombosis in pediatric patients with primary and secondary APS who received anticoagulation (± antiplatelet therapy) versus those who did not receive anticoagulation. Anticoagulant agents in these studies included UFH, LMWH, VKAs, fondaparinux, and DOACs. Patients who only received antiplatelet agents (e.g. aspirin and clopidogrel) were excluded from the evidence profile. The panel additionally considered a single-center, retrospective study by Avila et al.[63], but was unable to include these data in the analysis for this recommendation given that details on anticoagulation were not available for the entire cohort.

Only a subgroup analysis of the phase 2B/3 DIVERSITY trial reported bleeding in children with APS who were treated with Dabigatran. To address this gap, we utilized an expert evidence approach by systematically gathering clinical experience through a survey sent to panel members.[29] This survey estimated the number of patients with APS managed by each expert, as well as the bleeding rates associated with anticoagulation use.

Benefits

Based on the pooled data from the four studies, recurrent thrombosis was reported in 33/155 (21.3%) children with APS. This included 23/131 (17.6%) children receiving anticoagulation (± antiplatelet therapy), versus 10/24 (41.7%) children not receiving anticoagulation for a RR: 0.41 (95% CI: 0.23 –

0.76). There were 246 fewer recurrent thrombotic events (95% CI: 321 fewer to 100 fewer) per 1000 patients receiving anticoagulation (± antiplatelet therapy), compared to those who did not receive anticoagulation.

Rao et al. reported 17 pediatric patients with APS in a single center, retrospective study, with a median follow-up of 4.3 years (range: 0.8 – 16.9 years). Anticoagulant agents used included LMWH and VKA. Recurrent thrombotic events were reported in 5/12 (41.6%) patients on therapeutic anticoagulation (± antiplatelet therapy), compared to 4/4 (100%) patients not on anticoagulation.[60]

Ma et al. described 67 thrombotic events in 43 pediatric patients with APS in a single-center, retrospective study. Anticoagulant agents used included UFH, LMWH, VKA, and Rivaroxaban. Recurrent thrombotic events were reported in 1/31 (3.2%) patients receiving anticoagulation (± antiplatelet therapy), versus 4/10 (40%) patients who did not receive anticoagulation.[59]

In an international, multicenter cross-sectional study, Avcin et al. reported clinical outcomes in 121 pediatric patients with APS. The mean duration of follow-up was 6.1 years (range: 0.7 – 24.7 years). Eighty-eight patients received anticoagulation (± antiplatelet therapy), though details on anticoagulant agents used were not provided in the study. Recurrent thrombosis was reported in 17/88 (19%) patients receiving anticoagulation (± antiplatelet therapy) versus 2/10 (20%) patients not receiving anticoagulation.[61]

Brandao et al. reported three patients with APS enrolled in the phase 2b/3 DIVERSITY trial, who were rolled over to a single-arm, phase 3, secondary VTE prevention study with dabigatran. Recurrent thrombosis was reported in one patient, a month after stopping anticoagulation.[62]

In summary, anticoagulation was associated with a significant reduction in the risk of recurrent thrombosis when analyzing the pooled data. A major limitation of these data is the non-randomized study design resulting in a serious risk of bias. Additionally, the small sample size results in serious imprecision and a low certainty of evidence for the benefits of anticoagulation.

Harms and burden

Only Brandao et al. reported bleeding as an outcome in three patients with APS enrolled in the phase 2b/3 DIVERSITY trial, who were rolled over to a single-arm, phase 3, secondary VTE prevention study with dabigatran. No bleeding events were reported. In response to the expert survey, thirteen responses were received, providing data on 157 pediatric patients with APS who had been treated with secondary anticoagulant (± antiplatelet) prophylaxis. The panel reported major bleeding events in 2

(1.27%) patients and CRNMB events in 12 (7.6%) patients. Overall, there was very low certainty in the estimate of the risk of adverse effects due to a critical risk of recall and perception bias.

Other EtD criteria and considerations

The panel did not think there were feasibility or acceptability considerations that would impair the implementation of this recommendation. The resources required were considered to be moderate. Evidence profiles (EP) and Evidence to Decision (EtD) Frameworks are available online for Recommendation 7.

Conclusions and research needs for this recommendation

There are no pediatric RCTs to provide evidence on the benefits of anticoagulation for secondary VTE prophylaxis in children with APS. The recommendation was based on data from four non-randomized studies. The rate of recurrent thrombosis in children with APS was 21.3%, and anticoagulation was associated with a significant reduction in the risk of recurrent events. The desirable effects of anticoagulation were consequently deemed to be moderate in this cohort. These studies did not provide data on the rate of bleeding in children receiving anticoagulation, but through a subgroup analysis of the DIVERSITY trial and panel survey the undesirable effects of anticoagulation were deemed to be trivial. The panel therefore *suggests* using anticoagulation in pediatric patients with APS. This is a conditional recommendation based on very low certainty in the evidence of effects due to risk of bias, including recall and perception bias with the survey, and serious imprecision.

Based on current evidence, DOACs are not recommended in adult patients with APS, specifically triple-positive APS, and a history of arterial thrombosis. While similar data are not available for pediatric patients, based on extrapolation of adult data, LMWH and VKA are typically the anticoagulants of choice in these patients. The panel acknowledges that the burden of treatment in this cohort is likely to be significant, given the use of injectable drugs (LMWH), food and drug interactions (VKA), need for laboratory monitoring (LMWH and VKA), and the extended period of anticoagulation required in children with APS. Lastly, the panel was unable to make any recommendations on dose intensity for secondary prophy in APS as there are no published data to guide such recommendation. The decision on dose intensity (low dose vs. full-dose) for secondary VTE prophylaxis needs to be made on a case-by-case basis based on the perceived individual patient's risk for recurrent VTE and bleeding, the patient's lifestyle and the patient's and family's preferences and values.

Of note, the panel made an a priori decision to exclude patients treated solely with antiplatelet therapy from the systematic review and evidence profiles. Therefore, the panel did not make a recommendation on the benefit:risk ratio of using antiplatelet agents alone in this cohort.

The following research priorities were identified by the panel:

1. Prospective cohort studies to investigate the natural history of APS in children, specifically the risk of recurrent thrombosis in children with single versus double and triple positive APS.
2. Diagnostic criteria for APS need to be prospectively validated in children.
3. Studies investigating the safety and efficacy of different types of anticoagulant agents (LMWH, VKA and DOACs) in children with low-risk APS.
4. Studies to determine the magnitude of undesirable effects of anticoagulation in children with APS, including bleeding and reduced QoL.

Question: In pediatric patients with persistent antiphospholipid antibodies and without history of thrombosis, should primary anticoagulant prophylaxis vs. no primary anticoagulant prophylaxis be used?

Recommendation 8. In pediatric patients with persistently positive antiphospholipid antibodies (APLA) without a history of thrombosis, the ASH ISTH Guideline Panel ***suggests*** no primary anticoagulant prophylaxis rather than primary anticoagulant prophylaxis (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

- An a-priori decision was made to exclude pediatric patients receiving antiplatelet therapy, and therefore the panel cannot comment on the benefits and risk of using antiplatelet agents in this cohort.
- The panel acknowledges that evolving definitions of APS may influence clinical decision making and emphasizes that individual patient characteristics—such as the presence of an underlying autoimmune disorder, double or triple antibody positivity, the strength of

antibody titers, and microvascular manifestations should be considered when evaluating the need for primary anticoagulant prophylaxis.

Summary of the evidence

Through a systematic review, no studies were identified that specifically addressed the question of anticoagulant prophylaxis versus no anticoagulant prophylaxis in pediatric patients with persistently positive APLA and no history of thromboembolism. Evidence from a single open-label RCT comparing low-dose aspirin to low-dose aspirin plus low-intensity warfarin in adult patients with positive APLA[64] was considered. While this trial reported no differences in the incidence of VTE between the groups, it found a higher rate of bleeding events in patients receiving anticoagulation prophylaxis. However, this study did not include the pediatric population in question. To address this gap, the panel adopted an expert evidence approach, systematically gathering clinical experience through a survey distributed to panel members. The survey included targeted questions to estimate the number of patients managed by each expert and the rates of thrombosis and bleeding in these patients. Sixteen responses were received, providing data on 88 pediatric patients. Among these, five out of 88 (6%) received primary anticoagulant prophylaxis for persistently positive antiphospholipid antibodies without thrombosis, while 83 out of 88 (94%) did not. The survey did not include questions regarding the use of short-term prophylaxis at times of increased VTE risk (i.e., hospitalization). The panel acknowledged that, while this approach offered valuable insights in the absence of published studies, it was inherently limited by potential recall and perception bias.

Benefits

The expert survey evaluated the use of primary anticoagulant prophylaxis vs. no anticoagulant prophylaxis in pediatric patients with persistently positive antiphospholipid antibodies and no history of thrombosis. Based on panel member responses, symptomatic VTE events were reported in one out of five (20%) patients in the anticoagulant prophylaxis group and in two out of 83 (2%) in the no-anticoagulant prophylaxis group. The certainty of the estimated effects is very low owing to recall and perception bias.

Harms and burden

According to panel member responses to the expert survey, no major bleeding events were reported in either group: zero out of five patients in the anticoagulant prophylaxis group and zero out of 83 patients in the no-anticoagulant group. CRNMB occurred in one out of five patients (20%) in the anticoagulant prophylaxis group, compared to zero out of 83 patients in the no-anticoagulant group. Overall, there was very low certainty in the estimate of the risk of adverse effects due to a critical risk of recall and perception bias.

Other EtD criteria and considerations

The panel acknowledged that there was probably no important uncertainty or variability in the acceptability of anticoagulant prophylaxis for pediatric patients with persistently positive APLA. This was primarily because anticoagulation options for patients with APLA are often limited to LMWH or VKAs, which have high burdens of use and may be unacceptable to patients. However, the panel also noted that the acceptability could vary depending on factors such as the duration of anticoagulation, the perceived risk of thrombosis, or whether the concern was arterial vs venous thrombosis. Evidence profiles (EP) and Evidence to Decision (EtD) Frameworks are available online for Recommendation 8.

Conclusions and research needs for this recommendation

Because the overall guideline scope is focused on the management of anticoagulant prophylaxis in pediatric patients, the panel made a deliberate decision to exclude patients treated solely with antiplatelet therapy from the systematic review and evidence profiles. Therefore, the panel did not make a recommendation on the benefit:risk ratio of using antiplatelet agents in this cohort.

The panel used an expert survey to gather clinical experience as the best available means to provide evidence in the absence of studies. While acknowledging the numerous limitations of this approach, the panel also noted that the majority of patients included in the survey did not receive anticoagulant prophylaxis, suggesting that most experts do not routinely prescribe anticoagulation for pediatric patients with persistence of APLA in the absence of thrombotic history.

The group evaluated the balance between the desirable and undesirable effects of primary anticoagulant prophylaxis in pediatric patients with persistently positive APLA and concluded that it favored no anticoagulation. While the panel made a conditional recommendation for no primary

anticoagulant prophylaxis for persistently positive APLA, panel members emphasized the importance of considering individual patient circumstances where anticoagulation might be appropriate. Such situations could include patients with underlying autoimmune conditions, double or triple-positive APLA, or additional thrombophilic risk factors. Further, the expert survey did not include questions specifically addressing the need for anticoagulant prophylaxis during high-risk VTE periods such as hospitalization, prolonged immobility, serious active infection or presence of a CVAD. Panel members emphasized that the decision to start anticoagulation should be individualized based on balancing the risk of thrombotic complications with the underlying bleeding risk.

The research priority identified was:

1. Prospective studies to evaluate risk stratification strategies and the prognostic impact of primary anticoagulant prophylaxis in pediatric patients with persistently positive APLA and no history of thrombosis, at baseline and during periods of high VTE risk.

TRAUMA PATIENTS

Question: In pediatric patients with trauma, should anticoagulant prophylaxis vs. no anticoagulant prophylaxis be used?

Recommendation 9: In pediatric patients with trauma, the ASH ISTH Guideline Panel ***suggests*** no anticoagulant prophylaxis rather than anticoagulant prophylaxis (conditional recommendation based on very low certainty in the evidence about effects ⨁◯◯◯).

Remarks:

- The evidence does not support the universal use of anticoagulant prophylaxis in pediatric trauma patients who comprise a heterogenous population in whom the overall prevalence of VTE is low.
- There are, however, subgroups in the included studies (patients deemed “high risk”) that had higher reported rates of VTE who may benefit from prophylactic anticoagulation. These specific “high-risk” criteria included presence of shock, age > 12

years (or younger ages with multiple risk factors), immobility, intubation, and presence of a CVAD.

- While the risk for bleeding from anticoagulant prophylaxis in pediatric trauma patients is overall low, it was noted to be higher in patients receiving prophylactic anticoagulation in one study.

Summary of the evidence

Ten studies evaluating the rate of VTE in trauma patients receiving anticoagulant prophylaxis (n= 11541) vs those receiving no anticoagulant prophylaxis (n=171308) were included in the evidence profile.[65-74] Anticoagulant agents used for prophylaxis included UFH, LMWH and rivaroxaban. The pooled absolute risk difference was 0.01 (95%CI 0-0.03), with 20 more events per 1000 in the patients receiving anticoagulant prophylaxis. Pooled studies suggested an increased all-cause mortality (2% vs 1%, risk difference 0.01) and higher rate of symptomatic (1.9% vs 0.1%, risk difference 0.02) and asymptomatic VTE (1.8% vs 0.1%, risk difference 0.03) in patients receiving anticoagulant prophylaxis. Since these were observational studies and subject to selection bias, the higher rates of VTE in the anticoagulant prophylaxis arm may indicate confounding by indication, i.e., patients with perceived higher baseline VTE risk received anticoagulant prophylaxis. Two studies attempted to adjust for the heterogeneity in VTE risk of the population (see other EtD considerations, below).[65,66] However, the studies reported inconsistent results, with one study (adjusting for age) suggesting lower risk of VTE (OR 0.7, 95%CI 0.22-2.16)[65] and the other (matching cohorts for risk) showing higher risk of VTE with anticoagulant prophylaxis (IRR 2.3, 95%CI 1.66-3.18).[66]

While a systematic search for studies on prevalence of VTE in pediatric trauma patients was not performed, the overall prevalence of VTE in the included studies was low (n=254947; median 0.3%, range [0.05%-3%]). The overall low VTE incidence in these studies suggests that the potential absolute VTE risk reduction with anticoagulant prophylaxis is small to trivial.

A subgroup of patients labeled as “high-risk” was reported in four studies.[65,69,71,74] VTE occurred in 128/995 (12.9%) “high-risk” patients with a median rate of 17% (range 5.5-24%). Each study had different definitions of “high risk”, but there were similarities among them. Landisch et al. defined “high-risk” as age over 13 years OR age less than 13 years with ≥4 risk factors for VTE (with risk factors including presence of CVAD, predicted immobility > 5 days, operative pelvic fracture, known

thrombophilia, and current malignancy). Based on this definition 20/99 (10%) “high-risk” patients developed VTE.[65] Leeper et al. reported development of VTE in 78/315 “very-high risk” and “high-risk” patients. The study defined “very-high risk” patients as those identified at 36 hours after injury who either are over 13 years with one risk factor (intubated with CVAD, non-ambulatory pelvic or lower extremity fracture, obesity, use of inotropes, or use of exogenous estrogen) OR patients less than 13 years with a personal or family history of DVT or known thrombophilia in addition to one of the defined risk factors. These very-high risk patients were stated to meet criteria for anticoagulant prophylaxis. “High-risk” patients were defined as those who did not meet the prophylaxis criteria at 36 hours but had ongoing risk factors on post-trauma day five.[71] Tobias et al. had 5/21 (23.8%) “high-risk” patients develop VTE.[69] The study used a published risk model[75] that utilizes 10 clinical variables (including presence of CVAD, pelvic fracture, intubation, age, and intensive care unit [ICU] admission) and weighted scores to predict overall risk of VTE. Patients identified with a score ≥523 (predicted risk of VTE of 1%) were designated “high risk”. Finally, Witte et al. defined “high risk” patients as those unable to ambulate within 48 hours from their injury and either age > 8 years with one additional risk factor or age ≤ 8 years with 2 or more additional risk factors. Additional risk factors included obesity, central venous line, ICU stay anticipated > 48 hours, spinal cord injury, current use of estrogen, personal or family history of VTE, and vascular injury. The rate of VTE in this “high-risk” group was 5.5% (n=25/460) with similar rates among those who did and did not receive anticoagulant prophylaxis (5.6% vs 5.3%, respectively). Further the study noted that in those with anticoagulant prophylaxis initiated within 24 hours of the injury, the rate of VTE (1.6%) was lower than if anticoagulant prophylaxis was initiated >24 hours after the injury (6.9%). The group receiving anticoagulant prophylaxis within 24 hours of injury had shorter ICU lengths of stays and shorter time on mechanical ventilation compared with those with anticoagulant prophylaxis initiation >24 hours after the injury.[74] This suggests that the populations in these groups were likely different, implying that the data may have been impacted by confounding by indication.

The panel noted that all studies were unable to fully account for confounding by indication, which likely account for the poor outcomes observed in patient receiving anticoagulant prophylaxis. The panel does acknowledge that there are subgroups of pediatric trauma patients at very high risk of developing VTE but concludes that the benefit of anticoagulant prophylaxis is uncertain.

Benefits

There was no reduction in VTE in patients who received anticoagulant prophylaxis, with higher rates of VTE in the anticoagulant prophylaxis groups as described above and therefore, the beneficial effects from the included studies were considered trivial. The risk of bias in these studies was serious to very serious, and certainty of these estimated effects was low to very low.

Harms and burden

The undesirable effects from the included studies were considered small. Mahajerin et al. reported increased risk of bleeding in patients receiving anticoagulant prophylaxis (n=61/11165) compared with those not receiving anticoagulant prophylaxis (n=309/169767; 0.5% vs. 0.2%, respectively; RR for bleeding 3.00 [95%CI 2.28 to 3.95]).[66] There was serious risk of bias and certainty of this estimated effect was moderate. In considering potential burdens, while the intervention was considered probably acceptable, the panel did note that oral medications are rarely used for anticoagulant prophylaxis in trauma patients and thus the need for an injectable medication was considered.

Other EtD criteria and considerations

The panel did not think there were feasibility or acceptability considerations that would impair the implementation of this recommendation. The resources required were considered to be moderate. Evidence profiles (EP) and Evidence to Decision (EtD) Frameworks are available online for Recommendation 9.

Conclusions and research needs for this recommendation

Overall, the rate of VTE in hospitalized children with trauma was low. The panel determined that the evidence did not support a net benefit from using universal anticoagulant prophylaxis in unselected hospitalized children following trauma. The panel did note that trauma patients designated as “high risk” based on institutional protocols had higher rates of VTE and required consideration for anticoagulant prophylaxis. Further, there are clinical differences when comparing patients admitted in the ICU with those who have been deemed high-risk at their institution compared with the general trauma population. Therefore, the panel recommends that clinicians consider the individual patient risks for development of VTE as there may be patients in whom the potential benefit of anticoagulant prophylaxis may outweigh the risks.

The panel identified the following additional research priorities:

1. Characterization of the prevalence of VTE according to pediatric trauma severity
2. Collaborations to standardize VTE risk assessment models, timing and intensity of anticoagulation used in research studies on hospitalized children following trauma
3. Subsequently, multi-center prospective studies to evaluate the safety and efficacy of anticoagulant prophylaxis in high-risk patients using prospectively validated risk scores

HOSPITALIZED PATIENTS

Question: In hospitalized pediatric patients, should anticoagulant prophylaxis vs. no anticoagulant prophylaxis be used?

Recommendation 10. In hospitalized pediatric patients, the ASH ISTH Guideline Panel ***suggests*** no anticoagulant prophylaxis rather than anticoagulant prophylaxis (conditional recommendation based on low certainty in the evidence about effects ⊕⊕◯◯).

Remarks:

- Hospitalized pediatric patients encompass an extremely heterogeneous population with respect to age, underlying medical conditions and baseline risk of thrombosis.
- The panel acknowledged that there may be certain pediatric patients that may benefit from anticoagulant prophylaxis (e.g., immobility, use of estrogen, infection, obesity, inflammation), though additional studies are needed.
- Several subgroups (cancer, CVAD, surgery, trauma) are addressed in separate recommendations.

Summary of the evidence

The review team identified a single RCT (n=186) that compared LMWH to SoC (no anticoagulant prophylaxis) to prevent CVAD-related VTE in hospitalized pediatric patients. In this trial the rate of VTE was 12% with anticoagulant prophylaxis [3.3% symptomatic, 8.7% asymptomatic] vs 10% without [3.2% symptomatic, 7.4% asymptomatic], RR: 1.12 (0.5-2.5). There was one major bleed in the SoC arm. The trial was closed prematurely due to slow accrual.[57]

Additionally, the review team identified 4 non-randomized observational studies, that evaluated thromboprophylaxis in hospitalized children.[76-79] In the studies that reported VTE, the combined rate of VTE in children who received anticoagulant prophylaxis was 6.5% (14/214) compared to 3.7% (68/1853), risk difference 0.04 (-0.01-0.08). One study used a large database to evaluate rates of bleeding using International Classification of Disease codes in patients who received anticoagulant prophylaxis.[79] The combined rate of bleeding in the observational studies was 5.6% (589/10544) in patients with anticoagulation and 4.7% without (2783/58768).

Benefits

The beneficial effects from the included studies were considered trivial. There was no reduction in VTE in patients who received anticoagulant prophylaxis, although the risk of bias in the randomized trial was serious and very serious in the non-randomized studies. Overall, the certainty of these estimated effects was judged to be low.

Harms and burden

The harmful effects from the included studies were considered trivial. Rates of bleeding in patients who received anticoagulant prophylaxis did not appear to be higher compared to those who did not receive prophylaxis. However, these estimates were judged to be low due to risk of bias and imprecision.

Other EtD criteria and considerations

Several subgroups at high-risk of VTE are addressed separately in this manuscript. In addition, there may be select hospitalized patients, such as adolescents with additional pro-thrombotic risk factors (e.g., immobility, use of estrogen, infection, obesity, inflammation) who may benefit from anticoagulant prophylaxis. The ASH adult VTE prophylaxis guidelines in non-critically ill hospitalized medical patients suggest using anticoagulation rather than no anticoagulation.

The required resources associated with the intervention (anticoagulant prophylaxis) were judged to be moderate, although there were no available studies addressing this. Additionally, the panel did not identify equity, feasibility, or acceptability considerations that would impair implementation of the intervention. Evidence profiles (EP) and Evidence to Decision (EtD) Frameworks are available online for Recommendation 10.

Conclusions and research needs for this recommendation

Overall, there was very little evidence addressing this question. While the balance of effects did not clearly favor the intervention or the comparison, and while in the included studies there was no difference in bleeding, this data had significant bias and imprecision. The known potential for increased bleeding with anticoagulant prophylaxis influenced the decision to suggest against anticoagulation. The panel determined that the evidence did not support a net benefit from using anticoagulant prophylaxis in unselected hospitalized children.

The panel identified the following additional research priorities:

1. Pediatric risk scores that allow stratification of hospitalized children based on risk of VTE should be prospectively validated.
2. Multi-center prospective studies should be conducted to evaluate the safety and efficacy of anticoagulant prophylaxis in high-risk patients using these risk scores.

CRITICALLY ILL PATIENTS

Question: In pediatric patients who are critically ill with or without a CVAD, should primary anticoagulant prophylaxis over no prophylaxis be used?

Recommendation 11. In pediatric patients who are critically ill with or without a CVAD, the ASH ISTH Guideline Panel ***suggests*** no anticoagulant prophylaxis rather than anticoagulant prophylaxis (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯)

Remarks:

- The current evidence does not support the universal use of prophylactic anticoagulation in critically ill children for which there is insufficient data for formal stratification of the risks of VTE and the risk of bleeding.
- However, the panel acknowledged that there may be subgroups of critically ill children (children ≥1 year old with an untunneled CVAD and low risk of bleeding and children

receiving invasive mechanical ventilation), in whom the risk of VTE may outweigh the risk of bleeding, who could potentially benefit from prophylactic anticoagulation.

Summary of the evidence

The review team identified six studies comparing the use of anticoagulant prophylaxis to no anticoagulant prophylaxis in critically ill children, both with and without CVADs. These included one RCT[52] and five non-randomized studies of interventions (NRSI).[54-56,80,81] All studies enrolled critically ill pediatric patients, although the specific age ranges varied.

The RCT by Faustino et al.[52] and two prospective cohort studies by Jones et al.[54] and Quinn et al.[55] evaluated a total of 273 children with jugular or femoral untunneled CVADs. These studies assessed the use of enoxaparin, UFH or any anticoagulant as primary prophylaxis for the prevention of CVAD-related VTE. A mixed retrospective and prospective cohort study by Harney et al.[56] also evaluated VTE outcomes in children with untunneled CVADs. This study included 198 hospitalized patients aged one month to 21 years and compared those who received enoxaparin or UFH prophylaxis with those who received no anticoagulant prophylaxis. However, the study did not distinguish between children admitted to the intensive care or surgical units, limiting its applicability to critically ill population. Despite this limitation, a sensitivity analysis conducted by our panel found results consistent with those from studies exclusively involving critically ill children.

Sochet et al.[81] conducted a case-control study of 456 children <21 years who received invasive mechanical ventilation (IMV). The study compared cases with VTE versus controls without VTE matched by age group regarding the use of anticoagulant prophylaxis defined as any anticoagulant given at prophylactic doses. Lastly, Gupta et al.[80] conducted a retrospective cohort study of 622 adolescents aged 12–17 years who received cardiopulmonary support. This study assessed the incidence of VTE in those who did and did not receive anticoagulant prophylaxis.

Several of the included studies also involved patients receiving mechanical VTE prophylaxis, either in combination with anticoagulant agents or as the sole preventive measure, although this factor was not accounted for in the panel's analysis.

Benefits

The RCT by Faustino et al.[52] reported a reduced risk of developing a CVAD-related VTE (including both symptomatic and asymptomatic) in critically ill children who received anticoagulant prophylaxis (RR:

0.56, 95% CI: 0.27 to 1.15). A greater reduction in risk was observed when the analysis was limited to symptomatic CVAD-related VTE (RR: 0.13; 95% CI: 0.02 to 0.96). However, the certainty of these estimated effects is very low due to serious to very serious imprecision owing to the small number of events and enrolled patients. These limitations raised concerns regarding generalizability and residual confounding. Importantly, only 2.5% of all patients with a CVAD were ultimately randomized. Nearly 60% were deemed ineligible due to a high risk of bleeding, which was defined by factors such as active or recent clinically relevant bleeding, recent surgery or major trauma, coagulopathy, or renal failure. Additionally, 4 of the 27 children randomized to receive enoxaparin did not receive the intervention, further limiting the internal validity of the trial. Among the NRSI, the study by Sochet et al. reported that anticoagulant prophylaxis was associated with significantly lower odds of VTE in critically ill children requiring invasive mechanical ventilation after adjusting for CVAD presence, duration of mechanical ventilation, and immobility (adjusted OR: 0.20; 95% CI: 0.06 to 0.70).[81]

Despite these individual findings, pooled analysis of the RCT and NRSI did not demonstrate a lower risk of VTE (symptomatic and asymptomatic combined) with anticoagulant prophylaxis (RR: 1.29; 95% CI: 0.48 to 3.45). The panel rated the certainty of this estimate as very low, citing serious imprecision related to high risk of bias across studies, small event counts, and limited sample sizes. These factors contributed to wide confidence intervals, inconsistent point estimates, and uncertainty regarding the true effect.

Harms and burden

Adverse events, including bleeding and mortality, were reported in four of the included studies. In the RCT by Faustino et al.[52], the risk of clinically relevant bleeding, defined as CRNMB or major bleeding, did not differ significantly between patients receiving prophylactic enoxaparin and those who received no anticoagulation (risk difference: 0.04; 95% CI: –0.06 to 1.14). One patient in the enoxaparin group discontinued treatment due to upper airway bleeding. The certainty of this evidence was rated very low, primarily due to the exclusion of patients at high risk of bleeding and a singular bleeding event.

Among the NRSI, Quinn et al.[55], Jones et al.[54], and Harney et al.[56] evaluated bleeding outcomes in their cohorts. Both Quinn and Jones reported a higher risk of clinically relevant bleeding among patients receiving anticoagulant prophylaxis compared with those who did not (RR: 1.81; 95% CI: 0.43 to 7.56). Harney et al. found no meaningful difference in bleeding risk, though bleeding severity was not specified, between patients who received enoxaparin or UFH and those who did not (risk difference:

0.03; 95% CI: –0.04 to 0.11). All three studies were judged to have low certainty of evidence due to potential selection bias and serious imprecision, resulting from the small number of bleeding events (11 events in those who received anticoagulant prophylaxis and 30 events in those who did not).

Mortality outcomes were reported in two studies: Faustino et al.[52] and Jones et al.[54] In the RCT by Faustino et al., more deaths occurred in the enoxaparin group compared to the control group (5 of 27 [18.5%] vs. 2 of 24 [8.3%]), though none were attributed to anticoagulation. Similarly, Jones et al. observed a higher mortality risk in patients who received anticoagulant prophylaxis (RR: 1.43; 95% CI: 0.18 to 11.43). However, the certainty of this evidence was rated very low due to a high risk of selection bias and the very small number of mortality events, leading to serious imprecision.

Based on the available data, the panel concluded that the risk of adverse effects from anticoagulant prophylaxis in this population is most likely small.

Other EtD criteria and considerations

The panel considered the question of prescribing anticoagulant prophylaxis to prevent VTE or CVAD-related VTE in critically ill children to be of high importance. However, after evaluating the current body of evidence, the panel concluded that the potential benefit, namely, a reduced risk of VTE, was likely small, given the very low certainty of the evidence among a highly heterogenous population. This uncertainty includes a lack of clarity around the optimal type of anticoagulant used and appropriate dosing regimen. Given the potential for significant bleeding in critically ill children, anticoagulant prophylaxis is likely to offer the most benefit in patients with a high risk of VTE but with a low risk of bleeding.

The panel noted that the risk of bleeding associated with anticoagulant prophylaxis was small. However, bleeding events were infrequent across the included studies, limiting the precision and certainty of the estimated risk. Furthermore, patients with an elevated risk of bleeding were excluded from participation in the RCT by Faustino et al.[52], making it difficult to accurately determine the absolute risk of bleeding with anticoagulant prophylaxis in critically ill children.

The RCT by Faustino et al.[52] also highlighted challenges related to the acceptability of anticoagulant prophylaxis. Among the 27 patients randomized to receive enoxaparin, treatment was refused by the

parents of two patients, and by the physician in an additional two patients. Further, only a small number of screened patients were enrolled, primarily due to risk of bleeding.

The required resources associated with the intervention (anticoagulant prophylaxis) were judged to be moderate, although there were no available studies addressing this. Evidence profiles (EP) and Evidence to Decision (EtD) Frameworks are available online for Recommendation 11 (RCT Data and NRSI Data).

Conclusions and research needs for this recommendation

The panel concluded that there is low certainty of evidence supporting a net benefit from the use of primary anticoagulant prophylaxis to prevent VTE in critically ill children, with or without CVADs. This recommendation is based on findings from a single RCT and a pooled analysis of five NRSI. Although the RCT by Faustino et al.[52], which enrolled critically ill children with a CVAD, and the case-control study by Sochet et al.[81], which included critically ill children receiving IMV, both reported reduced risk of VTE with anticoagulant prophylaxis, the overall certainty of evidence for efficacy remains low due to study limitations, imprecision, and risk of bias.

Across the included studies, the overall prevalence of VTE in critically ill children was substantially higher (median 35%, range 1.3%–54%) than in the general pediatric population. However, this potential benefit must be weighed against the risk of bleeding, which was also elevated with anticoagulant prophylaxis (median 3.7%, range 0%–33%). Two studies found a higher bleeding risk in children receiving anticoagulant prophylaxis compared to those who did not[52,56], while two other studies found no difference.[54,55] Overall, the panel rated the certainty of evidence for harm as low to very low, due to methodological limitations, selection bias, and small event counts.

Critically ill children at high risk of VTE are often also at high risk of bleeding, making it difficult to determine who might benefit from prophylaxis. Consequently, the panel does not recommend universal use of anticoagulant prophylaxis in all critically ill children. This position was a key factor in the panel's overall recommendation. However, the panel acknowledged that certain subgroups of critically ill children, particularly those at high risk of VTE but at low risk of bleeding, might still benefit from individualized consideration.

Overall, the critically ill pediatric population is highly heterogeneous, and there is insufficient evidence to formally stratify VTE and bleeding risks. Therefore, the decision to initiate anticoagulant prophylaxis

should be individualized, based on a careful assessment of each child's specific risk of VTE, risk of bleeding, and potential for net clinical benefit.

The panel identified several key research priorities:

1. Studies to determine the absolute risks of VTE and bleeding with prophylactic anticoagulation in critically ill children with and without CVAD
2. Studies to determine optimal timing for initiating prophylactic anticoagulation in critically ill children, particularly for those who were initially assessed to be at high risk of bleeding
3. Studies to determine optimal choice of prophylactic anticoagulation, including oral anticoagulants, to improve the acceptability of prophylactic anticoagulation among patients, families, and healthcare providers
4. Studies to determine the efficacy of mechanical thromboprophylaxis alone or in addition to prophylactic anticoagulation

SURGERY PATIENTS

Question: In pediatric patients undergoing noncardiac surgery, should anticoagulant prophylaxis vs. no anticoagulant prophylaxis be used?

Recommendation 12. In children undergoing noncardiac surgery, the ASH ISTH Guideline Panel ***suggests*** no anticoagulant prophylaxis rather than anticoagulant prophylaxis (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯)

Remarks:

- The panel did not assess VTE risk by specific type of surgical procedure (e.g., orthopedic, bariatric, laparoscopic, etc.). Rather, the panel grouped available pediatric surgical data to assess the risk for postoperative VTE and found a low incidence in this heterogeneous group.
- Procedure-related and patient-related factors that increase the risk for VTE include longer operative time, prolonged immobilization, greater than seven days of central venous access, obesity, congenital thrombophilia, and the use of combined OCP.

Summary of the evidence

The review team identified five observational studies that addressed this question in pediatric patients (1 prospective non-randomized comparative study in children with long-gap esophageal atresia[82] and 4 retrospective comparative studies in children after splenectomy, orthopedic surgeries, scoliosis surgery, and pelvic osteotomy[83-86]). Anticaogulant agents used for prophylaxis in these studies included UFH, LMWH, VKAs, Fondaparinux and DOACs. All studies assessed VTE, 1 study reported data on symptomatic VTE and CVAD-related VTE[82], 1 study reported data on DVT[85], 2 studies reported data on PE[84,85], 1 study reported data on major bleeding and CRNMB[82], and 1 study reported data on bleeding (unspecified).[83] The panel concluded that both the desirable and undesirable effects of prophylactic anticoagulation were trivial for most pediatric patients undergoing noncardiac surgery. Based on the low-risk difference of 0.01 in these studies, anticoagulant prophylaxis is likely not indicated. Therefore, the panel made a conditional recommendation to use no anticoagulant prophylaxis over anticoagulant prophylaxis for pediatric patients undergoing noncardiac surgery, noting the very low certainty of evidence due to risk of bias concerns and imprecision.

Benefits

Combining five observational studies[82-86], 6/572 (1.0%) of patients receiving anticoagulant prophylaxis had VTE compared to 18/2075 (0.9%) of patients who did not receive anticoagulant prophylaxis (risk difference: 0.01; 95% CI -0.04 – 0.02).

One observational study by Kelly of a very specific population, evaluated anticoagulant prophylaxis in children with long gap esophageal atresia[82], 2/27 (7.4%) of patients receiving anticoagulant prophylaxis had symptomatic VTE compared to 13/40 (32.5%) of patients who did not receive anticoagulant prophylaxis (RR: 0.23; 95% CI 0.06 – 0.93). All symptomatic VTEs were CVAD-related VTEs.

One observational study in children who underwent scoliosis surgery reported data on DVT.[85] No DVTs were reported; 0/49 (0.0%) of patients receiving anticoagulant prophylaxis had DVT compared to 0/24 (0.0%) of patients who did not receive anticoagulant prophylaxis (risk difference: 0.00; 95% CI -0.06 – 0.06).

No PE was observed in the two included observational studies of children having varied orthopedic procedures and children with scoliosis surgery.[84,85] 0/91 (0.0%) of patients receiving anticoagulant

prophylaxis had PE compared to 0/1323 (0.0%) of patients who did not receive anticoagulant prophylaxis (risk difference 0.00; 95% CI -0.03 – 0.03).

In the five included observational studies, overall outcomes may have been affected by differing risk profiles for patients who received anticoagulant prophylaxis compared to those who did not receive anticoagulant prophylaxis. The certainty of the data was low given the serious imprecision for all outcomes and the serious to very serious risk of bias.

Harms and burden

No major bleeding, CRNMB, or bleeding (unspecified) were reported. Two observational studies[82,83], reported no major bleeding or CRNMB (0/27) or unspecified bleeding (0/51) of patients receiving anticoagulant prophylaxis compared to 0/40 (major/CRNMB) and 0/1 (unspecified) of patients who did not receive anticoagulant prophylaxis respectively .

The certainty of the data was low to very low given the very serious imprecision due to no events being observed, the small sample size, and the serious risk of bias.

Other EtD criteria and considerations

The panel did not think there were feasibility or acceptability considerations that would impair the implementation of these recommendations regarding noncardiac surgical anticoagulant prophylaxis. Patients and providers may weigh the risks and benefits of anticoagulant prophylaxis differently based on specific patient characteristics and surgical settings. For those patients receiving anticoagulant prophylaxis after noncardiac surgery, the resources required were moderate with probable acceptability and feasibility. Evidence profiles (EP) and Evidence to Decision (EtD) Frameworks are available online for Recommendation 12.

Conclusions and research needs for this recommendation

The panel reviewed comparative and noncomparative studies on a diverse, non-exhaustive group of noncardiac surgical procedures that likely confer different risks for VTE and bleeding. The panel determined that there is very low certainty evidence for a net health benefit from using anticoagulant prophylaxis in noncardiac surgery. Based on the body of available evidence, it is likely that the risk of postoperative VTE is low in most children undergoing noncardiac surgery irrespective of procedure type, and thus routine anticoagulant prophylaxis is not indicated. Yet, there are pediatric surgical subgroups

that may be at higher risk for VTE and thus may benefit from anticoagulant prophylaxis. The panel recommends that providers consider individual risks for VTE based on the combination of the surgical and individual patient risks. These risks include duration of the procedure, use of muscle paralytic agents, prolonged immobilization, presence of CVAD, post-pubertal age, obesity, congenital thrombophilia, personal or family history of VTE, and the use of combined OCP. Because of the low certainty of evidence and 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 areas:

1. Development of a tool to risk stratify pediatric non cardiac surgical scenarios for anticoagulant prophylaxis. Such studies should consider surgery-specific risk factors for VTE such as limb tourniquet or patient positioning, and other surgical risk factors such as duration of the procedure, requirement of muscle relaxation, and extent of immobility post-surgery.
2. Subsequent studies in high-risk patients to determine the ideal anticoagulant regimen: type of anticoagulant, dose intensity, timing of initiation of prophylaxis (before or after the procedure), and if initiation is after the procedure, how many hours post-surgery is ideal.

Anticoagulant Agents and Regimens

The selection of an anticoagulant agent and regimen for VTE prophylaxis in children is complex and must take into consideration several factors including the patient's age, clinical status, comorbidities, bleeding risk profile, ability to tolerate oral intake, impact on QoL with the administration of parenteral agents and/or limitations in age-appropriate activities, long-term off-target effects from anticoagulant agents and the patient/families' preferences and values. Given these complexities, the panel sought to provide further guidance on the use of anticoagulant agents and regimens for VTE prophylaxis in the pediatric population based on the regimens reported in the studies informing these guidelines. However, However, the panel was unable to do so due to significant heterogeneity in regimens reported across studies, even within the same agent and patient subgroup. Additionally, there was a considerable lack of detailed information, particularly regarding monitoring strategies, timing of initiation and duration of anticoagulant prophylaxis. Instead, a summary of the anticoagulant regimens reported in the studies informing these guidelines is provided below by type of agent and in **Table 2** by patient subgroups.

LMWH

As expected, LMWH was the most commonly investigated agent across nearly all of pediatric subgroups, with 72% (36/50) of studies reporting LMWH use. Dosing exhibited substantial variability in unit dosages and frequency. Reported regimens included doses from 0.5 mg/kg/dose twice daily to 1.5 mg/kg/day, as well as various weight-tiered regimens and regimens with fixed dosing based on age and weight thresholds. Peak anti-Xa levels were monitored in 33% (12/36) studies with varied target ranges (i.e., ≤0.4 U/L, 0.1 – 0.3 IU/mL, 0.1 to 0.4 IU/mL, 0.2 to 0.5 IU/mL and 0.1 to 0.5 IU/mL).

UFH

The use of UFH was reported in 16% (8/50) of the included studies. This agent was more commonly used in the trauma, critically ill and short-term CVAD populations, likely due to its short half-life which makes it a better choice for patients who are at high risk of bleeding or who may require urgent discontinuation or reversal of the anticoagulant effect. UFH dosing, route of administration and monitoring was not provided in the majority of the studies. In the only study providing information regarding dosing, the mean dose of UFH was 10.4 u/kg/hr (standard deviation 3.8 u/kg/hr) among critically ill patients, while a different study, also in the critically ill pediatric population, targeted an anti-Xa level of 0.2 – 0.4 IU/mL.

VKAs

The use of VKAs was reported in 18% (9/50) studies. Given their oral administration, these agents were most commonly used in pediatric subgroups who are likely to require long-term or indefinite anticoagulant prophylaxis including the APS and home TPN pediatric populations. INR target range was 2 to 3 for studies reporting this information.

DOACs

Apixaban, rivaroxaban and dabigatran were investigated in 12% (6/50) of studies including in the Leukemia/Lymphoblastic Lymphoma, APS, trauma and surgery subgroups. Dosing regimens for these agents were weight-based in the studies reporting this information.

Notably, four of the included studies did not provide any detail on the anticoagulant regimen used for prophylaxis. Given the observed marked heterogeneity in anticoagulant regimens, and the considerable amount of missing data, the panel was unable to provide further guidance on specific anticoagulant agents and regimens for VTE prophylaxis in pediatric patients. The panel identified the urgent need to investigate the safety and efficacy of different anticoagulant agents, and to determine their optimal dosing, timing and duration for VTE prevention across different pediatric subgroups. The panel also

recognized the need for guidance and standardization in the reporting of anticoagulant regimens within pediatric studies to ensure that comprehensive and uniform information is provided.

Limitations of these guidelines

The recommendations in these guidelines were limited in every case by very low or low certainty in the evidence. For certain recommendations, there was scarce or no published direct or relevant indirect evidence, and the panel was anonymously surveyed to provide unpublished collective data to use for decision-making. This process was performed in agreement with all panel members and is explicitly identified for relevant recommendations.

Summary of Conclusions and Future Research Recommendations

There is a lack of high-quality evidence to guide the use of anticoagulant prophylaxis for VTE prevention across diverse pediatric subgroups. Overall, the heterogeneity of pediatric patients in terms of VTE and bleeding risk profiles, even within specific subgroups, precludes the ability to make a universal recommendation for the use or no use of anticoagulant prophylaxis for the majority of the pediatric populations addressed in these guidelines. Instead, until more evidence becomes available, the panel emphasizes that the decision to use anticoagulant prophylaxis for VTE prevention in pediatric patients should be individualized and based on a careful assessment of the individual patient's thrombotic and bleeding risks, and the patient's values and preferences. While specific subgroups of pediatric patients within the broader pediatric populations assessed in these guidelines might benefit from anticoagulant prophylaxis, these subgroups of patients require better definitions and the investigation of targeted anticoagulant strategies.

Throughout the guidelines, the panel emphasized the urgent need for high-quality evidence, including evidence derived from adequately powered RCT investigating the safety and efficacy of anticoagulant prophylaxis for VTE prevention across different pediatric subgroups. Additionally, the panel identified the critical need for the development, validation and further refinement of risk assessment models that can permit the early identification of those subgroups of pediatric patients at high risk of VTE and low risk of bleeding who may benefit from anticoagulant prophylaxis. Furthermore, future research is

needed to evaluate the safety and efficacy of different anticoagulant agents, particularly DOACs, and to determine their optimal dosing, timing and duration across various clinical scenarios. Finally, there is a need to better understand the impact of long-term anticoagulant prophylaxis on the QoL of pediatric patients.

Revision or adaptation of the guidelines

Plans for updating these guidelines

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

Updating or adapting recommendations locally

Adaptation of these guidelines will be necessary in many circumstances. These adaptations should be based on the associated EtD frameworks.[87]

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Authorship contributions

All panel members contributed to specific subsections of text for both recommendations and implementation guidelines. Marisol Betensky, Paul Monagle and Leslie Raffini organised and then revised these subsections into the first draft of this manuscript and subsequently revised the manuscript based on authors' suggestions. All guideline panel members critically reviewed the manuscript and provided suggestions for improvement. Members of the systematic review team (Muayad Azzam, Hassan Kawtharany, and Jana Khawandi) contributed evidence summaries to the guidelines. All authors

approved of the content. Paul Monagle (co-chair), Reem Mustafa (co-chair) and Marisol Betensky ("co-chair in-training") led the panel meetings.

Disclosures of conflicts of interest

All authors were members of the guideline panel or members of the systematic review team or both. As such, they completed a disclosure of interest form, which was reviewed by ASH/ISTH and is available as supplements 2 and 3.

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Table 2 Summary of Anticoagulant Regimens Reported in Included Studies by PICO Question

Author, year	Agent	Dose	Route	Monitoring	Duration
PICO 1 Acute Lymphoblastic Leukemia / Lymphoma Pediatric Population					
O'Brien, 2024[31]	Apixaban	≥35 kg: 2.5 mg bid 25 to <35 kg: 2 mg bid 18 to <25 kg 1.5 mg bid 10.5 to <18 kg: 1 mg bid 6 to <10.5 kg: 0.5 mg bid	PO	No	28 days
Ruiz-Llobet, 2024[32]	LMWH	NR	NR	NR	During peg-ASP administration
Greiner, 2019[30]	LMWH	80-100 IU/kg qd	S.Q.	Target anti-Xa level ≤0.4 U/L	Day 8 – Day 33 of induction chemotherapy
Mitchell, 2010[34]	LMWH	1 mg/kg/day	NR	NR	During ALL induction
Elhasid, 2001[33]	LMWH	Median: 0.84 mg/kg/day Range: 0.45-1.33 mg/kg/day	S.Q.	NR	From first dose ASP until 1 week after last dose of ASP
PICO 2 Solid tumors / Hodgkin's Lymphoma Pediatric Population					
Giertz, 2025[41]	LMWH	NR	NR	NR	NR
Sarangi, 2021[40]	LMWH	1.5 mg/kg qd	S.Q.	No	From diagnosis of mediastinal mass until >50% reduction in size was achieved. Median: 49 days
Schönning, 2017[39]	LMWH	NR	NR	NR	NR
Abate, 2014[38]	LMWH	body weight-based dosing	NR	NR	Median: 117 days Range: 7-478 days
PICO 3 Total Parenteral Nutrition (>60 days) Pediatric Population					
Nagelkerke, 2022[46]	LMWH	<10 kg: 70 IU/kg/day 10 to 20 kg: 40 IU/kg/day 20 to 30 kg: 950 IU/day 30 to 50 kg: 1900 IU/day >50 kg: 2850 IU/day	S.Q.	Target anti-Xa level 0.1 to 0.3 IU/mL	Indefinite
	VKA	NR	PO	INR 2 to 3	
Vegting, 2012[44]	LMWH	80 IU/kg	S.Q.	Target anti-Xa level 0.1 to 0.3 IU/mL	Indefinite
	VKA	NR	PO	INR 2 to 3	

Demirok, 2025[43]	LMWH	<2 months: 150 u/kg/day 2 months to <2 years: 120 u/kg/day 2 to <12 years: 100 u/kg/day 12 to 18 years: 85.5 u/kg/day	S.Q.	Target anti-Xa level 0.1 to 0.4 IU/mL	Indefinite
	VKA	NR	PO	INR 2 to 3	
PICO 4 Central Venous Access Device: Short-term Pediatric Population					
Faustino, 2021[52]	LMWH	≤2 months: 0.75 mg/kg/bid >2 months: 0.5 mg/kg/bid	S.Q.	Target anti-Xa level 0.2 to 0.5 IU/mL	First dose <24 hours after CVAD placement until line removal or earlier upon discharge from ICU, radiologic diagnosis of CADVT, start of therapeutic anticoagulation, or 28 days after insertion of CVAD.
Faustino, 2013[53]	LMWH, UFH, VKA	NR	NR	NR	NR
Jones, 2019**[54]	UFH	Mean dose: 10.4 u/kg/hr (S.D. 3.8 u/kg/hr)	IV	NR	Started within 12 hours of CVAD insertion
Quinn, 2024**[55]	NR	NR	NR	NR	NR
Massicotte, 2003*[57]	LMWH (Reviparin)	<3 months old: 50 IU/kg/bid ≥3 months old: 30 IU/kg/bid	S.Q.	No***	NR
Harney, 2010**[56]	LMWH, UFH, VKA	NR	NR	NR	Day 1 to Day 17 of admission (median day 3)
PICO 5 Central Venous Access Device: Medium to Long-Term Pediatric Population (Massicotte, 2003)					
PICO 6 Antiphospholipid Antibody Syndrome Pediatric Population					
Nageswara, 2017[60]	LMWH, VKA	NR	NR	Yes	Indefinite
Avcin, 2008[61]	NR	NR	NR	NR	NR
Brandão, 2022[62]	Dabigatran	Age and weight-adjusted nomogram	Oral	Yes	Up to 12 months
Ma, 2018[59]	VKA, “others”	NR	NR	INR 2-3	NR
PICO 7 Trauma Pediatric Population					
Landisch, 2017[65]	LMWH	0.5 mg/kg bid	S.Q.	No	Until discharge
Mahajerin, 2022[66]	LMWH, UFH	NR	NR	NR	NR
Hanson, 2010[67]	NR	NR	NR	NR	NR

Karahan, 2023[68]	LMWH	5-45 kg: 0.5 mg/kg bid >45 kg: 40 mg qd (50% reduced dose for CrCl <30 mL/min)	S.Q.	No	At least 15 days
Tobias, 2023[69]	LMWH	NR	NR	NR	NR
Hanson, 2012[70]	LMWH	0.5 mg/kg bid	S.Q.	No	Until discharge
Leeper, 2017[71]	LMWH	1 mg/kg qd (Max 40 mg qd)	S.Q.	No	NR
Alturki, 2019[72]	LMWH	NR	NR	NR	NR
Witte, 2024[74]	LMWH	0.5 mg/kg bid (max 30 mg qd)	NR	No	NR
	UFH, rivaroxban	NR	NR	NR	
Bigelow, 2018[73]	NR	NR	NR	NR	NR
PICO 8 Hospitalized Pediatric Population					
Story, 2021**[76]	LMWH	1 mg/kg/dose bid	S.Q.	Target anti-Xa level 0.1 to 0.3 IU/mL	During admission
Walker, 2023**[77]	LMWH, UFH	age- and weight-based	NR	NR	NR
Levine, 2022**[78]	LMWH	NR	NR	NR	NR
Amos, 2019**[79]	LMWH	NR	NR	NR	NR
PICO 9 Critically ill Pediatric Population					
Gupta, 2021[80]	None	NA	NA	NA	NA
Sochet, 2024[81]	LMWH	NR	NR	Target anti-Xa level 0.1 to 0.5 IU/mL	NR
	UFH	NR	NR	Target anti-Xa level 0.2 to 0.4 IU/mL	NR
PICO 10 Surgical Pediatric Population					
MacNevin, 2021[84]	LMWH, dalteparin, rivaroxaban	NR	NR	NR	NR
Kelly, 2016[82]	LMWH	<2 months old: 0.75 mg/kg bid ≥2 months old: 0.5 mg/kg bid	S.Q.	Target anti-Xa level 0.1 to 0.4 IU/mL	Median: 16 days Interquartile range: 12 - 21.5 days
Allahabadi, 2021[86]	LMWH, UFH, VKA, apixaban, Fondaparinux	NR	NR	NR	NR
Zvizdic, 2020[83]	LMWH	NR	S.Q.	NR	NR
Kochai, 2019[85]	LMWH	NR	NR	NR	NR

VTE: Venous Thromboembolism; LMWH: Low Molecular Weight Heparin; NR: Not Reported; PO: Per Os (by mouth); IV: Intravenous; S.Q.: Subcutaneous; IU: International Units; ASP: Asparaginase; CADVT: Catheter-Associated Deep Venous Thrombosis; UFH: Unfractionated Heparin; VKA: Vitamin K Antagonist; INR: International Normalized Ratio; CrCl: Creatinine Clearance; kg= kilogram; bid: Twice a Day; qd: Once a Day; NA: Not Applicable; PICU: Pediatric Intensive Care Unit; S.D.: Standard Deviation.

* Also included in PICO 5 and 8

**Also included in PICO 9

***anti-Xa levels obtained but dose was not adjusted based on levels