# ASH/ISTH Draft Recommendations for Treatment of Pediatric Patients with Venous Thromboembolism (VTE) (Revision)

## INTRODUCTION

American Society of Hematology (ASH) and International Society on Thrombosis and Haemostasis (ISTH) guidelines are based on a systematic review of available evidence. Through a structured process, a guideline panel makes judgements about the evidence and forms recommendations.

The public comment period occurs after recommendations are formed but before a manuscript report of the guidelines has been finalized and before ASH/ISTH organizational approval of the guidelines. Comments collected during the open comment period are provided to the guideline panel for review prior to finalizing the guidelines.

These draft recommendations are not final and therefore are not intended for use or citation.

To submit comments on the draft recommendations, **please email guidelines@hematology.org**. Only comments submitted via email will be reviewed by the guideline panel.

The public comment period for these draft recommendations is **April 9 – May 9, 2024**.

## RECOMMENDATIONS

### SYMPTOMATIC AND ASYMPTOMATIC DVT

- Question 1: *Should anticoagulation versus no anticoagulation be used in pediatric patients with symptomatic DVT or PE?*
  - **Recommendation 1**: In pediatric patients with symptomatic deep vein thrombosis (DVT) or pulmonary embolism (PE) the ASH/ISTH Guideline Panel *suggests* using anticoagulation rather than no anticoagulation (conditional recommendation based on very low certainty in the evidence about effects.)
    - **Remarks:** Although there remains limited direct evidence in pediatric patients, there is strong indirect evidence in adults that symptomatic VTE requires treatment. However, based on recently published observational studies in children, there may be specific clinical scenarios such as neonatal CVC-associated VTE or trauma associated VTE where anticoagulation may yield either no significant benefit or potentially an increased risk of harm. Children who are not anticoagulated warrant follow-up monitoring, because extension of thrombus or organ dysfunction may require reconsideration of treatment options. Outside of these specific clinical scenarios, the panel agrees that in a majority of pediatric patients with symptomatic DVT and PE, anticoagulation is warranted. Therefore, the panel made a conditional recommendation with low certainty of evidence.
  - Evidence Profile
  - Evidence to Decision Framework
- Question 2: *Should anticoagulation vs. no anticoagulation be used for pediatric patients with clinically unsuspected (previously asymptomatic) DVT or PE?*
  - **Recommendation 2:** In pediatric patients with clinically unsuspected (previously asymptomatic) DVT or PE, the ASH/ISTH Guideline Panel *suggests either* using anticoagulation *or* no

anticoagulation (conditional recommendation based on very low certainty in the evidence about effects)

- **Remarks**: The natural history of clinically unsuspected DVT or PE in children appears to carry a lower risk of acute and long-term sequelae, especially in certain pediatric sub-populations. The recommendation is based on studies that report outcomes for children with clinically unsuspected DVT or PE. Single institution, observational and retrospective studies in select sub-populations of pediatric patients suggest that not using anticoagulation for clinically unsuspected DVT or PE does not cause severe outcomes. The benefits or harms of anticoagulation or no anticoagulation vary as they pertain to different populations including neonates, critically ill children, cardiac patients, or trauma. However, if clinically unsuspected DVT or PE is detected, the decision to treat or not treat should be individualized. Children who are not anticoagulated warrant follow-up monitoring, because extension of thrombus or organ dysfunction may require reconsideration of treatment options. Research to better understand the natural history of clinically unsuspected DVT or PE, benefits, and harms of treatment in a variety of subgroups and clinical settings in pediatrics is a high priority.

- Evidence Profile
- Evidence to Decision Framework

## Duration Provoked and Unprovoked

- Question 3: *Should anticoagulation for 6 weeks vs 3 months be used for pediatric patients with provoked VTE?*
  - **Recommendation 3:** In select pediatric patients with provoked VTE, the ASH/ISTH guideline panel *suggests* 6 weeks rather than 3 months of anticoagulation. Exclusions to this recommendation include (i) PE, (ii) recurrent VTE, (iii) persistent occlusive thrombus at 6 weeks, (iv) cancer-associated thrombosis, (v) patients with persistent antiphospholipid antibodies (APA) or major thrombophilia and (vi) ongoing VTE risk factors (conditional recommendation based on very low certainty in the evidence of effects)
    - **Remarks:** This recommendation is based mainly on the Kids-DOTT RCT that evaluated duration of anticoagulation therapy in children with provoked VTE. Importantly, criteria for inclusion and randomization were stringent, and many children with provoked VTE were excluded. The recommendation reflects the population that was studied and cannot be extrapolated to all patients with provoked VTE. For patients with provoked VTE not meeting these low-risk criteria, the panel suggests the use of anticoagulation therapy for 3 months, and for those with persistent provoking VTE risk factors, longer duration of anticoagulation can be considered.
  - Evidence Profile
  - Evidence to Decision Framework
- Question 4: *Should anticoagulation for 6 to 12 months vs indefinite anticoagulation be used in pediatric patients with unprovoked DVT or PE?*
  - **Recommendation 4:** In pediatric patients with unprovoked DVT or PE, the ASH/ISTH guideline panel *suggests* using anticoagulation for 6 to 12 months rather than indefinite anticoagulation (conditional recommendation based on very low certainty in the evidence of effects).
    - **Remarks**: Unprovoked VTE is rare in pediatric patients. While studies suggest that rates of recurrent VTE in children > 1yr with unprovoked VTE are relatively high (21-36% at 3.5 years), there are no pediatric studies evaluating duration of therapy in this cohort (1,

2). Although extrapolation of adult data might favor indefinite treatment in terms of VTE recurrence, in the absence of pediatric data the panel felt that the impact of indefinite anticoagulation on bleeding risk and quality of life would more negatively affect children compared to adults. Patient values and preferences should be considered when making this decision.

- Evidence Profile
- Evidence to Decision Framework

## CVST

- Question 5: *Should anticoagulation vs no anticoagulation be used in pediatric patients with CSVT?*
  - **Recommendation 5:** In pediatric patients with CSVT with and without hemorrhage secondary to venous congestion, the ASH/ISTH guideline panel *suggests* using anticoagulation rather than no anticoagulation (conditional recommendation based on very low certainty in the evidence based on pediatric data).
    - **Remarks:** Observational studies suggest lower mortality and improved neurologic outcomes in patients with CSVT treated with anticoagulation. However, the panel recognized different populations of patients with CSVT (e.g. neonates, infection-associated, trauma, surgery, cancer) may have different risks for bleeding and poor neurologic outcomes that should be considered in the decision to use anticoagulation. Patients with venous congestion secondary to thrombus obstruction with or without hemorrhage likely benefit from anticoagulation, however extensive hemorrhage may preclude anticoagulation. Children who are not anticoagulated warrant follow-up monitoring, because extension of thrombus or organ dysfunction may require reconsideration of treatment options. The panel notes that when anticoagulation is prescribed, it is important that appropriate therapy for additional comorbid conditions (e.g. surgical interventions and antimicrobial therapy for infection-associated CSVT) be used.
  - Evidence Profile
  - Evidence to Decision Framework

## Right Atrial Thrombosis

- Question 6: *Should anticoagulation vs no anticoagulation be used in neonates and pediatric patients with right atrial thrombosis?*
  - **Recommendation 6a:** In neonates and pediatric patients with right atrial thrombosis (RAT) with high-risk features, the ASH/ISTH Guideline Panel *suggests* anticoagulation over no anticoagulation (conditional recommendation based on very low certainty in the evidence about effects)
    - **Remarks:** Insufficient data are available for formal risk stratification of RAT. Based on available literature and experience of panel members, high-risk features of RAT to consider include large size, shape (snake-shaped or pedunculated), mobility, location (e.g. involvement of tricuspid valve or restricting blood flow), presence of intra-cardiac right to left shunt, presence of a central venous catheter, or associated with symptoms (arrhythmias, hemodynamic compromise, etc.).
  - **Recommendation 6b:** In neonates and pediatric patients with RAT and the absence of high-risk features, the ASH/ISTH Guideline Panel *suggests* no anticoagulation over anticoagulation (conditional recommendation based on very low certainty in the evidence about effects).

        - **Remarks:** Studies in patients without high-risk features treated with anticoagulation did not demonstrate clear clinical benefits compared to patients not treated with anticoagulation. The studies are not randomized, are small, and are subject to significant bias. Study subjects treated with anticoagulation had an increased risk of bleeding. However, neonates and children who are not anticoagulated warrant follow-up monitoring, because extension of thrombus or organ dysfunction may require reconsideration of treatment options.
    - Evidence Profile
    - Evidence to Decision Framework
- Question 7: *Should thrombolysis followed by standard anticoagulation vs anticoagulation alone be used in neonates with right atrial thrombosis?*
    - **Recommendation 7:** In pediatric patients with RAT requiring antithrombotic treatment, the ASH/ISTH guideline panel *suggests* using anticoagulation alone over thrombolysis followed by anticoagulation (conditional recommendation based on very low certainty in the evidence of effects).
        - **Remarks:** In most cases, anticoagulation alone is adequate. However, in some cases hemodynamic status, size, and mobility of the thrombus may dictate more aggressive therapy. The choice to use thrombolysis will depend on feasibility of the intervention and patient and family acceptability of the expected risks and benefits of thrombolysis.
    - Evidence Profile
    - Evidence to Decision Framework

## Renal vein Thrombosis

- Question 8: *Should anticoagulation vs no anticoagulation be used in neonates with renal vein thrombosis?*
    - **Recommendation 8:** In neonates with renal vein thrombosis (RVT), the ASH/ISTH guideline panel *suggests* using anticoagulation, rather than no anticoagulation (conditional recommendation based on very low certainty in the evidence about effects).
        - **Remarks:** The panel considers anticoagulation to have a potential beneficial effect if the long-term outcomes of avoiding hypertension, chronic kidney disease, and renal failure are considered. Anticoagulation is likely more important with thrombus extension into the inferior vena cava or bilateral renal vein involvement. Severity of disease, gestational age, presence of intraventricular hemorrhage, underlying co-morbidities, and degree of thrombocytopenia may impact bleeding risk with treatment. Neonates with RVT who are not anticoagulated warrant follow-up monitoring, because extension of thrombus or organ dysfunction may require reconsideration of treatment options.
    - Evidence Profile
    - Evidence to Decision Framework
- Question 9: *Should thrombolysis followed by anticoagulation vs anticoagulation alone be used in neonates with RVT?*
    - **Recommendation 9a:** In neonates with unilateral RVT with or without IVC extension, the ASH/ISTH guideline panel *recommends* anticoagulation alone rather than thrombolysis followed by anticoagulation (strong recommendation based on very low certainty in the evidence of effects).
        - **Remarks:** Available evidence is derived from observational studies in which patients treated with thrombolysis were typically more critically ill, and the studies did not adjust

for this bias. The panel placed a high value on avoiding the potential bleeding risks of thrombolysis in neonates, and therefore made this a strong recommendation for cases with low mortality risk (i.e. unilateral RVT with or without IVC extension), despite very low-quality evidence.

- **Recommendation 9b:** In neonates with life-threatening RVT, the ASH/ISTH guideline panel *suggests* using thrombolysis followed by anticoagulation rather than anticoagulation alone (conditional recommendation based on very low certainty in the evidence about effects).
  - **Remarks:** When RVT is life-threatening (i.e. bilateral thrombosis with potential or actual compromised renal function), the panel considered that the beneficial effects of thrombolysis may outweigh the undesirable consequences of the intervention. Gestational age, presence of intraventricular hemorrhage, underlying co-morbidities, and degree of thrombocytopenia may impact bleeding risk with thrombolysis.
- Evidence Profile
- Evidence to Decision Framework

## Portal Vein Thrombosis

- Question 10: *Should anticoagulation vs no anticoagulation be used for pediatric patients with PVT?*
  - **Recommendation 10a:** In neonates and children with occlusive PVT, and in children with non-occlusive PVT, post-liver transplant PVT, or unprovoked PVT, the ASH/ISTH guideline panel *suggests* using anticoagulation rather than no anticoagulation (conditional recommendation based on very low certainty in the evidence of effects)
  - **Recommendation 10b:** In neonates with non-occlusive PVT and in children who have already developed portal hypertension, the ASH/ISTH guideline panel *suggests* no anticoagulation rather than using anticoagulation (conditional recommendation based on very low certainty in the evidence of effects)
    - **Remarks for recommendations 10a and 10b**: Neonates and children who are not anticoagulated warrant follow-up monitoring, because extension of thrombus or organ dysfunction may require reconsideration of treatment options. Evidence from the available observational studies describe (complete or partial) PVT resolution in subjects who did receive anticoagulation, as well as those who did not receive anticoagulation, and therefore does not allow for assessment of the degree of benefit from anticoagulation. However, the panel placed value on avoiding the potential increased risk of long-term complications associated with persistent occlusive thrombus, and therefore favored treatment in this setting. The panel also recognized the potential increased risk of bleeding in children with portal hypertension and development of esophageal varices and therefore did not recommend anticoagulation in that setting.
  - Evidence Profile
  - Evidence to Decision Framework

## Superficial VTE

- Question 11: *Should anticoagulation vs no anticoagulation be used in pediatric patients with superficial VT (SVT)?*
  - **Recommendation 11:** In pediatric patients with superficial venous thrombosis (SVT), the ASH/ISTH guideline panel *suggests* no anticoagulation over anticoagulation (conditional recommendation based on very low certainty in the evidence about effects).

        - **Remarks:** There were no direct and only limited indirect data upon which to base this recommendation. The panel's collective experience suggested that in most instances (e.g., peripheral intravenous (PIV)- or CVAD-related events in the upper extremity), no anticoagulation may be required. However, anticoagulation could be considered in select patients (e.g., non-PIV/CVAD-related, cancer, varicose vein, lower limb events) or scenarios (e.g., PIV/CVAD permanence and/or symptom progression). The panel notes that when anticoagulation is prescribed, there is uncertainty about the optimal intensity (e.g., prophylactic vs. full-dose) and duration of therapy.
    - Evidence Profile
    - Evidence to Decision Framework

## THROMBOLYSIS

- Question 12: *Should thrombolysis followed by anticoagulation vs. anticoagulation alone be used for pediatric patients with proximal DVT?*
    - **Recommendation 12:** In pediatric patients with proximal DVT, the ASH/ISTH guideline panel *suggests* using anticoagulation alone rather than thrombolysis followed by anticoagulation (conditional recommendation based on very low certainty in the evidence about effects).
        - **Remarks:** The panel considered issues, such as the size and clinical impact of VTE, as important in deciding the relative risk benefit ratio of thrombolysis. In most cases, the risks of bleeding seem too high for the potential benefit; however, there may be individuals in whom the opposite is true. Extrapolation of adult data was difficult. There are insufficient data to address the relative risk benefit of local thrombolysis via interventional radiology compared with systemic thrombolysis, and the panel noted that the centers with access to pediatric interventional radiology were often stronger advocates of thrombolysis.
    - Evidence Profile
    - Evidence to Decision Framework
- Question 13: *Should thrombolysis followed by standard anticoagulation vs. anticoagulation alone be used for pediatric patients with cerebral sinus venous thrombosis?*
    - **Recommendation 13:** In pediatric patients with CSVT, the ASH/ISTH guideline panel *suggests* using anticoagulation alone rather than thrombolysis followed by anticoagulation (conditional recommendation based on very low certainty in the evidence about effects)
        - **Remarks:** The evidence is sparse for the balance of benefits and harms of thrombolysis compared to anticoagulation in pediatric patients with CSVT. The panel's collective experience is to use anticoagulation rather than thrombolysis for children with CSVT who have no evidence of ischemia. However, thrombolysis may be considered for neurologic deterioration, particularly in the instance of anticoagulation refractoriness; the use of reperfusion therapies such catheter-directed thrombolysis would depend on local resources and experience.
    - Evidence Profile
    - Evidence to Decision Framework
- Question 14: *Should thrombolysis followed by anticoagulation vs. anticoagulation alone be used for pediatric patients with sub-massive PE?*
    - **Recommendation 14:** In pediatric patients with PE with echocardiographic or biochemical evidence of right ventricular dysfunction but without hemodynamic compromise, the ASH/ISTH guideline panel *suggests* using anticoagulation alone rather than thrombolysis followed by anticoagulation (conditional recommendation based on very low certainty in the evidence about effects).

- **Remarks:** The panel considered sub-massive/intermediate-risk PE to represent children with PE who DO NOT have hemodynamic compromise (i.e., systemic hypotension or other signs of shock) but who DO have echocardiographic (e.g., right ventricular dilation or intraventricular septal stiffness, etc.) or biochemical (e.g., elevated troponin or brain.
- Evidence Profile
- Evidence to Decision Framework

➢ Question 15: *Should thrombolysis followed by anticoagulation vs. anticoagulation alone be used for pediatric patients with PE with hemodynamic compromise?*

- **Recommendation 15:** In pediatric patients with PE with hemodynamic compromise, the ASH/ ISTH guideline panel *suggests* using thrombolysis followed by anticoagulation rather than anticoagulation alone (conditional recommendation based on very low certainty in the evidence about effects).
  - **Remarks:** The panel considered massive/high-risk PE to represent children with PE who DO have hemodynamic compromise that may be life-threatening, with limited time to respond to standard anticoagulation, and so conditionally recommended thrombolysis followed by anticoagulation, based predominantly on extrapolation from adult data and three small pediatric studies that suggested a trend toward decreased mortality with thrombolysis.
- Evidence Profile
- Evidence to Decision Framework

## CENTRAL VENOUS ACCESS DEVICE

➢ Question 16: *Should immediate removal of a non-functioning or unneeded central venous access device (CVAD) vs. delayed removal be used in pediatric patients with symptomatic CVAD related thrombosis?*

- **Recommendation 16:** In pediatric patients with CVAD-related thrombosis, the ASH/ISTH Guideline Panel *suggests either* immediate removal *or* delayed removal of a CVAD if the patient no longer require venous access or the CVAD is non-functioning (conditional recommendation based on low certainty in the evidence about effects).
  - **Remarks:** Recent observational studies provided data that >48 hours of anticoagulation prior to CVAD removal vs. immediate CVAD removal are comparable in terms of potential risk of emboli leading to PE or paradoxical stroke. The panel recognized that some clinical scenarios, such as children with a large thrombotic burden or those with right-to-left cardiac shunts, may benefit from at least 48 hours of anticoagulation prior to CVAD removal to decrease the risk of embolism.
- Evidence Profile
- Evidence to Decision Framework

## HOW TO ANTICOAGULATE

➢ Question 17: *Should DOAC vs Standard of Care be used for Venous Thromboembolism in Pediatric Patients?*

- **Recommendation 17:** In pediatric patients with Venous Thromboembolism (VTE), the ASH/ISTH guideline panel *suggests* using DOACs (Rivaroxaban/Dabigatran) over Standard of Care (LMWH, UFH, VKA, Fondaparinux) (conditional recommendation based on low certainty in the evidence about effects).
  - **Remarks:** The panel concluded that there was a small benefit of DOACs over Standard of Care (SOC), in relation to reduced thrombus recurrence rate and increased rate of thrombus resolution. The undesirable effects of DOACs vs SOC were felt to be small, with a reduction in major bleeding albeit with an increase in clinically relevant non-major bleeding (CRNMB). The panel notes that in pediatric trials DOACs were not used as initial therapy. The panel acknowledged the limitations in generalizability of these data given the exclusions from and underrepresented populations in the trials. The panel also acknowledged the limitations of these data when evaluating the outcomes of

mortality, recurrence, post thrombotic syndrome (PTS) and major/clinically relevant non-major bleeding due to the small number of events reported. Given the natural history of PTS and thrombus recurrence, evaluation at 3-6 months was considered to be too soon to provide accurate representation of these outcomes. Although data on QoL, cost-effectiveness and acceptability of an oral agent that does not require monitoring were lacking, the panel felt that these were important factors when making this recommendation. However, given the limitations discussed, there remain pediatric patients and clinical situations in which SOC is preferred.

  - Evidence Profile
  - Evidence to Decision Framework
- Question 18: *Should Rivaroxaban vs Standard of Care be used for Venous Thromboembolism in Pediatric Patients?*
  - **Recommendation 18:** In pediatric patients with Venous Thromboembolism (VTE), the ASH/ISTH guideline panel *suggests* using Rivaroxaban over Standard of Care (LMWH, UFH, VKA, Fondaparinux) (conditional recommendation based on very low certainty in the evidence about effects).
    - **Remarks:** The panel concluded that there was a small benefit of Rivaroxaban over SOC, in relation to reduced thrombus recurrence and improved thrombus resolution. The undesirable effects of Rivaroxaban vs SOC were felt to be small, with a reduction in major bleeding countered by an increase in CRNMB. The panel noted that in the Einstein Jr. trial, Rivaroxaban was not commenced until after 5-9 days of heparinoid therapy. These data were limited by the small number of important outcomes that were reported, i.e. mortality, recurrence, PTS and major bleeding/CRNMB. The panel noted that some populations were excluded from the EINSTEIN Junior trial, including those with low birth weight and those with severe liver or renal impairment. In addition, there were underrepresented populations in the trials. The panel also noted reports of heavier menstrual bleeding whilst on Rivaroxaban and felt that this was an important consideration when choosing an anticoagulant.
  - Evidence Profile
  - Evidence to Decision Framework
- Question 19: *Should Dabigatran vs Standard of Care be used for Venous Thromboembolism in Pediatric Patients?*
  - **Recommendation 19:** In pediatric patients with Venous Thromboembolism (VTE), the ASH/ISTH guideline panel suggests using Dabigatran over Standard of Care (LMWH, UFH, VKA, Fondaparinux) (conditional recommendation based on very low certainty in the evidence about effects).
    - **Remarks:** The panel concluded that there was a small benefit of Dabigatran over SOC, in relation to reduced thrombus recurrence and improved thrombus resolution. The undesirable effects were felt to be trivial, with major bleeding reported in fewer patients treated with Dabigatran and an equivalent frequency of CRNMB. The panel noted that in the DIVERSITY trial, Dabigatran was not commenced until after 5-21 days of heparinoid therapy. The panel noted that some populations were excluded from the DIVERSITY trial, including those <2 years of age with low bodyweight, infants less than 3 months of age, and those with severe liver or renal impairment. In addition, there were underrepresented populations in the trials. The monitoring and dose adjustment of Dabigatran during the DIVERSITY trial raised concern about the potential effect on efficacy and safety of routine use according to current approvals which do not require

such monitoring. The panel also noted reports of gastrointestinal side effects whilst on Dabigatran and felt that this was an important consideration when choosing an anticoagulant.

- Evidence Profile
- Evidence to Decision Framework

- Question 20: *Should either Rivaroxaban or Dabigatran be used preferentially in the treatment of Pediatric VTE?*
  - **Recommendation 20:** In pediatric patients with Venous Thromboembolism (VTE), the ASH/ISTH guideline panel *suggests* using *either* Rivaroxaban *or* Dabigatran, although there may be patient populations or jurisdictional availability that would lead clinicians to choose one agent over the other (conditional recommendation based on very low certainty in the evidence about effects).
    - **Remarks:** The Panel undertook an exercise to review the EtDs for Rivaroxaban vs. SOC and Dabigatran vs. SOC to examine if one of these agents (given the available data) would be a preferred agent to use in treatment of pediatric VTE. To accomplish this, the Panel first assigned weights to the summary of judgements. Balance of effects, certainty of evidence, acceptability and feasibility of implementation were given the highest weighting, with resources required given moderate weighting and cost effectiveness and equity given the lowest weighting. There was no difference between agents overall.
  - Evidence Profile
  - Evidence to Decision Framework

**Author(s):**
**Question:** Anticoagulation compared to no anticoagulation in pediatric patients with symptomatic DVT or PE
**Setting:** Inpatient
**Bibliography:** American Society of Hematology 2024 Guidelines for Management of Venous Thromboembolism: Treatment of Pediatric Venous Thromboembolism

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | anticoagulation | no anticoagulation | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality (All-Cause) (follow-up: mean 54 days)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 3/24 (12.5%) [c] | 2/19 (10.5%) | **RR 1.18** (0.22 to 6.40) | **19 more per 1,000** (from 82 fewer to 568 more) | ⨁◯◯◯ Very low | CRITICAL |
| **Mortality (follow-up: 3 months)** | | | | | | | | | | | | |
| 2[2,3] | non-randomised studies | serious[d] | not serious | not serious | very serious[b] | none | 3/651 (0.5%) [e] | - | - | - | ⨁◯◯◯ Very low | CRITICAL |
| **Recurrence of VTE (follow-up: mean 54 days)** | | | | | | | | | | | | |
| 2[1,4] | non-randomised studies | serious[a] | not serious | not serious | serious[b] | none | 7/223 (3.1%) | 4/47 (8.5%) | **RR 0.37** (0.11 to 1.21) | **54 fewer per 1,000** (from 76 fewer to 18 more) | ⨁⨁◯◯ Low | CRITICAL |
| **Recurrence of VTE (follow-up: 3 months)** | | | | | | | | | | | | |
| 2[2,3] | non-randomised studies | serious[d] | not serious | not serious | very serious[b] | none | 22/651 (3.4%) [f] | - | - | - | ⨁◯◯◯ Very low | CRITICAL |
| **Resolution (follow-up: mean 54 days)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | serious[b] | none | 21/24 (87.5%) | 11/13 (84.6%) | **RR 1.02** (0.60 to 1.74) | **17 more per 1,000** (from 338 fewer to 626 more) | ⨁⨁◯◯ Low | CRITICAL |
| **Extension of Thrombus (follow-up: mean 54 days)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 0/24 (0.0%) | 9/28 (32.1%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Extension of Thrombus (follow-up: 3 months)** | | | | | | | | | | | | |
| 2[2,3] | non-randomised studies | serious[d] | not serious | not serious | very serious[b] | none | 10/651 (1.5%) [g] | - | - | - | ⨁◯◯◯ Very low | CRITICAL |
| **Pulmonary Embolism (follow-up: 3 months)** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2[2,3] | non-randomised studies | serious[d] | not serious | not serious | very serious[b] | none | 0/384 (0.0%) | - | - | - | ⨁◯◯◯ Very low | CRITICAL |
| **Major Bleeding (follow-up: mean 54 days)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 2/33 (6.1%) | 0/19 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Major Bleeding (follow-up: 3 months)** | | | | | | | | | | | | |
| 2[2,3] | non-randomised studies | serious[d] | not serious | not serious | very serious[b] | none | 8/767 (1.0%) [h] | - | - | - | ⨁◯◯◯ Very low | CRITICAL |
| **Clinically Relevant Non-Major Bleed (follow-up: mean 54 days)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 1/33 (3.0%) | 0/19 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Clinically Relevant Non-Major Bleed (follow-up: 3 months)** | | | | | | | | | | | | |
| 2[2,3] | non-randomised studies | serious[d] | not serious | not serious | very serious[d] | none | 14/767 (1.8%) [i] | - | - | - | ⨁◯◯◯ Very low | CRITICAL |
| **Post Thrombotic Syndrome (follow-up: 3 months)** | | | | | | | | | | | | |
| 2[2,3] | non-randomised studies | serious[d] | not serious | not serious | very serious[d] | none | 3/767 (0.4%) [j] | - | - | - | ⨁◯◯◯ Very low | CRITICAL |

**CI:** confidence interval; **RR:** risk ratio

**Explanations**

a. Risk of bias, assessed using ROBINS-I tool, was judged to be serious due to selection bias without adjustment for confounding.
b. Imprecision due to small number of included patients and patients with events in the evaluated studies.
c. None of the 3 patients that died were due to therapy or VTE related causes.
d. Both studies, DIVERSITY trial and EINSTEIN-JR, compared a direct oral anticoagulant versus standard of care anticoagulation (Heparin, Low Molecular Weight Heparin, Fondaparinux, Vitamin-K antagonists. Both arms of the trials were pooled to evaluate the outcome for patients using anticoagulation.
e. 1 out of 262 occurred in patients taking Rivaroxaban, 0 out of 177 occurred in patients taking Dabigatran, 2 out of 212 occurred in patients taking Standard of Care
f. 4 out of 262 occurred in patients that took Rivaroxaban, 7 out of 177 in patients that took Dabigatran, 11 out of 212 in patients that took Standard of Care (LMWH, UFH, VKA)
g. 4 out of 262 occurred in patients taking Rivaroxaban, 5 out of 177 occurred in patients taking Dabigatran, 4 out of 212 occurred in patients taking Standard of Care
h. 0 out of 262 occurred in patients that took Rivaroxaban, 4 out of 177 in patients that took Dabigatran, 4 out of 212 in patients that took Standard of Care (LMWH, UFH, VKA)
i. 10 out of 335 occurred in patients that took Rivaroxaban, 2 out of 177 in patients that took Dabigatran, 2 out of 255 in patients that took Standard of Care (LMWH, UFH, VKA)
j. 2 out of 335 occurred in patients that took Rivaroxaban, 1 out of 177 in patients that took Dabigatran, 0 out of 255 in patients that took Standard of Care (LMWH, UFH, VKA)

**References**


1.CH, van,Ommen, KA, Bergman, M, Boerma, HA, Bouma, AE, Donker, M, Gouvernante, CV, Hulzebos, D, Khandour, R, Knol, MA, Raets, KD, Liem, RA, van,Lingen, M, van,de,Loo, E, Lopriore, M, van,der,Putten, JJ, Sol, MH, Suijker, DC, Vijlbrief, R, Visser, MM, van,Weissenbruch. NEOnatal Central-venous Line Observational study on Thrombosis (NEOCLOT): . Journal of thrombosis and haemostasis : JTH; 2023.
2.C, Male, AWA, Lensing, JS, Palumbo, R, Kumar, I, Nurmeev, K, Hege, D, Bonnet, P, Connor, HL, Hooimeijer, M, Torres, AKC, Chan, G, Kenet, S, Holzhauer, A, Santamaría, P, Amedro, E, Chalmers, P, Simioni, RV, Bhat, DL, Yee, O, Lvova, J, Beyer-Westendorf, TT, Biss, I, Martinelli, P, Saracco, M, Peters, K, Kállay, CA, Gauger, MP, Massicotte, G, Young, AF, Pap, M, Majumder, WT, Smith, JF, Heubach, SD, Berkowitz, K, Thelen, D, Kubitza, M, Crowther, MH, Prins, P, Monagle, Investigators, EINSTEIN-Jr,Phase,3. Rivaroxaban compared with standard anticoagulants for the treatment of acute . The Lancet. Haematology; 2020.
3.J, Halton, LR, Brandão, M, Luciani, L, Bomgaars, E, Chalmers, LG, Mitchell, I, Nurmeev, A, Sharathkumar, P, Svirin, K, Gorbatikov, I, Tartakovsky, M, Simetzberger, F, Huang, Z, Sun, J, Kreuzer, S, Gropper, P, Reilly, M, Brueckmann, M, Albisetti, Investigators, DIVERSITY,Trial. Dabigatran etexilate for the treatment of acute venous thromboembolism in . The Lancet. Haematology; 2021.
4.Chan, Anthony, Lensing, Anthonie W. A., Kubitza, Dagmar, Brown, Grahaem, Elorza, Dolores, Ybarra, Marta, Halton, Jacqueline, Grunt, Sebastian, Kenet, Gili, Bonnet, Damien, Santamaria, Amparo, Saracco, Paola, Biss, Tina, Climent, Francesco, Connor, Philip, Palumbo, Joseph, Thelen, Kirstin, Smith, William T., Mason, Amy, Adalbo, Ivet, Berkowitz, Scott D., Hurst, Eva, van Kesteren, Jeroen, Young, Guy, Monagle, Paul. Clinical presentation and therapeutic management of venous thrombosis in young children: a retrospective analysis. Thrombosis Journal; 2018.

## QUESTION

| Should anticoagulation vs. no anticoagulation be used for pediatric patients with symptomatic DVT or PE ? | |
|---|---|
| **POPULATION:** | pediatric patients with symptomatic DVT or PE |
| **INTERVENTION:** | anticoagulation |
| **COMPARISON:** | no anticoagulation |
| **MAIN OUTCOMES:** | |
| **SETTING:** | Inpatient |
| **PERSPECTIVE:** | Clinical recommendation – Population perspective |
| **BACKGROUND:** | Venous thromboembolism (VTE) in pediatric patients is becoming recognized as a major complication among hospitalized infants and children. The incidence of symptomatic VTE in hospitalized children is 5.3 per 10,000, with an overall incidence of 0.7 per 10,000 across all pediatric patients. Pediatric VTE most commonly occurs as a central venous catheter (CVC)-related thrombosis. There is a paucity of pediatric-specific evidence for treatment of VTE and data is often extrapolated from adult literature. It is important to determine whether anticoagulation therapy is warranted for symptomatic VTE (1)(2). |
| **CONFLICT OF INTEREST:** | |

## ASSESSMENT

**Problem**
Is the problem a priority?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ No<br>○ Probably no<br>○ Probably yes<br>● Yes<br>○ Varies<br>○ Don't know | Anticoagulation is the mainstay therapy in pediatric patients with venous thromboembolism. Most decisions and recommendations in clinical guidelines are based on evidence from adult populations and observational studies in pediatric patients.(3) | |
| | Adolopment | |

| | | |
|---|---|---|
| ○ No<br>○ Probably no<br>○ Probably yes<br>● Yes<br>○ Varies<br>○ Don't know | Anticoagulation is the mainstay therapy in pediatric patients with venous thromboembolism. Most decisions and recommendations in clinical guidelines are based on evidence from adult populations and observational studies in pediatric patients.(3) | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Desirable Effects

How substantial are the desirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

○ Trivial
○ Small
○ Moderate
● Large
○ Varies
○ Don't know

| Outcomes | № of participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects* (95% CI) | |
|---|---|---|---|---|---|
| | | | | Risk with no anticoagulation | Risk difference with anticoagulation |
| Mortality - not reported[a] | - | - | - | - | - |
| Mortality assessed with: mortality in adults[b] | 35 (1 RCT) | ⨁◯◯◯ VERY LOW[c,d,e] | **RR 0.24** (0.03 to 1.83) | Study population | |
| | | | | 263 per 1,000 | **200 fewer per 1,000** (255 fewer to 218 more) |
| Pulmonary embolism - Severe | 30 (1 observational study) | ⨁◯◯◯ VERY LOW[g,h] | not estimable | Study population | |
| | | | | - | - |

The panel judged that the desirable anticipated effects of anticoagulation are large in pediatric patients with symptomatic DVT or PE.

The panel also considered that pediatric baseline rates of VTE vary and differ from adult rates (adult data is reported for recurrent VTE and mortality).

| | | | | | |
|---|---|---|---|---|---|
| follow up: 3 months[f] | | | | | |
| | (2 observational studies) | ⨁◯◯◯ VERY LOW[h] | not estimable | Study population | |
| | | | | - | - |
| Recurrent VTE assessed with: any VTE[j] | 940 (18 observational studies) | ⨁◯◯◯ VERY LOW[h] | not estimable | Study population | |
| | | | | - | - |
| Recurrent VTE assessed with: recurrent VTE in adults[b] | 35 (1 RCT) | ⨁◯◯◯ VERY LOW[c,d,e] | **RR 0.11** (0.01 to 1.80) | Study population | |
| | | | | 263 per 1,000 | **234 fewer per 1,000** (261 fewer to 211 more) |
| DVT - Severe follow up: 3 months[f] | 30 (1 observational study)[k] | ⨁◯◯◯ VERY LOW[g,h] | not estimable | Study population | |
| | | | | - | -[k] |
| DVT - Severe [i] | 237 (2 observational studies) | ⨁◯◯◯ VERY LOW[h] | not estimable | Study population | |
| | | | | - | - |
| Major bleeding [j] | 940 (18 observational studies) | ⨁◯◯◯ VERY LOW[h] | not estimable | Study population | |
| | | | | - | - |
| Major bleeding follow up: 3 months[f] | 30 (1 observational study) | ⨁◯◯◯ VERY LOW[g,h] | not estimable | Study population | |
| | | | | - | - |

| | | | | | |
|---|---|---|---|---|---|
| Major bleeding [i,l,m] | 590 (4 observational studies) | ⨁◯◯◯ VERY LOW[h] | not estimable | Study population | |
| | | | | - | - |

a. One Cochrane review aimed to determine the efficacy of UFH or LMWH in comparison to placebo/no treatment in neonates with clinical or imaging diagnosis of thromboembolism. No RCTs or quasi-randomized trials were identified (Romantsik 2016).
b. Barritt & Jordan 1960. Single study evaluating intravenous heparin/oral VKA vs. no Tx for patients with PE.
c. Inadequate random sequence generation and allocation concealment. Authors reported, "envelopes were prepared containing an equal number of cards marked " anticoagulant " or " no anticoagulant ", and when a patient was admitted to the trial a card was drawn."
d. Barritt & Jordan (1960) was a randomised controlled trial including adult patients with PE.
e. Wide confidence intervals which do not exclude thresholds for plausible benefit or harm.
f. Andrew (1994). Single study evaluating treatment with heparin.
g. Andrew 1994 included patients with various indications for heparin. Thirty children had DVT and/or PE; 11 had arterial thrombi, most frequently after diagnostic angiography; and the remaining 24 received heparin prophylactically for congenital heart disease.
h. Single-arm studies with no comparison group to detect an effect.
i. Streif 1999 evaluated treatment with warfarin. Bonduel 2003 evaluated treatment with acenocoumarol.
j. Bidlingmaier 2011 systematic review; Fiamoli 2011 and O'Brien 2014 evaluated treatment with LMWH.
k. Recurrent event was a catheter-related DVT.
l. Newall 2005. Conference abstract evaluating treatment with warfarin.
m. Spoor 2012 evaluated treatment with phenprocoumon and acenocoumarol. Duration of follow-up varied from <3 months to 12 months.

Note: for a complete set of outcomes see the corresponding evidence profile.

| | | |
|---|---|---|
| | | |
| | Adolopment | |
| ○ Trivial<br>○ Small<br>○ Moderate<br>● Large<br>○ Varies<br>○ Don't know | *See Appendix 2See Appendix 3* | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Undesirable Effects

How substantial are the undesirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

○ Large
○ Moderate
● Small
○ Trivial
○ Varies
○ Don't know

| Outcomes | № of participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects* (95% CI) | |
|---|---|---|---|---|---|
| | | | | Risk with no anticoagulation | Risk difference with anticoagulation |
| Mortality - not reported[a] | - | - | - | - | - |
| Mortality assessed with: mortality in adults[b] | 35 (1 RCT) | ⨁◯◯◯ VERY LOW[c,d,e] | **RR 0.24** (0.03 to 1.83) | Study population | |
| | | | | 263 per 1,000 | **200 fewer per 1,000** (255 fewer to 218 more) |

The panel judged that the undesirable anticipated effects of anticoagulation are small in pediatric patients with symptomatic DVT or PE.

| | | | | | |
|---|---|---|---|---|---|
| Pulmonary embolism - Severe follow up: 3 months[f] | 30 (1 observational study) | ⨁◯◯◯ VERY LOW[g,h] | not estimable | Study population | |
| | | | | - | - |
| | (2 observational studies) | ⨁◯◯◯ VERY LOW[h] | not estimable | Study population | |
| | | | | - | - |
| Recurrent VTE assessed with: any VTE[j] | 940 (18 observational studies) | ⨁◯◯◯ VERY LOW[h] | not estimable | Study population | |
| | | | | - | - |
| Recurrent VTE assessed with: recurrent VTE in adults[b] | 35 (1 RCT) | ⨁◯◯◯ VERY LOW[c,d,e] | **RR 0.11** (0.01 to 1.80) | Study population | |
| | | | | 263 per 1,000 | **234 fewer per 1,000** (261 fewer to 211 more) |
| DVT - Severe follow up: 3 months[f] | 30 (1 observational study)[k] | ⨁◯◯◯ VERY LOW[g,h] | not estimable | Study population | |
| | | | | - | -[k] |
| DVT - Severe [i] | 237 (2 observational studies) | ⨁◯◯◯ VERY LOW[h] | not estimable | Study population | |
| | | | | - | - |
| Major bleeding [j] | 940 (18 observational studies) | ⨁◯◯◯ VERY LOW[h] | not estimable | Study population | |
| | | | | - | - |
| | | | | Study population | |

| | | | | | |
|---|---|---|---|---|---|
| Major bleeding follow up: 3 months[f] | 30 (1 observational study) | ⨁◯◯◯ VERY LOW[g,h] | not estimable | - | - |
| Major bleeding [i,l,m] | 590 (4 observational studies) | ⨁◯◯◯ VERY LOW[h] | not estimable | Study population | |
| | | | | - | - |

a. One Cochrane review aimed to determine the efficacy of UFH or LMWH in comparison to placebo/no treatment in neonates with clinical or imaging diagnosis of thromboembolism. No RCTs or quasi-randomized trials were identified (Romantsik 2016).
b. Barritt & Jordan 1960. Single study evaluating intravenous heparin/oral VKA vs. no Tx for patients with PE.
c. Inadequate random sequence generation and allocation concealment. Authors reported, "envelopes were prepared containing an equal number of cards marked " anticoagulant " or " no anticoagulant ", and when a patient was admitted to the trial a card was drawn."
d. Barritt & Jordan (1960) was a randomised controlled trial including adult patients with PE.
e. Wide confidence intervals which do not exclude thresholds for plausible benefit or harm.
f. Andrew (1994). Single study evaluating treatment with heparin.
g. Andrew 1994 included patients with various indications for heparin. Thirty children had DVT and/or PE; 11 had arterial thrombi, most frequently after diagnostic angiography; and the remaining 24 received heparin prophylactically for congenital heart disease.
h. Single-arm studies with no comparison group to detect an effect.
i. Streif 1999 evaluated treatment with warfarin. Bonduel 2003 evaluated treatment with acenocoumarol.
j. Bidlingmaier 2011 systematic review; Fiamoli 2011 and O'Brien 2014 evaluated treatment with LMWH.
k. Recurrent event was a catheter-related DVT.
l. Newall 2005. Conference abstract evaluating treatment with warfarin.
m. Spoor 2012 evaluated treatment with phenprocoumon and acenocoumarol. Duration of follow-up varied from <3 months to 12 months.

| | | |
|---|---|---|
| | Note: for a complete set of outcomes see the corresponding evidence profile. | |
| | Adolopment | |
| ○ Large<br>○ Moderate<br>● Small<br>○ Trivial<br>○ Varies<br>○ Don't know | *See Appendix 1* | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Certainty of evidence

What is the overall certainty of the evidence of effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | Certainty of the evidence of effects was judged as 'very low' due to risk of bias, indirectness and imprecision. | The panel judged that the overall certainty of the evidence of effects is very low.<br><br>The panel also considered that equipoise to conduct additional research and randomized trials to obtain higher certainty of the evidence are unlikely. |
| | Adolopment | |

| | | |
|---|---|---|
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | Certainty of the evidence of effects was judged as 'very low' due to risk of bias, and imprecision. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Values

Is there important uncertainty about or variability in how much people value the main outcomes?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Important uncertainty or variability<br>○ Possibly important uncertainty or variability<br>● Probably no important uncertainty or variability<br>○ No important uncertainty or variability | **<u>Utility related information:</u>**<br><br>**The relative importance of outcomes:**<br><br>**<u>Results from Panel Members' Utility Rating Survey</u>**:<br><br>Utilities rated on the visual analog scale, where 0 represents death and 1 represents full health, were as follows.<br><br>Pulmonary embolism – Severe marker state: 0.31<br><br>Pulmonary embolism – Moderate marker state: 0.49<br><br>Deep vein thrombosis (proximal) – Severe marker state: 0.49<br><br>Deep vein thrombosis (proximal) – Moderate marker state: 0.61<br><br>Deep vein thrombosis (distal) – Severe marker state: 0.56<br><br>Deep vein thrombosis (distal) – Moderate marker state: 0.68 | The panel judged that there is probably no important uncertainty or variability in how much people value the main outcomes.<br><br>The panel also considered that specific outcomes could have different utilities for pediatric patients than that for adults.<br><br>Based on the non-utility information, values and preferences related to anticoagulation treatment could differ in pediatric patients as compared to adults. |

| | | |
|---|---|---|
| | Major bleeding: 0.30<br><br>Neonatal Bleeding – Severe: 0.30<br><br>Infant Bleeding – Severe: 0.26<br><br>**We did not identify utility related information or non-utility information for the outcomes of interest specific to the pediatric population in the literature.**<br><br>**<u>Additional information from the adult population:</u>**<br><br>**Our systematic review for the adult population found that the relative importance of the outcomes is as follows:** Pulmonary embolism: 0.63-0.93 (different methods) (Hogg et al., 2014, Hogg et al., 2013, Locadia et al., 2004)<br><br>Deep vein thrombosis: 0.64-0.99 (different methods) (Hogg et al., 2014, Hogg et al., 2013, Locadia et al., 2004)(Marvig et al., 2015)(Utne et al., 2016)<br><br>Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) (Hogg et al., 2013, Locadia et al., 2004)<br><br>Muscular bleeding: 0.76 (time trade off) (Locadia et al., 2004)<br><br>Minor intracranial bleeding event: 0.75 (standard gamble) (Hogg et al., 2013)<br><br>Major intracranial bleeding event: 0.15 (standard gamble) (Hogg et al., 2013)<br><br>Central nervous system bleeding: 0.29-0.60 (standard gamble) (Lenert et al., 1997)(O'Meara et al., 1994)<br><br>Treatment with LMWH: 0.993 (time trade off) (Marchetti et al., 2001)<br><br>Treatment with warfarin (as a surrogate): 0.989 (time trade off) (Marchetti et al., 2001) | |

| | | |
|---|---|---|
| | **<u>We also identified in the systematic review the following non-utility information from the adult population:</u>**<br><br>**Anticoagulant therapy**<br><br>Adult patients highly value the benefits of risk reduction in VTE recurrence and post-thrombosis syndrome (Locadia et al., 2004). Patients would favor efficacy and safety over convenience of route of administration (Noble et al., 2015). Further, patients would like to avoid adverse events but most of them are "not afraid of" the adverse events (Barcellona et al., 2000)(Noble et al., 2015)(O'Meara et al., 1994). For anticoagulant therapy in general, most patients would prefer the oral doses compared with injections, this is mainly because of treatment burden due to injection. For patients with venographically proven deep venous thrombosis, 15 of the 19 patients expressed a preference for the subcutaneous route for administration of heparin over intravenous administration(Robinson et al., 1993). **Warfarin**<br><br>Adult patients would like to switch to another anticoagulant if it is as effective as warfarin; this is mainly due to the treatment burden associated with monitoring, injection and dietary change due to warfarin use. In another study approximately half of the patients did not consider VKA therapy particularly difficult to manage. (Attaya et al., 2012)(Wild et al., 2009) **LMWH**<br><br>For adult patients receiving low molecular weight heparin, patients placed a high score on "importance of ease of use", "expectations of symptom relief", and "confidence in the treatment to prevent blood clots" while they had a low score of treatment-related side effects (bruise, bleeding). (Baba et al., 2015) | |
| | Adolopment | |
| ○ Important uncertainty or variability<br>○ Possibly important uncertainty or variability<br>● Probably no important uncertainty or variability<br>○ No important uncertainty or variability | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>● Favors the intervention<br>○ Varies<br>○ Don't know | see table above | The panel judged that the balance between desirable and undesirable effects favors anticoagulation in pediatric patients with symptomatic DVT or PE. |
| | Adolopment | |
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>● Favors the intervention<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Resources required

How large are the resource requirements (costs)?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

| | | |
|---|---|---|
| ○ Large costs<br>● Moderate costs<br>○ Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br>○ Varies<br>○ Don't know | The following economic analyses were identified (U.S. setting):<br><br>Data from the 2009 Thomson Reuters MarketScan Commercial Database and MultiState Medicaid database were used to estimate annual expenditures for children 1–17 years of age with VTE. Medicaid-enrolled and privately insured children with VTE had an average of 1–2 inpatient admissions and 8–10 non-emergency department visits. Unadjusted mean total expenditures were similar for Medicaid-enrolled and privately insured children with VTE, $105,359 and $87,767, respectively. Adjusted mean expenditures for children with secondary VTE were five times higher than for children with idiopathic VTE (Boulet et al., 2012)<br><br>Another economic analysis identified at-risk children 1 to 17 years old with inpatient discharges in the Nationwide Inpatient Sample and estimated differences in the length of stay and costs for comparable pediatric patients with and without VTE. Patients with VTE had an increased 8.1 inpatient days (95% confidence interval [CI]: 3.9 to 12.3) and excess average costs of $27,686 (95% CI: $11,137 to $44,235) compared with matched controls.(Goudie et al., 2015) | The panel judged the resource requirements (costs) for anticoagulation to be moderate in pediatric patients with symptomatic DVT or PE. |
| | Adolopment | |
| ○ Large costs<br>● Moderate costs<br>○ Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

| | | |
|---|---|---|
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | Certainty of the evidence of resource requirements is very low, due to indirect evidence. | The panel judged the certainty of the evidence of resource requirements (costs) to be very low. |
| | Adolopment | |
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

| | | |
|---|---|---|
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>● Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>○ No included studies | No research evidence was identified. | The panel judged that cost-effectiveness probably favors anticoagulation in pediatric patients with symptomatic DVT or PE. |
| | Adolopment | |
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>● Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>○ No included studies | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Equity

What would be the impact on health equity?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Reduced<br>○ Probably reduced<br>○ Probably no impact<br>○ Probably increased<br>○ Increased<br>● Varies<br>○ Don't know | No research evidence was identified. | The panel judged that there is probably no impact on health equity with anticoagulation in pediatric patients with symptomatic DVT or PE. |
| | Adolopment | |

| | | |
|---|---|---|
| ○ Reduced<br>○ Probably reduced<br>○ Probably no impact<br>○ Probably increased<br>○ Increased<br>● Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Acceptability

Is the intervention acceptable to key stakeholders?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ No<br>○ Probably no<br>● Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | Observational research suggests the following regarding acceptability and barriers associated with the intervention: In Australia a prospective chart audit in a tertiary paediatric centre assessed the level of compliance of antithrombotic medication use in current practice with guidelines across a 100-day prospective chart audit in 2008-2009. The study showed that the level of compliance for use of antithrombotic medications for the indications of DVT and PE was 98.8% and 61.5%, respectively. High compliance was correlated with strong recommendations, with low compliance found especially in areas where recommendations were based on 'weak' evidence. This reflects clinician confidence in the strength of evidence currently available for paediatric antithrombotic therapy where there may be barriers associated with the use of the intervention where only low-quality, inconsistent, or indirect evidence extrapolated from adult data is available. (Peng et al., 2011)<br><br>Another study conducted at a large pediatric tertiary care hospital in the United States showed that implementation of a patient-care policy helped to improve compliance with guidelines, specifically for VTE prophylaxis, from a baseline compliance rate of 22% to an average rate of 83% during the 4-year study period. (Raffini et al., 2011) While assessed for VTE prophylaxis similar patient-care policies may help to address acceptability concerns for VTE treatment in the pediatric population. | The panel judged that anticoagulation for pediatric patients with symptomatic DVT or PE is probably acceptable to key stakeholders. |
| | Adolopment | |

| | | |
|---|---|---|
| ○ No<br>○ Probably no<br>● Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Feasibility

Is the intervention feasible to implement?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ No<br>○ Probably no<br>● Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | No research evidence was identified. | The panel judged that anticoagulation for pediatric patients with symptomatic DVT or PE is probably feasible to implement. |
| | Adolopment | |
| ○ No<br>○ Probably no<br>○ Probably yes<br>● Yes<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## SUMMARY OF JUDGEMENTS

| CRITERIA | ORIGINAL | IMPORTANCE FOR DECISION | ADOLOPMENT | IMPORTANCE FOR DECISION |
|---|---|---|---|---|
| PROBLEM | Yes | | Yes | |
| DESIRABLE EFFECTS | Large | | Large | |
| UNDESIRABLE EFFECTS | Small | | Small | |

| CRITERIA | ORIGINAL | IMPORTANCE FOR DECISION | ADOLOPMENT | IMPORTANCE FOR DECISION |
|---|---|---|---|---|
| CERTAINTY OF EVIDENCE | Very low | | Very low | |
| VALUES | Probably no important uncertainty or variability | | Probably no important uncertainty or variability | |
| BALANCE OF EFFECTS | Favors the intervention | | Favors the intervention | |
| RESOURCES REQUIRED | Moderate costs | | Moderate costs | |
| CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES | Very low | | Very low | |
| COST EFFECTIVENESS | Probably favors the intervention | | Probably favors the intervention | |
| EQUITY | Varies | | Varies | |
| ACCEPTABILITY | Probably yes | | Probably yes | |
| FEASIBILITY | Probably yes | | Yes | |

## TYPE OF RECOMMENDATION

Original

| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | **Strong recommendation for the intervention** |
|---|---|---|---|---|
| ○ | ○ | ○ | ○ | ● |

Adolopment

| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | **Conditional recommendation for the intervention** | Strong recommendation for the intervention |
|---|---|---|---|---|
| ○ | ○ | ○ | ● | ○ |

# CONCLUSIONS

Original

## Recommendation

**The ASH guideline panel recommends using anticoagulation rather than no anticoagulation in pediatric patients with symptomatic proximal DVT or PE (strong recommendation based on very low certainty in the evidence about effects).**

## Justification

While there remains limited direct evidence in children, there is very strong indirect evidence from adults that symptomatic VTE requires treatment. Further, given that the majority of VTE occurs in sick hospitalized children, in whom VTE is often life-threatening, low quality evidence suggesting benefit justifiies a strong recommendation based on extrapolation from adults, and potential consequences of sympotmatic VTE in children, despite very low certainty in the evidence.

Adolopment

## Recommendation

The American Society of Hematology (ASH)/International Society on Thrombosis and Haemostasis (ISTH) Guideline Panel ***suggests*** using anticoagulation rather than no anticoagulation in pediatric patients with symptomatic deep vein thrombosis (DVT) or pulmonary embolism (PE) (conditional recommendation based on very low certainty in the evidence about effects.

## Justification

Although there remains limited direct evidence in children, there is strong indirect evidence in adults that symptomatic VTE requires treatment. However, based on observational studies in children, there may be specific clinical scenarios where anticoagulation may yield either no significant benefit or potentially an increased risk of harm. Hence, the panel made a conditional recommendation based on extrapolation from adults, observational trials in specific pediatric subgroups, as well as unclear benefit/potential risk of harm of anticoagulation, with low certainty of evidence.

## Subgroup considerations

## Implementation considerations

## Monitoring and evaluation

## Research priorities

## REFERENCES SUMMARY

1. Kotsakis, A., Cook, D., Griffith, L., Anton, N., Massicotte, P., MacFarland, K., Farrell, R., Hutchison, J., Canadian Critical Care Trials, Group. Clinically important venous thromboembolism in pediatric critical care: a Canadian survey. J Crit Care; Dec 2005.
2. Albisetti, M., Chan, A. K.. Venous thrombosis and thromboembolism in infants and children: Risk factors and clinical manifestations. 2016.
3. Monagle, P, Chan, AK, Goldenberg, NA, Ichord, RN, Journeycake, JM, Nowak-Gottl, U. Antithrombotic therapy in neonates and children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest; 2012.

# APPENDICES

## Appendix 1

**Author(s):**
**Question:** Anticoagulation compared to no anticoagulation in pediatric patients with symptomatic DVT or PE
**Setting:** Inpatient
**Bibliography:** American Society of Hematology 2024 Guidelines for Management of Venous Thromboembolism: Treatment of Pediatric Venous Thromboembolism

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | anticoagulation | no anticoagulation | Relative (95% CI) | Absolute (95% CI) | | |
| **Major Bleeding (follow-up: mean 54 days)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 2/33 (6.1%) | 0/19 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Major Bleeding (follow-up: 3 months)** | | | | | | | | | | | | |
| 2[2,3] | non-randomised studies | serious[c] | not serious | not serious | very serious[b] | none | 8/767 (1.0%) [d] | - | - | - | ⨁◯◯◯ Very low | CRITICAL |
| **Clinically Relevant Non-Major Bleed (follow-up: mean 54 days)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 1/33 (3.0%) | 0/19 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Clinically Relevant Non-Major Bleed (follow-up: 3 months)** | | | | | | | | | | | | |
| 2[2,3] | non-randomised studies | serious[c] | not serious | not serious | very serious[c] | none | 14/767 (1.8%) [e] | - | - | - | ⨁◯◯◯ Very low | CRITICAL |

**CI:** confidence interval; **RR:** risk ratio

**Explanations**

a. Risk of bias, assessed using ROBINS-I tool, was judged to be serious due to selection bias without adjustment for confounding.
b. Imprecision due to small number of included patients and patients with events in the evaluated studies.
c. Both studies, DIVERSITY trial and EINSTEIN-JR, compared a direct oral anticoagulant versus standard of care anticoagulation (Heparin, Low Molecular Weight Heparin, Fondaparinux, Vitamin-K antagonists. Both arms of the trials were pooled to evaluate the outcome for patients using anticoagulation.
d. 0 out of 262 occurred in patients that took Rivaroxaban, 4 out of 177 in patients that took Dabigatran, 4 out of 212 in patients that took Standard of Care (LMWH, UFH, VKA)
e. 10 out of 335 occurred in patients that took Rivaroxaban, 2 out of 177 in patients that took Dabigatran, 2 out of 255 in patients that took Standard of Care (LMWH, UFH, VKA)

**References**


1.CH, van,Ommen, KA, Bergman, M, Boerma, HA, Bouma, AE, Donker, M, Gouvernante, CV, Hulzebos, D, Khandour, R, Knol, MA, Raets, KD, Liem, RA, van,Lingen, M, van,de,Loo, E, Lopriore, M, van,der,Putten, JJ, Sol, MH, Suijker, DC, Vijfbrief, R, Visser, MM, van,Weissenbruch. NEOnatal Central-venous Line Observational study on Thrombosis (NEOCLOT): . Journal of thrombosis and haemostasis : JTH; 2023.
2.C, Male, AWA, Lensing, JS, Palumbo, R, Kumar, I, Nurmeev, K, Hege, D, Bonnet, P, Connor, HL, Hooimeijer, M, Torres, AKC, Chan, G, Kenet, S, Holzhauer, A, Santamaría, P, Amedro, E, Chalmers, P, Simioni, RV, Bhat, DL, Yee, O, Lvova, J, Beyer-Westendorf, TT, Biss, I, Martinelli, P, Saracco, M, Peters, K, Kállay, CA, Gauger, MP, Massicotte, G, Young, AF, Pap, M, Majumder, WT, Smith, JF, Heubach, SD, Berkowitz, K, Thelen, D, Kubitza, M, Crowther, MH, Prins, P, Monagle, Investigators, EINSTEIN-Jr,Phase,3. Rivaroxaban compared with standard anticoagulants for the treatment of acute . The Lancet. Haematology; 2020.
3.J, Halton, LR, Brandão, M, Luciani, L, Bomgaars, E, Chalmers, LG, Mitchell, I, Nurmeev, A, Sharathkumar, P, Svirin, K, Gorbatikov, I, Tartakovsky, M, Simetzberger, F, Huang, Z, Sun, J, Kreuzer, S, Gropper, P, Reilly, M, Brueckmann, M, Albisetti, Investigators, DIVERSITY,Trial. Dabigatran etexilate for the treatment of acute venous thromboembolism in . The Lancet. Haematology; 2021.

Appendix 2

**Author(s):**
**Question:** Anticoagulation compared to no anticoagulation in pediatric patients with symptomatic DVT or PE
**Setting:** Inpatient
**Bibliography:** American Society of Hematology 2024 Guidelines for Management of Venous Thromboembolism: Treatment of Pediatric Venous Thromboembolism

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | anticoagulation | no anticoagulation | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality (All-Cause) (follow-up: mean 54 days)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 3/24 (12.5%) [c] | 2/19 (10.5%) | **RR 1.18** (0.22 to 6.40) | **19 more per 1,000** (from 82 fewer to 568 more) | ⨁◯◯◯ Very low | CRITICAL |
| **Mortality (follow-up: 3 months)** | | | | | | | | | | | | |
| 2[2,3] | non-randomised studies | serious[d] | not serious | not serious | very serious[b] | none | 3/651 (0.5%) [e] | - | - | - | ⨁◯◯◯ Very low | CRITICAL |
| **Recurrence of VTE (follow-up: mean 54 days)** | | | | | | | | | | | | |
| 2[1,4] | non-randomised studies | serious[a] | not serious | not serious | serious[b] | none | 7/223 (3.1%) | 4/47 (8.5%) | **RR 0.37** (0.11 to 1.21) | **54 fewer per 1,000** (from 76 fewer to 18 more) | ⨁⨁◯◯ Low | CRITICAL |
| **Recurrence of VTE (follow-up: 3 months)** | | | | | | | | | | | | |
| 2[2,3] | non-randomised studies | serious[d] | not serious | not serious | very serious[b] | none | 22/651 (3.4%) [f] | - | - | - | ⨁◯◯◯ Very low | CRITICAL |
| **Resolution (follow-up: mean 54 days)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | serious[b] | none | 21/24 (87.5%) | 11/13 (84.6%) | **RR 1.02** (0.60 to 1.74) | **17 more per 1,000** (from 338 fewer to 626 more) | ⨁⨁◯◯ Low | CRITICAL |
| **Extension of Thrombus (follow-up: mean 54 days)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 0/24 (0.0%) | 9/28 (32.1%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Extension of Thrombus (follow-up: 3 months)** | | | | | | | | | | | | |
| 2[2,3] | non-randomised studies | serious[d] | not serious | not serious | very serious[b] | none | 10/651 (1.5%) [g] | - | - | - | ⨁◯◯◯ Very low | CRITICAL |
| **Pulmonary Embolism (follow-up: 3 months)** | | | | | | | | | | | | |

Appendix 3

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2[2,3] | non-randomised studies | serious[d] | not serious | not serious | very serious[b] | none | 0/384 (0.0%) | - | - | - | ⨁◯◯◯ Very low | CRITICAL |
| **Post Thrombotic Syndrome (follow-up: 3 months)** | | | | | | | | | | | | |
| 2[2,3] | non-randomised studies | serious[d] | not serious | not serious | very serious[d] | none | 3/767 (0.4%) [h] | - | - | - | ⨁◯◯◯ Very low | CRITICAL |

**CI:** confidence interval; **RR:** risk ratio

**Explanations**

a. Risk of bias, assessed using ROBINS-I tool, was judged to be serious due to selection bias without adjustment for confounding.
b. Imprecision due to small number of included patients and patients with events in the evaluated studies.
c. None of the 3 patients that died were due to therapy or VTE related causes.
d. Both studies, DIVERSITY trial and EINSTEIN-JR, compared a direct oral anticoagulant versus standard of care anticoagulation (Heparin, Low Molecular Weight Heparin, Fondaparinux, Vitamin-K antagonists. Both arms of the trials were pooled to evaluate the outcome for patients using anticoagulation.
e. 1 out of 262 occurred in patients taking Rivaroxaban, 0 out of 177 occurred in patients taking Dabigatran, 2 out of 212 occurred in patients taking Standard of Care
f. 4 out of 262 occurred in patients that took Rivaroxaban, 7 out of 177 in patients that took Dabigatran, 11 out of 212 in patients that took Standard of Care (LMWH, UFH, VKA)
g. 4 out of 262 occurred in patients taking Rivaroxaban, 5 out of 177 occurred in patients taking Dabigatran, 4 out of 212 occurred in patients taking Standard of Care
h. 2 out of 335 occurred in patients that took Rivaroxaban, 1 out of 177 in patients that took Dabigatran, 0 out of 255 in patients that took Standard of Care (LMWH, UFH, VKA)

**References**


1.CH, van,Ommen, KA, Bergman, M, Boerma, HA, Bouma, AE, Donker, M, Gouvernante, CV, Hulzebos, D, Khandour, R, Knol, MA, Raets, KD, Liem, RA, van,Lingen, M, van,de,Loo, E, Lopriore, M, van,der,Putten, JJ, Sol, MH, Suijker, DC, Villbrief, R, Visser, MM, van,Weissenbruch. NEOnatal Central-venous Line Observational study on Thrombosis (NEOCLOT): . Journal of thrombosis and haemostasis : JTH; 2023.
2.C, Male, AWA, Lensing, JS, Palumbo, R, Kumar, I, Nurmeev, K, Hege, D, Bonnet, P, Connor, HL, Hoolmeijer, M, Torres, AKC, Chan, G, Kenet, S, Holzhauer, A, Santamaria, P, Amedro, E, Chalmers, P, Simioni, RV, Bhat, DL, Yee, O, Lvova, J, Beyer-Westendorf, TT, Biss, I, Martinelli, P, Saracco, M, Peters, K, Kállay, CA, Gauger, MP, Massicotte, G, Young, AF, Pap, M, Majumder, WT, Smith, JF, Heubach, SD, Berkowitz, K, Thelen, D, Kubitza, M, Crowther, MH, Prins, P, Monagle, Investigators, EINSTEIN-Jr,Phase,3. Rivaroxaban compared with standard anticoagulants for the treatment of acute . The Lancet. Haematology; 2020.
3.J, Halton, LR, Brandão, M, Luciani, L, Bomgaars, E, Chalmers, LG, Mitchell, I, Nurmeev, A, Sharathkumar, P, Svirin, K, Gorbatikov, I, Tartakovsky, M, Simetzberger, F, Huang, Z, Sun, J, Kreuzer, S, Gropper, P, Reilly, M, Brueckmann, M, Albisetti, Investigators, DIVERSITY,Trial. Dabigatran etexilate for the treatment of acute venous thromboembolism in . The Lancet. Haematology; 2021.
4.Chan, Anthony, Lensing, Anthonie W. A., Kubitza, Dagmar, Brown, Grahaem, Elorza, Dolores, Ybarra, Marta, Halton, Jacqueline, Grunt, Sebastian, Kenet, Gili, Bonnet, Damien, Santamaria, Amparo, Saracco, Paola, Biss, Tina, Climent, Francesco, Connor, Philip, Palumbo, Joseph, Thelen, Kirstin, Smith, William T., Mason, Amy, Adalbo, Ivet, Berkowitz, Scott D., Hurst, Eva, van Kesteren, Jeroen, Young, Guy, Monagle, Paul. Clinical presentation and therapeutic management of venous thrombosis in young children: a retrospective analysis. Thrombosis Journal; 2018.

**Author(s):**
**Question:** Anticoagulation compared to no anticoagulation in pediatric patients with asymptomatic DVT or PE?
**Setting:** Inpatient
**Bibliography:** American Society of Hematology 2024 Guidelines for Management of Venous Thromboembolism: Treatment of Pediatric Venous Thromboembolism

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | anticoagulation | no anticoagulation | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality (All Cause) (follow-up: mean 54 days)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | extremely serious[b] | none | 1/1 (100.0%) [c] | 0/3 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Mortality (follow-up: 2 years)** | | | | | | | | | | | | |
| 1[2] | non-randomised studies | serious[d] | not serious | not serious | serious[b] | none | | 4/32 (12.5%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Recurrence (follow-up: 54 days)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 0/1 (0.0%) | 0/3 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Resolution (follow-up: 2 years; assessed with: Complete Resolution)** | | | | | | | | | | | | |
| 1[2] | non-randomised studies | serious[d] | not serious | not serious | serious[b] | none | | 19/24 (79.2%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Extension of thrombus (follow-up: 54 days)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 0/1 (0.0%) | 2/5 (40.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Resolution (follow-up: mean 54 days)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 1/1 (100.0%) | 3/3 (100.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Post-Thrombotic Syndrome (follow-up: 2 years)** | | | | | | | | | | | | |
| 1[2] | non-randomised studies | serious[d] | not serious | not serious | serious[b] | none | | 6/32 (18.8%) [e] | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Major Bleeding (follow-up: 54 days)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 1/3 (33.3%) | 0/3 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Clinically Relevant Non-Major Bleed (follow-up: 54 days)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 0/3 (0.0%) | 0/3 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |

**CI:** confidence interval

**Explanations**

a. Risk of bias, assessed using ROBINS-I, was judged to be serious due to selection bias.
b. Imprecision due to small number of included patients and patients with events in the included studies.
c. The patient that died was not due to therapy or VTE related causes.
d. Risk of bias due to non-comparative studies.
e. For these 32 children, 1 child had clinically significant PTS, 5 others had PTS.

**References**

1.CH, van,Ommen, KA, Bergman, M, Boerma, HA, Bouma, AE, Donker, M, Gouvernante, CV, Hulzebos, D, Khandour, R, Knol, MA, Raets, KD, Liem, RA, van,Lingen, M, van,de,Loo, E, Lopriore, M, van,der,Putten, JJ, Sol, MH, Suijker, DC, Vijlbrief, R, Visser, MM, van,Weissenbruch. NEOnatal Central-venous Line Observational study on Thrombosis (NEOCLOT): . Journal of thrombosis and haemostasis : JTH; 2023.
2.S, Jones, W, Butt, P, Monagle, T, Cain, F, Newall. The natural history of asymptomatic central venous catheter-related thrombosis in . Blood; 2019.

## QUESTION

| Should anticoagulation vs. no anticoagulation be used for pediatric patients with asymptomatic DVT or PE?? | |
|---|---|
| **POPULATION:** | pediatric patients with asymptomatic DVT or PE? |
| **INTERVENTION:** | anticoagulation |
| **COMPARISON:** | no anticoagulation |
| **MAIN OUTCOMES:** | |
| **SETTING:** | Inpatient |
| **PERSPECTIVE:** | Clinical recommendation - Population perspective |
| **BACKGROUND:** | Asymptomatic venous thromboemoblism is common among infants and children, and often occurs in the presence of a central venous catheter. According to the Canadian registry, the incidence of CVC-related VTE is 3.5 per 10000 hospitalizations, representing 60% of all pediatric VTE. Asymptomatic VTE in children is associated with increased morbidity and death, and anticoagulant therapies may be effective in reducing these outcomes.(1)(2) |
| **CONFLICT OF INTEREST:** | **ASH conflict of interest declaration and management policies were applied and the following panel members were voting panel members (determining the direction and strength of the recommendation):**<br><br>**Panel members recused as a result of risk of conflicts of interest:** |

## ASSESSMENT

**Problem**
Is the problem a priority?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ No<br>○ Probably no<br>○ Probably yes<br>● Yes<br>○ Varies<br>○ Don't know | Although the rate of symptomatic CVC-related DVT in pediatric patients has been reported to be as high as 12%, the majority of studies report a much lower rate of 0% to 3.1%. The incidence of CVC-related DVT assessed by venography has been reported to vary from 27% to 66%. Most of the thrombi in these studies were asymptomatic. (Verso M, 2003) | |
| | Adolopment | |

| | | |
|---|---|---|
| ○ No<br>○ Probably no<br>○ Probably yes<br>● Yes<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Desirable Effects

How substantial are the desirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

○ Trivial
○ Small
○ Moderate
○ Large
○ Varies
● Don't know

| Outcomes | № of participants (studies) Follow up | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects* (95% CI) | |
|---|---|---|---|---|---|
| | | | | Risk with no anticoagulation | Risk difference with anticoagulation |
| Mortality follow up: 2 years[a] | 146 (1 observational study) | ⨁◯◯◯ VERY LOW[b] | - | [n=31] Ultrasounds of 146 children in the PICU determined a 22.6% incidence of CVC-related thrombosis. Only two children were symptomatic. Among 31 untreated children with asymptomatic CVC-related thrombosis, there were 0 deaths from thromboembolic complications. | |
| Mortality - not reported[c] | - | - | - | - | - |
| Pulmonary embolism - Severe follow up: 3 months[d] | 30 (1 observational study) | ⨁◯◯◯ VERY LOW[e,f,g] | not estimable | Study population | |
| | | | | 0 per 1,000 | **0 fewer per 1,000** (0 fewer to 0 fewer) |
| Pulmonary embolism - Severe [h] | 237 (2 observational studies) | ⨁◯◯◯ VERY LOW[e,g] | not estimable | Study population | |
| | | | | 0 per 1,000 | **0 fewer per 1,000** (0 fewer to 0 fewer) |
| | | | | Study population | |

The panel judged that the desirable anticipated effects of anticoagulation are unknown based on the available data in pediatric patients with asymptomatic DVT or PE.
The expert panel members were surveyed about their practice. From a total of 8000 patients managed in their practice, ~3500 (44%) had asymptomatic clots and ~1600 (50%) of patients with asymptomatic clots were not treated. Of the untreated patients, ~6% had a recurrent DVT/PE and 10% died due to all-cause mortality, with 1% of the deaths due to the clot.
Based on the survey, the panel considered that the rate of recurrent DVT/PE with anticoagulation is 2-3% and with no anticoagulation is 6%.

| | | | | | |
|---|---|---|---|---|---|
| DVT - Severe follow up: 3 months[d] | 30 (1 observational study) | ⨁◯◯◯ VERY LOW[e,f,g] | not estimable | 0 per 1,000 | **0 fewer per 1,000** (0 fewer to 0 fewer) |
| DVT - Severe [h] | 237 (2 observational studies) | ⨁◯◯◯ VERY LOW[e,g] | not estimable | Study population | |
| | | | | 0 per 1,000 | **0 fewer per 1,000** (0 fewer to 0 fewer) |
| Major bleeding follow up: 3 months[d] | 30 (1 observational study) | ⨁◯◯◯ VERY LOW[e,f,i] | not estimable | Study population | |
| | | | | 0 per 1,000 | **0 fewer per 1,000** (0 fewer to 0 fewer) |
| Major bleeding [h,j] | 483 (3 observational studies) | ⨁◯◯◯ VERY LOW[e,k] | not estimable | Study population | |
| | | | | 0 per 1,000 | **0 fewer per 1,000** (0 fewer to 0 fewer) |
| Thrombosis extension or clinical embolization follow up: 2 years[a] | 126 (1 observational study) | ⨁◯◯◯ VERY LOW[b] | - | [n=31] Among 31 untreated children with asymptomatic CVC-related thrombosis, there were 0 thrombosis extensions or clinical embolizations. | |
| Post-thrombotic syndrome follow up: 2 years[a] | 0 (1 observational study) | ⨁◯◯◯ VERY LOW[b] | - | [n=31] Among 31 untreated children with asymptomatic CVC-related thrombosis, clinically significant post-thrombotic syndrome was reported in 1 child. | |
| Post-thrombotic syndrome follow up: median 13 months | 0 (1 observational study) | ⨁◯◯◯ VERY LOW[e,l] | - | [n=59] Among 65 pediatric trauma patients with VTE, 24 (36.9%) were asymptomatic. Of the 59 patients who survived to hospital discharge, post-thrombotic syndrome occurred in 9/59 (15.8%) patients. Post-thrombotic syndrome was not associated with clot resolution (P = 0.782), or symptomatic DVT (P = 0.598), or duration or frequency of anticoagulation therapy (P = 0.588). | |

a. Jones 2017 ISTH conference abstract evaluating untreated asymptomatic CVC-related thrombosis.
b. Published conference abstract - single arm with no comparison group to detect an effect.

| | | |
|---|---|---|
| | c. One Cochrane review aimed to determine the efficacy of UFH or LMWH in comparison to placebo/no treatment in neonates with clinical or imaging diagnosis of thromboembolism. No RCTs or quasi-randomized trials were identified (Romantsik 2016).<br>d. Andrew (1994). Single study evaluating Tx with heparin.<br>e. Single-arm studies with no comparison group to detect an effect.<br>f. Andrew 1994 included patients with various indications for heparin. Thirty children had DVT and/or PE; 11 had arterial thrombi, most frequently after diagnostic angiography; and the remaining 24 received heparin prophylactically for congenital heart disease.<br>g. Single study with few events.<br>h. Streif 1999 evaluated Tx with warfarin. Bonduel 2003 evaluated Tx with acenocoumarol.<br>i. No events reported in a single study.<br>j. Newall 2005. Conference abstract.<br>k. Two studies with few patients and events.<br>l. Post-thrombotic syndrome was reported for the full cohort of patients with symptomatic and asymptomatic VTE.<br><br>NOTE: For a complete set of outcomes see the EVIDENCE PROFILE | |
| | Adolopment | |
| ○ Trivial<br>○ Small<br>○ Moderate<br>○ Large<br>● Varies<br>○ Don't know | *See Appendix 1*<br><br>**Explanations** a. Van Ommen 2023 had a critical risk of bias b. Low number of patients with event c. Therapy related mortality was 0 d. Evidence based on case series e. Van Ommen was found to have critical risk of bias<br><br>**References**<br>1.CH, van,Ommen, KA, Bergman, M, Boerma, HA, Bouma, AE, Donker, M, Gouvernante, CV, Hulzebos, D, Khandour, R, Knol, MA, Raets, KD, Liem, RA, van,Lingen, M, van,de,Loo, E, Lopriore, M, van,der,Putten, JJ, Sol, MH, Suijker, DC, Vijlbrief, R, Visser, MM, van,Weissenbruch. NEOnatal Central-venous Line Observational study on Thrombosis (NEOCLOT): . Journal of thrombosis and haemostasis : JTH; 2023. 2.S, Jones, W, Butt, P, Monagle, T, Cain, F, Newall. The | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

natural history of asymptomatic central venous catheter-related thrombosis in . Blood; 2019.

## Undesirable Effects

How substantial are the undesirable anticipated effects?

**JUDGEMENT**

○ Large
○ Moderate
● Small
○ Trivial
○ Varies
○ Don't know

**RESEARCH EVIDENCE**

Original

| Outcomes | № of participants (studies) Follow up | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects* (95% CI) | |
|---|---|---|---|---|---|
| | | | | Risk with no anticoagulation | Risk difference with anticoagulation |
| Mortality follow up: 2 years[a] | 146 (1 observational study) | ⨁◯◯◯ VERY LOW[b] | - | [n=31] Ultrasounds of 146 children in the PICU determined a 22.6% incidence of CVC-related thrombosis. Only two children were symptomatic. Among 31 untreated children with asymptomatic CVC-related thrombosis, there were 0 deaths from thromboembolic complications. | |
| Mortality - not reported[c] | - | - | - | - | - |
| Pulmonary embolism - Severe follow up: 3 months[d] | 30 (1 observational study) | ⨁◯◯◯ VERY LOW[e,f,g] | not estimable | Study population | |
| | | | | 0 per 1,000 | **0 fewer per 1,000** (0 fewer to 0 fewer) |
| Pulmonary embolism - Severe [h] | 237 (2 observational studies) | ⨁◯◯◯ VERY LOW[e,g] | not estimable | Study population | |
| | | | | 0 per 1,000 | **0 fewer per 1,000** (0 fewer to 0 fewer) |
| DVT - Severe follow up: 3 months[d] | 30 (1 observational study) | ⨁◯◯◯ VERY LOW[e,f,g] | not estimable | Study population | |
| | | | | 0 per 1,000 | **0 fewer per 1,000** (0 fewer to 0 fewer) |
| | | | | Study population | |

**ADDITIONAL CONSIDERATIONS**

The panel judged that the undesirable anticipated effects of anticoagulation are small in pediatric patients with asymptomatic DVT or PE.

| | | | | | |
|---|---|---|---|---|---|
| DVT - Severe [h] | 237 (2 observational studies) | ⨁◯◯◯ VERY LOW[e,g] | not estimable | 0 per 1,000 | **0 fewer per 1,000** (0 fewer to 0 fewer) |
| Major bleeding follow up: 3 months[d] | 30 (1 observational study) | ⨁◯◯◯ VERY LOW[e,f,i] | not estimable | Study population | |
| | | | | 0 per 1,000 | **0 fewer per 1,000** (0 fewer to 0 fewer) |
| Major bleeding [h,j] | 483 (3 observational studies) | ⨁◯◯◯ VERY LOW[e,k] | not estimable | Study population | |
| | | | | 0 per 1,000 | **0 fewer per 1,000** (0 fewer to 0 fewer) |
| Thrombosis extension or clinical embolization follow up: 2 years[a] | 126 (1 observational study) | ⨁◯◯◯ VERY LOW[b] | - | [n=31] Among 31 untreated children with asymptomatic CVC-related thrombosis, there were 0 thrombosis extensions or clinical embolizations. | |
| Post-thrombotic syndrome follow up: 2 years[a] | 0 (1 observational study) | ⨁◯◯◯ VERY LOW[b] | - | [n=31] Among 31 untreated children with asymptomatic CVC-related thrombosis, clinically significant post-thrombotic syndrome was reported in 1 child. | |
| Post-thrombotic syndrome follow up: median 13 months | 0 (1 observational study) | ⨁◯◯◯ VERY LOW[e,l] | - | [n=59] Among 65 pediatric trauma patients with VTE, 24 (36.9%) were asymptomatic. Of the 59 patients who survived to hospital discharge, post-thrombotic syndrome occurred in 9/59 (15.8%) patients. Post-thrombotic syndrome was not associated with clot resolution (P = 0.782), or symptomatic DVT (P = 0.598), or duration or frequency of anticoagulation therapy (P = 0.588). | |

a. Jones 2017 ISTH conference abstract evaluating untreated asymptomatic CVC-related thrombosis.
b. Published conference abstract - single arm with no comparison group to detect an effect.
c. One Cochrane review aimed to determine the efficacy of UFH or LMWH in comparison to placebo/no treatment in neonates with clinical or imaging diagnosis of thromboembolism. No RCTs or quasi-randomized trials were identified (Romantsik 2016).
d. Andrew (1994). Single study evaluating Tx with heparin.

| | | |
|---|---|---|
| | e. Single-arm studies with no comparison group to detect an effect.<br>f. Andrew 1994 included patients with various indications for heparin. Thirty children had DVT and/or PE; 11 had arterial thrombi, most frequently after diagnostic angiography; and the remaining 24 received heparin prophylactically for congenital heart disease.<br>g. Single study with few events.<br>h. Streif 1999 evaluated Tx with warfarin. Bonduel 2003 evaluated Tx with acenocoumarol.<br>i. No events reported in a single study.<br>j. Newall 2005. Conference abstract.<br>k. Two studies with few patients and events.<br>l. Post-thrombotic syndrome was reported for the full cohort of patients with symptomatic and asymptomatic VTE.<br><br>NOTE: For a complete set of outcomes see the EVIDENCE PROFILE | |
| | Adolopment | |
| ○ Large<br>○ Moderate<br>● Small<br>○ Trivial<br>○ Varies<br>○ Don't know | *See Appendix 2*<br><br>**Explanations** a. Low number of patients with event b. Van Ommen was found to have critical risk of bias<br><br>**References** 1.CH, van,Ommen, KA, Bergman, M, Boerma, HA, Bouma, AE, Donker, M, Gouvernante, CV, Hulzebos, D, Khandour, R, Knol, MA, Raets, KD, Liem, RA, van,Lingen, M, van,de,Loo, E, Lopriore, M, van,der,Putten, JJ, Sol, MH, Suijker, DC, Vijlbrief, R, Visser, MM, van,Weissenbruch. NEOnatal Central-venous Line Observational study on Thrombosis (NEOCLOT): . Journal of thrombosis and haemostasis : JTH; 2023. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Certainty of evidence

What is the overall certainty of the evidence of effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

| | | |
|---|---|---|
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | Certainty of the evidence of effects was judged as 'very low' due to serious risk of bias, and imprecision. | The panel judged that the overall certainty of the evidence of effects is very low in pediatric patients with asymptomatic DVT or PE. |
| | Adolopment | |
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Values

Is there important uncertainty about or variability in how much people value the main outcomes?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Important uncertainty or variability<br>● Possibly important uncertainty or variability<br>○ Probably no important uncertainty or variability<br>○ No important uncertainty or variability | **Utility related information:**<br><br>**The relative importance of outcomes:**<br>**Results from Panel Members' Utility Rating Survey**:<br>Utilities rated on the visual analog scale, where 0 represents death and 1 represents full health, were as follows.<br>Pulmonary embolism – Severe marker state: 0.31<br>Pulmonary embolism – Moderate marker state: 0.49<br>Deep vein thrombosis (proximal) – Severe marker state: 0.49<br>Deep vein thrombosis (proximal) – Moderate marker state: 0.61<br>Deep vein thrombosis (distal) – Severe marker state: 0.56<br>Deep vein thrombosis (distal) – Moderate marker state: 0.68<br>Major bleeding: 0.30 | The panel judged that there is possibly important uncertainty or variability in how much people value the main outcomes.<br>The panel also considered the outcome of post-thrombotic syndrome for the question of anticoagulation vs. no anticoagulation in pediatric patients with asymptomatic DVT or PE. |

Neonatal Bleeding – Severe: 0.30
Infant Bleeding – Severe: 0.26
Post-thrombotic syndrome: 0.58

**We did not identify utility related information or non-utility information for the outcomes of interest specific to the pediatric population in the literature.**

**Additional information from the adult population:**
**Our systematic review for the adult population found that the relative importance of the outcomes is as follows:**
Pulmonary embolism: 0.63-0.93 (different methods) (Hogg et al., 2014, Hogg et al., 2013, Locadia et al., 2004)
Deep vein thrombosis: 0.64-0.99 (different methods) (Hogg et al., 2014, Hogg et al., 2013, Locadia et al., 2004, Marvig et al., 2015, Utne et al., 2016)
Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) (Hogg et al., 2013, Locadia et al., 2004)
Muscular bleeding: 0.76 (time trade off) (Locadia et al., 2004)
Minor intracranial bleeding event: 0.75 (standard gamble) (Hogg et al., 2013)
Major intracranial bleeding event: 0.15 (standard gamble) (Hogg et al., 2013)
Central nervous system bleeding: 0.29-0.60 (standard gamble) (Lenert et al., 1997, O'Meara et al., 1994)
Treatment with LMWH: 0.993 (time trade off) (Marchetti et al., 2001)
Treatment with warfarin (as a surrogate): 0.989 (time trade off) (Marchetti et al., 2001)

**We also identified in the systematic review the following non-utility information from the adult population:**

**Anticoagulant therapy**
Adult patients highly value the benefits of risk reduction in VTE recurrence and post-thrombosis syndrome (Locadia et al., 2004). Patients would favor efficacy and safety over convenience of route of administration (Noble et al., 2015). Further, patients would like to avoid adverse events but most of them are "not afraid of" the adverse events (Barcellona et al., 2000, Noble et al., 2015, O'Meara et al., 1994). For anticoagulant therapy in general, most patients would prefer the oral doses compared with injections, this is mainly because of treatment burden due to injection.(Barcellona et al., 2000) For patients with venographically proven deep venous thrombosis, 15 of the 19 patients expressed a preference for the

| | | |
|---|---|---|
| | subcutaneous route for administration of heparin over intravenous administration. (Robinson et al., 1993) | |
| | Adolopment | |
| ○ Important uncertainty or variability<br>● Possibly important uncertainty or variability<br>○ Probably no important uncertainty or variability<br>○ No important uncertainty or variability | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>● Don't know | Not applicable | The panel judged that the balance between desirable and undesirable effects are unknown based on the available data for pediatric patients with asymptomatic DVT or PE.<br>It was noted that the available data is mostly on CVC-related thrombi and it is unclear how many were occlusive, or near occlusive at the time of diagnoses. The panel discussed that VTE in specific populations (cardiac, CVC dependent for nutrition) may benefit from treatment. |
| | Adolopment | |
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>● Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Resources required

| How large are the resource requirements (costs)? | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| | Original | |
| ○ Large costs<br>● Moderate costs<br>○ Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br>○ Varies<br>○ Don't know | The following economic analyses were identified (U.S. setting): Data from the 2009 Thomson Reuters MarketScan Commercial Database and MultiState Medicaid database were used to estimate annual expenditures for children 1–17 years of age with VTE. Medicaid-enrolled and privately insured children with VTE had an average of 1–2 inpatient admissions and 8–10 non-emergency department visits. Unadjusted mean total expenditures were similar for Medicaid-enrolled and privately insured children with VTE, $105,359 and $87,767, respectively. Adjusted mean expenditures for children with secondary VTE were five times higher than for children with idiopathic VTE. (Boulet et al., 2012)Another economic analysis identified at-risk children 1 to 17 years old with inpatient discharges in the Nationwide Inpatient Sample and estimated differences in the length of stay and costs for comparable pediatric patients with and without VTE. Patients with VTE had an increased 8.1 inpatient days (95% confidence interval [CI]: 3.9 to 12.3) and excess average costs of $27,686 (95% CI: $11,137 to $44,235) compared with matched controls.(Goudie et al., 2015) | The panel judged that the resource requirements (costs) of anticoagulation are moderate in pediatric patients with asymptomatic DVT or PE. |
| | Adolopment | |
| ○ Large costs<br>● Moderate costs<br>○ Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
|---|---|---|
| | Original | |

| | | |
|---|---|---|
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | Only indirect evidence. | The panel judged that the certainty of the evidence of resource requirements (costs) is very low in pediatric patients with asymptomatic DVT or PE. |
| | Adolopment | |
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |
| **Cost effectiveness**<br>Does the cost-effectiveness of the intervention favor the intervention or the comparison? | | |
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| | Original | |

| | | |
|---|---|---|
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>● No included studies | No research evidence was identified. | |
| | Adolopment | |
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>● No included studies | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Equity

What would be the impact on health equity?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Reduced<br>○ Probably reduced<br>● Probably no impact<br>○ Probably increased<br>○ Increased<br>○ Varies<br>○ Don't know | No research evidence was identified. | |
| | Adolopment | |
| ○ Reduced<br>○ Probably reduced<br>● Probably no impact<br>○ Probably increased<br>○ Increased | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

| | | |
|---|---|---|
| ○ Varies<br>○ Don't know | | |
| **Acceptability**<br>Is the intervention acceptable to key stakeholders? | | |
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| | Original | |
| ○ No<br>○ Probably no<br>● Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | Observational research suggests the following regarding acceptability and barriers associated with the intervention:<br><br>In Australia a prospective chart audit in a tertiary paediatric centre assessed the level of compliance of antithrombotic medication use in current practice with guidelines across a 100-day prospective chart audit in 2008-2009. The study showed that the level of compliance for use of antithrombotic medications for the indications of DVT and PE was 98.8% and 61.5%, respectively. High compliance was correlated with strong recommendations, with low compliance found especially in areas where recommendations were based on 'weak' evidence. This reflects clinician confidence in the strength of evidence currently available for paediatric antithrombotic therapy where there may be barriers associated with the use of the intervention where only low-quality, inconsistent, or indirect evidence extrapolated from adult data is available. (Peng et al., 2011)<br><br>Another study conducted at a large pediatric tertiary care hospital in the United States showed that implementation of a patient-care policy helped to improve compliance with guidelines, specifically for VTE prophylaxis, from a baseline compliance rate of 22% to an average rate of 83% during the 4-year study period. (Raffini et al., 2011) While assessed for VTE prophylaxis similar patient-care policies may help to address acceptability concerns for VTE treatment in the pediatric population. | The panel judged that anticoagulation in pediatric patients with asymptomatic DVT or PE is probably acceptable to key stakeholders. |
| | Adolopment | |
| ○ No<br>○ Probably no<br>● Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |
| **Feasibility** | | |

| Is the intervention feasible to implement? | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| | Original | |
| ○ No<br>○ Probably no<br>● Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | No research evidence was identified. | The panel judged that anticoagulation in pediatric patients with asymptomatic DVT or PE is probably feasible to implement. |
| | Adolopment | |
| ○ No<br>○ Probably no<br>○ Probably yes<br>● Yes<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## SUMMARY OF JUDGEMENTS

| CRITERIA | ORIGINAL | IMPORTANCE FOR DECISION | ADOLOPMENT | IMPORTANCE FOR DECISION |
|---|---|---|---|---|
| **PROBLEM** | Yes | | Yes | |
| **DESIRABLE EFFECTS** | Don't know | | Varies | |
| **UNDESIRABLE EFFECTS** | Small | | Small | |
| **CERTAINTY OF EVIDENCE** | Very low | | Very low | |
| **VALUES** | Possibly important uncertainty or variability | | Possibly important uncertainty or variability | |
| **BALANCE OF EFFECTS** | Don't know | | Don't know | |
| **RESOURCES REQUIRED** | Moderate costs | | Moderate costs | |
| **CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES** | Very low | | Very low | |
| **COST EFFECTIVENESS** | No included studies | | No included studies | |

| CRITERIA | ORIGINAL | IMPORTANCE FOR DECISION | ADOLOPMENT | IMPORTANCE FOR DECISION |
|---|---|---|---|---|
| **EQUITY** | Probably no impact | | Probably no impact | |
| **ACCEPTABILITY** | Probably yes | | Probably yes | |
| **FEASIBILITY** | Probably yes | | Yes | |

## TYPE OF RECOMMENDATION

Original

| Strong recommendation against the intervention | Conditional recommendation against the intervention | **Conditional recommendation for either the intervention or the comparison** | Conditional recommendation for the intervention | Strong recommendation for the intervention |
|---|---|---|---|---|
| ○ | ○ | ● | ○ | ○ |

Adolopment

| Strong recommendation against the intervention | Conditional recommendation against the intervention | **Conditional recommendation for either the intervention or the comparison** | Conditional recommendation for the intervention | Strong recommendation for the intervention |
|---|---|---|---|---|
| ○ | ○ | ● | ○ | ○ |

## CONCLUSIONS

Original

**Recommendation**

**The ASH guideline panel suggests either using anticoagulation or no anticoagulation in pediatric patients with asymptomatic DVT or PE (conditional recommendation based on very low certainty in the evidence about effects).**

**Justification**

The adult data would suggest that treatment of most asymptomatic VTE is not required. However, there are major epidemiological, anatomical, and pathophysiological differences between VTE in adults and children that make extrapolation in this regard very difficult. The unknown benefits of anticoagulation therapy relative to the known potential risks associated with therapy do not support routine radiological screening for asymptomatic VTE. However, if detected, the decision to treat or not treat should be individualised. Research to understand the natural history of asymptomatic VTE in a variety of sub-groups is a high priority.

Adolopment

**Recommendation**

**The ASH/ISTH guideline panel suggests either using anticoagulation or no anticoagulation in pediatric patients with asymptomatic DVT or PE (conditional recommendation based on very low certainty in the evidence about effects).**

## Justification

Despite new data, data remains of very low certainty

## Subgroup considerations

## Implementation considerations

## Monitoring and evaluation

## Research priorities

Well-conducted studies assessing the effect of treating vs not treating asymptomatic VTE are needed.
Identifying subgroups of patients who may benefit or who may be harmed by anticoagulation of asymptomatic VTE is a research priority.

## REFERENCES SUMMARY

1. Albisetti, M., Chan, A. K.. Venous thrombosis and thromboembolism in infants and children: Risk factors and clinical manifestations. 2016.
2. Kotsakis, A., Cook, D., Griffith, L., Anton, N., Massicotte, P., MacFarland, K., Farrell, R., Hutchison, J., Canadian Critical Care Trials, Group. Clinically important venous thromboembolism in pediatric critical care: a Canadian survey. J Crit Care; Dec 2005.

# APPENDICES

## Appendix 1

**Author(s):**
**Question:** Anticoagulation compared to no anticoagulation in pediatric patients with asymptomatic DVT or PE?
**Setting:** Inpatient
**Bibliography:** American Society of Hematology 2024 Guidelines for Management of Venous Thromboembolism: Treatment of Pediatric Venous Thromboembolism

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | anticoagulation | no anticoagulation | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality (All Cause) (follow-up: mean 54 days)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | extremely serious[b] | none | 1/1 (100.0%) [c] | 0/3 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Mortality (follow-up: 2 years)** | | | | | | | | | | | | |
| 1[2] | non-randomised studies | serious[d] | not serious | not serious | serious[b] | none | | 4/32 (12.5%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Recurrence (follow-up: 54 days)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 0/1 (0.0%) | 0/3 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Resolution (follow-up: 2 years; assessed with: Complete Resolution)** | | | | | | | | | | | | |
| 1[2] | non-randomised studies | serious[d] | not serious | not serious | serious[b] | none | | 19/24 (79.2%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Extension of thrombus (follow-up: 54 days)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 0/1 (0.0%) | 2/5 (40.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Resolution (follow-up: mean 54 days)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 1/1 (100.0%) | 3/3 (100.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Post-Thrombotic Syndrome (follow-up: 2 years)** | | | | | | | | | | | | |
| 1[2] | non-randomised studies | serious[d] | not serious | not serious | serious[b] | none | | 6/32 (18.8%) [e] | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Major Bleeding (follow-up: 54 days)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 1/3 (33.3%) | 0/3 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Clinically Relevant Non-Major Bleed (follow-up: 54 days)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 0/3 (0.0%) | 0/3 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |

**CI:** confidence interval

**Explanations**

a. Risk of bias, assessed using ROBINS-I, was judged to be serious due to selection bias.
b. Imprecision due to small number of included patients and patients with events in the included studies.
c. The patient that died was not due to therapy or VTE related causes.
d. Risk of bias due to non-comparative studies.
e. For these 32 children, 1 child had clinically significant PTS, 5 others had PTS.

**References**

1.CH, van,Ommen, KA, Bergman, M, Boerma, HA, Bouma, AE, Donker, M, Gouvernante, CV, Hulzebos, D, Khandour, R, Knol, MA, Raets, KD, Liem, RA, van,Lingen, M, van,de,Loo, E, Lopriore, M, van,der,Putten, JJ, Sol, MH, Suijker, DC, Vijlbrief, R, Visser, MM, van,Weissenbruch. NEOnatal Central-venous Line Observational study on Thrombosis (NEOCLOT): . Journal of thrombosis and haemostasis : JTH; 2023.
2.S, Jones, W, Butt, P, Monagle, T, Cain, F, Newall. The natural history of asymptomatic central venous catheter-related thrombosis in . Blood; 2019.

Appendix 2

**Author(s):**
**Question:** Anticoagulation compared to no anticoagulation in pediatric patients with asymptomatic DVT or PE?
**Setting:** Inpatient
**Bibliography:** American Society of Hematology 2024 Guidelines for Management of Venous Thromboembolism: Treatment of Pediatric Venous Thromboembolism

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | anticoagulation | no anticoagulation | Relative (95% CI) | Absolute (95% CI) | | |
| **Major Bleeding (follow-up: 54 days)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 1/3 (33.3%) | 0/3 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Clinically Relevant Non-Major Bleed (follow-up: 54 days)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 0/3 (0.0%) | 0/3 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |

**CI:** confidence interval

**Explanations**

a. Risk of bias, assessed using ROBINS-I, was judged to be serious due to selection bias.
b. Imprecision due to small number of included patients and patients with events in the included studies.

**References**

1.CH, van,Ommen, KA, Bergman, M, Boerma, HA, Bouma, AE, Donker, M, Gouvernante, CV, Hulzebos, D, Khandour, R, Knol, MA, Raets, KD, Liem, RA, van,Lingen, M, van,de,Loo, E, Lopriore, M, van,der,Putten, JJ, Sol, MH, Suijker, DC, Vijlbrief, R, Visser, MM, van,Weissenbruch. NEOnatal Central-venous Line Observational study on Thrombosis (NEOCLOT): . Journal of thrombosis and haemostasis : JTH; 2023.

2.S, Jones, W, Butt, P, Monagle, T, Cain, F, Newall. The natural history of asymptomatic central venous catheter-related thrombosis in . Blood; 2019.

**Author(s):**
**Question:** Anticoagulation for less than 3 months compared to anticoagulation 3 months in pediatric patients with VTE
**Setting:** Inpatient
**Bibliography:** American Society of Hematology 2024 Guidelines for Management of Venous Thromboembolism: Treatment of Pediatric Venous Thromboembolism

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | anticoagulation for less than 3 months | anticoagulation 3 months | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality (follow-up: 94 days; assessed with: All Cause Mortality)[a]** | | | | | | | | | | | | |
| 1[1] | randomised trials | not serious[b] | not serious | not serious | very serious[c] | none | 4/206 (1.9%) | 4/206 (1.9%) | **RR 1.00** (0.25 to 3.94) | **0 fewer per 1,000** (from 15 fewer to 57 more) | ⨁⨁◯◯ Low | CRITICAL |
| **Symptomatic recurrent venous thromboembolism (follow-up: 1 years)** | | | | | | | | | | | | |
| 1[1] | randomised trials | not serious[b] | not serious | not serious | very serious[c] | none | 1/154 (0.6%) | 2/143 (1.4%) | **RR 0.46** (0.04 to 5.07) | **8 fewer per 1,000** (from 13 fewer to 57 more) | ⨁⨁◯◯ Low | CRITICAL |
| **Recurrence (follow-up: range 6 weeks to 3 months)** | | | | | | | | | | | | |
| 2[2,3] | non-randomised studies | serious[d] | not serious | not serious | very serious[c] | none | 0/21 (0.0%) | 0/32 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Resolution (Complete or Partial Resolution) (follow-up: range 6 weeks to 3 months)** | | | | | | | | | | | | |
| 2[2,3] | non-randomised studies | serious[d] | not serious | not serious | serious[c] | none | 20/38 (52.6%) [e] | 17/45 (37.8%) [f] | **RR 1.38** (0.23 to 8.38) | **144 more per 1,000** (from 291 fewer to 1,000 more) | ⨁⨁◯◯ Low | CRITICAL |
| **Extension (follow-up: range 6 weeks to 3 months)** | | | | | | | | | | | | |
| 2[2,3] | non-randomised studies | serious[d] | not serious | not serious | very serious[c] | none | 0/38 (0.0%) | 2/45 (4.4%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Post-thrombotic syndrome (follow-up: 1 years)** | | | | | | | | | | | | |
| 1[1] | randomised trials | not serious[b] | not serious | not serious | serious[c] | none | 35/120 (29.2%) | 32/108 (29.6%) | **RR 1.30** (0.86 to 1.97) | **89 more per 1,000** (from 41 fewer to 287 more) | ⨁⨁⨁◯ Moderate | CRITICAL |
| **Post Thrombotic (assessed with: Clinical Judgement)** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[2] | non-randomised studies | serious[d] | not serious | not serious | very serious[c] | none | 2/16 (12.5%) | 2/21 (9.5%) | **RR 1.3** (0.2 to 8.3) | **29 more per 1,000** (from 76 fewer to 695 more) | ⨁◯◯◯ Very low | CRITICAL |

**Clinically Relevant Bleed (follow-up: 1 years; assessed with: Major bleeding and clinically relevant non-major bleed )**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[1] | randomised trials | not serious[b] | not serious | not serious | very serious[c] | none | 1/154 (0.6%) | 1/143 (0.7%) | **RR 0.93** (0.06 to 14.71) | **0 fewer per 1,000** (from 7 fewer to 96 more) | ⨁⨁◯◯ Low | CRITICAL |

**Bleeding (Unspecified) (follow-up: 6 months)**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[3] | non-randomised studies | serious[d] | not serious | not serious | very serious[c] | none | 0/5 (0.0%) | 0/11 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |

**CI:** confidence interval; **RR:** risk ratio

**Explanations**

a. All cases were reported to be unrelated to intervention or comparison
b. Although the study was found to have some concerns for risk of bias due to missing outcomes, the loss to follow up was equal in both interventions and therefore was not considered "serious"
c. Imprecision due to small number of included patients and patients with events in the included studies.
d. Risk of bias, assessed using ROBINS-I, was judged to be serious due to selection bias.
e. 15 out of 38 had complete resolution while 5 out of 38 had partial resolution.
f. 12 out of 45 had complete resolution while 5 out of 45 had partial resolution.

**References**

1.Goldenberg, Neil A., Kittelson, John M., Abshire, Thomas C., Bonaca, Marc, Casella, James F., Dale, Rita A., Halperin, Jonathan L., Hamblin, Frances, Kessler, Craig M., Manco-Johnson, Marilyn J., Sidonio, Robert F., Spyropoulos, Alex C., Steg, P. Gabriel, Turpie, Alexander G. G., Schulman, Sam, Group, Kids-DOTT,Trial,Investigators,and,the,ATLAS. Effect of Anticoagulant Therapy for 6 Weeks vs 3 Months on Recurrence and Bleeding Events in Patients Younger Than 21 Years of Age With Provoked Venous Thromboembolism: The Kids-DOTT Randomized Clinical Trial. JAMA; 2022.
2.R, Smith, S, Jones, F, Newall. Six Weeks Versus 3 Months of Anticoagulant Treatment for Pediatric Central Venous . Journal of pediatric hematology/oncology; 2017.
3.Hassan, . Single Centre Study on Safety and Efficacy of Rivaroxaban in Paediatric Venous Thromboembolism. 2022.

## QUESTION

| Should anticoagulation for less than 3 months vs. anticoagulation 3 months be used for pediatric patients with VTE? | |
|---|---|
| **POPULATION:** | pediatric patients with VTE |
| **INTERVENTION:** | anticoagulation for less than 3 months |
| **COMPARISON:** | anticoagulation 3 months |
| **MAIN OUTCOMES:** | |
| **SETTING:** | Inpatient or outpatient setting |
| **PERSPECTIVE:** | Clinical recommendation - Population perspective |
| **BACKGROUND:** | |
| **CONFLICT OF INTEREST:** | |

## ASSESSMENT

**Problem**
Is the problem a priority?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ No<br>○ Probably no<br>○ Probably yes<br>● Yes<br>○ Varies<br>○ Don't know | Anticoagulation is the mainstay therapy in pediatric patients with venous thromboembolism. Most decisions and recommendations in clinical guidelines are based on evidence from adult populations and observational studies in pediatric patients. There is especially a scarcity of evidence regarding duration and optimal management. (Monagle et al., 2012) | |
| | Adolopment | |
| ○ No<br>○ Probably no<br>○ Probably yes<br>● Yes<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Desirable Effects

How substantial are the desirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

● Trivial
○ Small
○ Moderate
○ Large
○ Varies
○ Don't know

| Outcomes | № of participants (studies) Follow up | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects* (95% CI) | |
|---|---|---|---|---|---|
| | | | | Risk with anticoagulation for up to 3 months | Risk difference with anticoagulation for longer than 3 months |
| Recurrent VTE (> 6 months VERSUS 3-6 months) (enoxaparin) [a] | 83 (1 observational study) | ⨁◯◯◯ VERY LOW[b,c] | not pooled | Study population | |
| | | | | not pooled | not pooled |
| Recurrent VTE (3 months) (LMWH or UFH) follow up: 3 months[d] | 76 (1 RCT) | ⨁⨁◯◯ LOW[e] | not pooled | Study population | |
| | | | | not pooled | not pooled |
| [ADULTS] Recurrent VTE (6 months VERSUS 3 months) (VKA) | 145 (1 RCT) | ⨁⨁◯◯ LOW[g,h] | **RR 0.51** (0.16 to 1.66) | Study population | |
| | | | | 100 per 1,000 | **49 fewer per 1,000** (84 fewer to 66 more) |

The panel judged the desirable anticipated effects to be trivial.

| | | | | | |
|---|---|---|---|---|---|
| follow up: 6 months[f] | | | | | |
| Major Bleeding (3 months) (LMWH or UFH) follow up: 3 months[d] | 76 (1 RCT) | ⨁⨁◯◯ LOW[e] | not pooled | Study population | |
| | | | | not pooled | not pooled |
| [ADULTS] Major Bleeding (6 months VERSUS 3 months) (VKA) follow up: 6 months[f] | 145 (1 RCT) | ⨁⨁◯◯ LOW[g,i] | **RR 2.80** (0.12 to 67.68) | Study population | |
| | | | | 0 per 1,000 | **0 fewer per 1,000** (0 fewer to 0 fewer) |
| Mortality (3 months) (LMWH or UFH) follow up: 3 months[d] | 76 (1 RCT) | ⨁⨁◯◯ LOW[e] | not pooled | Study population | |
| | | | | not pooled | not pooled |
| [ADULTS] Mortality (3 months VERSUS 6 months) (VKA) follow up: 6 months[f] | 145 (1 RCT) | ⨁⨁◯◯ LOW[g,i] | **RR 8.41** (0.47 to 153.39) | Study population | |
| | | | | 0 per 1,000 | **0 fewer per 1,000** (0 fewer to 0 fewer) |
| PE - severe - not reported | - | - | - | **-** | **-** |

| | | | | | | |
|---|---|---|---|---|---|---|
| DVT - severe - not reported | - | - | - | - | - | |

a. [Estepp 2012] 7% unprovoked
b. very small sample sizes
c. not exactly 3 month comparison
d. [Massicotte 2003 - REVIVE]
e. Only reported both arms of data together
f. [Agnelli 2003 - WODIT-PE] PE Hx rather than DVT
g. adult population
h. 95% confidence interval contains both null effect and threshold for plausible benefit or harm.
i. very low number of events

NOTE: For a complete assessment see the EVIDENCE PROFILE.

Adolopment

● Trivial
○ Small
○ Moderate
○ Large
○ Varies
○ Don't know

*See Appendix 1*

Desirable effects would also

## Undesirable Effects

How substantial are the undesirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

○ Large
○ Moderate
● Small
○ Trivial
○ Varies
○ Don't know

| Outcomes | № of participants (studies) Follow up | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects* (95% CI) | |
|---|---|---|---|---|---|
| | | | | Risk with anticoagulation for up to 3 months | Risk difference with anticoagulation for longer than 3 months |
| Recurrent VTE (> 6 months VERSUS 3-6 months) (enoxaparin) [a] | 83 (1 observational study) | ⨁◯◯◯ VERY LOW[b,c] | not pooled | Study population | |
| | | | | not pooled | not pooled |
| Recurrent VTE (3 months) (LMWH or UFH) follow up: 3 months[d] | 76 (1 RCT) | ⨁⨁◯◯ LOW[e] | not pooled | Study population | |
| | | | | not pooled | not pooled |
| [ADULTS] Recurrent VTE (6 months VERSUS 3 months) (VKA) follow up: 6 months[f] | 145 (1 RCT) | ⨁⨁◯◯ LOW[g,h] | **RR 0.51** (0.16 to 1.66) | Study population | |
| | | | | 100 per 1,000 | **49 fewer per 1,000** (84 fewer to 66 more) |
| Major Bleeding (3 months) (LMWH or UFH) | 76 (1 RCT) | ⨁⨁◯◯ LOW[e] | not pooled | Study population | |
| | | | | not pooled | not pooled |

The panel judged the undesirable anticipated effects to be small.

| | | | | | |
|---|---|---|---|---|---|
| follow up: 3 months[d] | | | | | |
| [ADULTS] Major Bleeding (6 months VERSUS 3 months) (VKA) follow up: 6 months[f] | 145 (1 RCT) | ⨁⨁◯◯ LOW[g,i] | **RR 2.80** (0.12 to 67.68) | Study population | |
| | | | | 0 per 1,000 | **0 fewer per 1,000** (0 fewer to 0 fewer) |
| Mortality (3 months) (LMWH or UFH) follow up: 3 months[d] | 76 (1 RCT) | ⨁⨁◯◯ LOW[e] | not pooled | Study population | |
| | | | | not pooled | not pooled |
| [ADULTS] Mortality (3 months VERSUS 6 months) (VKA) follow up: 6 months[f] | 145 (1 RCT) | ⨁⨁◯◯ LOW[g,i] | **RR 8.41** (0.47 to 153.39) | Study population | |
| | | | | 0 per 1,000 | **0 fewer per 1,000** (0 fewer to 0 fewer) |
| PE - severe - not reported | - | - | - | **-** | **-** |
| DVT - severe - not reported | - | - | - | **-** | **-** |

a. [Estepp 2012] 7% unprovoked
b. very small sample sizes
c. not exactly 3 month comparison
d. [Massicotte 2003 - REVIVE]
e. Only reported both arms of data together
f. [Agnelli 2003 - WODIT-PE] PE Hx rather than DVT

| | | |
|---|---|---|
| | g. adult population<br>h. 95% confidence interval contains both null effect and threshold for plausible benefit or harm.<br>i. very low number of events<br><br>NOTE: For a complete assessment see the EVIDENCE PROFILE. | |
| | Adolopment | |
| ○ Large<br>○ Moderate<br>○ Small<br>● Trivial<br>○ Varies<br>○ Don't know | *See Appendix 2* | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Certainty of evidence

What is the overall certainty of the evidence of effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | Overall certainty of the evidence of effects was 'very low' due to indirectness and imprecision. | The panel judged the overall certainty of evidence of effects as very low. |

| | | |
|---|---|---|
| | Adolopment | |
| ○ Very low<br>● Low<br>○ Moderate<br>○ High<br>○ No included studies | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Values

Is there important uncertainty about or variability in how much people value the main outcomes?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Important uncertainty or variability<br>○ Possibly important uncertainty or variability<br>● Probably no important uncertainty or variability<br>○ No important uncertainty or variability | **Utility related information:**<br><br>**The relative importance of outcomes:**<br><br>**Results from Panel Members' Utility Rating Survey**:<br><br>Utilities rated on the visual analog scale, where 0 represents death and 1 represents full health, were as follows.<br><br>Pulmonary embolism – Severe marker state: 0.31<br><br>Pulmonary embolism – Moderate marker state: 0.49<br><br>Deep vein thrombosis (proximal) – Severe marker state: 0.49<br><br>Deep vein thrombosis (proximal) – Moderate marker state: 0.61<br><br>Deep vein thrombosis (distal) – Severe marker state: 0.56<br><br>Deep vein thrombosis (distal) – Moderate marker state: 0.68<br><br>Major bleeding: 0.30<br><br>Neonatal Bleeding – Severe: 0.30 | The panel judged that there was probably no important uncertainty or variability in how much people value the main outcomes. |

Infant Bleeding – Severe: 0.26

**We did not identify utility related information or non-utility information for the outcomes of interest specific to the pediatric population in the literature.**

**Additional information from the adult population:**

**Our systematic review for the adult population found that the relative importance of the outcomes is as follows:**

Pulmonary embolism: 0.63-0.93 (different methods) (Hogg et al., 2013, Hogg et al., 2014, Locadia et al., 2004)

Deep vein thrombosis: 0.64-0.99 (different methods) (Hogg et al., 2014, Hogg et al., 2013, Locadia et al., 2004, Marvig et al., 2015, Utne et al., 2016)

Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) (Hogg et al., 2013, Hogg et al., 2014, Locadia et al., 2004)

Muscular bleeding: 0.76 (time trade off) (Locadia et al., 2004)

Minor intracranial bleeding event: 0.75 (standard gamble) (Hogg et al., 2013)

Major intracranial bleeding event: 0.15 (standard gamble) (Hogg et al., 2013)

Central nervous system bleeding: 0.29-0.60 (standard gamble) ((Lenert et al., 1997)(O'Meara et al., 1994)

Treatment with LMWH: 0.993 (time trade off)(Marchetti et al., 2001)

Treatment with warfarin (as a surrogate): 0.989 (time trade off) (Marchetti et al., 2001)

**We also identified in the systematic review the following non-utility information from the adult population:**

**Anticoagulant therapy**

Adult patients highly value the benefits of risk reduction in VTE recurrence and post-thrombosis syndrome (Locadia et al., 2004). Patients would favor efficacy and safety over convenience of route of administration (Noble et al., 2015). Further, patients would like to avoid adverse events but most of them are “not afraid of” the adverse events (Barcellona et al., 2000, Noble et al., 2015, O'Meara

| | | |
|---|---|---|
| | et al., 1994). For anticoagulant therapy in general, most patients would prefer the oral doses compared with injections, this is mainly because of treatment burden due to injection (Barcellona et al., 2000, Noble et al., 2015). For patients with venographically proven deep venous thrombosis, 15 of the 19 patients expressed a preference for the subcutaneous route for administration of heparin over intravenous administration (Robinson et al., 1993). | |
| | Adolopment | |
| ○ Important uncertainty or variability<br>○ Possibly important uncertainty or variability<br>● Probably no important uncertainty or variability<br>○ No important uncertainty or variability | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Favors the comparison<br>● Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>○ Don't know | | The panel judged the balance between desirable and undesirable effects to probably favor the comparsion. |
| | Adolopment | |

| | | |
|---|---|---|
| ○ Favors the comparison<br>○ Probably favors the comparison<br>● Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | 6 weeks only considered in a specific subset of patients<br><br>Shorter duration assumed to be mor acceptable for patients and family |

## Resources required

How large are the resource requirements (costs)?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Large costs<br>● Moderate costs<br>○ Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br>○ Varies<br>○ Don't know | No research evidence was identified addressing the cost of 3 month duration of anticoagulation as compared to greater than 3 month duration. **Additional information from adult population:** In relation to the reported costs of anticoagulation, the direct cost per week with warfarin in adults ranges from $3.54 to $11.44 USD while this number in Canada decreases to $0.49 to $0.84 CAD per week. (Biskupiak et al., 2013, Kearon C, 2014, Klarenbach et al., 2016, Guanella et al., 2011) With heparin, the costs per unit range from $0.18 per 10 units, to $0.212 per 1000 units [(Medicare, 2017) with a cost per week of $37.00 USD and $11.14 CAD per day in Canada. (Klarenbach et al., 2016, Guanella et al., 2011) LMWH (enoxaparin) cost varies. The wholesale cost in low and middle income economies is reported at about $13 to $75 USD per week. (IMPPG, 2016) In the United States the wholesale cost is about $98.91 USD per day as of 2016. (NADAC, 2017) | The panel judged resource costs to be moderate. |
| | Adolopment | |

| | | |
|---|---|---|
| ○ Large costs<br>○ Moderate costs<br>○ Negligible costs and savings<br>● Moderate savings<br>○ Large savings<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | | The panel judged the certainty of evidence of resource requirements as very low. |
| | Adolopment | |

| | | |
|---|---|---|
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Favors the comparison<br>● Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>○ No included studies | No research evidence identified. | The panel judged that cost-effectiveness probably favors the comparison. |
| | Adolopment | |
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>● Varies<br>○ No included studies | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Treated for 6 weeks may come for additional imaging depending on institutional pracitice. |

## Equity

What would be the impact on health equity?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Reduced<br>○ Probably reduced<br>● Probably no impact<br>○ Probably increased<br>○ Increased<br>○ Varies<br>○ Don't know | No research evidence was identified. | The panel judged that there would probably be no impact on health equity. If people are paying for the drug, then inequity if treated for longer. |
| | Adolopment | |
| ○ Reduced<br>○ Probably reduced<br>● Probably no impact<br>○ Probably increased<br>○ Increased<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | The panel judged that there would probably be no impact on health equity. If people are paying for the drug, then increase equity if treated for shorter. |

## Acceptability

Is the intervention acceptable to key stakeholders?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ No<br>○ Probably no<br>● Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | Observational research suggests the following regarding acceptability and barriers associated with the intervention:<br><br>In Australia a prospective chart audit in a tertiary paediatric centre assessed the level of compliance of antithrombotic medication use in current practice with guidelines across a 100-day prospective chart audit in 2008-2009. The study showed that the level of compliance for use of antithrombotic medications for the indications of DVT and PE was 98.8% and 61.5%, respectively. High compliance was correlated with strong recommendations, with low compliance | The panel judged that the intervention would probably be acceptable to key stakeholders. |

| | | |
|---|---|---|
| | found especially in areas where recommendations were based on ‘weak’ evidence. This reflects clinician confidence in the strength of evidence currently available for paediatric antithrombotic therapy where there may be barriers associated with the use of the intervention where only low-quality, inconsistent, or indirect evidence extrapolated from adult data is available. (Peng et al., 2011) | |
| | Adolopment | |
| ○ No<br>○ Probably no<br>○ Probably yes<br>● Yes<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Shorter duration would probably be favored by the patients and their parents. |

## Feasibility

Is the intervention feasible to implement?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ No<br>○ Probably no<br>● Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | No research evidence identifed. | The panel judged that the intervention would probably be feasible to implement. |
| | Adolopment | |
| ○ No<br>○ Probably no<br>○ Probably yes<br>● Yes<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |



## SUMMARY OF JUDGEMENTS

| CRITERIA | ORIGINAL | IMPORTANCE FOR DECISION | ADOLOPMENT | IMPORTANCE FOR DECISION |
|---|---|---|---|---|
| **PROBLEM** | Yes | | Yes | |
| **DESIRABLE EFFECTS** | Trivial | | Trivial | |
| **UNDESIRABLE EFFECTS** | Small | | Trivial | |
| **CERTAINTY OF EVIDENCE** | Very low | | Low | |
| **VALUES** | Probably no important uncertainty or variability | | Probably no important uncertainty or variability | |
| **BALANCE OF EFFECTS** | Probably favors the comparison | | Does not favor either the intervention or the comparison | |
| **RESOURCES REQUIRED** | Moderate costs | | Moderate savings | |
| **CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES** | Very low | | Very low | |
| **COST EFFECTIVENESS** | Probably favors the comparison | | Varies | |
| **EQUITY** | Probably no impact | | Probably no impact | |
| **ACCEPTABILITY** | Probably yes | | Yes | |
| **FEASIBILITY** | Probably yes | | Yes | |

## TYPE OF RECOMMENDATION

Original

| | | | | |
|---|---|---|---|---|
| Strong recommendation against the intervention | **Conditional recommendation against the intervention** | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | Strong recommendation for the intervention |

| | | | | |
|---|---|---|---|---|
| ○ | ● | ○ | ○ | ○ |

Adolopment

| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | **Conditional recommendation for the intervention** | Strong recommendation for the intervention |
|---|---|---|---|---|
| ○ | ○ | ○ | ● | ○ |

## CONCLUSIONS

Original

**Recommendation**

**The ASH guideline panel suggests using anticoagulation for 3 months or less rather than anticoagulation for longer than 3 months in pediatric patients with provoked DVT or PE (conditional recommendation based on very low certainty in the evidence about effects).**

**Justification**

The panel noted that the exact duration for optimal anticoagulation was unknown and there are ongoing studies comparing durations within this timeframe. In cases where the provoking factor is resolved, treatment for longer than 3 months is unjustified. However, in patients who have persistence of the causative risk factor for provoked DVT/PE, longer anticoagulation could be considered.

Adolopment

**Recommendation**

**The ASH/ISTH guideline panel suggests using anticoagulation for 6 weeks rather than anticoagulation for 3 months in (select) pediatric patients with provoked VTE(conditional recommendation based on low certainty in the evidence about effects).**

**Remarks:**

**Without persistant provoking (risk) factors**

**U/s after 6 weeks resolved or non-occlussive**

**Without cancer**

**Without persistent APLA or thrombophilia.**

**Without PE without DVT**

**The ASH/ISTH guidelines suggests 6-weeks of anticoagulation over 3-months in patients with clearly provoked VTE, who have radiological thrombus resolution by 6-weeks. Important exclusions to this recommendation include (i) PE, (ii) cancer-associated thrombosis (iii) patients with positive anti-phospholipid antibodies or major thrombophilia and (iv) ongoing VTE risk factors.**

## Justification

## Subgroup considerations

## Implementation considerations

## Monitoring and evaluation

## Research priorities

**REFERENCES SUMMARY**

# APPENDICES

Appendix 1

**Author(s):**
**Question:** Anticoagulation for less than 3 months compared to anticoagulation 3 months in pediatric patients with VTE
**Setting:** Inpatient
**Bibliography:** American Society of Hematology 2024 Guidelines for Management of Venous Thromboembolism: Treatment of Pediatric Venous Thromboembolism

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | anticoagulation for less than 3 months | anticoagulation 3 months | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality (follow-up: 94 days; assessed with: All Cause Mortality)**[a] | | | | | | | | | | | | |
| 1[1] | randomised trials | not serious[b] | not serious | not serious | very serious[c] | none | 4/206 (1.9%) | 4/206 (1.9%) | **RR 1.00** (0.25 to 3.94) | **0 fewer per 1,000** (from 15 fewer to 57 more) | ⨁⨁◯◯ Low | CRITICAL |
| **Symptomatic recurrent venous thromboembolism (follow-up: 1 years)** | | | | | | | | | | | | |
| 1[1] | randomised trials | not serious[b] | not serious | not serious | very serious[c] | none | 1/154 (0.6%) | 2/143 (1.4%) | **RR 0.46** (0.04 to 5.07) | **8 fewer per 1,000** (from 13 fewer to 57 more) | ⨁⨁◯◯ Low | CRITICAL |
| **Recurrence (follow-up: range 6 weeks to 3 months)** | | | | | | | | | | | | |
| 2[2,3] | non-randomised studies | serious[d] | not serious | not serious | very serious[c] | none | 0/21 (0.0%) | 0/32 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Resolution (Complete or Partial Resolution) (follow-up: range 6 weeks to 3 months)** | | | | | | | | | | | | |
| 2[2,3] | non-randomised studies | serious[d] | not serious | not serious | serious[c] | none | 20/38 (52.6%) [e] | 17/45 (37.8%) [f] | **RR 1.38** (0.23 to 8.38) | **144 more per 1,000** (from 291 fewer to 1,000 more) | ⨁⨁◯◯ Low | CRITICAL |
| **Extension (follow-up: range 6 weeks to 3 months)** | | | | | | | | | | | | |
| 2[2,3] | non-randomised studies | serious[d] | not serious | not serious | very serious[c] | none | 0/38 (0.0%) | 2/45 (4.4%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Post-thrombotic Syndrome (follow-up: 1 years)** | | | | | | | | | | | | |
| 1[1] | randomised trials | not serious[b] | not serious | not serious | serious[c] | none | 35/120 (29.2%) | 32/108 (29.6%) | **RR 1.30** (0.86 to 1.97) | **89 more per 1,000** (from 41 fewer to 287 more) | ⨁⨁⨁◯ Moderate | CRITICAL |
| **Post Thrombotic Syndrome (assessed with: Clinical Judgement)** | | | | | | | | | | | | |
| 1[2] | non-randomised studies | serious[d] | not serious | not serious | very serious[c] | none | 2/16 (12.5%) | 2/21 (9.5%) | **RR 1.3** (0.2 to 8.3) | **29 more per 1,000** (from 76 fewer to 695 more) | ⨁◯◯◯ Very low | CRITICAL |

**CI:** confidence interval; **RR:** risk ratio

**Explanations**

a. All cases were reported to be unrelated to intervention or comparison
b. Although the study was found to have some concerns for risk of bias due to missing outcomes, the loss to follow up was equal in both interventions and therefore was not considered "serious"
c. Imprecision due to small number of included patients and patients with events in the included studies.
d. Risk of bias, assessed using ROBINS-I, was judged to be serious due to selection bias.
e. 15 out of 38 had complete resolution while 5 out of 38 had partial resolution.
f. 12 out of 45 had complete resolution while 5 out of 45 had partial resolution.

**References**


1.Goldenberg, Neil A., Kittelson, John M., Abshire, Thomas C., Bonaca, Marc, Casella, James F., Dale, Rita A., Halperin, Jonathan L., Hamblin, Frances, Kessler, Craig M., Manco-Johnson, Marilyn J., Sidonio, Robert F., Spyropoulos, Alex C., Steg, P. Gabriel, Turpie, Alexander G. G., Schulman, Sam, Group, Kids-DOTT,Trial,Investigators,and,the,ATLAS . Effect of Anticoagulant Therapy for 6 Weeks vs 3 Months on Recurrence and Bleeding Events in Patients Younger Than 21 Years of Age With Provoked Venous Thromboembolism: The Kids-DOTT Randomized Clinical Trial. JAMA; 2022.
2.R, Smith, S, Jones, F, Newall. Six Weeks Versus 3 Months of Anticoagulant Treatment for Pediatric Central Venous , Journal of pediatric hematology/oncology; 2017.
3.Hassan, , Single Centre Study on Safety and Efficacy of Rivaroxaban in Paediatric Venous Thromboembolism. 2022.

Appendix 2

**Author(s):**
**Question:** Anticoagulation for less than 3 months compared to anticoagulation 3 months in pediatric patients with VTE
**Setting:** Inpatient
**Bibliography:** American Society of Hematology 2024 Guidelines for Management of Venous Thromboembolism: Treatment of Pediatric Venous Thromboembolism

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | anticoagulation for less than 3 months | anticoagulation 3 months | Relative (95% CI) | Absolute (95% CI) | | |
| **Bleeding (follow-up: 1 years; assessed with: Major bleeding and clinically relevant non-major bleed )** | | | | | | | | | | | | |
| 1[1] | randomised trials | not serious[a] | not serious | not serious | very serious[b] | none | 1/154 (0.6%) | 1/143 (0.7%) | **RR 0.93** (0.06 to 14.71) | **0 fewer per 1,000** (from 7 fewer to 96 more) | ⨁⨁◯◯ Low | CRITICAL |
| **Bleeding (Unspecified) (follow-up: 6 months)** | | | | | | | | | | | | |
| 1[2] | non-randomised studies | serious[c] | not serious | not serious | very serious[b] | none | 0/5 (0.0%) | 0/11 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |

**CI:** confidence interval; **RR:** risk ratio

**Explanations**

a. Although the study was found to have some concerns for risk of bias due to missing outcomes, the loss to follow up was equal in both interventions and therefore was not considered "serious"
b. Imprecision due to small number of included patients and patients with events in the included studies.
c. Risk of bias, assessed using ROBINS-I, was judged to be serious due to selection bias.

**References**

1.Goldenberg, Neil A., Kittelson, John M., Abshire, Thomas C., Bonaca, Marc, Casella, James F., Dale, Rita A., Halperin, Jonathan L., Hamblin, Frances, Kessler, Craig M., Manco-Johnson, Marilyn J., Sidonio, Robert F., Spyropoulos, Alex C., Steg, P. Gabriel, Turpie, Alexander G. G., Schulman, Sam, Group, Kids-DOTT,Trial,Investigators,and,the,ATLAS. Effect of Anticoagulant Therapy for 6 Weeks vs 3 Months on Recurrence and Bleeding Events in Patients Younger Than 21 Years of Age With Provoked Venous Thromboembolism: The Kids-DOTT Randomized Clinical Trial. JAMA; 2022.
2.Hassan, . Single Centre Study on Safety and Efficacy of Rivaroxaban in Paediatric Venous Thromboembolism. 2022.

Appendix 3

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2[2,3] | observational studies | serious[e] | not serious | not serious | serious[f] | none | 18/38 (47.4%) [g] | 29/45 (64.4%) [h] | **RR 0.68** (0.47 to 0.98) | **206 fewer per 1,000** (from 342 fewer to 13 fewer) | ⨁⨁◯◯ Low | CRITICAL |
| **Post-thrombotic syndrome (follow-up: 1 years)** | | | | | | | | | | | | |
| 1[1] | randomised trials | not serious[b] | not serious | not serious | serious[c] | none | 35/120 (29.2%) | 32/108 (29.6%) | not estimable | **18 fewer per 1,000** (from 112 fewer to 147 more)[d] | ⨁⨁⨁◯ Moderate | CRITICAL |
| **Post Thrombotic (assessed with: Clinical Judgement)** | | | | | | | | | | | | |
| 1[2] | observational studies | serious[e] | not serious | not serious | very serious[f] | none | 2/16 (12.5%) | 2/21 (9.5%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |

**CI:** confidence interval; **RR:** risk ratio

**Explanations**

a. All cases were reported to be unrelated to intervention or comparison
b. Although the study was found to have some concerns for risk of bias due to missing outcomes, the loss to follow up was equal in both interventions and therefore was not considered "serious"
c. Small number of events
d. Relative Risk was not provided
e. Critical Risk of Bias due to selection bias
f. Small number of events and patients
g. 6/11 improved on long term follow up, 1/11 had extension
h. 4/11 improved on long term benefit, 0/11 had extension

**References**

1.Goldenberg, Neil A., Kittelson, John M., Abshire, Thomas C., Bonaca, Marc, Casella, James F., Dale, Rita A., Halperin, Jonathan L., Hamblin, Frances, Kessler, Craig M., Manco-Johnson, Marilyn J., Sidonio, Robert F., Spyropoulos, Alex C., Steg, P. Gabriel, Turpie, Alexander G. G., Schulman, Sam, Group, Kids-DOTT,Trial,Investigators,and,the,ATLAS. Effect of Anticoagulant Therapy for 6 Weeks vs 3 Months on Recurrence and Bleeding Events in Patients Younger Than 21 Years of Age With Provoked Venous Thromboembolism: The Kids-DOTT Randomized Clinical Trial. JAMA: 2022.
2.R, Smith, S, Jones, F, Newall. Six Weeks Versus 3 Months of Anticoagulant Treatment for Pediatric Central Venous . Journal of pediatric hematology/oncology: 2017.
3.Hassan, . Single Centre Study on Safety and Efficacy of Rivaroxaban in Paediatric Venous Thromboembolism. 2022.

**Author(s):**
**Question:** Anticoagulation for longer than 6 to 12 months compared to indefinite anticoagulation in pediatric patients with unprovoked DVT or PE
**Setting:** Inpatient
**Bibliography:** American Society of Hematology 2024 Guidelines for Management of Venous Thromboembolism: Treatment of Pediatric Venous Thromboembolism

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | anticoagulation for longer than 6 to 12 months | indefinite anticoagulation | Relative (95% CI) | Absolute (95% CI) | | |
| **Recurrent VTE (>6 months VERSUS 3-6 months) (enoxaparin) (follow-up: 1 years)[a]** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | not serious | not serious | serious[b] | serious[c] | none | 13/56 (23.2%) | 4/27 (14.8%) | **OR 1.74** (0.51 to 5.95) | **84 more per 1,000** (from 67 fewer to 360 more) | ⨁◯◯◯ Very low | CRITICAL |
| **[ADULTS] Recurrent VTE (24 months VERSUS 6 months) (VKA) (follow-up: 12 months; assessed with: after finishing anticoagulation)[d]** | | | | | | | | | | | | |
| 1[2] | randomised trials | not serious | not serious | serious[e] | serious[c] | none | 1/32 (3.1%) | 7/32 (21.9%) | **RR 0.14** (0.02 to 1.10) | **188 fewer per 1,000** (from 214 fewer to 22 more) | ⨁⨁◯◯ Low | CRITICAL |
| **[ADULTS] Recurrent VTE (12 months VERSUS 6 months) (VKA) (follow-up: 1 years)[f]** | | | | | | | | | | | | |
| 1[3] | randomised trials | not serious | not serious | serious[e] | serious[c] | none | 11/90 (12.2%) | 11/91 (12.1%) | **RR 1.01** (0.46 to 2.21) | **1 more per 1,000** (from 65 fewer to 146 more) | ⨁⨁◯◯ Low | CRITICAL |
| **[ADULTS] Recurrent VTE (2 years longer than 6-18 months (32-37% @6mo) VERSUS 6-18 months (32-37%@6months)) (aspirin 100mg daily) (follow-up: 2 years)[g]** | | | | | | | | | | | | |
| 1[4] | randomised trials | not serious | not serious | serious[b,e] | not serious | none | 28/205 (13.7%) | 43/197 (21.8%) | **RR 0.63** (0.41 to 0.97) | **81 fewer per 1,000** (from 129 fewer to 7 fewer) | ⨁⨁⨁◯ Moderate | CRITICAL |
| **[ADULTS] Major Bleeding (12 months VERSUS 6 months (VKA) (follow-up: 1 years)[f]** | | | | | | | | | | | | |
| 1[3] | randomised trials | not serious | not serious | serious[e] | serious[h] | none | 2/90 (2.2%) | 1/91 (1.1%) | **RR 2.02** (0.19 to 21.91) | **11 more per 1,000** (from 9 fewer to 230 more) | ⨁⨁◯◯ Low | CRITICAL |
| **[ADULTS] Major Bleeding (24 months VERSUS 6 months) (VKA) (follow-up: 12 months; assessed with: after finishing anticoagulation)[d]** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[2] | randomised trials | not serious | not serious | serious[e] | serious[h] | none | 2/32 (6.3%) | 2/32 (6.3%) | **RR 1.00** (0.15 to 6.67) | **0 fewer per 1,000** (from 53 fewer to 354 more) | ⨁⨁◯◯ Low | CRITICAL |

**[ADULTS] Major Bleeding (2 years longer than 6-18 months (32-37% @6mo) VERSUS 6-18 months (32-37% @6mo)) (aspirin 100mg daily) (follow-up: 2 years)[g]**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[4] | randomised trials | not serious | not serious | serious[b,e] | serious[h] | none | 1/205 (0.5%) | 1/197 (0.5%) | **RR 0.96** (0.06 to 15.26) | **0 fewer per 1,000** (from 5 fewer to 72 more) | ⨁⨁◯◯ Low | CRITICAL |

**[ADULTS] Mortality (12 months VERSUS 6 months) (VKA) (follow-up: 1 years)[f]**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[3] | randomised trials | not serious | not serious | serious[e] | serious[c] | none | 8/90 (8.9%) | 7/91 (7.7%) | **RR 1.16** (0.44 to 3.05) | **12 more per 1,000** (from 43 fewer to 158 more) | ⨁⨁◯◯ Low | CRITICAL |

**[ADULTS] Mortality (24 months VERSUS 6 months) (VKA) (follow-up: 12 months; assessed with: after finishing anticoagulation)[d]**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[2] | randomised trials | not serious | not serious | serious[e] | serious[h] | none | 0/32 (0.0%) | 0/32 (0.0%) | not estimable | | ⨁⨁◯◯ Low | CRITICAL |

**[ADULTS] Mortality (2 years longer than 6-18 months (32-37% @6mo) VERSUS 6-18 months (32-37% @6mo)) (aspirin 100mg daily) (follow-up: 2 years)[g]**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[4] | randomised trials | not serious | not serious | serious[b] | serious[c] | none | 6/205 (2.9%) | 5/197 (2.5%) | **RR 1.15** (0.36 to 3.72) | **4 more per 1,000** (from 16 fewer to 69 more) | ⨁⨁◯◯ Low | CRITICAL |

**PE - severe - not reported**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| - | - | - | - | - | - | - | - | - | - | - | - | CRITICAL |

**DVT - severe - not reported**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| - | - | - | - | - | - | - | - | - | - | - | - | CRITICAL |

**CI:** confidence interval; **OR:** odds ratio; **RR:** risk ratio

**Explanations**

a. Based on Estepp 2012 (7% unprovoked)
b. not exactly 6 month time point
c. 95% confidence interval contains both an effect and no effect
d. Based on Ferraj 2004 study
e. adult population
f. Based on Agnelli 2003 - WODIT-PE study; PE rather than DVT History
g. Based on Becattini 2012 study
h. very low number of events

**References**

1.Estepp JH, Smeltzer M,Reiss UM. The impact of quality and duration of enoxaparin therapy on recurrent venous thrombosis in children. Pediatric Blood and Cancer. 2012;59:105-9..
2.RS, Farraj. Anticoagulation period in idiopathic venous thromboembolism. How long is enough? Saudi Med J. 2004;25:848-51..
3.Agnelli G, Prandoni P,Becattini C,Silingardi M,Taliani M,Miccio M,et al. Extended oral anticoagulant therapy after a first episode of pulmonary embolism. Ann Intern Med 2003. p. 19-25.
4.Becattini C, Agnelli G,Schenone A,Eichinger S,Bucherini E,Silingardi M,et al.. Aspirin for preventing the recurrence of venous thromboembolism. N Engl J Med. 2012;366:1959-67..

## QUESTION

| Should anticoagulation for longer than 6 to 12 months vs. indefinite anticoagulation be used for pediatric patients with unprovoked DVT or PE? | |
|---|---|
| **POPULATION:** | pediatric patients with unprovoked DVT or PE |
| **INTERVENTION:** | anticoagulation for longer than 6 to 12 months |
| **COMPARISON:** | indefinite anticoagulation |
| **MAIN OUTCOMES:** | Recurrent VTE (PE or DVT); Major Bleeding; Mortality; PTS |
| **SETTING:** | Inpatient or outpatient setting |
| **PERSPECTIVE:** | Clinical recommendation - Population perspective |
| **BACKGROUND:** | |
| **CONFLICT OF INTEREST:** | |

## ASSESSMENT

**Problem**
Is the problem a priority?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ No<br>○ Probably no<br>○ Probably yes<br>● Yes<br>○ Varies<br>○ Don't know | Anticoagulation is the mainstay therapy in pediatric patients with venous thromboembolism. Most decisions and recommendations in clinical guidelines are based on evidence from adult populations and observational studies in pediatric patients. There is especially a scarcity of evidence regarding duration and optimal management. (Monagle et al., 2012) | |
| | Adolopment | |
| ○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br>○ Varies | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

| | | |
|---|---|---|
| ○ Don't know | | |

## Desirable Effects

How substantial are the desirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

○ Trivial
● Small
○ Moderate
○ Large
○ Varies
○ Don't know

| Outcomes | № of participants (studies) Follow up | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects* (95% CI) | |
|---|---|---|---|---|---|
| | | | | Risk with anticoagulation for 6 to 12 months | Risk difference with anticoagulation for longer than 6 to 12 months |
| Recurrent VTE (>6 months VERSUS 3-6 months) (enoxaparin) follow up: 1 years[a] | 83 (1 observational study) | ⨁◯◯◯ VERY LOW[b,c] | **OR 1.74** (0.51 to 5.95) | Study population | |
| | | | | 148 per 1,000 | **84 more per 1,000** (67 fewer to 360 more) |
| [ADULTS] Recurrent VTE (24 months VERSUS 6 months) (VKA) assessed with: after finishing anticoagulation follow up: 12 months[d] | 64 (1 RCT) | ⨁⨁◯◯ LOW[c,e] | **RR 0.14** (0.02 to 1.10) | Study population | |
| | | | | 219 per 1,000 | **188 fewer per 1,000** (214 fewer to 22 more) |
| [ADULTS] Recurrent VTE (12 months VERSUS 6 months) (VKA) follow up: 1 years[f] | 181 (1 RCT) | ⨁⨁◯◯ LOW[c,e] | **RR 1.01** (0.46 to 2.21) | Study population | |
| | | | | 121 per 1,000 | **1 more per 1,000** (65 fewer to 146 more) |

The panel judged that the desirable anticipated effects as small. There is available data related to outcomes of mortality, recurrent PE, and indirect data from adults.

| | | | | | |
|---|---|---|---|---|---|
| [ADULTS] Recurrent VTE (2 years longer than 6-18 months (32-37% @6mo) VERSUS 6-18 months (32-37%@6months)) (aspirin 100mg daily)<br>follow up: 2 years[g] | 402<br>(1 RCT) | ⊕⊕⊕◯<br>MODERATE[b,e] | **RR 0.63**<br>(0.41 to 0.97) | Study population | |
| | | | | 218 per 1,000 | **81 fewer per 1,000**<br>(129 fewer to 7 fewer) |
| [ADULTS] Major Bleeding (12 months VERSUS 6 months (VKA)<br>follow up: 1 years[f] | 181<br>(1 RCT) | ⊕⊕◯◯<br>LOW[e,h] | **RR 2.02**<br>(0.19 to 21.91) | Study population | |
| | | | | 11 per 1,000 | **11 more per 1,000**<br>(9 fewer to 230 more) |
| [ADULTS] Major Bleeding (24 months VERSUS 6 months) (VKA) assessed with: after finishing anticoagulation<br>follow up: 12 months[d] | 64<br>(1 RCT) | ⊕⊕◯◯<br>LOW[e,h] | **RR 1.00**<br>(0.15 to 6.67) | Study population | |
| | | | | 63 per 1,000 | **0 fewer per 1,000**<br>(53 fewer to 354 more) |
| [ADULTS] Major Bleeding (2 years longer than 6-18 months (32-37% @6mo) VERSUS 6-18 months (32-37% @6mo)) (aspirin 100mg daily)<br>follow up: 2 years[g] | 402<br>(1 RCT) | ⊕⊕◯◯<br>LOW[b,e,h] | **RR 0.96**<br>(0.06 to 15.26) | Study population | |
| | | | | 5 per 1,000 | **0 fewer per 1,000**<br>(5 fewer to 72 more) |
| [ADULTS] Mortality (12 months VERSUS 6 months) (VKA)<br>follow up: 1 years[f] | 181<br>(1 RCT) | ⊕⊕◯◯<br>LOW[c,e] | **RR 1.16**<br>(0.44 to 3.05) | Study population | |
| | | | | 77 per 1,000 | **12 more per 1,000**<br>(43 fewer to 158 more) |

| | | | | | | |
|---|---|---|---|---|---|---|
| [ADULTS] Mortality (24 months VERSUS 6 months) (VKA) assessed with: after finishing anticoagulation follow up: 12 months[d] | 64 (1 RCT) | ⨁⨁◯◯ LOW[e,h] | not estimable | Study population | | |
| | | | | 0 per 1,000 | **0 fewer per 1,000** (0 fewer to 0 fewer) | |
| [ADULTS] Mortality (2 years longer than 6-18 months (32-37% @6mo) VERSUS 6-18 months (32-37% @6mo)) (aspirin 100mg daily) follow up: 2 years[g] | 402 (1 RCT) | ⨁⨁◯◯ LOW[b,c] | **RR 1.15** (0.36 to 3.72) | Study population | | |
| | | | | 25 per 1,000 | **4 more per 1,000** (16 fewer to 69 more) | |
| PE - severe - not reported | - | - | - | - | - | |
| DVT - severe - not reported | - | - | - | - | - | |

a. [Estepp 2012] (7% unprovoked)
b. not exactly 6 month time point
c. 95% confidence interval contains both an effect and no effect
d. [Ferraj 2004]
e. adult population
f. [Agnelli 2003 - WODIT-PE] PE rather than DVT Hx
g. [Becattini 2012]
h. very low number of events

NOTE: For a complete assessment see the EVIDENCE PROFILE.

| | | |
|---|---|---|
| | Adolopment | |
| ○ Trivial | | Add considerations made be the adoloping panel, |

| | | |
|---|---|---|
| ○ Small<br>○ Moderate<br>○ Large<br>○ Varies<br>○ Don't know | *See Appendix 2See Appendix 3* | including the justification for any change in judgment. |

## Undesirable Effects

How substantial are the undesirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

○ Large
● Moderate
○ Small
○ Trivial
○ Varies
○ Don't know

| Outcomes | № of participants (studies) Follow up | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects* (95% CI) | |
|---|---|---|---|---|---|
| | | | | Risk with anticoagulation for 6 to 12 months | Risk difference with anticoagulation for longer than 6 to 12 months |
| Recurrent VTE (>6 months VERSUS 3-6 months) (enoxaparin) follow up: 1 years[a] | 83 (1 observational study) | ⨁◯◯◯ VERY LOW[b,c] | **OR 1.74** (0.51 to 5.95) | Study population | |
| | | | | 148 per 1,000 | **84 more per 1,000** (67 fewer to 360 more) |
| [ADULTS] Recurrent VTE (24 months VERSUS 6 months) (VKA) assessed with: after finishing anticoagulation follow up: 12 months[d] | 64 (1 RCT) | ⨁⨁◯◯ LOW[c,e] | **RR 0.14** (0.02 to 1.10) | Study population | |
| | | | | 219 per 1,000 | **188 fewer per 1,000** (214 fewer to 22 more) |
| [ADULTS] | 181 | ⨁⨁◯◯ | **RR 1.01** | Study population | |

The panel judged that the undesirable effects are moderate. Longer treatment would reflect a higher bleeding rate.

| | | | | | | |
|---|---|---|---|---|---|---|
| Recurrent VTE (12 months VERSUS 6 months) (VKA) follow up: 1 years[f] | (1 RCT) | LOW[c,e] | (0.46 to 2.21) | 121 per 1,000 | **1 more per 1,000** (65 fewer to 146 more) | |
| [ADULTS] Recurrent VTE (2 years longer than 6-18 months (32-37% @6mo) VERSUS 6-18 months (32-37%@6months)) (aspirin 100mg daily) follow up: 2 years[g] | 402 (1 RCT) | ⨁⨁⨁◯ MODERATE[b,e] | **RR 0.63** (0.41 to 0.97) | Study population | | |
| | | | | 218 per 1,000 | **81 fewer per 1,000** (129 fewer to 7 fewer) | |
| [ADULTS] Major Bleeding (12 months VERSUS 6 months (VKA) follow up: 1 years[f] | 181 (1 RCT) | ⨁⨁◯◯ LOW[e,h] | **RR 2.02** (0.19 to 21.91) | Study population | | |
| | | | | 11 per 1,000 | **11 more per 1,000** (9 fewer to 230 more) | |
| [ADULTS] Major Bleeding (24 months VERSUS 6 months) (VKA) assessed with: after finishing anticoagulation follow up: 12 months[d] | 64 (1 RCT) | ⨁⨁◯◯ LOW[e,h] | **RR 1.00** (0.15 to 6.67) | Study population | | |
| | | | | 63 per 1,000 | **0 fewer per 1,000** (53 fewer to 354 more) | |
| [ADULTS] Major Bleeding (2 years longer than 6-18 months (32-37% @6mo) VERSUS 6-18 months (32-37% @6mo)) (aspirin 100mg daily) follow up: 2 years[g] | 402 (1 RCT) | ⨁⨁◯◯ LOW[b,e,h] | **RR 0.96** (0.06 to 15.26) | Study population | | |
| | | | | 5 per 1,000 | **0 fewer per 1,000** (5 fewer to 72 more) | |
| [ADULTS] Mortality | 181 | ⨁⨁◯◯ | **RR 1.16** | Study population | | |

| | | | | | |
|---|---|---|---|---|---|
| (12 months VERSUS 6 months) (VKA)<br>follow up: 1 years[f] | (1 RCT) | LOW[c,e] | (0.44 to 3.05) | 77 per 1,000 | **12 more per 1,000**<br>(43 fewer to 158 more) |
| [ADULTS] Mortality (24 months VERSUS 6 months) (VKA)<br>assessed with: after finishing anticoagulation<br>follow up: 12 months[d] | 64<br>(1 RCT) | ⨁⨁◯◯<br>LOW[e,h] | not estimable | Study population | |
| | | | | 0 per 1,000 | **0 fewer per 1,000**<br>(0 fewer to 0 fewer) |
| [ADULTS] Mortality (2 years longer than 6-18 months (32-37% @6mo) VERSUS 6-18 months (32-37% @6mo)) (aspirin 100mg daily)<br>follow up: 2 years[g] | 402<br>(1 RCT) | ⨁⨁◯◯<br>LOW[b,c] | **RR 1.15**<br>(0.36 to 3.72) | Study population | |
| | | | | 25 per 1,000 | **4 more per 1,000**<br>(16 fewer to 69 more) |
| PE - severe - not reported | - | - | - | - | - |
| DVT - severe - not reported | - | - | - | - | - |

a. [Estepp 2012] (7% unprovoked)
b. not exactly 6 month time point
c. 95% confidence interval contains both an effect and no effect
d. [Ferraj 2004]
e. adult population
f. [Agnelli 2003 - WODIT-PE] PE rather than DVT Hx
g. [Becattini 2012]
h. very low number of events

NOTE: For a complete assessment see the EVIDENCE PROFILE.

| | | |
|---|---|---|
| | Adolopment | |
| ○ Large<br>○ Moderate<br>○ Small<br>○ Trivial<br>○ Varies<br>○ Don't know | *See Appendix 1* | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Certainty of evidence

What is the overall certainty of the evidence of effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | Overall certainty of the evidence of effects was judged as 'very low' due to imprecision and indirectness | The panel judged the overall certainty of the evidence of effects as very low due to imprecision and indirectness. |
| | Adolopment | |
| ○ Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Values

Is there important uncertainty about or variability in how much people value the main outcomes?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Important uncertainty or variability<br>● Possibly important uncertainty or variability<br>○ Probably no important uncertainty or variability<br>○ No important uncertainty or variability | **<u>Utility related information:</u>**<br><br>**The relative importance of outcomes:**<br><br>**<u>Results from Panel Members' Utility Rating Survey</u>**:<br><br>Utilities rated on the visual analog scale, where 0 represents death and 1 represents full health, were as follows.<br><br>Pulmonary embolism – Severe marker state: 0.31<br><br>Pulmonary embolism – Moderate marker state: 0.49<br><br>Deep vein thrombosis (proximal) – Severe marker state: 0.49<br><br>Deep vein thrombosis (proximal) – Moderate marker state: 0.61<br><br>Deep vein thrombosis (distal) – Severe marker state: 0.56<br><br>Deep vein thrombosis (distal) – Moderate marker state: 0.68<br><br>Major bleeding: 0.30<br><br>Neonatal Bleeding – Severe: 0.30<br><br>Infant Bleeding – Severe: 0.26<br><br>**We did not identify utility related information or non-utility information for the outcomes of interest specific to the pediatric population in the literature.**<br><br>**<u>Additional information from the adult population:</u>**<br><br>**Our systematic review for the adult population found that the relative importance of the outcomes is as follows:**<br><br>Pulmonary embolism: 0.63-0.93 (different methods) (Hogg et al., 2013, Hogg et al., | The panel judged that there possibly was important uncertainty or variability in how much people value the main outcomes. |

| | | |
|---|---|---|
| | 2014, Locadia et al., 2004)<br><br>Deep vein thrombosis: 0.64-0.99 (different methods) (Hogg et al., 2014, Hogg et al., 2013, Locadia et al., 2004, Marvig et al., 2015, Utne et al., 2016)<br><br>Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off)(Hogg et al., 2013, Locadia et al., 2004)<br><br>Muscular bleeding: 0.76 (time trade off) (Locadia et al., 2004)<br><br>Minor intracranial bleeding event: 0.75 (standard gamble) (Hogg et al., 2013)<br><br>Major intracranial bleeding event: 0.15 (standard gamble)(Hogg et al., 2013)<br><br>Central nervous system bleeding: 0.29-0.60 (standard gamble) (Lenert et al., 1997, O'Meara et al., 1994)<br><br>Treatment with LMWH: 0.993 (time trade off)(Marchetti et al., 2001)<br><br>Treatment with warfarin (as a surrogate): 0.989 (time trade off)(Marchetti et al., 2001)<br><br>**<u>We also identified in the systematic review the following non-utility information from the adult population:</u>**<br><br>**Anticoagulant therapy**<br><br>Adult patients highly value the benefits of risk reduction in VTE recurrence and post-thrombosis syndrome (Locadia et al., 2004). Patients would favor efficacy and safety over convenience of route of administration (Noble et al., 2015). Further, patients would like to avoid adverse events but most of them are “not afraid of” the adverse events (Barcellona et al., 2000, Noble et al., 2015, O'Meara et al., 1994). For anticoagulant therapy in general, most patients would prefer the oral doses compared with injections, this is mainly because of treatment burden due to injection (Barcellona et al., 2000, Noble et al., 2015). For patients with venographically proven deep venous thrombosis, 15 of the 19 patients expressed a preference for the subcutaneous route for administration of heparin over intravenous administration (Robinson et al., 1993). | |
| | Adolopment | |
| ○ Important uncertainty or variability<br>○ Possibly important uncertainty or variability<br>○ Probably no important uncertainty or variability | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

| | | |
|---|---|---|
| ○ No important uncertainty or variability | | |

## Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Favors the comparison<br>● Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>○ Don't know | | The panel judged the balance between desirable and undesirable effects would probably favor the comparison. |
| | Adolopment | |
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Resources required

How large are the resource requirements (costs)?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

| | | |
|---|---|---|
| ○ Large costs<br>● Moderate costs<br>○ Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br>○ Varies<br>○ Don't know | No research evidence was identified addressing the cost of 6 month duration of anticoagulation as compared to greater than 6 months duration.<br><br>**Additional information from adult population:**<br><br>In relation to the reported costs of anticoagulation, the direct cost per week with warfarin in adults ranges from $3.54 to $11.44 USD while this number in Canada decreases to $0.49 to $0.84 CAD per week. (Biskupiak et al., 2013, Kearon C, 2014, Klarenbach et al., 2016, Guanella et al., 2011) With heparin, the costs per unit range from $0.18 per 10 units, to $0.212 per 1000 units [ASP] with a cost per week of $37.00 USD and $11.14 CAD per day in Canada. (Klarenbach et al., 2016, Guanella et al., 2011) LMWH (enoxaparin) cost varies. The wholesale cost in low and middle income economies is reported at about $13 to $75 USD per week.(IMPPG, 2016) In the United States the wholesale cost is about $98.91 USD per day as of 2016 (NADAC, 2017). | The panel judged the resource requirements as moderate. The panel felt costs would vary according to duration of anticoagulation. |
| | Adolopment | |
| ○ Large costs<br>○ Moderate costs<br>○ Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

| | | |
|---|---|---|
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | | The panel judged the certainty of evidence of resource requirements as very low. |
| | Adolopment | |
| ○ Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

| | | |
|---|---|---|
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>● No included studies | No research evidence was identified. | The panel judged this was a complex cost effectiveness question and would not be easy to make judgments without available studies in this case. Although, the panel felt this was an important question due to the small benefit and harms noted above. |
| | Adolopment | |
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>○ No included studies | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Equity

What would be the impact on health equity?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Reduced<br>● Probably reduced<br>○ Probably no impact<br>○ Probably increased<br>○ Increased<br>○ Varies<br>○ Don't know | No research evidence was identified. | The panel judged that health equity would probably be reduced. |
| | Adolopment | |
| ○ Reduced<br>○ Probably reduced<br>○ Probably no impact | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in |

| | | |
|---|---|---|
| ○ Probably increased<br>○ Increased<br>○ Varies<br>○ Don't know | | judgment. |
| **Acceptability**<br>Is the intervention acceptable to key stakeholders? | | |
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| | Original | |
| ○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br>● Varies<br>○ Don't know | Observational research suggests the following regarding acceptability and barriers associated with the intervention: In Australia a prospective chart audit in a tertiary paediatric centre assessed the level of compliance of antithrombotic medication use in current practice with guidelines across a 100-day prospective chart audit in 2008-2009. The study showed that the level of compliance for use of antithrombotic medications for the indications of DVT and PE was 98.8% and 61.5%, respectively. High compliance was correlated with strong recommendations, with low compliance found especially in areas where recommendations were based on 'weak' evidence. This reflects clinician confidence in the strength of evidence currently available for paediatric antithrombotic therapy where there may be barriers associated with the use of the intervention where only low-quality, inconsistent, or indirect evidence extrapolated from adult data is available. (Peng et al., 2011)(Peng 2011) | The panel judged that intervention acceptability would vary based on patients' perceived burden of treatment, life style and impact on quality of life. |
| | Adolopment | |
| ○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |
| **Feasibility**<br>Is the intervention feasible to implement? | | |
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| | Original | |

| | | |
|---|---|---|
| ○ No<br>○ Probably no<br>● Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | No research evidence was identified. | The panel judged that the intervention would probably be feasible to implement. |
| | Adolopment | |
| ○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## SUMMARY OF JUDGEMENTS

| CRITERIA | ORIGINAL | IMPORTANCE FOR DECISION | ADOLOPMENT | IMPORTANCE FOR DECISION |
|---|---|---|---|---|
| PROBLEM | Yes | | | |
| DESIRABLE EFFECTS | Small | | | |
| UNDESIRABLE EFFECTS | Moderate | | | |
| CERTAINTY OF EVIDENCE | Very low | | | |
| VALUES | Possibly important uncertainty or variability | | | |
| BALANCE OF EFFECTS | Probably favors the comparison | | | |
| RESOURCES REQUIRED | Moderate costs | | | |
| CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES | Very low | | | |
| COST EFFECTIVENESS | No included studies | | | |

| CRITERIA | ORIGINAL | IMPORTANCE FOR DECISION | ADOLOPMENT | IMPORTANCE FOR DECISION |
|---|---|---|---|---|
| EQUITY | Probably reduced | | | |
| ACCEPTABILITY | Varies | | | |
| FEASIBILITY | Probably yes | | | |

## TYPE OF RECOMMENDATION

Original

| Strong recommendation against the intervention | **Conditional recommendation against the intervention** | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | Strong recommendation for the intervention |
|---|---|---|---|---|
| ○ | ● | ○ | ○ | ○ |

Adolopment

| Strong recommendation against the intervention | **Conditional recommendation against the intervention** | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | Strong recommendation for the intervention |
|---|---|---|---|---|
| ○ | ● | ○ | ○ | ○ |

## CONCLUSIONS

Original

**Recommendation**

**The ASH guideline panel suggests using anticoagulation for 6 to 12 months rather than anticoagulation for longer than 6 to 12 months in pediatric patients with unprovoked DVT or PE (conditional recommendation based on very low certainty in the evidence about effects).**

**Justification**

There was little pediatric data. Extrapolation of adult data might favor prolonged treatment periods in terms of VTE recurrence. However, the bleeding risk and impact on quality of life of prolonged therapy was judged to be significantly higher in children compared to adults. Patients' values and preferences should always be considered.

Adolopment

## Recommendation

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

## Justification

## Subgroup considerations

## Implementation considerations

## Monitoring and evaluation

## Research priorities

**REFERENCES SUMMARY**

# APPENDICES

Appendix 1

**Author(s):**
**Question:** Anticoagulation for longer than 6 to 12 months compared to indefinite anticoagulation in pediatric patients with unprovoked DVT or PE
**Setting:** Inpatient
**Bibliography:** American Society of Hematology 2024 Guidelines for Management of Venous Thromboembolism: Treatment of Pediatric Venous Thromboembolism

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | anticoagulation for longer than 6 to 12 months | indefinite anticoagulation | Relative (95% CI) | Absolute (95% CI) | | |
| **[ADULTS] Major Bleeding (12 months VERSUS 6 months (VKA) (follow-up: 1 years)[a]** | | | | | | | | | | | | |
| 1[1] | randomised trials | not serious | not serious | serious[b] | serious[d] | none | 2/90 (2.2%) | 1/91 (1.1%) | **RR 2.02** (0.19 to 21.91) | **11 more per 1,000** (from 9 fewer to 230 more) | ⨁⨁◯◯ Low | CRITICAL |
| **[ADULTS] Major Bleeding (24 months VERSUS 6 months) (VKA) (follow-up: 12 months; assessed with: after finishing anticoagulation)[c]** | | | | | | | | | | | | |
| 1[2] | randomised trials | not serious | not serious | serious[b] | serious[d] | none | 2/32 (6.3%) | 2/32 (6.3%) | **RR 1.00** (0.15 to 6.67) | **0 fewer per 1,000** (from 53 fewer to 354 more) | ⨁⨁◯◯ Low | CRITICAL |
| **[ADULTS] Major Bleeding (2 years longer than 6-18 months (32-37% @6mo) VERSUS 6-18 months (32-37% @6mo)) (aspirin 100mg daily) (follow-up: 2 years)[e]** | | | | | | | | | | | | |
| 1[3] | randomised trials | not serious | not serious | serious[b,f] | serious[d] | none | 1/205 (0.5%) | 1/197 (0.5%) | **RR 0.96** (0.06 to 15.26) | **0 fewer per 1,000** (from 5 fewer to 72 more) | ⨁⨁◯◯ Low | CRITICAL |

**CI:** confidence interval; **OR:** odds ratio; **RR:** risk ratio

**Explanations**

a. Based on Agnelli 2003 - WODIT-PE study; PE rather than DVT History
b. adult population
c. Based on Ferraj 2004 study
d. very low number of events
e. Based on Becattini 2012 study
f. not exactly 6 month time point

**References**

1.Agnelli G, Prandoni P,Becattini C,Silingardi M,Taliani M,Miccio M,et al. Extended oral anticoagulant therapy after a first episode of pulmonary embolism. Ann Intern Med 2003. p. 19-25.
2.RS, Farraj. Anticoagulation period in idiopathic venous thromboembolism. How long is enough? Saudi Med J. 2004;25:848-51..
3.Becattini C, Agnelli G,Schenone A,Eichinger S,Bucherini E,Silingardi M,et al.. Aspirin for preventing the recurrence of venous thromboembolism. N Engl J Med. 2012;366:1959-67..

Appendix 2

**Author(s):**
**Question:** Anticoagulation for longer than 6 to 12 months compared to indefinite anticoagulation in pediatric patients with unprovoked DVT or PE
**Setting:** Inpatient
**Bibliography:** American Society of Hematology 2024 Guidelines for Management of Venous Thromboembolism: Treatment of Pediatric Venous Thromboembolism

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | anticoagulation for longer than 6 to 12 months | indefinite anticoagulation | Relative (95% CI) | Absolute (95% CI) | | |
| **[ADULTS] Mortality (12 months VERSUS 6 months) (VKA) (follow-up: 1 years)[a]** | | | | | | | | | | | | |
| 1[1] | randomised trials | not serious | not serious | serious[b] | serious[c] | none | 8/90 (8.9%) | 7/91 (7.7%) | **RR 1.16** (0.44 to 3.05) | **12 more per 1,000** (from 43 fewer to 158 more) | ⨁⨁◯◯ Low | CRITICAL |
| **[ADULTS] Mortality (24 months VERSUS 6 months) (VKA) (follow-up: 12 months; assessed with: after finishing anticoagulation)[d]** | | | | | | | | | | | | |
| 1[2] | randomised trials | not serious | not serious | serious[b] | serious[e] | none | 0/32 (0.0%) | 0/32 (0.0%) | not estimable | | ⨁⨁◯◯ Low | CRITICAL |
| **[ADULTS] Mortality (2 years longer than 6-18 months (32-37% @6mo) VERSUS 6-18 months (32-37% @6mo)) (aspirin 100mg daily) (follow-up: 2 years)[f]** | | | | | | | | | | | | |
| 1[3] | randomised trials | not serious | not serious | serious[g] | serious[c] | none | 6/205 (2.9%) | 5/197 (2.5%) | **RR 1.15** (0.36 to 3.72) | **4 more per 1,000** (from 16 fewer to 69 more) | ⨁⨁◯◯ Low | CRITICAL |
| **Recurrent VTE (>6 months VERSUS 3-6 months) (enoxaparin) (follow-up: 1 years)[h]** | | | | | | | | | | | | |
| 1[4] | non-randomised studies | not serious | not serious | serious[g] | serious[c] | none | 13/56 (23.2%) | 4/27 (14.8%) | **OR 1.74** (0.51 to 5.95) | **84 more per 1,000** (from 67 fewer to 360 more) | ⨁◯◯◯ Very low | CRITICAL |
| **[ADULTS] Recurrent VTE (24 months VERSUS 6 months) (VKA) (follow-up: 12 months; assessed with: after finishing anticoagulation)[d]** | | | | | | | | | | | | |
| 1[2] | randomised trials | not serious | not serious | serious[b] | serious[c] | none | 1/32 (3.1%) | 7/32 (21.9%) | **RR 0.14** (0.02 to 1.10) | **188 fewer per 1,000** (from 214 fewer to 22 more) | ⨁⨁◯◯ Low | CRITICAL |
| **[ADULTS] Recurrent VTE (12 months VERSUS 6 months) (VKA) (follow-up: 1 years)[a]** | | | | | | | | | | | | |

Appendix 3

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[1] | randomised trials | not serious | not serious | serious[b] | serious[c] | none | 11/90 (12.2%) | 11/91 (12.1%) | **RR 1.01** (0.46 to 2.21) | **1 more per 1,000** (from 65 fewer to 146 more) | ⨁⨁◯◯ Low | CRITICAL |

**[ADULTS] Recurrent VTE (2 years longer than 6-18 months (32-37% @6mo) VERSUS 6-18 months (32-37%@6months)) (aspirin 100mg daily) (follow-up: 2 years)[f]**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[3] | randomised trials | not serious | not serious | serious[b,g] | not serious | none | 28/205 (13.7%) | 43/197 (21.8%) | **RR 0.63** (0.41 to 0.97) | **81 fewer per 1,000** (from 129 fewer to 7 fewer) | ⨁⨁⨁◯ Moderate | CRITICAL |

**CI:** confidence interval; **OR:** odds ratio; **RR:** risk ratio

**Explanations**

a. Based on Agnelli 2003 - WODIT-PE study; PE rather than DVT History
b. adult population
c. 95% confidence interval contains both an effect and no effect
d. Based on Ferraj 2004 study
e. very low number of events
f. Based on Becattini 2012 study
g. not exactly 6 month time point
h. Based on Estepp 2012 (7% unprovoked)

**References**


1.Agnelli G, Prandoni P,Becattini C,Silingardi M,Taliani M,Miccio M,et al. Extended oral anticoagulant therapy after a first episode of pulmonary embolism. Ann Intern Med 2003. p. 19-25.
2.RS, Farraj. Anticoagulation period in idiopathic venous thromboembolism. How long is enough? Saudi Med J. 2004;25:848-51..
3.Becattini C, Agnelli G,Schenone A,Eichinger S,Bucherini E,Silingardi M,et al.. Aspirin for preventing the recurrence of venous thromboembolism. N Engl J Med. 2012;366:1959-67..
4.Estepp JH, Smeltzer M,Reiss UM. The impact of quality and duration of enoxaparin therapy on recurrent venous thrombosis in children. Pediatric Blood and Cancer. 2012;59:105-9..

**Author(s):**
**Question:** Anticoagulation compared to no anticoagulation in pediatric patients with cerebral sinus venous thrombosis
**Setting:** Inpatient
**Bibliography:**

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | anticoagulation | no anticoagulation | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality (assessed with: All-Cause Mortality)** | | | | | | | | | | | | |
| 4[1,2,3,4] | non-randomised studies | serious[a] | not serious | not serious | serious[b] | none | 5/366 (1.4%) | 9/82 (11.0%) | **RR 0.12** (0.04 to 0.36) | **97 fewer per 1,000** (from 105 fewer to 70 fewer) | ⨁⨁◯◯ Low | CRITICAL |
| **Mortality (follow-up: 3 months)** | | | | | | | | | | | | |
| 1[5] | non-randomised studies | serious[c] | not serious | not serious | serious[b] | none | 0/114 (0.0%) | - | - | - | ⨁◯◯◯ Very low | CRITICAL |
| **Neurological Outcome (assessed with: Neurological Deficit)** | | | | | | | | | | | | |
| 6[1,2,4,6,7,8] | non-randomised studies | serious[a] | not serious | not serious | very serious[d] | none | 119/371 (32.1%) | 31/91 (34.1%) | **RR 0.95** (0.69 to 1.30) | **17 fewer per 1,000** (from 106 fewer to 102 more) | ⨁◯◯◯ Very low | CRITICAL |
| **Neurological Outcome (follow-up: 3 months; assessed with: Neurological Deficit)** | | | | | | | | | | | | |
| 1[5] | non-randomised studies | serious[c] | not serious | not serious | serious[b] | none | 21/114 (18.4%) | - | - | - | ⨁◯◯◯ Very low | CRITICAL |
| **Resolution (assessed with: Complete and Partial Resolution)** | | | | | | | | | | | | |
| 7[1,3,4,6,7,9,10] | non-randomised studies | serious[a] | not serious | not serious | serious[e] | none | 64/79 (81.0%) | 38/71 (53.5%) | **RR 1.5** (1.2 to 1.9) | **268 more per 1,000** (from 107 more to 482 more) | ⨁⨁◯◯ Low | CRITICAL |
| **Recurrence** | | | | | | | | | | | | |
| 2[8,11] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 0/37 (0.0%) | 0/19 (0.0%) | not pooled | see comment | ⨁◯◯◯ Very low | CRITICAL |
| **Reccurence (follow-up: 3 months)** | | | | | | | | | | | | |
| 1[5] | non-randomised studies | serious[c] | not serious | not serious | very serious[b] | none | 1/114 (0.9%) | - | - | - | ⨁◯◯◯ Very low | CRITICAL |
| **Bleeding (assessed with: Unspecified)** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 5[1,6,7,9,12] | non-randomised studies | serious[a] | not serious | not serious | very serious[d] | none | 3/64 (4.7%) | 1/31 (3.2%) | **RR 1.90** (0.27 to 13.31) | **29 more per 1,000** (from 24 fewer to 397 more) | ⨁◯◯◯ Very low | CRITICAL |

**Bleeding (follow-up: 3 months; assessed with: MB and CRNMB)[f]**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[5] | non-randomised studies | serious[d] | not serious | not serious | serious[g] | none | 6/114 (5.3%) | - | - | - | ⨁◯◯◯ Very low | CRITICAL |

**CI:** confidence interval; **RR:** risk ratio

**Explanations**

a. Risk of bias, assessed using ROBINS-I, was judged to be serious due to selection bias.
b. Imprecision due to small number of included patients and patients with events in the included studies.
c. Single arm study, no comparative group.
d. Wide 95% confidence interval, ranging from effect to no effect
e. Imprecision due to small number of patients in the included studies.
f. 1 MB, 5 CRNMB
g. Small Number of Events

**References**


1.C, Karakas, Y, Hajiyev, HC, Skrehot, SF, Kralik, EM, Lambert, D, Pehlivan. Clinical Profile and Long-Term Outcomes in Pediatric Cavernous Sinus Thrombosis.. Pediatric neurology; 2022.
2.RJ, Felling, SMA, Hassanein, J, Armstrong, L, Aversa, L, Billinghurst, NA, Goldenberg, JE, Lee, EC, Maxwell, MJ, Noetzel, W, Lo. Treatment and outcome of childhood cerebral sinovenous thrombosis.. Neurology. Clinical practice; 2020.
3.MA, Aardoom, RCW, Klomberg, P, Kemos, FM, Ruemmele, CHH, van,Ommen, L, de,Ridder, NM, Croft, Group, PIBD-VTE, Consortium, PIBD-SETQuality. The Incidence and Characteristics of Venous Thromboembolisms in Paediatric-Onset . Journal of Crohn's & colitis; 2022.
4.Tenente, J., Lopes, S., Bem, P., Vila-Real, M., Ferreira, D., Geraldo, A.F., Santos, F.. Cerebral venous thrombosis in children an 18-year review of a Portuguese hospital. Neurología; 2022.
5.P, Connor, M, Sánchez,van,Kammen, AWA, Lensing, E, Chalmers, K, Kállay, K, Hege, P, Simioni, T, Biss, F, Bajolle, D, Bonnet, S, Grunt, R, Kumar, O, Lvova, R, Bhat, A, Van,Damme, J, Palumbo, A, Santamaria, P, Saracco, J, Payne, S, Baird, K, Godder, V, Labarque, C, Male, I, Martinelli, M, Morales,Soto, J, Motwani, S, Shah, HL, Hooimeijer, MH, Prins, D, Kubitza, WT, Smith, SD, Berkowitz, AF, Pap, M, Majumder, P, Monagle, JM, Coutinho. Safety and efficacy of rivaroxaban in pediatric cerebral venous thrombosis . Blood advances; 2020.
6.DB, Harrar, M, Goss, MT, Donofrio, J, Murnick, JG, Reitz, A, Zhang, Y, Diab, J, Meldau, P, Sinha, C, Yerebakan, JL, Carpenter. Cerebral Sinus Venous Thrombosis in Infants after Surgery for Congenital Heart . The Journal of pediatrics; 2022.
7.D, Petrov, MY, Uohara, R, Ichord, Z, Ali, L, Jastrzab, SS, Lang, L, Billinghurst. Pediatric cerebral sinovenous thrombosis following cranial surgery.. Child's nervous system : ChNS : official journal of the International Society for ; 2017.
8.S, Schneider, J, Kapelushnik, M, Kraus, S, El,Saied, I, Levi, DM, Kaplan. The association between otogenic lateral sinus thrombosis and thrombophilia - A . American journal of otolaryngology; 2018.
9.H, Roth, R, Ränsch, M, Kossorotoff, A, Chahine, O, Tirel, D, Brossier, I, Wroblewski, G, Orliaguet, S, Chabrier, G, Mortamet. Post traumatic cerebral sinovenous thrombosis in children: A retrospective and . European journal of paediatric neurology : EJPN : official journal of the ; 2023.
10.I, Herman, C, Karakas, TA, Webber, SF, Kralik, DS, Takacs, KS, Fisher, EA, Edmondson, JJ, Riviello, GD, Clark, D, Pehlivan. Clinical Profile and Long-Term Outcome in Neonatal Cerebral Sinus Venous . Pediatric neurology; 2021.
11.SG, Rodrigues, D, Vieira, F, Bernardo, J, Coelho, JA, Ribeiro, F, Palavra, C, Robalo, A, Levy, S, Quintas. Pediatric cerebral sinus venous thrombosis: clinical characterization of a . Acta neurologica Belgica; 2022.
12.MI, Engelhardt, N, Phan, H, Zavala, S, Chinnadurai, BB, Roby. Head and neck venous thrombosis secondary to pediatric otolaryngologic infection.. International journal of pediatric otorhinolaryngology; 2023.

**Author(s):**
**Question:** Thrombolysis followed by standard anticoagulation compared to anticoagulation alone in pediatric patients with cerebral sinus venous thrombosis
**Setting:** Inpatient
**Bibliography:** American Society of Hematology 2024 Guidelines for Management of Venous Thromboembolism: Treatment of Pediatric Venous Thromboembolism

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | thrombolysis followed by standard anticoagulation | anticoagulation alone | Relative (95% CI) | Absolute (95% CI) | | |
| **All-cause mortality (follow-up: mean 3.5 years)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 0/6 (0.0%) | 0/4 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Complete resolution of the thrombus (follow-up: mean 3.5 years; assessed with: imaging)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 6/6 (100.0%) | 3/4 (75.0%) | **RR 1.33** (0.72 to 2.44) | **248 more per 1,000** (from 210 fewer to 1,000 more) | ⨁◯◯◯ Very low | CRITICAL |
| **Resolution of the thrombus (follow-up: mean 3.5 years; assessed with: Complete and partial resolution )** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 6/6 (100.0%) | 4/4 (100.0%) | **RR 1.00** (0.70 to 1.43) | **0 fewer per 1,000** (from 300 fewer to 430 more) | ⨁◯◯◯ Very low | CRITICAL |
| **Thrombus recurrence (follow-up: mean 3.5 years)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 0/6 (0.0%) | 0/4 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |

**CI:** confidence interval; **RR:** risk ratio

**Explanations**

a. The risk of bias was assessed using ROBINs I. We downgraded for ROB selection bias and not adjusted for confounding
b. We downgraded twice for imprecision because of small sample size and small number of events

**References**

1.Rong L, Chen L,Dong Z,Zhuang H,Lin Z,Mo Y,Jiang X. .. Analysis of 10 Pediatric Nephrotic Syndrome Cases With Complications of Cerebral Sinovenous Thrombosis. Front Pediatr.; 2020 Dec 23.

# QUESTION

| Should thrombolysis followed by standard anticoagulation vs. anticoagulation alone be used for pediatric patients with cerebral sinus venous thrombosis? | |
|---|---|
| **POPULATION:** | pediatric patients with cerebral sinus venous thrombosis |
| **INTERVENTION:** | thrombolysis followed by standard anticoagulation |
| **COMPARISON:** | anticoagulation alone |
| **MAIN OUTCOMES:** | Mortality; Cerebral Venous Thrombosis – Severe; Major bleeding; Neurological sequelae. |
| **SETTING:** | Inpatient |
| **PERSPECTIVE:** | Clinical recommendation - population perspective |
| **BACKGROUND:** | Cerebral sinus venous thrombosis (CSVT) is a relatively rare yet critical condition affecting neonates and children with a wide-range clinical presentation, aetiology, and prognosis. It is usually diagnosed by imaging when venous blood flow is impaired or absent in one of the cerebral sinuses. (1) The condition has an incidence of 0.34 to 0.67/100,000 children per year while in neonates the incidence is reported at 40.7 per 100,000 live births per year. (1) (2, 3) Mortality can be in the range of 3% to 12% while neurological sequelae can affect up to 62% of survivors. (4)<br><br>There are many local (head and neck infections, cranial trauma or recent intracranial surgery) and systemic causes (i.e., perinatal disease, surgery, drugs toxicity, acute disease, dehydration, renal failure, nephrotic syndrome, neoplasm, hematological / prothrombotic disorders) of CSVT, and this varied aetiolgy makes the CSVT a difficult condition to detect initially. Better imaging in current practice detects parenchymal lesions in about 60% of the infants, and their location depends on the sinuses involved. (5) (6) |
| **CONFLICT OF INTEREST:** | **ASH conflict of interest declaration and management policies were applied, and the following panel members were voting panel members (determining the direction and strength of the recommendation):**<br>Paul Monagle<br>Sara Vesely<br>Manuela Bonduel<br>Leonardo Brandao<br>Sheila Hanson<br>Fiona Newall<br>John Wiernikowski |

| | |
|---|---|
| | Suzan Williams<br>Tammy Capman<br>Joerg Meerphol<br>Caitlin Augustine<br>Anthony KC Chan<br>Christoph Male<br>Sarah O'Brien<br>Heleen van Ommen<br>Leslie Raffini<br>**Panel members recused as a result of risk of conflicts of interest:**<br>None |

## ASSESSMENT

| **Problem**<br>Is the problem a priority? | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| | Original | |
| ○ No<br>○ Probably no<br>○ Probably yes<br>● Yes<br>○ Varies<br>○ Don't know | Thrombolysis or thrombolytic therapy (either with tPA, alteplase, urokinase) has theoretical advantages over anticoagulation in pediatric patients with CSVT, such as a more rapid resolution or re-canalization of the thrombus. However, there is a scarcity of randomized trials or observational comparative studies to be considered. It is usually reserved as a second line therapy reserved for severe or non-respondent cases. (7) | |
| | Adolopment | |
| ○ No<br>○ Probably no<br>○ Probably yes<br>● Yes<br>○ Varies | Thrombolysis or thrombolytic therapy (either with tPA, alteplase, urokinase) has theoretical advantages over anticoagulation in pediatric patients with CSVT, such as a more rapid resolution or re-canalization of the thrombus. However, there is a scarcity of randomized trials or observational comparative studies to be considered. It is usually reserved as a second line therapy reserved for severe or non- | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

| | | |
|---|---|---|
| ○ Don't know | respondent cases. (7) | |

## Desirable Effects

How substantial are the desirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

● Trivial
○ Small
○ Moderate
○ Large
○ Varies
○ Don't know

| Outcomes | № of participants (studies) Follow up | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects* (95% CI) | |
|---|---|---|---|---|---|
| | | | | Risk with anticoagulation alone | Risk difference with thrombolysis followed by standard anticoagulation |
| Mortality assessed with: overall mortality in neonates and children follow up: range 1 days to 3 years | 769 (7 observational studies) | ⨁◯◯◯ VERY LOW[a,b,c] | - | A total of 17 patients were included from 7 case series and reports. Three patients (17.6%) died. For the anticoagulation arm the risk of death is 15/752 (2%) deaths. | |
| Cerebral Venous Thrombosis – Severe assessed with: 'no re-canalization', thrombus progression, or 'no resolution' follow up: range 1 weeks to 3 years | 769 (7 observational studies) | ⨁◯◯◯ VERY LOW[a,b,c] | - | A total of 17 patients were included from 7 case series and reports. One patient (5.8%) had no resolution of the thrombosis. For the anticoagulation arm the risk is 20/462 (4.3%) | |

The panel considered that the effect of thrombolysis is trivial in patients with CSVT, although this could vary in different subgroups (i.e., those with hemorrhagic lesions)

| | | | | | | |
|---|---|---|---|---|---|---|
| Infant bleeding – Severe assessed with: any major bleeding in neonates and children follow up: range 1 days to 3 years | 769 (7 observational studies) | ⨁◯◯◯ VERY LOW[a,b,c] | - | A total of 17 patients were included from 7 case series and reports. Eight patients (47%) had a major bleeding. For the anticoagulation arm the risk is 12/515 (2.3%) | | |
| Mortality (Adult population) assessed with: overall mortality in adult populations follow up: range 1 weeks to 4 years | 205 (16 observational studies) | ⨁◯◯◯ VERY LOW[c,d,e] | not pooled | Study population | | |
| | | | | not pooled | not pooled | |
| Cerebral Venous Thrombosis – Severe (Adult population) assessed with: as no re-canalization, thrombus progression, no resolution, in adults follow up: range 1 weeks to 4 years | 205 (16 observational studies) | ⨁◯◯◯ VERY LOW[c,d,e] | not pooled | Study population | | |
| | | | | not pooled | not pooled | |
| Major bleeding (Adult population) assessed with: major bleeding in adult populations | 205 (16 observational studies) | ⨁◯◯◯ VERY LOW[c,d,e] | not pooled | Study population | | |
| | | | | not pooled | not pooled | |

| | | | | | |
|---|---|---|---|---|---|
| Neurological sequelae follow up: range 2 weeks to 3 months | 0 (7 observational studies) | ⨁◯◯◯ VERY LOW[a,b,c] | - | Of 17 patients with CSVT who underwent thrombolysis, 4 (23.5%) had neurological sequelae. | |

a. All pediatric studies are case series or case reports with no arms of comparison.
b. Some concerns on different aetiologies and age across the pediatric populations
c. Low number of events and participants. No confidence intervals are calculated.
d. Except for one study [Siddiqui 2014] all studies are case series with a single arm of study. All have high risk of bias due to confounding, selection of participants and loss to follow-up.
e. All studies include adult populations.

NOTE: For a complete assessment see the EVIDENCE PROFILE.

Adolopment

● Trivial
○ Small
○ Moderate
○ Large
○ Varies
○ Don't know

*See Appendix 1*

Add considerations made be the adoloping panel, including the justification for any change in judgment.

## Undesirable Effects

How substantial are the undesirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

● Large
○ Moderate
○ Small
○ Trivial
○ Varies
○ Don't know

| Outcomes | № of participants (studies) Follow up | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects* (95% CI) | |
|---|---|---|---|---|---|
| | | | | Risk with anticoagulation alone | Risk difference with thrombolysis followed by standard anticoagulation |
| Mortality assessed with: overall mortality in neonates and children follow up: range 1 days to 3 years | 769 (7 observational studies) | ⨁◯◯◯ VERY LOW[a,b,c] | - | A total of 17 patients were included from 7 case series and reports. Three patients (17.6%) died. For the anticoagulation arm the risk of death is 15/752 (2%) deaths. | |
| Cerebral Venous Thrombosis – Severe assessed with: 'no re-canalization', thrombus progression, or 'no resolution' follow up: range 1 weeks to 3 years | 769 (7 observational studies) | ⨁◯◯◯ VERY LOW[a,b,c] | - | A total of 17 patients were included from 7 case series and reports. One patient (5.8%) had no resolution of the thrombosis. For the anticoagulation arm the risk is 20/462 (4.3%) | |
| Infant bleeding – Severe assessed with: any major bleeding in neonates and children follow up: range 1 days to 3 years | 769 (7 observational studies) | ⨁◯◯◯ VERY LOW[a,b,c] | - | A total of 17 patients were included from 7 case series and reports. Eight patients (47%) had a major bleeding. For the anticoagulation arm the risk is 12/515 (2.3%) | |

Undesirable effects were considered large, mostly based on mortality and the major bleeding rate as compared to anticoagulation alone. Also, about use of tPA in CSVT when large ischemic infarctions are present.

| | | | | | |
|---|---|---|---|---|---|
| Mortality (Adult population) assessed with: overall mortality in adult populations follow up: range 1 weeks to 4 years | 205 (16 observational studies) | ⨁◯◯◯ VERY LOW[c,d,e] | not pooled | Study population | |
| | | | | not pooled | not pooled |
| Cerebral Venous Thrombosis – Severe (Adult population) assessed with: as no re-canalization, thrombus progression, no resolution, in adults follow up: range 1 weeks to 4 years | 205 (16 observational studies) | ⨁◯◯◯ VERY LOW[c,d,e] | not pooled | Study population | |
| | | | | not pooled | not pooled |
| Major bleeding (Adult population) assessed with: major bleeding in adult populations | 205 (16 observational studies) | ⨁◯◯◯ VERY LOW[c,d,e] | not pooled | Study population | |
| | | | | not pooled | not pooled |
| Neurological sequelae follow up: range 2 weeks to 3 months | 0 (7 observational studies) | ⨁◯◯◯ VERY LOW[a,b,c] | - | Of 17 patients with CSVT who underwent thrombolysis, 4 (23.5%) had neurological sequelae. | |

a. All pediatric studies are case series or case reports with no arms of comparison.
b. Some concerns on different aetiologies and age across the pediatric populations
c. Low number of events and participants. No confidence intervals are

| | | |
|---|---|---|
| | calculated.<br>d. Except for one study [Siddiqui 2014] all studies are case series with a single arm of study. All have high risk of bias due to confounding, selection of participants and loss to follow-up.<br>e. All studies include adult populations.<br><br>NOTE: For a complete assessment see the EVIDENCE PROFILE. | |
| | Adolopment | |
| ● Large<br>○ Moderate<br>○ Small<br>○ Trivial<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Certainty of evidence

What is the overall certainty of the evidence of effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | Certainty of the evidence of effects was judged as very low due to risk of bias (confounding, selection bias, loss to follow up). Also, other concerns were indirectness (indirect comparison and population), and imprecision due to low number of events and patients. | |
| | Adolopment | |

| | | |
|---|---|---|
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | Certainty of the evidence of effects was judged as very low due to risk of bias (confounding, selection bias) and due to imprecision (the evidence is based on one case series of 10 patients). | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Values

Is there important uncertainty about or variability in how much people value the main outcomes?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Important uncertainty or variability<br>○ Possibly important uncertainty or variability<br>● Probably no important uncertainty or variability<br>○ No important uncertainty or variability | **Utility related information:**<br><br>**The relative importance of outcomes:**<br><br>**Results from Panel Members' Utility Rating Survey**:<br><br>Utilities rated on the visual analog scale, where 0 represents death and 1 represents full health, were as follows.<br><br>Pulmonary embolism – Severe marker state: 0.31<br><br>Pulmonary embolism – Moderate marker state: 0.49<br><br>Deep vein thrombosis (proximal) – Severe marker state: 0.49<br><br>Deep vein thrombosis (proximal) – Moderate marker state: 0.61<br><br>Deep vein thrombosis (distal) – Severe marker state: 0.56<br><br>Deep vein thrombosis (distal) – Moderate marker state: 0.68<br><br>Major bleeding: 0.30<br><br>Neonatal Bleeding – Severe: 0.30<br><br>Infant Bleeding – Severe: 0.26<br><br>Cerebral venous thrombosis - Severe: 0.22<br><br>Cerebral venous thrombosis - Mild: 0.50 | Although some might consider differently the value of death versus neurologic disability, the panel noted that there would be no important uncertainty or variability on how patients and stakeholders value the outcomes. |

| | | |
|---|---|---|
| | Cognitive Impairment - Severe: 0.24<br><br>Cognitive Impairment - Mild: 0.46<br><br><br><br>**We did not identify utility related information or non-utility information for the outcomes of interest specific to the pediatric population in the literature.**<br><br>**<u>Additional information from the adult population:</u>**<br><br>**Our systematic review for the adult population found that the relative importance of the outcomes is as follows:**<br><br>Pulmonary embolism: 0.63-0.93 (different methods) (8, 9, 10)<br><br>Deep vein thrombosis: 0.64-0.99 (different methods) (8, 9, 10, 11, 12)<br><br>Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) (8, 9, 10)<br><br>Muscular bleeding: 0.76 (time trade off) (10)<br><br>Minor intracranial bleeding event: 0.75 (standard gamble) (9)<br><br>Major intracranial bleeding event: 0.15 (standard gamble) (9)<br><br>Central nervous system bleeding: 0.29-0.60 (standard gamble)(13, 14)<br><br>Treatment with LMWH: 0.993 (time trade off) (15)<br><br>Treatment with warfarin (as a surrogate): 0.989 (time trade off) (15) | |
| | Adolopment | |
| ○ Important uncertainty or variability<br>○ Possibly important uncertainty or variability<br>● Probably no important uncertainty or variability<br>○ No important uncertainty or variability | Utility related information: The relative importance of outcomes: Results from Panel Members' Utility Rating Survey: Utilities rated on the visual analog scale, where 0 represents death and 1 represents full health, were as follows. Pulmonary embolism – Severe marker state: 0.31 Pulmonary embolism – Moderate marker state: 0.49 Deep vein thrombosis (proximal) – Severe marker state: 0.49 Deep vein thrombosis (proximal) – Moderate marker state: 0.61 Deep vein thrombosis (distal) – Severe marker state: 0.56 Deep vein thrombosis (distal) – Moderate marker state: 0.68 Major bleeding: 0.30 Neonatal Bleeding – Severe: 0.30 Infant Bleeding – Severe: 0.26 Cerebral venous thrombosis - Severe: 0.22Cerebral venous thrombosis - Mild: 0.50Cognitive Impairment - Severe: 0.24Cognitive Impairment - Mild: 0.46We did not identify utility related information or non-utility information for the | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

| | | |
|---|---|---|
| | outcomes of interest specific to the pediatric population in the literature.Additional information from the adult population:Our systematic review for the adult population found that the relative importance of the outcomes is as follows: Pulmonary embolism: 0.63-0.93 (different methods) (8, 9, 10) Deep vein thrombosis: 0.64-0.99 (different methods) (8, 9, 10, 11, 12)Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) (8, 9, 10)Muscular bleeding: 0.76 (time trade off) (10) Minor intracranial bleeding event: 0.75 (standard gamble) (9) Major intracranial bleeding event: 0.15 (standard gamble) (9) Central nervous system bleeding: 0.29-0.60 (standard gamble)(13, 14) Treatment with LMWH: 0.993 (time trade off) (15) Treatment with warfarin (as a surrogate): 0.989 (time trade off) (15) | |

## Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Favors the comparison<br>● Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>○ Don't know | Probably favors the comparison (anticoagulation alone) | |
| | Adolopment | |
| ○ Favors the comparison<br>● Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Resources required

How large are the resource requirements (costs)?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ● Large costs<br>○ Moderate costs<br>○ Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br>○ Varies<br>○ Don't know | No research evidence was identified addressing directly the costs of thrombolytic therapy followed by anticoagulation as compared to anticoagulation alone in pediatric patients with CSVT.<br><br>**Additional information from adult population:**<br><br>In the adult population the cost of urokinase and equipment cost for the catheter directed thrombolysis is estimated to around $10,127 USD (16). In adult patients receiving stroke treatment, thrombolysis has been deemed as a cost-effective strategy, with direct cost of $2750 USD per dose. (17) However, the cost of thrombolytics might be different in treating children with CSVT.<br><br>For costs of anticoagulation in adult patients, the direct cost per week with warfarin in adults ranges from $3.54 to $11.44 USD while this number in Canada decreases to 0.49 to 0.84 CAD per week. (18, 19, 20, 21) With heparin, the costs per unit ranges from $0.18 per 10 units, to $0.212 per 1000 units (22) with a Cost per week: $37.00 USD and $11.14 CAD per day in Canada. (19, 21) LMWH (enoxaparin) cost varies. The wholesale cost in the low and middle income economies is about $13 to $75 USD per week. (23) In the United States the wholesale cost is about $98.91 USD per day as of 2016 (24) | The panel noted that the cost of thrombolysis drugs (e.g. tPA), and associated monitoring, labs, imaging leads to this judgment. |
| | Adolopment | |
| ● Large costs<br>○ Moderate costs<br>○ Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br>○ Varies<br>○ Don't know | No research evidence was identified addressing directly the costs of thrombolytic therapy followed by anticoagulation as compared to anticoagulation alone in pediatric patients with CSVT. Additional information from adult population: In the adult population the cost of urokinase and equipment cost for the catheter directed thrombolysis is estimated to around $10,127 USD (16). In adult patients receiving stroke treatment, thrombolysis has been deemed as a cost-effective strategy, with direct cost of $2750 USD per dose. (17) However, the cost of thrombolytics might be different in treating children with CSVT. For costs of anticoagulation in adult patients, the direct cost per week with warfarin in adults ranges from $3.54 to $11.44 USD while this number in Canada decreases to 0.49 to 0.84 CAD per week. (18, 19, 20, 21) With heparin, the costs per unit ranges from $0.18 per 10 units, to $0.212 per 1000 units (22) with a Cost per week: $37.00 USD and $11.14 CAD per day in Canada. (19, 21) LMWH (enoxaparin) cost varies. The wholesale cost in the | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

| | | |
|---|---|---|
| | low and middle income economies is about $13 to $75 USD per week. (23) In the United States the wholesale cost is about $98.91 USD per day as of 2016 (24) | |

## Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | No research identified. | |
| | Adolopment | |

| | | |
|---|---|---|
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | No research identified. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ● Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>○ No included studies | No research evidence was identified for cost-effectiveness in pediatric patients.<br><br>Only information from adult patients undergoing stroke treatment is available, where thrombolysis has been deemed as a cost-effective strategy, with direct cost of $2750 USD per dose.(17) However the cost and effectiveness of thrombolytics might differ in children with CSVT. | |
| | Adolopment | |
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>● No included studies | No research evidence was identified for cost-effectiveness in pediatric patients.<br>Only information from adult patients undergoing stroke treatment is available, where thrombolysis has been deemed as a cost-effective strategy, with direct cost of $2750 USD per dose.(17) However the cost and effectiveness of thrombolytics might differ in children with CSVT. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Equity

What would be the impact on health equity?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Reduced<br>● Probably reduced<br>○ Probably no impact<br>○ Probably increased<br>○ Increased<br>○ Varies<br>○ Don't know | No research evidence was identified. | |
| | Adolopment | |
| ○ Reduced<br>● Probably reduced<br>○ Probably no impact<br>○ Probably increased<br>○ Increased<br>○ Varies<br>○ Don't know | No research evidence was identified. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Acceptability

Is the intervention acceptable to key stakeholders?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ No<br>● Probably no<br>○ Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | A survey study suggests the following regarding acceptability and barriers associated with the intervention:One survey of American Society of Pediatric Hematology/Oncology members demonstrates the wide variation in treatment approaches between practitioners, in this case with respect to thrombolytic therapy of pediatric VTE. With respect to the preferred agent, the survey results confirm that tPA has become the thrombolytic drug of choice in pediatric patients, although a small percentage of respondents stated a preference for others, such as urokinase. In contrast, responses varied widely regarding the preferred mode of tPA delivery (systemic vs. catheter-directed vs. use of catheter-directed therapy on a salvage basis) without clear majority preference for any single modality. Since the overwhelming majority of respondents (95%) reported having access to pediatric | Probably not acceptable to all key stakeholders.<br><br>However, it is important to consider variations such as the presence of hemorrhage, or the use of catheter directed thrombolysis, and the size of the clot. The evidence, nonetheless, is scarce, even from the adult population. |

| | | |
|---|---|---|
| | interventional radiology services, preferences for a given mode of tPA administration clearly could not be ascribed to IR availability and were not associated with any of the other queried professional demographic data (25). | |
| | Adolopment | |
| ○ No<br>● Probably no<br>○ Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | A survey study suggests the following regarding acceptability and barriers associated with the intervention:One survey of American Society of Pediatric Hematology/Oncology members demonstrates the wide variation in treatment approaches between practitioners, in this case with respect to thrombolytic therapy of pediatric VTE. With respect to the preferred agent, the survey results confirm that tPA has become the thrombolytic drug of choice in pediatric patients, although a small percentage of respondents stated a preference for others, such as urokinase. In contrast, responses varied widely regarding the preferred mode of tPA delivery (systemic vs. catheter-directed vs. use of catheter-directed therapy on a salvage basis) without clear majority preference for any single modality. Since the overwhelming majority of respondents (95%) reported having access to pediatric interventional radiology services, preferences for a given mode of tPA administration clearly could not be ascribed to IR availability and were not associated with any of the other queried professional demographic data (25). | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Feasibility

Is the intervention feasible to implement?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br>● Varies<br>○ Don't know | No research evidence was identified. | It varies considering the availability of interventional radiology in setting, of thrombolytic drugs, and availability of 24 hr intensive care support and neuro imaging team. |
| | Adolopment | |
| ○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br>● Varies | No research evidence was identified. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

| | | |
|---|---|---|
| ○ Don't know | | |

## SUMMARY OF JUDGEMENTS

| CRITERIA | ORIGINAL | IMPORTANCE FOR DECISION | ADOLOPMENT | IMPORTANCE FOR DECISION |
|---|---|---|---|---|
| **PROBLEM** | Yes | | Yes | |
| **DESIRABLE EFFECTS** | Trivial | | Trivial | |
| **UNDESIRABLE EFFECTS** | Large | | Large | |
| **CERTAINTY OF EVIDENCE** | Very low | | Very low | |
| **VALUES** | Probably no important uncertainty or variability | | Probably no important uncertainty or variability | |
| **BALANCE OF EFFECTS** | Probably favors the comparison | | Probably favors the comparison | |
| **RESOURCES REQUIRED** | Large costs | | Large costs | |
| **CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES** | Very low | | Very low | |
| **COST EFFECTIVENESS** | Favors the comparison | | No included studies | |
| **EQUITY** | Probably reduced | | Probably reduced | |
| **ACCEPTABILITY** | Probably no | | Probably no | |
| **FEASIBILITY** | Varies | | Varies | |



## TYPE OF RECOMMENDATION

Original

| | | | | |
|---|---|---|---|---|
| Strong recommendation against the | **Conditional recommendation against the** | Conditional recommendation for either the | Conditional recommendation for the | Strong recommendation for the |

| | | | | |
|---|---|---|---|---|
| intervention<br>○ | **intervention**<br>● | intervention or the comparison<br>○ | intervention<br>○ | intervention<br>○ |

Adolopment

| | | | | |
|---|---|---|---|---|
| Strong recommendation against the intervention<br>○ | **Conditional recommendation against the intervention**<br>● | Conditional recommendation for either the intervention or the comparison<br>○ | Conditional recommendation for the intervention<br>○ | Strong recommendation for the intervention<br>○ |

## CONCLUSIONS

Original

**Recommendation**

**The ASH guideline panel suggests against using thrombolysis followed by standard anticoagulation, and rather use anticoagulation alone, in pediatric patients with cerebral sinus venous thrombosis (conditional recommendation based on very low certainty in the evidence about effects).**

**Justification**

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

Adolopment

**Recommendation**

**The ASH/ISTH guideline panel suggests using anticoagulation rather than thrombolysis followed by anticoagulation in pediatric patients with cerebral sinus venous thrombosis (conditional recommendation based on very low certainty in the evidence about effects).**

**Justification**

## Subgroup considerations

Original

Based on the panel collective experience, for children with CSVT without evidence of ischemia there is no rationale for using thrombolysis.

Insufficient data to support specific subgroups who would benefit from the intervention.

Adolopment

## Implementation considerations

Original

--

Adolopment

## Monitoring and evaluation

Original

--

Adolopment

## Research priorities

Original

More research from randomized or non-randomized studies assessing the effect of thrombolysis in children with CSVT.

Adolopment

# REFERENCES SUMMARY


1. Carducci, C, Colafati, GS, Figà-Talamanca, L, Longo, D, Lunardi, T, Randisi, F, Bernardi, B. Cerebral sinovenous thrombosis (CSVT) in children: what the pediatric radiologists need to know. Radiol Med; 2016.
2. Hedlund, G. L.. Cerebral sinovenous thrombosis in pediatric practice. Pediatr Radiol; Jan 2013.
3. deVeber, G., Andrew, M., Adams, C., Bjornson, B., Booth, F., Buckley, D. J., Camfield, C. S., David, M., Humphreys, P., Langevin, P., MacDonald, E. A., Gillett, J., Meaney, B., Shevell, M., Sinclair, D. B., Yager, J., Canadian Pediatric Ischemic Stroke Study, Group. Cerebral sinovenous thrombosis in children. N Engl J Med; Aug 09 2001.
4. Ichord, R.N., Benedict, S.L., Chan, A.K., Kirkham, FJ, Nowak-Gottl, U. Paediatric cerebral sinovenous thrombosis: findings of the International Paediatric Stroke Study. Arch Dis Child; 2015.
5. Fitzgerald, KC, Williams, L, Garg, BP, Carvalho, KS, Golomb, MR. Cerebral sinovenous thrombosis in the neonate. Arch Neurol; 2006.
6. van der Aa, N. E., Benders, M. J., Groenendaal, F., de Vries, L. S.. Neonatal stroke: a review of the current evidence on epidemiology, pathogenesis, diagnostics and therapeutic options. Acta Paediatr; Apr 2014.
7. Mallick, AA, Sharples, PM, Calvert, SE, Jones, RW, Leary, M, Lux, AL. Cerebral venous sinus thrombosis: a case series including thrombolysis. Arch Dis Child; 2009.
8. Hogg, K., Shaw, J., Coyle, D., Fallah, P., Carrier, M., Wells, P.. Validity of standard gamble estimated quality of life in acute venous thrombosis. Thromb Res; Oct 2014.
9. Hogg, K., Kimpton, M., Carrier, M., Coyle, D., Forgie, M., Wells, P.. Estimating quality of life in acute venous thrombosis. JAMA Intern Med; Jun 24 2013.
10. Locadia, M., Bossuyt, P. M., Stalmeier, P. F., Sprangers, M. A., van Dongen, C. J., Middeldorp, S., Bank, I., van der Meer, J., Hamulyak, K., Prins, M. H.. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. Thromb Haemost; Dec 2004.
11. Marvig, C. L., Verhoef, T. I., de Boer, A., Kamali, F., Redekop, K., Pirmohamed, M., Daly, A. K., Manolopoulos, V. G., Wadelius, M., Bouvy, M., Maitland-van der Zee, A. H., consortium, Eu-Pact. Quality of life in patients with venous thromboembolism and atrial fibrillation treated with coumarin anticoagulants. Thromb Res; Jul 2015.
12. Utne, K. K., Tavoly, M., Wik, H. S., Jelsness-Jorgensen, L. P., Holst, R., Sandset, P. M., Ghanima, W.. Health-related quality of life after deep vein thrombosis. Springerplus; 2016.
13. Lenert, L. A., Soetikno, R. M.. Automated computer interviews to elicit utilities: potential applications in the treatment of deep venous thrombosis. J Am Med Inform Assoc; Jan-Feb 1997.
14. O'Meara, J. J.,3rd, McNutt, R. A., Evans, A. T., Moore, S. W., Downs, S. M.. A decision analysis of streptokinase plus heparin as compared with heparin alone for deep-vein thrombosis. N Engl J Med; Jun 30 1994.
15. Marchetti, M., Pistorio, A., Barone, M., Serafini, S., Barosi, G.. Low-molecular-weight heparin versus warfarin for secondary prophylaxis of venous thromboembolism: a cost-effectiveness analysis. Am J Med; Aug 2001.
16. Karthikesalingam A, Young EL,Hinchliffe RJ,Loftus IM,Thompson MM,Holt PJ. A systematic review of percutaneous mechanical thrombectomy in the treatment of deep venous thrombosis. Eur J Vasc Endovasc Surg; 2011.
17. Kazley AS, Simpson KN,Simpson A,Jauch E,Adams RJ. Optimizing the Economic Impact of rtPA Use in a Stroke Belt State: The Case of South Carolina. Am Health Drug Benefits; 2013.
18. Biskupiak, J., Ghate, S. R., Jiao, T., Brixner, D.. Cost implications of formulary decisions on oral anticoagulants in nonvalvular atrial fibrillation. J Manag Care Pharm; Nov-Dec 2013.
19. Klarenbach, S., Lee, K., Boucher, M., So, H., Manns, B., Tonelli, M.. Direct Oral Anticoagulants for the Treatment of Venous Thromboembolic Events: Economic Evaluation. 2016.
20. Kearon C, Akl E. Duration of anticoagulant therapy for deep vein thrombosis and pulmonary embolism. Blood; 2014.
21. Guanella, R., Ducruet, T., Johri, M., Miron, M. J., Roussin, A., Desmarais, S., Joyal, F., Kassis, J., Solymoss, S., Ginsberg, J. S., Lamping, D. L., Shrier, I., Kahn, S. R.. Economic burden and cost determinants of deep vein thrombosis during 2 years following diagnosis: a prospective evaluation. J Thromb Haemost; Dec 2011.
22. Medicare, . 2017 ASP Drug Pricing files. available in: www.cms.gov/apps/physician-fee-schedule/overview.aspx [last accessed March 2018]; 2017.
23. IMPPG, . International Medical Products Price Guide. [Internet]; 2016.
24. NADAC, . National Average Drug Acquisition Cost. Available in: https://data.medicaid.gov/Drug-Pricing-and-Payment/NADAC-National-Average-Drug-Acquisition-Cost-/a4y5-998d [last accessed: March 2018]; 2017.
25. Yee DL, Chan AK,Williams S,Goldenberg NA,Massicotte MP,Raffini LJ. Varied opinions on thrombolysis for venous thromboembolism in infants and children: findings from a survey of pediatric hematology-oncology specialists. Pediatr Blood Cancer; 2009.

# APPENDICES

Appendix 1

**Author(s):**
**Question:** Thrombolysis followed by standard anticoagulation compared to anticoagulation alone in pediatric patients with cerebral sinus venous thrombosis
**Setting:** Inpatient
**Bibliography:** American Society of Hematology 2024 Guidelines for Management of Venous Thromboembolism: Treatment of Pediatric Venous Thromboembolism

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | thrombolysis followed by standard anticoagulation | anticoagulation alone | Relative (95% CI) | Absolute (95% CI) | | |
| **All-cause mortality (follow-up: mean 3.5 years)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 0/6 (0.0%) | 0/4 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Complete resolution of the thrombus (follow-up: mean 3.5 years; assessed with: imaging)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 6/6 (100.0%) | 3/4 (75.0%) | **RR 1.33** (0.72 to 2.44) | **248 more per 1,000** (from 210 fewer to 1,000 more) | ⨁◯◯◯ Very low | CRITICAL |
| **Resolution of the thrombus (follow-up: mean 3.5 years; assessed with: Complete and partial resolution )** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 6/6 (100.0%) | 4/4 (100.0%) | **RR 1.00** (0.70 to 1.43) | **0 fewer per 1,000** (from 300 fewer to 430 more) | ⨁◯◯◯ Very low | CRITICAL |
| **Thrombus recurrence (follow-up: mean 3.5 years)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 0/6 (0.0%) | 0/4 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |

**CI:** confidence interval; **RR:** risk ratio

**Explanations**

a. The risk of bias was assessed using ROBINs I. We downgraded for ROB selection bias and not adjusted for confounding
b. We downgraded twice for imprecision because of small sample size and small number of events

**References**

1.Rong L, Chen L,Dong Z,Zhuang H,Lin Z,Mo Y,Jiang X. .. Analysis of 10 Pediatric Nephrotic Syndrome Cases With Complications of Cerebral Sinovenous Thrombosis. Front Pediatr.; 2020 Dec 23.

**Author(s):**
**Question:** Anticoagulation compared to no anticoagulation in neonates and pediatric patients with right atrial thrombosis
**Setting:** Inpatient
**Bibliography:** American Society of Hematology 2024 Guidelines for Management of Venous Thromboembolism: Treatment of Pediatric Venous Thromboembolism

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | anticoagulation | no anticoagulation | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality (assessed with: All-Cause Mortality)** | | | | | | | | | | | | |
| 2[1,2] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 9/31 (29.0%) [c] | 0/4 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Resolution (Complete or Partial Resolution) [de]** | | | | | | | | | | | | |
| 3[1,2,3] | non-randomised studies | serious[a] | not serious | not serious | very serious[f] | none | 32/42 (76.2%) [g] | 23/25 (92.0%) [h] | **RR 0.83** (0.67 to 1.01) | **156 fewer per 1,000** (from 304 fewer to 9 more) | ⨁◯◯◯ Very low | IMPORTANT |
| **Recurrence** | | | | | | | | | | | | |
| 2[1,3] | non-randomised studies | serious[a] | not serious | not serious | very serious[f] | none | 1/16 (6.3%) | 1/25 (4.0%) | **RR 1.56** (0.10 to 23.24) | **22 more per 1,000** (from 36 fewer to 890 more) | ⨁◯◯◯ Very low | CRITICAL |
| **Extension (follow-up: median 40 days)** | | | | | | | | | | | | |
| 1[3] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 3/14 (21.4%) | 5/28 (17.9%) | **RR 1.20** (0.33 to 4.31) | **36 more per 1,000** (from 120 fewer to 591 more) | ⨁◯◯◯ Very low | CRITICAL |
| **Bleeding (assessed with: (Unspecified))** | | | | | | | | | | | | |
| 3[1,2,3] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 7/46 (15.2%) | 0/27 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Major Bleeding** | | | | | | | | | | | | |
| 2[1,3] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 3/41 (7.3%) | 0/25 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Clinically Relevant Non-Major Bleed** | | | | | | | | | | | | |
| 1[3] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 0/15 (0.0%) | 0/23 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |

**CI:** confidence interval; **RR:** risk ratio

**Explanations**

a. Risk of bias, assessed using ROBINS-I, was judged to be serious due to selection bias without adjusting for confounding.
b. Imprecision due to small number of included patients and patients with events in the included studies.
c. 2 Therapy-Related Deaths, 0 Thrombus-Related Deaths
d. Van Ommen 2023 mean follow-up time was 40 days
e. Agarwal 2023 median follow-up time was 46 days
f. Wide 95% confidence interval, ranging from positive effect to negative effect
g. 13 out of 37 had complete resolution, 15 out of 37 had partial resolution
h. 11 out of 23 had complete resolution, 10 out of 23 had partial resolution

**References**

1.Agarwal, . Intracardiac Thrombosis in Pediatrics: Anticoagulation Approach and Treatment Outcomes. 2023.
2.M, Garcia-Nicoletti, MD, Sinha, A, Savis, S, Adalat, N, Karunanithy, F, Calder. Silent and dangerous: catheter-associated right atrial thrombus (CRAT) in children on chronic haemodialysis.. Pediatric nephrology (Berlin, Germany); 2021.
3.CH, van,Ommen, KA, Bergman, M, Boerma, HA, Bouma, AE, Donker, M, Gouvernante, CV, Hulzebos, D, Khandour, R, Knol, MA, Raets, KD, Liem, RA, van,Lingen, M, van,de,Loo, E, Lopriore, M, van,der,Putten, JJ, Sol, MH, Suijker, DC, Vijlbrief, R, Visser, MM, van,Weissenbruch. NEOnatal Central-venous Line Observational study on Thrombosis (NEOCLOT): . Journal of thrombosis and haemostasis : JTH; 2023.

**Author(s):**
**Question:** Thrombolysis followed by standard anticoagulation compared to anticoagulation alone in neonates and pediatric patients with right atrial thrombosis
**Setting:** Inpatient
**Bibliography:** American Society of Hematology 2024 Guidelines for Management of Venous Thromboembolism: Treatment of Pediatric Venous Thromboembolism

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | thrombolysis followed by standard anticoagulation | anticoagulation alone | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality** | | | | | | | | | | | | |
| 2[1,2] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 2/11 (18.2%) | 1/13 (7.7%) | **RR 1.14** (0.15 to 8.99) | **11 more per 1,000** (from 65 fewer to 615 more) | ⨁◯◯◯ Very low | CRITICAL |
| **Resolution (assessed with: Complete or Partial Resolution)** | | | | | | | | | | | | |
| 3[1,2,3] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 16/17 (94.1%) [c] | 25/27 (92.6%) [d] | **RR 1.02** (0.87 to 1.19) | **19 more per 1,000** (from 120 fewer to 176 more) | ⨁◯◯◯ Very low | CRITICAL |
| **Recurrence** | | | | | | | | | | | | |
| 1[3] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 0/6 (0.0%) | 0/14 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Bleeding (assessed with: Unspecified)** | | | | | | | | | | | | |
| 2[1,3] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 3/10 (30.0%) | 1/23 (4.3%) | **RR 4.53** (0.67 to 30.87) | **153 more per 1,000** (from 14 fewer to 1,000 more) | ⨁◯◯◯ Very low | CRITICAL |
| **Major Bleed** | | | | | | | | | | | | |
| 1[3] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 1/6 (16.7%) | 1/14 (7.1%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Clinically Relevant Non-major Bleed** | | | | | | | | | | | | |
| 1[3] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 0/6 (0.0%) | 0/14 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |

**CI:** confidence interval; **RR:** risk ratio

**Explanations**

a. Risk of bias, assessed using ROBINS-I, was judged to be serious due to selection bias without adjustment for confounders.

b. Imprecision due to small number of included patients and patients with events in the included studies.
c. 13 out of 17 had complete resolution while 3 had partial resolution
d. 14 out of 27 had complete resolution while 11 out of 27 had partial resolution

**References**

1.I, Odaman,Al, Y, Oymak, M, Erdem, N, Tahta, S, Okur,Acar, T, Mese, MM, Yilmazer, S, Gözmen, C, Zihni, S, Calkavur, TH, Karapinar. Assessment of clinical characteristics and treatment outcomes of pediatric . Blood coagulation & fibrinolysis : an international journal in haemostasis and ; 2022.
2.M, Kara, M, Güler, Z, Keskin,Yildirim, K, Tekgunduz, F, Laloglu, N, Ceviz. Clinical features and treatment results in preterm infants with intracardiac . The journal of maternal-fetal & neonatal medicine : the official journal of the ; 2021.
3.CH, van,Ommen, KA, Bergman, M, Boerma, HA, Bouma, AE, Donker, M, Gouvernante, CV, Hulzebos, D, Khandour, R, Knol, MA, Raets, KD, Liem, RA, van,Lingen, M, van,de,Loo, E, Lopriore, M, van,der,Putten, JJ, Sol, MH, Suijker, DC, Vijlbrief, R, Visser, MM, van,Weissenbruch. NEOnatal Central-venous Line Observational study on Thrombosis (NEOCLOT): . Journal of thrombosis and haemostasis : JTH; 2023.

## QUESTION

| Should anticoagulation vs. no anticoagulation be used for neonates and pediatric patients with right atrial thrombosis? | |
|---|---|
| **POPULATION:** | neonates and pediatric patients with right atrial thrombosis |
| **INTERVENTION:** | anticoagulation |
| **COMPARISON:** | no anticoagulation |
| **MAIN OUTCOMES:** | Death; Pulmonary embolism - Severe; Major Bleeding; Heparin Induced Thrombocytopenia. |
| **SETTING:** | Inpatient |
| **PERSPECTIVE:** | Clinical recommendation - Population perspective |
| **BACKGROUND:** | Intracardiac thrombus are being recognized more frequently due to increase awareness and more common use of echocardiographic evaluations in high risk patients (i.e., critically ill neonates and infants). (1) Right atrial thrombosis is a relatively common complication of indwelling central venous catheters in infants and children (2) with approximately 90% being related to central venous lines. High-risk features on echocardiogram are large size, more than 2 cm in any dimension, pedunculated, mobile, or snake-shaped, and mobile. |
| **CONFLICT OF INTEREST:** | |

## ASSESSMENT

| **Problem**<br>Is the problem a priority? | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| | Original | |
| ○ No<br>○ Probably no<br>○ Probably yes<br>● Yes<br>○ Varies<br>○ Don't know | Intracardiac thrombus are being recognized more frequently due to increase awareness and more common use of echocardiographic evaluations in high risk patients (i.e., critically ill neonates and infants). (1). Specific treatment and recommendations are based mostly on indirect evidence from observational data. | |
| | Adolopment | |
| ○ No<br>○ Probably no | Intracardiac thrombus are being recognized more frequently due to increase awareness and more common use of echocardiographic evaluations in high risk | Add considerations made be the adoloping panel, including the justification for any change in |

| | | |
|---|---|---|
| ○ Probably yes<br>● Yes<br>○ Varies<br>○ Don't know | patients (i.e., critically ill neonates and infants). (1). Specific treatment and recommendations are based mostly on indirect evidence from observational data. | judgment. |

## Desirable Effects

How substantial are the desirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

○ Trivial
● Small
○ Moderate
○ Large
○ Varies
○ Don't know

| Outcomes | № of participants (studies) Follow up | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects* (95% CI) | |
|---|---|---|---|---|---|
| | | | | Risk with no anticoagulation | Risk difference with anticoagulation |
| Death<br>assessed with: all-cause mortality | 71<br>(28 observational studies)[a] | ⨁◯◯◯<br>VERY LOW[b,c] | - | There were 30 patients exposed to anticoagulation and 41 to observation alone or observation plus catheter removal in 28 studies. In the anticoagulation group 2/30 (6.7%) patients died (all deemed not to be VTE related) vs 4/41 (9.8%) in the control group (VTE related). | |
| Pulmonary embolism - Severe<br>assessed with: as pulmonary embolism by imaging<br>follow up: range 7 days to 6 weeks | 66<br>(28 observational studies) | ⨁◯◯◯<br>VERY LOW[b,c] | - | There were zero events out of 25 in the anticoagulation group vs 4/41 (9.7%) in the observation group. | |
| Major Bleeding<br>assessed with: clinical evaluation<br>follow up: range 1 weeks to 12 weeks | 71<br>(28 observational studies) | ⨁◯◯◯<br>VERY LOW[b,c] | - | No reported events of major bleedings in any group of study. | |

The panel considered that desirable anticipated effects would be small, although no deaths related to VTE were present in the evidence available.

| | | | | | | |
|---|---|---|---|---|---|---|
| Heparin Induced Thrombocytopenia - not reported[d] | - | - | - | - | - | |

a. A systematic review (Yang 2010) identified 25 reports of pediatric patients with right atrial thrombosis. An update for this review yielded another 3 studies. [Bronzetti 2009, Cetin 2014, Choi 2010] Overall, 30 patients were exposed to anticoagulation while 41 to observation or observation plus catheter removal
b. All studies are case series or case reports without any adjustment for confounders.
c. There were altogether 71 patients in all studies reported.
d. Two observational studies reported the risk of HIT varies for pediatric patients. The risk is estimated to be close to 0% in children receiving standard heparin or LMWH. The risk of HIT is 2.3% (14/612) in children receiving heparin in the PICU.

NOTE: For a complete set of outcomes see the EVIDENCE PROFILE.

**Additional information about undesirable effects:**

Bleeding risk in patients with VTE treated with LMWH is reported at 3% for major bleeding and 23.4% for minor bleedings in one review (Nowak-Gottl et al., 2008) while another with enoxaparin in newborns report major bleeding in 13 of 240 (5%) treated neonates. (Malowany et al., 2008)

Bleeding risks with UFH has a comparable risk of bleeding complications to LMWH. (McCrory et al., 2011) One cohort study reports major bleeding of 1.5% in children treated with UFH for VTE (DVT and PE) (Andrew et al., 1994) although this number is higher (24%) in ICU treated patients. (Kuhle et al., 2007)

VKAs have a bleeding incidence rate of 0.5% per patient-year (Streif et al., 1999)



| | | |
|---|---|---|
| | Adolopment | |
| ○ Trivial<br>● Small<br>○ Moderate<br>○ Large<br>○ Varies | *See Appendix 2* | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

| | | |
|---|---|---|
| ○ Don't know | | |

## Undesirable Effects

How substantial are the undesirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

○ Large
○ Moderate
○ Small
● Trivial
○ Varies
○ Don't know

Undesirable effects are considered trivial by panel members.

| Outcomes | № of participants (studies) Follow up | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects* (95% CI) | |
|---|---|---|---|---|---|
| | | | | Risk with no anticoagulation | Risk difference with anticoagulation |
| Death<br>assessed with: all-cause mortality | 71<br>(28 observational studies)[a] | ⨁◯◯◯<br>VERY LOW[b,c] | - | There were 30 patients exposed to anticoagulation and 41 to observation alone or observation plus catheter removal in 28 studies. In the anticoagulation group 2/30 (6.7%) patients died (all deemed not to be VTE related) vs 4/41 (9.8%) in the control group (VTE related). | |
| Pulmonary embolism - Severe<br>assessed with: as pulmonary embolism by imaging<br>follow up: range 7 days to 6 weeks | 66<br>(28 observational studies) | ⨁◯◯◯<br>VERY LOW[b,c] | - | There were zero events out of 25 in the anticoagulation group vs 4/41 (9.7%) in the observation group. | |
| Major Bleeding<br>assessed with: clinical evaluation<br>follow up: range 1 weeks to 12 weeks | 71<br>(28 observational studies) | ⨁◯◯◯<br>VERY LOW[b,c] | - | No reported events of major bleedings in any group of study. | |
| Heparin Induced Thrombocytopenia | - | - | - | - | - |

| | | | | | | |
|---|---|---|---|---|---|---|
| - not reported[d] | | | | | | |

a. A systematic review (Yang 2010) identified 25 reports of pediatric patients with right atrial thrombosis. An update for this review yielded another 3 studies. [Bronzetti 2009, Cetin 2014, Choi 2010] Overall, 30 patients were exposed to anticoagulation while 41 to observation or observation plus catheter removal
b. All studies are case series or case reports without any adjustment for confounders.
c. There were altogether 71 patients in all studies reported.
d. Two observational studies reported the risk of HIT varies for pediatric patients. The risk is estimated to be close to 0% in children receiving standard heparin or LMWH. The risk of HIT is 2.3% (14/612) in children receiving heparin in the PICU.

NOTE: For a complete set of outcomes see the EVIDENCE PROFILE.

**Additional information about undesirable effects:**

Bleeding risk in patients with VTE treated with LMWH is reported at 3% for major bleeding and 23.4% for minor bleedings in one review (Nowak-Gottl et al., 2008) while another with enoxaparin in newborns report major bleeding in 13 of 240 (5%) treated neonates. (Malowany et al., 2008)

Bleeding risks with UFH has a comparable risk of bleeding complications to LMWH. (McCrory et al., 2011) One cohort study reports major bleeding of 1.5% in children treated with UFH for VTE (DVT and PE) (Andrew et al., 1994) although this number is higher (24%) in ICU treated patients. (Kuhle et al., 2007)

VKAs have a bleeding incidence rate of 0.5% per patient-year (Streif et al., 1999)

Adolopment

| | | |
|---|---|---|
| ○ Large<br>○ Moderate<br>● Small<br>○ Trivial<br>○ Varies<br>○ Don't know | *See Appendix 1* | Discussion between moderate to small. |

## Certainty of evidence

What is the overall certainty of the evidence of effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | Certainty of the evidence of effects was judged as 'very low'. All evidence consisted of case reports and case studies that were considered at high risk of bias. | |
| | Adolopment | |
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | Certainty of the evidence of effects was judged as 'very low' due to impression and high risk of bias | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Values

Is there important uncertainty about or variability in how much people value the main outcomes?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Important uncertainty or variability<br>○ Possibly important uncertainty or variability<br>● Probably no important uncertainty or variability<br>○ No important uncertainty or variability | **<u>Utility related information:</u>**<br><br>**The relative importance of outcomes:**<br><br>**<u>Results from Panel Members' Utility Rating Survey</u>**:<br><br>Utilities rated on the visual analog scale, where 0 represents death and 1 represents full health, were as follows.<br><br>Pulmonary embolism – Severe marker state: 0.31<br><br>Pulmonary embolism – Moderate marker state: 0.49<br><br>Deep vein thrombosis (proximal) – Severe marker state: 0.49<br><br>Deep vein thrombosis (proximal) – Moderate marker state: 0.61<br><br>Deep vein thrombosis (distal) – Severe marker state: 0.56<br><br>Deep vein thrombosis (distal) – Moderate marker state: 0.68<br><br>Major bleeding: 0.30<br><br>Neonatal Bleeding – Severe: 0.30<br><br>Infant Bleeding – Severe: 0.26<br><br>Heparin-induced thrombocytopenia: 0.59<br><br>**We did not identify utility related information or non-utility information for the outcomes of interest specific to the pediatric population in the literature.**<br><br>**<u>Additional information from the adult population:</u>**<br><br>**Our systematic review for the adult population found that the relative importance of the outcomes is as follows:**<br><br>Pulmonary embolism: 0.63-0.93 (different methods) (Hogg et al., 2014, Hogg et al., 2013, Locadia et al., 2004)<br><br>Deep vein thrombosis: 0.64-0.99 (different methods) (Hogg et al., 2014, Hogg et al., 2013, Locadia et al., 2004, Marvig et al., 2015, Utne et al., 2016) | Considerations must be taken on whether mortality would be valued consistently in certain specific cases, for example, in a neonate with complex medical condition requiring a central line. |

Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off)(Hogg et al., 2013, Locadia et al., 2004)

Muscular bleeding: 0.76 (time trade off)(Locadia et al., 2004)

Minor intracranial bleeding event: 0.75 (standard gamble) (Hogg et al., 2013)

Major intracranial bleeding event: 0.15 (standard gamble)(Hogg et al., 2013)

Central nervous system bleeding: 0.29-0.60 (standard gamble)(Lenert et al., 1997, O'Meara et al., 1994)

Treatment with LMWH: 0.993 (time trade off) (Marchetti et al., 2001)

Treatment with warfarin (as a surrogate): 0.989 (time trade off) (Marchetti et al., 2001)

**We also identified in the systematic review the following non-utility information from the adult population:**

**Anticoagulant therapy**

Adult patients highly value the benefits of risk reduction in VTE recurrence and post-thrombosis syndrome (Locadia et al., 2004). Patients would favor efficacy and safety over convenience of route of administration (Noble et al., 2015). Further, patients would like to avoid adverse events but most of them are "not afraid of" the adverse events (Barcellona et al., 2000, Noble et al., 2015, O'Meara et al., 1994). For anticoagulant therapy in general, most patients would prefer the oral doses compared with injections, this is mainly because of treatment burden due to injection (Barcellona et al., 2000, Noble et al., 2015). For patients with venographically proven deep venous thrombosis, 15 of the 19 patients expressed a preference for the subcutaneous route for administration of heparin over intravenous administration (Robinson et al., 1993).

**Warfarin**

Adult patients would like to switch to another anticoagulant if it is as effective as warfarin; this is mainly due to the treatment burden associated with monitoring, injection and dietary change due to warfarin use (Attaya et al., 2012). In another study approximately half of the patients did not consider VKA therapy particularly difficult to manage (Wild et al., 2009).

**LMWH**

For adult patients receiving low molecular weight heparin, patients placed a high score on "importance of ease of use", "expectations of symptom relief", and "confidence in the treatment to prevent blood clots" while they had a low score of

| | | |
|---|---|---|
| | treatment-related side effects (bruise, bleeding). (Baba et al., 2015) (Cajfinger et al., 2016). | |
| | Adolopment | |
| ○ Important uncertainty or variability<br>○ Possibly important uncertainty or variability<br>● Probably no important uncertainty or variability<br>○ No important uncertainty or variability | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>● Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>○ Don't know | | Balance could be impacted based on individual cases with different risks and clinical presentations (e.g., size and mobility of cloth, patient's characteristics, etc.) |
| | Adolopment | |
| ○ Favors the comparison<br>○ Probably favors the comparison<br>● Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Central Line --- Favors no anticoagulation<br><br>Data on cause of death<br><br>**Discussion regarding does not favor versus varies**<br><br>Use the literature to look at definitions for high risk versus low risk |

## Resources required

How large are the resource requirements (costs)?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Large costs<br>● Moderate costs<br>○ Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br>○ Varies<br>○ Don't know | No research evidence was identified for the resource requirements for anticoagulation for right atrial or intra-cardiac thromboses.<br><br>Two studies reported the costs of disease from pediatric patients with any VTE. One reported for 834 pediatric patients with VTE a median annual expenditure of $25,258 and $24,934 USD in Medicaid and private insurance patients respectively.(Boulet et al., 2012) Another study found that patients with VTE had an increased 8.1 inpatient days and excess average costs of $27,686 USD. (Goudie et al., 2015) | All children will present with VTE in hospital, and costs of anticoagulation as treatment will be added. Costs for management of pediatric VTE patients without anticoagulation is not available from the research evidence. |
| | Adolopment | |
| ○ Large costs<br>● Moderate costs<br>○ Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

| | | |
|---|---|---|
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | No research evidence was identified. | |
| | Adolopment | |
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

| | | |
|---|---|---|
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>● Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>○ No included studies | No research evidence was identified. | |
| | Adolopment | |
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>● Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>○ No included studies | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Equity

What would be the impact on health equity?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Reduced<br>○ Probably reduced<br>● Probably no impact<br>○ Probably increased<br>○ Increased<br>○ Varies<br>○ Don't know | No research evidence was identified. | |
| | Adolopment | |
| ○ Reduced<br>○ Probably reduced<br>● Probably no impact | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in |

| | | |
|---|---|---|
| ○ Probably increased<br>○ Increased<br>○ Varies<br>○ Don't know | | judgment. |

## Acceptability

Is the intervention acceptable to key stakeholders?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ No<br>○ Probably no<br>● Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | A prospective patient-safety and quality improvement project performed at a large pediatric tertiary care hospital. A patient-care policy was developed to assess VTE risk and prescribe the appropriate thromboprophylaxis regimen. The primary outcome measure was compliance with thromboprophylaxis guidelines in patients at risk for VTE. Over the 4-year study period, the observed rate of VTE prophylaxis in patients at risk increased from a baseline of 22% to an average rate of 82%, and there were intermittent improvements up to 100%. Despite the fact that the risk of VTE in hospitalized children is much lower than that in adults, there are patients in pediatric hospitals who deserve systematic screening and thoughtful application of preventative measures. (Raffini et al., 2011)<br><br>A UK survey has identified nonconformity of approach in terms of the timing of CVAD insertion in relation to induction therapy. Almost half of UK centers defer CVAD insertion until after completion of induction therapy due to concerns that the risk of thrombosis during induction therapy, as a result of administration of 2 doses of asparaginase during induction, may be increased by early CVAD placement. (Biss et al., 2016)<br><br>Heparin prophylaxis (HP) is commonly used for prevention of central venous catheter (CVC)-related complications among pediatric intensivists, yet efficacy of this therapy is unknown. A survey was conducted on pediatric intensivists and their experiences with HP in USA. A total of 96 responses were received. Almost half of the respondents regularly used HP in patients with CVCs, yet most were unsure of its benefit. The majority of respondents claimed to experience no adverse effects; the complications that were reported to occur were related to bleeding or suspected heparin-induced thrombocytopenia (HIT). Overall, participants felt CVC-associated HP was safe in pediatric critical illness, while acknowledging the paucity | Intervention would probably be accepatable to all key stakeholders. |

| | | |
|---|---|---|
| | of compelling data. (Clarke et al., 2011) | |
| | Adolopment | |
| ○ No<br>○ Probably no<br>● Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Feasibility

Is the intervention feasible to implement?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ No<br>○ Probably no<br>● Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | No research evidence was identified. | Consideration about treatment extending past hospital discharge. |
| | Adolopment | |
| ○ No<br>○ Probably no<br>○ Probably yes<br>● Yes<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## SUMMARY OF JUDGEMENTS

| CRITERIA | ORIGINAL | IMPORTANCE FOR DECISION | ADOLOPMENT | IMPORTANCE FOR DECISION |
|---|---|---|---|---|
| PROBLEM | Yes | | Yes | |

| CRITERIA | ORIGINAL | IMPORTANCE FOR DECISION | ADOLOPMENT | IMPORTANCE FOR DECISION |
|---|---|---|---|---|
| DESIRABLE EFFECTS | Small | | Small | |
| UNDESIRABLE EFFECTS | Trivial | | Small | |
| CERTAINTY OF EVIDENCE | Very low | | Very low | |
| VALUES | Probably no important uncertainty or variability | | Probably no important uncertainty or variability | |
| BALANCE OF EFFECTS | Probably favors the intervention | | Does not favor either the intervention or the comparison | |
| RESOURCES REQUIRED | Moderate costs | | Moderate costs | |
| CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES | Very low | | Very low | |
| COST EFFECTIVENESS | Probably favors the intervention | | Probably favors the intervention | |
| EQUITY | Probably no impact | | Probably no impact | |
| ACCEPTABILITY | Probably yes | | Probably yes | |
| FEASIBILITY | Probably yes | | Yes | |

## TYPE OF RECOMMENDATION

Original

| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | **Conditional recommendation for the intervention** | Strong recommendation for the intervention |
|---|---|---|---|---|
| ○ | ○ | ○ | ● | ○ |

Adolopment

| Strong recommendation against the intervention | Conditional recommendation against the intervention | **Conditional recommendation for either the intervention or the comparison** | Conditional recommendation for the intervention | Strong recommendation for the intervention |
|---|---|---|---|---|
| ○ | ○ | ● | ○ | ○ |

# CONCLUSIONS

Original

## Recommendation

**The ASH guideline panel suggests using anticoagulation rather than no anticoagulation in pediatric patients with right atrial thrombosis (conditional recommendation based on very low certainty in the evidence about effects).**

## Justification

The panel was unable to distinguish between symptomatic and asymptomatic VTE in this instance because many right atrial thromboses are discovered during routine imaging, especially in cardiac surgical patients. Factors such as size and mobility of the thrombus, patient's hemodynamic status, and bleeding risk are important considerations but there is insufficient data to define specific subgroup effects.

Adolopment

## Recommendation

**Recommendation a.** In neonates and pediatric patients with right atrial thrombosis (RAT) with high-risk features and low perceived risk of bleeding, the ASH/ISTH Guideline Panel *suggests* anticoagulation over no anticoagulation (conditional recommendation based on very low certainty in the evidence about effects

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

## Justification

## Subgroup considerations

Factors such as size and mobility of the clot, patient's hemodynamic status, and bleeding risks are important considerations but there is insufficient data to define specific subgroup's effect.

## Implementation considerations

## Monitoring and evaluation

## Research priorities

## REFERENCES SUMMARY

1. Cetin, II, Ekici, F, Unal, S, Kocabas, A, Sahin, S, Yazici, MU. Intracardiac thrombus in children: the fine equilibrium between the risk and the benefit. Pediatr Hematol Oncol; 2014.
2. Yang, JY, Williams, S, Brandao, LR, Chan, AK. Neonatal and childhood right atrial thrombosis: recognition and a risk-stratified treatment approach. Blood Coagul Fibrinolysis; 2010.

# APPENDICES

Appendix 1

**Author(s):**
**Question:** Anticoagulation compared to no anticoagulation in neonates and pediatric patients with right atrial thrombosis
**Setting:** Inpatient
**Bibliography:** American Society of Hematology 2024 Guidelines for Management of Venous Thromboembolism: Treatment of Pediatric Venous Thromboembolism

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | anticoagulation | no anticoagulation | Relative (95% CI) | Absolute (95% CI) | | |
| **Bleeding (assessed with: (Unspecified))** | | | | | | | | | | | | |
| 3[1,2,3] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 7/46 (15.2%) | 0/27 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Major Bleeding** | | | | | | | | | | | | |
| 2[1,3] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 3/41 (7.3%) | 0/25 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Clinically Relevant Non-Major Bleed** | | | | | | | | | | | | |
| 1[3] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 0/15 (0.0%) | 0/23 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |

**CI:** confidence interval; **RR:** risk ratio

**Explanations**

a. Risk of bias, assessed using ROBINS-I, was judged to be serious due to selection bias without adjusting for confounding.
b. Imprecision due to small number of included patients and patients with events in the included studies.

**References**


1.Agarwal, . Intracardiac Thrombosis in Pediatrics: Anticoagulation Approach and Treatment Outcomes. 2023.
2.M, García-Nicoletti, MD, Sinha, A, Savis, S, Adalat, N, Karunanithy, F, Calder. Silent and dangerous: catheter-associated right atrial thrombus (CRAT) in children on chronic haemodialysis.. Pediatric nephrology (Berlin, Germany); 2021.
3.CH, van,Ommen, KA, Bergman, M, Boerma, HA, Bouma, AE, Donker, M, Gouvernante, CV, Hulzebos, D, Khandour, R, Knol, MA, Raets, KD, Liem, RA, van,Lingen, M, van,de,Loo, E, Lopriore, M, van,der,Putten, JJ, Sol, MH, Suijker, DC, Vijlbrief, R, Visser, MM, van,Weissenbruch. NEOnatal Central-venous Line Observational study on Thrombosis (NEOCLOT): . Journal of thrombosis and haemostasis : JTH; 2023.

Appendix 2

**Author(s):**
**Question:** Anticoagulation compared to no anticoagulation in neonates and pediatric patients with right atrial thrombosis
**Setting:** Inpatient
**Bibliography:** American Society of Hematology 2024 Guidelines for Management of Venous Thromboembolism: Treatment of Pediatric Venous Thromboembolism

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | anticoagulation | no anticoagulation | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality (assessed with: All-Cause Mortality)** | | | | | | | | | | | | |
| 2[1,2] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 9/31 (29.0%) [c] | 0/4 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Resolution (Complete or Partial Resolution) [de]** | | | | | | | | | | | | |
| 3[1,2,3] | non-randomised studies | serious[a] | not serious | not serious | very serious[f] | none | 32/42 (76.2%) [g] | 23/25 (92.0%) [h] | **RR 0.83** (0.67 to 1.01) | **156 fewer per 1,000** (from 304 fewer to 9 more) | ⨁◯◯◯ Very low | IMPORTANT |
| **Recurrence** | | | | | | | | | | | | |
| 2[1,3] | non-randomised studies | serious[a] | not serious | not serious | very serious[f] | none | 1/16 (6.3%) | 1/25 (4.0%) | **RR 1.56** (0.10 to 23.24) | **22 more per 1,000** (from 36 fewer to 890 more) | ⨁◯◯◯ Very low | CRITICAL |
| **Extension (follow-up: median 40 days)** | | | | | | | | | | | | |
| 1[3] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 3/14 (21.4%) | 5/28 (17.9%) | **RR 1.20** (0.33 to 4.31) | **36 more per 1,000** (from 120 fewer to 591 more) | ⨁◯◯◯ Very low | CRITICAL |

**CI:** confidence interval; **RR:** risk ratio

**Explanations**

a. Risk of bias, assessed using ROBINS-I, was judged to be serious due to selection bias without adjusting for confounding.
b. Imprecision due to small number of included patients and patients with events in the included studies.
c. 2 Therapy-Related Deaths, 0 Thrombus-Related Deaths
d. Van Ommen 2023 mean follow-up time was 40 days
e. Agarwal 2023 median follow-up time was 46 days
f. Wide 95% confidence interval, ranging from positive effect to negative effect
g. 13 out of 37 had complete resolution, 15 out of 37 had partial resolution
h. 11 out of 23 had complete resolution, 10 out of 23 had partial resolution

**References**

1.Agarwal, . Intracardiac Thrombosis in Pediatrics: Anticoagulation Approach and Treatment Outcomes. 2023.
2.M, Garcia-Nicoletti, MD, Sinha, A, Savis, S, Adalat, N, Karunanithy, F, Calder. Silent and dangerous: catheter-associated right atrial thrombus (CRAT) in children on chronic haemodialysis.. Pediatric nephrology (Berlin, Germany); 2021.
3.CH, van,Ommen, KA, Bergman, M, Boerma, HA, Bouma, AE, Donker, M, Gouvernante, CV, Hulzebos, D, Khandour, R, Knol, MA, Raets, KD, Liem, RA, van,Lingen, M, van,de,Loo, E, Lopriore, M, van,der,Putten,

JJ, Sol, MH, Suijker, DC, Vijlbrief, R, Visser, MM, van,Weissenbruch. NEOnatal Central-venous Line Observational study on Thrombosis (NEOCLOT): . Journal of thrombosis and haemostasis : JTH; 2023.

## QUESTION

| Should thrombolysis followed by standard anticoagulation vs. anticoagulation alone be used for neonates and pediatric patients with right atrial thrombosis? | |
|---|---|
| **POPULATION:** | neonates and pediatric patients with right atrial thrombosis |
| **INTERVENTION:** | thrombolysis followed by standard anticoagulation |
| **COMPARISON:** | anticoagulation alone |
| **MAIN OUTCOMES:** | Death; Pulmonary embolism - Severe; Neonatal bleeding - Severe; Heparin Induced Thrombocytopenia |
| **SETTING:** | Inpatient |
| **PERSPECTIVE:** | Clinical recommendation - Population perspective |
| **BACKGROUND:** | Intracardiac thrombus are being recognized more frequently due to increase awareness and more common use of echocardiographic evaluations in high risk patients (i.e., critically ill neonates and infants).(1) Right atrial thrombosis is a relatively common complication of indwelling central venous catheters in infants and children(2) with approximately 90% being related to central venous lines. High-risk features on echocardiogram are large size, more than 2 cm in any dimension, pedunculated, mobile, or snake-shaped, and mobile. |
| **CONFLICT OF INTEREST:** | |

## ASSESSMENT

**Problem**
Is the problem a priority?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ No<br>○ Probably no<br>○ Probably yes<br>● Yes<br>○ Varies<br>○ Don't know | Intracardiac thrombus are being recognized more frequently due to increase awareness and more common use of echocardiographic evaluations in high risk patients (i.e., critically ill neonates and infants). Specific treatment and recommendations are based mostly on indirect evidence from observational data. | |
| | Adolopment | |
| ○ No | Example:'no additional research evidence, local or global considered': or 'additional | Add considerations made be the adoloping panel, |

| | | |
|---|---|---|
| ○ Probably no<br>○ Probably yes<br>● Yes<br>○ Varies<br>○ Don't know | local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | including the justification for any change in judgment. |

## Desirable Effects

How substantial are the desirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

● Trivial
○ Small
○ Moderate
○ Large
○ Varies
○ Don't know

| Outcomes | № of participants (studies) Follow up | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects* (95% CI) | |
|---|---|---|---|---|---|
| | | | | Risk with anticoagulation alone | Risk difference with thrombolysis or surgical thrombectomy followed by standard anticoagulation |
| Death<br>assessed with: all-cause mortality<br>follow up: range 1 weeks to 12 weeks | 99 (28 observational studies)[a] | ⨁◯◯◯ VERY LOW[b,c] | - | 10/65 (15.4%) died in the thrombolysis (4 patients) or thrombectomy (6 patients); while 2/30 (6.7%) died amongst those exposed to anticoagulation alone. | |
| Pulmonary embolism - Severe<br>assessed with: as pulmonary embolism by imaging or no resolution of thrombus<br>follow up: range 1 weeks to 6 weeks | 99 (28 observational studies) | ⨁◯◯◯ VERY LOW[b,c] | - | There were 13/69 (18.8%) reported cases of pulmonary embolism in the thrombolysis group vs 0/30 in the anticoagulation group. | |

The panel noted that there would be trivial desirable effects from thrombectomy.

| | | | | | |
|---|---|---|---|---|---|
| Neonatal bleeding - Severe assessed with: any major bleeding follow up: range 1 weeks to 10 weeks | 99 (28 observational studies) | ⨁◯◯◯ VERY LOW[b,c] | - | There were 8/69 (11.59%) reported events of major bleeding in the thrombolysis group, and no reported events of major bleeding in the anticoagulation group. | |
| Heparin Induced Thrombocytopenia - not reported[d] | - | - | - | - | - |

a. A systematic review (Yang 2010) identified 25 reports of pediatric patients with right atrial thrombosis. An update for this review yielded another 3 studies. [Cetin 2014, Choi 2010, Alvarez 2015] On these, 65 patients were exposed to thrombolysis or surgical thrombectomy while 30 to anticoagulation alone.
b. All studies are either case reports or case series.
c. There were few events and cases reported.
d. Two observational studies reported the risk of HIT varies for pediatric patients. The risk is estimated to be close to 0% in children receiving standard heparin or LMWH. The risk of HIT is 2.3% (14/612) in children receiving heparin in the PICU.

NOTE: For a complete assessment, please see the EVIDENCE PROFILE

Adolopment

| | | |
|---|---|---|
| ● Trivial<br>○ Small<br>○ Moderate<br>○ Large<br>○ Varies<br>○ Don't know | *See Appendix 2* | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Undesirable Effects

## How substantial are the undesirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

○ Large
● Moderate
○ Small
○ Trivial
○ Varies
○ Don't know

| Outcomes | № of participants (studies) Follow up | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects* (95% CI) | |
|---|---|---|---|---|---|
| | | | | Risk with anticoagulation alone | Risk difference with thrombolysis or surgical thrombectomy followed by standard anticoagulation |
| Death<br>assessed with: all-cause mortality<br>follow up: range 1 weeks to 12 weeks | 99<br>(28 observational studies)[a] | ⨁◯◯◯<br>VERY LOW[b,c] | - | 10/65 (15.4%) died in the thrombolysis (4 patients) or thrombectomy (6 patients); while 2/30 (6.7%) died amongst those exposed to anticoagulation alone. | |
| Pulmonary embolism - Severe<br>assessed with: as pulmonary embolism by imaging or no resolution of thrombus<br>follow up: range 1 weeks to 6 weeks | 99<br>(28 observational studies) | ⨁◯◯◯<br>VERY LOW[b,c] | - | There were 13/69 (18.8%) reported cases of pulmonary embolism in the thrombolysis group vs 0/30 in the anticoagulation group. | |
| Neonatal bleeding - Severe<br>assessed with: any major bleeding<br>follow up: range 1 weeks to 10 weeks | 99<br>(28 observational studies) | ⨁◯◯◯<br>VERY LOW[b,c] | - | There were 8/69 (11.59%) reported events of major bleeding in the thrombolysis group, and no reported events of major bleeding in the anticoagulation group. | |

Although more patients in the thrombolysis/thrombectomy group had undesirable consequences (death, PE, bleeding), this could be due to higher risk patients being selected to the intervention arm. For example, sicker patients with larger, mobile thrombi may be more likely to receive thrombolysis.

| | | | | | | |
|---|---|---|---|---|---|---|
| Heparin Induced Thrombocytopenia - not reported[d] | - | - | - | - | - | |

a. A systematic review (Yang 2010) identified 25 reports of pediatric patients with right atrial thrombosis. An update for this review yielded another 3 studies. [Cetin 2014, Choi 2010, Alvarez 2015] On these, 65 patients were exposed to thrombolysis or surgical thrombectomy while 30 to anticoagulation alone.
b. All studies are either case reports or case series.
c. There were few events and cases reported.
d. Two observational studies reported the risk of HIT varies for pediatric patients. The risk is estimated to be close to 0% in children receiving standard heparin or LMWH. The risk of HIT is 2.3% (14/612) in children receiving heparin in the PICU.

NOTE: For a complete assessment, please see the EVIDENCE PROFILE

Adolopment

| | | |
|---|---|---|
| ○ Large<br>● Moderate<br>○ Small<br>○ Trivial<br>○ Varies<br>○ Don't know | *See Appendix 1* | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Certainty of evidence

What is the overall certainty of the evidence of effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|

| | | |
|---|---|---|
| | Original | |
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | Certainty of the evidence of effects was judged as 'very low'. All evidence consists of case reports and case studies that are considered at high risk of bias. | |
| | Adolopment | |
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | Certainty of the evidence of effects was judged as 'very low' due to risk of bias and imprecision. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Values

Is there important uncertainty about or variability in how much people value the main outcomes?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Important uncertainty or variability<br>○ Possibly important uncertainty or variability<br>● Probably no important uncertainty or variability<br>○ No important uncertainty or variability | **Utility related information:**<br><br>**The relative importance of outcomes:**<br><br>**Results from Panel Members' Utility Rating Survey**:<br><br>Utilities rated on the visual analog scale, where 0 represents death and 1 represents full health, were as follows. | Some co-morbidities in premature population may influence the value placed on mortality. |

| | | |
|---|---|---|
| | Pulmonary embolism – Severe marker state: 0.31<br><br>Pulmonary embolism – Moderate marker state: 0.49<br><br>Deep vein thrombosis (proximal) – Severe marker state: 0.49<br><br>Deep vein thrombosis (proximal) – Moderate marker state: 0.61<br><br>Deep vein thrombosis (distal) – Severe marker state: 0.56<br><br>Deep vein thrombosis (distal) – Moderate marker state: 0.68<br><br>Major bleeding: 0.30<br><br>Neonatal Bleeding – Severe: 0.30<br><br>Infant Bleeding – Severe: 0.26<br><br>Heparin-induced thrombocytopenia: 0.59<br><br>**We did not identify utility related information or non-utility information for the outcomes of interest specific to the pediatric population in the literature.**<br><br>**<u>Additional information from the adult population:</u>**<br><br>**Our systematic review for the adult population found that the relative importance of the outcomes is as follows:**<br><br>Pulmonary embolism: 0.63-0.93 (different methods)(Hogg et al., 2014, Hogg et al., 2013, Locadia et al., 2004)<br><br>Deep vein thrombosis: 0.64-0.99 (different methods) (Hogg et al., 2014, Hogg et al., 2013, Locadia et al., 2004, Marvig et al., 2015, Utne et al., 2016)<br><br>Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) (Hogg et al., 2013, Locadia et al., 2004)<br><br>Muscular bleeding: 0.76 (time trade off) (Locadia et al., 2004)<br><br>Minor intracranial bleeding event: 0.75 (standard gamble) (Hogg et al., 2013)<br><br>Major intracranial bleeding event: 0.15 (standard gamble)(Hogg et al., 2013)<br><br>Central nervous system bleeding: 0.29-0.60 (standard gamble) (Lenert et al., 1997, O'Meara et al., 1994) | |

| | | |
|---|---|---|
| | Adolopment | |
| ○ Important uncertainty or variability<br>○ Possibly important uncertainty or variability<br>● Probably no important uncertainty or variability<br>○ No important uncertainty or variability | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Favors the comparison<br>● Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>○ Don't know | | The panel noted that the balance between desirable and undesirable effects probably favor the standard anticoagulation. |
| | Adolopment | |
| ○ Favors the comparison<br>● Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Resources required

How large are the resource requirements (costs)?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ● Large costs<br>○ Moderate costs<br>○ Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br>○ Varies<br>○ Don't know | No research evidence was identified for thrombolysis as compared to surgical thrombectomy for treatment of right atrial or intra-cardiac thromboses.<br><br>**Additional information from adult population on thrombolysis:** In the adult population the cost of urokinase and equipment cost for the catheter directed thrombolysis is estimated to around $10,127 USD (Karthikesalingam A, 2011) In adult patients receiving stroke treatment, thrombolysis has been deemed as a cost-effective strategy, with direct cost of $2750 USD per dose. (Kazley AS, 2013)<br><br>However, the cost of thrombolytics might differ in children with right atrial or intra-cardiac thromboses. No research evidence was identified for cost of surgical thrombectomy. | The cost of thrombolysis, including monitoring and administration may be significant, as well as the cost of surgical thrombectomy. |
| | Adolopment | |
| ● Large costs<br>○ Moderate costs<br>○ Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

| | | |
|---|---|---|
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | No research on costs found on right atrial or intracardiac thromboses although some from indirect evidence. (see above) | |
| | Adolopment | |
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

| | | |
|---|---|---|
| ○ Favors the comparison<br>● Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>○ No included studies | No research evidence was identified for cost-effectiveness. | |
| | Adolopment | |
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>● No included studies | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Equity

What would be the impact on health equity?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Reduced<br>● Probably reduced<br>○ Probably no impact<br>○ Probably increased<br>○ Increased<br>○ Varies<br>○ Don't know | No research evidence was identified. | Although more patients in the thrombolysis/thrombectomy group had undesirable consequences (death, PE, bleeding), this could be due to higher risk patients being selected to the intervention arm. For example,, sicker patients with larger, mobile thrombi may be more likely to receive thrombolysis. |
| | Adolopment | |
| ○ Reduced<br>● Probably reduced | Example:'no additional research evidence, local or global considered': or 'additional | Add considerations made be the adoloping panel, including the justification for any change in |

| | | |
|---|---|---|
| ○ Probably no impact<br>○ Probably increased<br>○ Increased<br>○ Varies<br>○ Don't know | local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | judgment. |

## Acceptability

Is the intervention acceptable to key stakeholders?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ No<br>○ Probably no<br>● Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | A prospective patient-safety and quality improvement project performed at a large pediatric tertiary care hospital. A patient-care policy was developed to assess VTE risk and prescribe the appropriate thromboprophylaxis regimen. The primary outcome measure was compliance with thromboprophylaxis guidelines in patients at risk for VTE. Over the 4-year study period, the observed rate of VTE prophylaxis in patients at risk increased from a baseline of 22% to an average rate of 82%, and there were intermittent improvements up to 100%. Despite the fact that the risk of VTE in hospitalized children is much lower than that in adults, there are patients in pediatric hospitals who deserve systematic screening and thoughtful application of preventative measures (Raffini et al., 2011).<br><br>A UK survey has identified nonconformity of approach in terms of the timing of CVAD insertion in relation to induction therapy. Almost half of UK centers defer CVAD insertion until after completion of induction therapy due to concerns that the risk of thrombosis during induction therapy, as a result of administration of 2 doses of asparaginase during induction, may be increased by early CVAD placement (Biss et al., 2016).<br><br>Heparin prophylaxis (HP) is commonly used for prevention of central venous catheter (CVC)-related complications among pediatric intensivists, yet efficacy of this therapy is unknown. A survey was conducted on pediatric intensivists and their experiences with HP in USA. A total of 96 responses were received. Almost half of the respondents regularly used HP in patients with CVCs, yet most were unsure of its benefit. The majority of respondents claimed to experience no adverse effects; the complications that were reported to occur were related to bleeding or suspected heparin-induced thrombocytopenia (HIT). Overall, participants felt CVC-associated HP was safe in pediatric critical illness, while acknowledging the paucity of compelling data(Clarke et al., 2011).<br><br>One survey of American Society of Pediatric Hematology/Oncology members demonstrates the wide variation in treatment approaches between practitioners, in | Acceptability may vary depending on the 'aggressiveness' of the interventions. |

| | | |
|---|---|---|
| | this case with respect to thrombolytic therapy of pediatric VTE. No clear consensus prevails as to indication, mode of drug delivery, dose regimen or maximum duration of therapy. With respect to the preferred agent, the survey results confirm that tPA has become the thrombolytic drug of choice in pediatric patients, although a small percentage of respondents stated a preference for others, such as urokinase. In contrast, responses varied widely regarding the preferred mode of tPA delivery (systemic vs. catheter-directed vs. use of catheter-directed therapy on a salvage basis) without clear majority preference for any single modality. Since the overwhelming majority of respondents (95%) reported having access to pediatric interventional radiology services, preferences for a given mode of tPA administration clearly could not be ascribed to IR availability and were not associated with any of the other queried professional demographic data(Yee DL, 2009). | |
| | Adolopment | |
| ○ No<br>○ Probably no<br>● Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |
| **Feasibility**<br>Is the intervention feasible to implement? | | |
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| | Original | |
| ○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br>● Varies<br>○ Don't know | No research evidence was identified. | |
| | Adolopment | |
| ○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

| | | |
|---|---|---|
| ● Varies<br>○ Don't know | | |

## SUMMARY OF JUDGEMENTS

| CRITERIA | ORIGINAL | IMPORTANCE FOR DECISION | ADOLOPMENT | IMPORTANCE FOR DECISION |
|---|---|---|---|---|
| PROBLEM | Yes | | Yes | |
| DESIRABLE EFFECTS | Trivial | | Trivial | |
| UNDESIRABLE EFFECTS | Moderate | | Moderate | |
| CERTAINTY OF EVIDENCE | Very low | | Very low | |
| VALUES | Probably no important uncertainty or variability | | Probably no important uncertainty or variability | |
| BALANCE OF EFFECTS | Probably favors the comparison | | Probably favors the comparison | |
| RESOURCES REQUIRED | Large costs | | Large costs | |
| CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES | Very low | | Very low | |
| COST EFFECTIVENESS | Probably favors the comparison | | No included studies | |
| EQUITY | Probably reduced | | Probably reduced | |
| ACCEPTABILITY | Probably yes | | Probably yes | |
| FEASIBILITY | Varies | | Varies | |



## TYPE OF RECOMMENDATION

Original

| Strong recommendation against the intervention | **Conditional recommendation against the intervention** | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | Strong recommendation for the intervention |
|---|---|---|---|---|
| ○ | ● | ○ | ○ | ○ |

Adolopment

| Strong recommendation against the intervention | **Conditional recommendation against the intervention** | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | Strong recommendation for the intervention |
|---|---|---|---|---|
| ○ | ● | ○ | ○ | ○ |

## CONCLUSIONS

Original

**Recommendation**

**The ASH guideline panel suggests against using thrombolysis or surgical thrombectomy followed by standard anticoagulation, and rather use anticoagulation alone in pediatric patients with right atrial thrombosis (conditional recommendation based on very low certainty in the evidence about effects).**

**Justification**

In most cases anticoagulation alone is adequate, however there will be individual cases in which the haemodynamic status, size and mobility of the thrombus might dictate more aggressive therapy. The choice of thrombectomy vs thrombolysis will depend on patient and family acceptability and feasibility of the interventions

Adolopment

**Recommendation**

**The ASH/ISTH guideline panel suggests using anticoagulation alone rather than thrombolysis followed by anticoagulation in pediatric patients with right atrial thrombosis (conditional recommendation based on very low certainty in the evidence about effects).**

**Justification**

## Subgroup considerations

Factors such as size mobility of the clot and patient's hemodynamic status, patient diagnosis, and bleeding risk are important considerations, but there is insufficient data to define specific subgroup effects.

## Implementation considerations

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

## Monitoring and evaluation

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## Research priorities

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## REFERENCES SUMMARY

1. Cetin, II, Ekici, F, Unal, S, Kocabas, A, Sahin, S, Yazici, MU. Intracardiac thrombus in children: the fine equilibrium between the risk and the benefit. Pediatr Hematol Oncol; 2014.
2. Yang, JY, Williams, S, Brandao, LR, Chan, AK. Neonatal and childhood right atrial thrombosis: recognition and a risk-stratified treatment approach. Blood Coagul Fibrinolysis; 2010.

# APPENDICES

Appendix 1

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | thrombolysis followed by standard anticoagulation | anticoagulation alone | Relative (95% CI) | Absolute (95% CI) | | |
| **Bleeding (assessed with: Unspecified)** | | | | | | | | | | | | |
| 2[1,2] | observational studies | serious[a] | not serious | not serious | very serious[b] | none | 3/10 (30.0%) | 1/23 (4.3%) | **RR 4.53** (0.67 to 30.87) | **153 more per 1,000** (from 14 fewer to 1,000 more) | ⨁◯◯◯ Very low | |
| **Major Bleed** | | | | | | | | | | | | |
| 1[1] | observational studies | serious[a] | not serious | not serious | very serious[b] | none | 1/6 (16.7%) | 1/14 (7.1%) | not estimable | | ⨁◯◯◯ Very low | |
| **Clinically Relevant Non-major Bleed** | | | | | | | | | | | | |
| 1[1] | observational studies | serious[a] | not serious | not serious | very serious[b] | none | 0/6 (0.0%) | 0/14 (0.0%) | not estimable | | ⨁◯◯◯ Very low | |

**CI:** confidence interval; **RR:** risk ratio

Appendix 2

**Author(s):**
**Question:** Thrombolysis followed by standard anticoagulation compared to anticoagulation alone in neonates and pediatric patients with right atrial thrombosis
**Setting:** Inpatient
**Bibliography:** American Society of Hematology 2024 Guidelines for Management of Venous Thromboembolism: Treatment of Pediatric Venous Thromboembolism

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | thrombolysis followed by standard anticoagulation | anticoagulation alone | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality** | | | | | | | | | | | | |
| 2[1,2] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 2/11 (18.2%) | 1/13 (7.7%) | **RR 1.14** (0.15 to 8.99) | **11 more per 1,000** (from 65 fewer to 615 more) | ⨁◯◯◯ Very low | CRITICAL |
| **Resolution (assessed with: Complete or Partial Resolution)** | | | | | | | | | | | | |
| 3[1,2,3] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 16/17 (94.1%) [c] | 25/27 (92.6%) [d] | **RR 1.02** (0.87 to 1.19) | **19 more per 1,000** (from 120 fewer to 176 more) | ⨁◯◯◯ Very low | CRITICAL |
| **Recurrence** | | | | | | | | | | | | |
| 1[3] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 0/6 (0.0%) | 0/14 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |

**CI:** confidence interval; **RR:** risk ratio

**Explanations**

a. Risk of bias, assessed using ROBINS-I, was judged to be serious due to selection bias without adjustment for confounders.
b. Imprecision due to small number of included patients and patients with events in the included studies.
c. 13 out of 17 had complete resolution while 3 had partial resolution
d. 14 out of 27 had complete resolution while 11 out of 27 had partial resolution

**References**

1.I, Odaman,Al, Y, Oymak, M, Erdem, N, Tahta, S, Okur,Acar, T, Mese, MM, Yilmazer, S, Gözmen, C, Zihni, S, Calkavur, TH, Karapinar. Assessment of clinical characteristics and treatment outcomes of pediatric . Blood coagulation & fibrinolysis : an international journal in haemostasis and ; 2022.
2.M, Kara, M, Güler, Z, Keskin,Yildirim, K, Tekgunduz, F, Laloglu, N, Ceviz. Clinical features and treatment results in preterm infants with intracardiac . The journal of maternal-fetal & neonatal medicine : the official journal of the ; 2021.
3.CH, van,Ommen, KA, Bergman, M, Boerma, HA, Bouma, AE, Donker, M, Gouvernante, CV, Hulzebos, D, Khandour, R, Knol, MA, Raets, KD, Liem, RA, van,Lingen, M, van,de,Loo, E, Lopriore, M, van,der,Putten, JJ, Sol, MH, Suijker, DC, Vijlbrief, R, Visser, MM, van,Weissenbruch. NEOnatal Central-venous Line Observational study on Thrombosis (NEOCLOT): . Journal of thrombosis and haemostasis : JTH; 2023.

**Author(s):**
**Question:** Anticoagulation compared to no anticoagulation in neonates with renal vein thrombosis
**Setting:** Inpatient
**Bibliography:** ASH/ISTH 2024 Guidelines for Management of Venous Thromboembolism: Treatment of Pediatric Venous Thromboembolism

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | anticoagulation | no anticoagulation | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality (follow-up: median 5.7 years; assessed with: all-cause mortality)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 1/19 (5.3%) | 0/2 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Chronic kidney disease (follow-up: median 5.7 years)** | | | | | | | | | | | | |
| 2[1,2] | non-randomised studies | serious[a] | not serious | not serious | extremely serious[b] | none | 2/8 (25.0%) | 4/5 (80.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **chronic kidney failure (follow-up: median 5.7 years)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | serious[b] | none | 1/23 (4.3%) | - | - | - | ⨁◯◯◯ Very low | CRITICAL |
| **Proteinuria on follow up (follow-up: median 5.7 years)** | | | | | | | | | | | | |
| 2[1,2] | non-randomised studies | serious[a] | not serious | not serious | extremely serious[b] | none | 0/6 (0.0%) | 0/4 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Proteinuria (follow-up: median 5.7 years)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | serious[b] | none | 2/17 (11.8%) | - | - | - | ⨁◯◯◯ Very low | CRITICAL |
| **High blood pressure (follow-up: median 5.7 years)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | extremely serious[b] | none | 0/3 (0.0%) | 0/1 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **High blood pressure (follow-up: median 5.7 years)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | serious[b] | none | 2/23 (8.7%) | - | - | - | ⨁◯◯◯ Very low | CRITICAL |
| **Kidney atrophy (follow-up: median 6 months)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | not serious[b] | none | 17/22 (77.3%) | - | - | - | ⨁◯◯◯ Very low | CRITICAL |
| **Kidney atrophy (follow-up: mean 3 months)** | | | | | | | | | | | | |
| 1[3] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | **Total number of patients for both AC and no AC was: 14**Rate of unilaterial kidney atrophy in AC arm was **81%** vs **66%** in the No AC arm. | | | | ⨁◯◯◯ Very low | CRITICAL |
| **eGFR (follow-up: median 4.7 years)** | | | | | | | | | | | | |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[1,2] | non-randomised studies | serious[a] | not serious | not serious | serious[b] | none | -Median (IQR) of eGFR in AC arm (n=5) was **111** (IQR: 81 – 126) vs **75** (IQR: 57 – 83) in the No AC arm. -Median (IQR) of eGFR in <6 weeks AC arm (n=8): **104** (90-107) -Median (IQR) of eGFR in >6 weeks AC arm (n=15) : **107** (90-110) | | | | ⨁◯◯◯ Very low | CRITICAL |
| **Long term pathological kidney features (assessed with: proteinuria or kidney atrophy or hypertension or CKD)** | | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | not serious[b] | none | 17/23 (73.9%) | - | - | - | ⨁◯◯◯ Very low | CRITICAL |
| **Thrombus recurrence (assessed with: Median follow up duration was 5.7 and 4.7 years respectively )** | | | | | | | | | | | | | |
| 2[1,2] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 1/26 (3.8%) | 0/7 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Neonatal bleeding (follow-up: median 5.7 years; assessed with: any bleeding, Median follow up duration was 5.7 and 4.7 years respectively )** | | | | | | | | | | | | | |
| 2[1,2] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 2/25 (8.0%) | 0/7 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Clot resolution (follow-up: median 5.7 years; assessed with: partial and complete resolution)** | | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 18/20 (90.0%) | 2/2 (100.0%) | not estimable | | ⨁◯◯◯ Very low | IMPORTANT |
| **Complete clot resolution (follow-up: median 5.7 years)** | | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 4/20 (20.0%) | 1/2 (50.0%) | not estimable | | ⨁◯◯◯ Very low | IMPORTANT |

**CI:** confidence interval

**Explanations**

a. All studies were found to have critical risk of bias (assessed by ROBINsI), mainly due to selection bias and confounding
b. We downgraded for imprecision because of concerns related to very small number of events and very small sample size.

**References**

1.Bellaure Ndoudi Likoho 1 , Romain Berthaud 2 ,Claire Dossier 3 ,Jean-Daniel Delbet 4 ,Olivia Boyer 2 ,Véronique Baudouin 3 ,Marianne Alison 5 ,Valérie Biran 6 ,Marie-Françoise Hurtaud 7 ,Julien Hogan 3 ,Theresa Kwon 3 ,Anne Couderc 3. Renal vein thrombosis in neonates: a case series of diagnosis, treatment and childhood kidney function follow-up. Pediatric Nephrology ; 2023.
2.Hilary Whitworth , Lauren A Beslow,Rebecca A Hubbard,Charles E Leonard ,Rebecca Scobell ,Char Witmer,Leslie Raffini. Outcomes in infants with unprovoked venous thromboembolism: A retrospective cohort study. Res Pract Thromb Haemost; 2023.
3.Lim, C., Alamelu, J., Roy, S., Melhem, N., Booth, C. J. Should we heparinise in neonatal renal vein thrombosis (RVT)? A single paediatric tertiary centre experience. Pediatric Nephrology ; 2023.

**Author(s):**
**Question:** Thrombolysis + Anticoagulation compared to Anticoagulation alone in patients with renal vein thrombosis
**Setting:** In-patient
**Bibliography:** ASH/ISTH 2024 Guidelines for Management of Venous Thromboembolism: Treatment of Pediatric Venous Thromboembolism

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Thrombolysis + Anticoagulation | Anticoagulation alone | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality (follow-up: range 6 months to 5.7 years; assessed with: all-cause mortality )** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 0/4 (0.0%) | 1/3 (33.3%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Bleeding (follow-up: median 5.7 years; assessed with: not specified)** | | | | | | | | | | | | |
| 2[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 3/4 (75.0%) | 0/3 (0.0%) | not estimable | | ⨁◯◯◯ Very low[c] | CRITICAL |
| **Thrombus recurrence (follow-up: mean 5.7 years)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 0/4 (0.0%) | 0/3 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Thrombus progression (follow-up: mean 6 months)** | | | | | | | | | | | | |
| 1[2] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 1/3 (33.3%) | - | - | - | ⨁◯◯◯ Very low | CRITICAL |
| **Proteinuria (follow-up: median 5.7 years)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 1/4 (25.0%) | 0/3 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Chronic kidney disease (follow-up: range 6 months to 5.7 years)** | | | | | | | | | | | | |
| 2[1,2] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 1/7 (14.3%) | 0/3 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **High blood pressure (follow-up: range 6 months to 5.7 years)** | | | | | | | | | | | | |
| 2[1,2] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 1/7 (14.3%) | 0/3 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Long-term pathological kidney features (follow-up: median 5.7 years; assessed with: Pathological kidney features: defined as proteinuria or kidney atrophy or hypertension or CKD)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 3/4 (75.0%) | 2/3 (66.7%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Atrophic non-functioning kidney (follow-up: mean 6 months; assessed with: renal scintigraphy)** | | | | | | | | | | | | |
| 1[2] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 3/3 (100.0%) | - | - | - | ⨁◯◯◯ Very low | CRITICAL |
| **Clot resolution (follow-up: range 6 months to 5.7 years; assessed with: complete or partial clot resolution)** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2[1,2] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 5/7 (71.4%) | 3/3 (100.0%) | not estimable | | ⨁◯◯◯ Very low | IMPORTANT |

**Complete clot resolution (follow-up: range 6 months to 5.7 years)**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2[1,2] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 1/7 (14.3%) | 1/3 (33.3%) | not estimable | | ⨁◯◯◯ Very low | IMPORTANT |

**CI:** confidence interval

**Explanations**

a. risk of bias was assessed using ROBINsI, we have concerns due to selection bias and confounding
b. we downgraded twice for imprecision due to small sample size and small number of events.
c. Niada et al: Dilated lateral ventricles on F/U: 1/3 Probably secondary to an intraventricular hemorrhage.

**References**

1.Bellaure Ndoudi Likoho 1 , Romain Berthaud 2 ,Claire Dossier 3 ,Jean-Daniel Delbet 4 ,Olivia Boyer 2 ,Véronique Baudouin 3 ,Marianne Alison 5 ,Valérie Biran 6 ,Marie-Françoise Hurtaud 7 ,Julien Hogan 3 ,Theresa Kwon 3 ,Anne Couderc 3. Renal vein thrombosis in neonates: a case series of diagnosis, treatment and childhood kidney function follow-up. Pediatric Nephrology ; 2023.
2.Fran¸cois Niada a, b,Rene´ Tabin a,Simon Kayemba-Kay's. Spontaneous neonatal renal vein thromboses: Should we treat them all? A report of five cases and a literature review. 2017.

## QUESTION

| Should anticoagulation vs. no anticoagulation be used for neonates with renal vein thrombosis? | |
|---|---|
| **POPULATION:** | neonates with renal vein thrombosis |
| **INTERVENTION:** | anticoagulation |
| **COMPARISON:** | no anticoagulation |
| **MAIN OUTCOMES:** | Mortality; Renal vein thrombosis; Neonatal bleeding - Severe; Renal damage; Hypertension. |
| **SETTING:** | Inpatients |
| **PERSPECTIVE:** | Clinical recommendation - population perspective |
| **BACKGROUND:** | Renal vein thrombosis (RVT) in the neonatal period is associated with low mortality, but long-term kidney dysfunction is common. Approximately 25% of cases are bilateral and 52% to 60% extend into the inferior vena cava. (1) In a review of RVT in neonates, kidney atrophy was seen in 70.6 % of participating neonates, hypertension in 20 % and chronic kidney disease requiring renal replacement therapy in 3% (most of the latter cases were sequelae of bilateral RVT).(2) |
| **CONFLICT OF INTEREST:** | |

## ASSESSMENT

**Problem**
Is the problem a priority?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ No<br>○ Probably no<br>○ Probably yes<br>● Yes<br>○ Varies<br>○ Don't know | Given the frequency and outcomes reported in the current literature, and that current direct evidence on anticoagulant and thrombolytic therapy remains controversial, it is important to weigh the different options for neonates with RVT. | |
| | Adolopment | |
| ○ No<br>○ Probably no | Given the frequency and outcomes reported in the current literature, and that current direct evidence on anticoagulant and thrombolytic therapy remains controversial, it is important to weigh the different options for neonates with RVT. | Add considerations made be the adoloping panel, |

| | | |
|---|---|---|
| ○ Probably yes<br>● Yes<br>○ Varies<br>○ Don't know | | including the justification for any change in judgment. |

## Desirable Effects

How substantial are the desirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

○ Trivial
● Small
○ Moderate
○ Large
○ Varies
○ Don't know

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Risk with no anticoagulation | Risk with anticoagulation | | | | |
| Mortality<br>assessed with: all-cause mortality<br>follow up: range 3 months to 15 years | Study population | | - | 151<br>(9 observational studies) | ⨁◯◯◯<br>VERY LOW[a,b] | |
| | see comment | see comment | | | | |
| Renal vein thrombosis<br>assessed with: no resolution of renal vein thrombosis<br>follow up: range 3 months to 15 years | Study population | | - | 151<br>(9 observational studies) | ⨁◯◯◯<br>VERY LOW[a,b] | |
| | see comment | see comment | | | | |
| Neonatal bleeding - Severe<br>assessed with: any major bleeding<br>follow up: range 1 weeks to 3 months | Study population | | - | 151<br>(9 observational studies) | ⨁◯◯◯<br>VERY LOW[a,b] | |
| | see comment | see comment | | | | |
| Renal damage<br>assessed with: as renal atrophy detected by imaging<br>follow up: range 6 months to | Study population | | - | 151<br>(9 observational studies) | ⨁◯◯◯<br>VERY LOW[a,b] | |
| | see comment | see comment | | | | |

The panel considered the desirable effects to be small, and also the following:

a) The bilateral compared to unilateral involvement of the thrombosis.

b) The progression to the inferior vena cava is an important consideration in prognosis. In these conditions, clinicians are more likely to anticoagulate.

c) Anticoagulant used for treatment, severity of disease, (ICU vs non-ICU), and age, will ultimately impact the bleeding risk.

d) Bleeding rates may be higher in neonates.

d) There is not enough data about the interaction between renal function and risk of bleeding.

| | | | | | | |
|---|---|---|---|---|---|---|
| 17 years | | | | | | |
| Hypertension<br>follow up: range 6 months to 17 years | Study population | | - | 40<br>(3 observational studies)[c] | ⨁◯◯◯<br>VERY LOW[a,d] | |
| | see comment | see comment | | | | |

a. All are observational studies with serious risk of bias due to confounding, selection of participants and measurement.
b. All case series and case reports with few cases and participants.
c. Bidadi 2016, Messinger 2006, Nuss 1994
d. Few cases and events.

NOTE: For a complete assessment, see the EVIDENCE PROFILE

Adolopment

○ Trivial
● Small
○ Moderate
○ Large
○ Varies
○ Don't know

The long term outcomes on the kidney function were comparable between AC and No AC arms, thats why we judged the desirable effects as small. All the outcomes were judged as critical for decision making expect clot resolution as it is not directly related to improved long term outcomes.

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | anticoagulation | no anticoagulation | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality (follow-up: median 5.7 years; assessed with: all-cause mortality)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 1/19 (5.3%) | 0/2 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Chronic kidney disease (follow-up: median 5.7 years)** | | | | | | | | | | | | |
| 2[1,2] | non-randomised studies | serious[a] | not serious | not serious | extremely serious[b] | none | 2/8 (25.0%) | 4/5 (80.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **chronic kidney failure (follow-up: median 5.7 years)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | serious[b] | none | 1/23 (4.3%) | - | - | - | ⨁◯◯◯ Very low | CRITICAL |
| **Proteinuria on follow up (follow-up: median 5.7 years)** | | | | | | | | | | | | |
| 2[1,2] | non-randomised studies | serious[a] | not serious | not serious | extremely serious[b] | none | 0/6 (0.0%) | 0/4 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Proteinuria (follow-up: median 5.7 years)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | serious[b] | none | 2/17 (11.8%) | - | - | - | ⨁◯◯◯ Very low | CRITICAL |
| **High blood pressure (follow-up: median 5.7 years)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | extremely serious[b] | none | 0/3 (0.0%) | 0/1 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **High blood pressure (follow-up: median 5.7 years)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | serious[b] | none | 2/23 (8.7%) | - | - | - | ⨁◯◯◯ Very low | CRITICAL |
| **Kidney atrophy (follow-up: median 6 months)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | not serious[b] | none | 17/22 (77.3%) | - | - | - | ⨁◯◯◯ Very low | CRITICAL |
| **Kidney atrophy (follow-up: mean 3 months)** | | | | | | | | | | | | |
| 1[3] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | **Total number of patients for both AC and no AC was: 14**Rate of unilateral kidney atrophy in AC arm was **81%** vs **66%** in the No AC arm. | | | | ⨁◯◯◯ Very low | CRITICAL |

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | anticoagulation | no anticoagulation | Relative (95% CI) | Absolute (95% CI) | | |
| **eGFR (follow-up: median 4.7 years)** | | | | | | | | | | | | |
| 1[1,2] | non-randomised studies | serious[a] | not serious | not serious | serious[b] | none | -Median (IQR) of eGFR in AC arm (n=5) was **111** (IQR: 81 – 126) vs **75** (IQR: 57 – 83) in the No AC arm. -Median (IQR) of eGFR in <6 weeks AC arm (n=8): **104** (90-107) -Median (IQR) of eGFR in >6 weeks AC arm (n=15) : **107** (90-110) | | | | ⨁◯◯◯ Very low | CRITICAL |
| **Long term pathological kidney features (assessed with: proteinuria or kidney atrophy or hypertension or CKD)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | not serious[b] | none | 17/23 (73.9%) | - | - | - | ⨁◯◯◯ Very low | CRITICAL |
| **Thrombus recurrence (assessed with: Median follow up duration was 5.7 and 4.7 years respectively )** | | | | | | | | | | | | |
| 2[1,2] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 1/26 (3.8%) | 0/7 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Clot resolution (follow-up: median 5.7 years; assessed with: partial and complete resolution)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 18/20 (90.0%) | 2/2 (100.0%) | not estimable | | ⨁◯◯◯ Very low | IMPORTANT |
| **Complete clot resolution (follow-up: median 5.7 years)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 4/20 (20.0%) | 1/2 (50.0%) | not estimable | | ⨁◯◯◯ Very low | IMPORTANT |

**CI:** confidence interval

## Explanations

a. All studies were found to have critical risk of bias (assessed by ROBINsI), mainly due to selection bias and confounding

b. We downgraded for imprecision because of concerns related to very small number of events and small sample size.

**References**

1.Bellaure Ndoudi Likoho 1 , Romain Berthaud 2 ,Claire Dossier 3 ,Jean-Daniel Delbet 4 ,Olivia Boyer 2 ,Véronique Baudouin 3 ,Marianne Alison 5 ,Valérie Biran 6 ,Marie-Françoise Hurtaud 7 ,Julien Hogan 3 ,Theresa Kwon 3 ,Anne Couderc 3. Renal vein thrombosis in neonates: a case series of diagnosis, treatment and childhood kidney function follow-up. Pediatric Nephrology ; 2023.

2.Hilary Whitworth , Lauren A Beslow,Rebecca A Hubbard,Charles E Leonard ,Rebecca Scobell ,Char Witmer,Leslie Raffini. Outcomes in infants with unprovoked venous thromboembolism: A retrospective cohort study. Res Pract Thromb Haemost; 2023.

3.Lim, C., Alamelu, J., Roy, S., Melhem, N., Booth, C. J. Should we heparinise in neonatal renal vein thrombosis (RVT)? A single paediatric tertiary centre experience. Pediatric Nephrology ; 2023.



## Undesirable Effects

## How substantial are the undesirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

○ Large
○ Moderate
○ Small
● Trivial
○ Varies
○ Don't know

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Risk with no anticoagulation | Risk with anticoagulation | | | | |
| Mortality<br>assessed with: all-cause mortality<br>follow up: range 3 months to 15 years | Study population | | - | 151<br>(9 observational studies) | ⨁◯◯◯<br>VERY LOW[a,b] | |
| | see comment | see comment | | | | |
| Renal vein thrombosis<br>assessed with: no resolution of renal vein thrombosis<br>follow up: range 3 months to 15 years | Study population | | - | 151<br>(9 observational studies) | ⨁◯◯◯<br>VERY LOW[a,b] | |
| | see comment | see comment | | | | |
| Neonatal bleeding - Severe<br>assessed with: any major bleeding<br>follow up: range 1 weeks to 3 months | Study population | | - | 151<br>(9 observational studies) | ⨁◯◯◯<br>VERY LOW[a,b] | |
| | see comment | see comment | | | | |
| Renal damage<br>assessed with: as renal atrophy detected by imaging<br>follow up: range 6 months to 17 years | Study population | | - | 151<br>(9 observational studies) | ⨁◯◯◯<br>VERY LOW[a,b] | |
| | see comment | see comment | | | | |
| Hypertension<br>follow up: range 6 months to 17 years | Study population | | - | 40<br>(3 observational studies)[c] | ⨁◯◯◯<br>VERY LOW[a,d] | |
| | see comment | see comment | | | | |

The undesirable anticipated effects were considered small. Bleeding rates will also depend on gestational age of the neonate.

It should be considered that neonatal bleeding rates may be as high as 2 to 3% and can also present with adrenal bleeding.

a. All are observational studies with serious risk of bias due to confounding, selection of participants and measurement.
b. All case series and case reports with few cases and participants.
c. Bidadi 2016, Messinger 2006, Nuss 1994
d. Few cases and events.

NOTE: For a complete assessment, see the EVIDENCE PROFILE



Adolopment

○ Large
○ Moderate
● Small
○ Trivial
○ Varies
○ Don't know

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | anticoagulation | no anticoagulation | Relative (95% CI) | Absolute (95% CI) | | |
| Neonatal bleeding (follow-up: median 5.7 years; assessed with: any bleeding, Median follow up duration was 5.7 and 4.7 years respectively ) | | | | | | | | | | | | |
| 2[1,2] | observational studies | serious[a] | not serious | not serious | very serious[b] | none | 2/25 (8.0%) | 0/7 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |

**CI:** confidence interval

## Explanations

a. All studies were found to have critical risk of bias (assessed by ROBINsI), mainly due to selection bias and confounding

b. We downgraded for imprecision because of concerns related to very small number of events and small sample size.

## References

Add considerations made be the adoloping panel, including the justification for any change in judgment.

| | | |
|---|---|---|
| | 1.Bellaure Ndoudi Likoho 1 , Romain Berthaud 2 ,Claire Dossier 3 ,Jean-Daniel Delbet 4 ,Olivia Boyer 2 ,Véronique Baudouin 3 ,Marianne Alison 5 ,Valérie Biran 6 ,Marie-Françoise Hurtaud 7 ,Julien Hogan 3 ,Theresa Kwon 3 ,Anne Couderc 3. Renal vein thrombosis in neonates: a case series of diagnosis, treatment and childhood kidney function follow-up. Pediatric Nephrology ; 2023.<br><br>2.Hilary Whitworth , Lauren A Beslow,Rebecca A Hubbard,Charles E Leonard ,Rebecca Scobell ,Char Witmer,Leslie Raffini. Outcomes in infants with unprovoked venous thromboembolism: A retrospective cohort study. Res Pract Thromb Haemost; 2023. | |

## Certainty of evidence

What is the overall certainty of the evidence of effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | Certainty of the evidence of effects was judged as 'very low' due to serious risk of bias, and imprecision. | |
| | Adolopment | |
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | Even though there was no studies addressing renal vein thrombosis, the certainty of the evidence of effects was judged as 'very low' due to concerns about risk of bias, and imprecision. This evidence was derived from study with very small sample size with concerns related to selection bias without any adjustmnet to confounders. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Values

Is there important uncertainty about or variability in how much people value the main outcomes?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Important uncertainty or variability<br>○ Possibly important uncertainty or variability<br>○ Probably no important uncertainty or variability<br>● No important uncertainty or variability | **Utility related information:**<br>**The relative importance of outcomes:**<br>**Results from Panel Members' Utility Rating Survey**:<br>Utilities rated on the visual analog scale, where 0 represents death and 1 represents full health, were as follows.<br>Pulmonary embolism – Severe marker state: 0.31<br>Pulmonary embolism – Moderate marker state: 0.49<br>Deep vein thrombosis (proximal) – Severe marker state: 0.49<br>Deep vein thrombosis (proximal) – Moderate marker state: 0.61<br>Deep vein thrombosis (distal) – Severe marker state: 0.56<br>Deep vein thrombosis (distal) – Moderate marker state: 0.68<br>Major bleeding: 0.30<br>Neonatal Bleeding – Severe: 0.30<br>Infant Bleeding – Severe: 0.26<br>Renal vein thrombosis in a child (unilateral): 0.64<br>Renal vein thrombosis in a child (bilateral): 0.32<br>**We did not identify utility related information or non-utility information for the outcomes of interest specific to the pediatric population in the literature.**<br>**Additional information from the adult population:**<br>**Our systematic review for the adult population found that the relative importance of the outcomes is as follows:**<br>Pulmonary embolism: 0.63-0.93 (different methods) (11, 12, 13)<br>Deep vein thrombosis: 0.64-0.99 (different methods) (11, 12, 13, 14, 15)<br>Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off)(12, 13) | The panel noted that even when some children surviving into adulthood with chronic conditions might rate their health states different than their parents, there would be no important uncertainty or variability. |

| | | |
|---|---|---|
| | Muscular bleeding: 0.76 (time trade off) (13)<br><br>Minor intracranial bleeding event: 0.75 (standard gamble) (12)<br><br>Major intracranial bleeding event: 0.15 (standard gamble) (12)<br><br>Central nervous system bleeding: 0.29-0.60 (standard gamble) (16, 5)<br><br>Treatment with LMWH: 0.993 (time trade off) (17)<br><br>Treatment with warfarin (as a surrogate): 0.989 (time trade off)(17)<br><br>**<u>We also identified in the systematic review the following non-utility information from the adult population:</u>**<br><br>**Anticoagulant therapy**<br><br>Adult patients highly value the benefits of risk reduction in VTE recurrence and post-thrombosis syndrome (13). Patients would favor efficacy and safety over convenience of route of administration (4). Further, patients would like to avoid adverse events but most of them are "not afraid of" the adverse events (3, 4, 5). For anticoagulant therapy in general, most patients would prefer the oral doses compared with injections, this is mainly because of treatment burden due to injection(3, 4) . For patients with venographically proven deep venous thrombosis, 15 of the 19 patients expressed a preference for the subcutaneous route for administration of heparin over intravenous administration (6).<br><br>**Warfarin**<br><br>Adult patients would like to switch to another anticoagulant if it is as effective as warfarin; this is mainly due to the treatment burden associated with monitoring, injection and dietary change due to warfarin use (7). In another study approximately half of the patients did not consider VKA therapy particularly difficult to manage (8).<br><br>**LMWH**<br><br>For adult patients receiving low molecular weight heparin, patients placed a high score on "importance of ease of use", "expectations of symptom relief", and "confidence in the treatment to prevent blood clots" while they had a low score of treatment-related side effects (bruise, bleeding). (9, 10). | |
| | Adolopment | |
| ○ Important uncertainty or variability<br>○ Possibly important uncertainty or variability<br>○ Probably no | Utility related information: The relative importance of outcomes: Results from Panel Members' Utility Rating Survey: Utilities rated on the visual analog scale, where 0 represents death and 1 represents full health, were as follows. Pulmonary embolism – Severe marker state: 0.31 Pulmonary embolism – Moderate marker state: 0.49 Deep vein thrombosis (proximal) – Severe marker state: 0.49 Deep vein thrombosis (proximal) – Moderate marker state: 0.61 Deep vein thrombosis (distal) – Severe marker state: 0.56 Deep vein thrombosis (distal) – Moderate marker state: 0.68 Major bleeding: 0.30 Neonatal Bleeding – Severe: 0.30 Infant Bleeding – Severe: 0.26 Renal vein thrombosis in a child (unilateral): 0.64Renal vein thrombosis in a child (bilateral): 0.32We did not identify utility related information or non-utility | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

| | | |
|---|---|---|
| important uncertainty or variability<br>● No important uncertainty or variability | information for the outcomes of interest specific to the pediatric population in the literature.Additional information from the adult population:Our systematic review for the adult population found that the relative importance of the outcomes is as follows: Pulmonary embolism: 0.63-0.93 (different methods) (11, 12, 13) Deep vein thrombosis: 0.64-0.99 (different methods) (11, 12, 13, 14, 15)Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off)(12, 13) Muscular bleeding: 0.76 (time trade off) (13) Minor intracranial bleeding event: 0.75 (standard gamble) (12)Major intracranial bleeding event: 0.15 (standard gamble) (12) Central nervous system bleeding: 0.29-0.60 (standard gamble) (16, 5) Treatment with LMWH: 0.993 (time trade off) (17) Treatment with warfarin (as a surrogate): 0.989 (time trade off)(17) We also identified in the systematic review the following non-utility information from the adult population:Anticoagulant therapy Adult patients highly value the benefits of risk reduction in VTE recurrence and post-thrombosis syndrome (13). Patients would favor efficacy and safety over convenience of route of administration (4). Further, patients would like to avoid adverse events but most of them are "not afraid of" the adverse events (3, 4, 5). For anticoagulant therapy in general, most patients would prefer the oral doses compared with injections, this is mainly because of treatment burden due to injection(3, 4) . For patients with venographically proven deep venous thrombosis, 15 of the 19 patients expressed a preference for the subcutaneous route for administration of heparin over intravenous administration (6). Warfarin Adult patients would like to switch to another anticoagulant if it is as effective as warfarin; this is mainly due to the treatment burden associated with monitoring, injection and dietary change due to warfarin use (7). In another study approximately half of the patients did not consider VKA therapy particularly difficult to manage (8). LMWH For adult patients receiving low molecular weight heparin, patients placed a high score on "importance of ease of use", "expectations of symptom relief", and "confidence in the treatment to prevent blood clots" while they had a low score of treatment-related side effects (bruise, bleeding). (9, 10). | |

## Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>● Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>○ Don't know | | For this decision, the size of the clot and kidney function should be considered. Also important is the location (unilateral versus bilateral) and the extension or not to the IVC. |

| | | |
|---|---|---|
| | Adolopment | |
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>● Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | For decision making, the size of the clot, extension to the inferior vena cava, and whether it is bilateral or unilateral clot. Although the bleeding rates were higher in the AC arm, the balance of effects probably favors AC, because of the desirable effects assocaited with AC in RVT. |

## Resources required

How large are the resource requirements (costs)?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Large costs<br>● Moderate costs<br>○ Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br>○ Varies<br>○ Don't know | No research evidence was identified for anticoagulation costs for renal vein thrombosis in neonates. Two studies reported the costs of disease from pediatric patients with any VTE. One reported for 834 pediatric patients with VTE a median annual expenditure of $25,258 and $24,934 USD in Medicaid and private insurance patients respectively. (18) Another study found that patients with VTE had an increased 8.1 inpatient days and excess average costs of $27,686 USD. (19)<br><br>**Additional information from adult population:**<br><br>In relation to the reported costs of anticoagulation, the direct cost per week with warfarin in adults ranges from 3.54 to 11.44 USD while this number in Canada decreases to 0.49 to 0.84 CAD per week. (20, 21, 22, 23) With heparin, the costs per unit range from $0.18 per 10 units, to $0.212 per 1000 units (24) with a cost per week of $37.00 USD and $11.14 CAD per day in Canada. (22, 23) LMWH (enoxaparin) cost varies. The wholesale cost in low and middle income economies is reported at about $13 to $75 USD per week. (25) In the United States the wholesale cost is about $98.91 USD per day as of 2016 (26). | Children will present with VTE in hospital, and the costs will be added when clinicians decide to give anticoagulation as treatment.<br><br>Costs for the management of pediatric VTE patients without anticoagulation is not available from the research evidence. |
| | Adolopment | |

| | | |
|---|---|---|
| ○ Large costs<br>● Moderate costs<br>○ Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br>○ Varies<br>○ Don't know | No research evidence was identified for anticoagulation costs for renal vein thrombosis in neonates. 3 studies reported the costs of disease from pediatric patients with any VTE. One reported for 834 pediatric patients with VTE a median annual expenditure of $25,258 and $24,934 USD in Medicaid and private insurance patients respectively. (18) Another study found that patients with VTE had an increased 8.1 inpatient days and excess average costs of $27,686 USD. (19) . Total mean healthcare expenditures for the 6- month follow-up period were 13-fold greater in the VTE group than in the group without VTE ($338,338 ± $544,045 vs. $25,171 ± $90,792; p < 0.0001). (bryce et al.201)Additional information from adult population:In relation to the reported costs of anticoagulation, the direct cost per week with warfarin in adults ranges from 3.54 to 11.44 USD while this number in Canada decreases to 0.49 to 0.84 CAD per week. (20, 21, 22, 23) With heparin, the costs per unit range from $0.18 per 10 units, to $0.212 per 1000 units (24) with a cost per week of $37.00 USD and $11.14 CAD per day in Canada. (22, 23) LMWH (enoxaparin) cost varies. The wholesale cost in low and middle income economies is reported at about $13 to $75 USD per week. (25) In the United States the wholesale cost is about $98.91 USD per day as of 2016 (26). | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Very low<br>○ Low<br>○ Moderate<br>○ High<br>● No included studies | No research evidence found. | |
| | Adolopment | |

| | | |
|---|---|---|
| ○ Very low<br>○ Low<br>○ Moderate<br>○ High<br>● No included studies | No research evidence found | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>● Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>○ No included studies | No research evidence was identified. | The panel considers the intervention to have a potential beneficial effect if we include the long terms benefits of avoiding hypertension and/or renal damage. |
| | Adolopment | |

| | | |
|---|---|---|
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>● Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>○ No included studies | No research evidence was identified. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Equity

What would be the impact on health equity?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Reduced<br>○ Probably reduced<br>● Probably no impact<br>○ Probably increased<br>○ Increased<br>○ Varies<br>○ Don't know | No research evidence was identified. | |
| | Adolopment | |
| ○ Reduced<br>○ Probably reduced<br>● Probably no impact<br>○ Probably increased<br>○ Increased<br>○ Varies<br>○ Don't know | No research evidence was identified. | Probably no impact on equity, as AC is widely available. |

## Acceptability

Is the intervention acceptable to key stakeholders?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ No<br>○ Probably no<br>● Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | No research evidence was identified | |
| | Adolopment | |
| ○ No<br>○ Probably no<br>● Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | No research evidence was identified | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Feasibility

Is the intervention feasible to implement?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ No<br>○ Probably no<br>● Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | No research evidence was identified | |
| | Adolopment | |
| ○ No<br>○ Probably no<br>○ Probably yes<br>● Yes<br>○ Varies<br>○ Don't know | No research evidence was identified | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## SUMMARY OF JUDGEMENTS

| CRITERIA | ORIGINAL | IMPORTANCE FOR DECISION | ADOLOPMENT | IMPORTANCE FOR DECISION |
|---|---|---|---|---|
| PROBLEM | Yes | | Yes | |
| DESIRABLE EFFECTS | Small | | Small | |
| UNDESIRABLE EFFECTS | Trivial | | Small | |
| CERTAINTY OF EVIDENCE | Very low | | Very low | |
| VALUES | No important uncertainty or variability | | No important uncertainty or variability | |
| BALANCE OF EFFECTS | Probably favors the intervention | | Probably favors the intervention | |
| RESOURCES REQUIRED | Moderate costs | | Moderate costs | |
| CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES | No included studies | | No included studies | |
| COST EFFECTIVENESS | Probably favors the intervention | | Probably favors the intervention | |
| EQUITY | Probably no impact | | Probably no impact | |
| ACCEPTABILITY | Probably yes | | Probably yes | |
| FEASIBILITY | Probably yes | | Yes | |

## TYPE OF RECOMMENDATION

Original

| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | **Conditional recommendation for the intervention** | Strong recommendation for the intervention |
|---|---|---|---|---|
| ○ | ○ | ○ | ● | ○ |

Adolopment

| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | **Conditional recommendation for the intervention** | Strong recommendation for the intervention |
|---|---|---|---|---|
| ○ | ○ | ○ | ● | ○ |

## CONCLUSIONS

Original

### Recommendation

**The ASH guideline panel suggests using anticoagulation rather than no anticoagulation in neonates with renal vein thrombosis (RVT) (conditional recommendation based on very low certainty in the evidence about effects).**

### Justification

The panel considers the intervention to have a potential beneficial effect if the long terms benefits of avoiding hypertension and/or renal damage are considered. Anticoagulation is likely more important with bilateral compared to unilateral involvement, or with progression to the inferior vena cava. Severity of disease, age, gestational age, and degree of thrombocytopenia will impact bleeding risk with treatment.

Adolopment

### Recommendation

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

### Justification

### Subgroup considerations

Original

Groups that may have additional benefit from treatment

-bilateral RVT

-IVC extension

Groups that require especial attention and care when treated:

-increased bleeding risk due to prematurity and thrombocytopenia

-abnormal renal function

Adolopment

## Implementation considerations

Original

--

Adolopment

## Monitoring and evaluation

Original

--

Adolopment

## Research priorities

Original

More high quality evidence for baseline risks, duration of treatment and agents used, as well as RCTs to assess AC vs no AC in RVT.

Adolopment

# REFERENCES SUMMARY


1. Zigman, A., Yazbeck, S., Emil, S., Nguyen, L.. Renal vein thrombosis: A 10-year review. Journal of Pediatric Surgery; 2000.
2. Lau, K. K., Stoffman, J. M., Williams, S., McCusker, P., Brandao, L., Patel, S., Chan, A. K., Canadian Pediatric, Thrombosis, Hemostasis, Network. Neonatal renal vein thrombosis: review of the English-language literature between 1992 and 2006. Pediatrics; Nov 2007.
3. Barcellona, D., Contu, P., Sorano, G. G., Pengo, V., Marongiu, F.. The management of oral anticoagulant therapy: the patient's point of view. Thromb Haemost; Jan 2000.
4. Noble, S., Matzdorff, A., Maraveyas, A., Holm, M. V., Pisa, G.. Assessing patients' anticoagulation preferences for the treatment of cancer-associated thrombosis using conjoint methodology. Haematologica; Nov 2015.
5. O'Meara, J. J.,3rd, McNutt, R. A., Evans, A. T., Moore, S. W., Downs, S. M.. A decision analysis of streptokinase plus heparin as compared with heparin alone for deep-vein thrombosis. N Engl J Med; Jun 30 1994.
6. Robinson, A. M., McLean, K. A., Greaves, M., Channer, K. S.. Subcutaneous versus intravenous administration of heparin in the treatment of deep vein thrombosis; which do patients prefer? A randomized cross-over study. Postgrad Med J; Feb 1993.
7. Attaya, S., Bornstein, T., Ronquillo, N., Volgman, R., Braun, L. T., Trohman, R., Volgman, A.. Study of warfarin patients investigating attitudes toward therapy change (SWITCH Survey). Am J Ther; Nov 2012.
8. Wild, D., Murray, M., Donatti, C.. Patient perspectives on taking vitamin K antagonists: a qualitative study in the UK, USA and Spain. Expert Rev Pharmacoecon Outcomes Res; Oct 2009.
9. Baba, M., Al-Masri, M., Salhab, M., El-Ghanem, M.. Patient's Compliance on the Use of Extended Low Molecular Weight Heparin Post Major Pelvic Surgeries in Cancer Patients at King Hussein Cancer Center. Gulf J Oncolog; Jan 2015.
10. Cajfinger, F, Debourdeau, P, Lamblin, A, Benatar, V, Falvo, N, Benhamou, Y. Low-molecular-weight heparins for cancer-associated thrombosis: Adherence to clinical practice guidelines and patient perception in TROPIQUE, a 409-patient prospective observational study. Thromb Res; 2016.
11. Hogg, K., Shaw, J., Coyle, D., Fallah, P., Carrier, M., Wells, P.. Validity of standard gamble estimated quality of life in acute venous thrombosis. Thromb Res; Oct 2014.
12. Hogg, K., Kimpton, M., Carrier, M., Coyle, D., Forgie, M., Wells, P.. Estimating quality of life in acute venous thrombosis. JAMA Intern Med; Jun 24 2013.
13. Locadia, M., Bossuyt, P. M., Stalmeier, P. F., Sprangers, M. A., van Dongen, C. J., Middeldorp, S., Bank, I., van der Meer, J., Hamulyak, K., Prins, M. H.. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. Thromb Haemost; Dec 2004.
14. Marvig, C. L., Verhoef, T. I., de Boer, A., Kamali, F., Redekop, K., Pirmohamed, M., Daly, A. K., Manolopoulos, V. G., Wadelius, M., Bouvy, M., Maitland-van der Zee, A. H., consortium, Eu-Pact. Quality of life in patients with venous thromboembolism and atrial fibrillation treated with coumarin anticoagulants. Thromb Res; Jul 2015.
15. Utne, K. K., Tavoly, M., Wik, H. S., Jelsness-Jorgensen, L. P., Holst, R., Sandset, P. M., Ghanima, W.. Health-related quality of life after deep vein thrombosis. Springerplus; 2016.
16. Lenert, L. A., Soetikno, R. M.. Automated computer interviews to elicit utilities: potential applications in the treatment of deep venous thrombosis. J Am Med Inform Assoc; Jan-Feb 1997.
17. Marchetti, M., Pistorio, A., Barone, M., Serafini, S., Barosi, G.. Low-molecular-weight heparin versus warfarin for secondary prophylaxis of venous thromboembolism: a cost-effectiveness analysis. Am J Med; Aug 2001.
18. Boulet, S. L., Amendah, D., Grosse, S. D., Hooper, W. C.. Health care expenditures associated with venous thromboembolism among children. Thromb Res; May 2012.
19. Goudie, A., Dynan, L., Brady, P. W., Fieldston, E., Brilli, R. J., Walsh, K. E.. Costs of Venous Thromboembolism, Catheter-Associated Urinary Tract Infection, and Pressure Ulcer. Pediatrics; Sep 2015.
20. Biskupiak, J., Ghate, S. R., Jiao, T., Brixner, D.. Cost implications of formulary decisions on oral anticoagulants in nonvalvular atrial fibrillation. J Manag Care Pharm; Nov-Dec 2013.
21. Kearon C, Akl E. Duration of anticoagulant therapy for deep vein thrombosis and pulmonary embolism. Blood; 2014.
22. Klarenbach, S., Lee, K., Boucher, M., So, H., Manns, B., Tonelli, M.. Direct Oral Anticoagulants for the Treatment of Venous Thromboembolic Events: Economic Evaluation. 2016.
23. Guanella, R., Ducruet, T., Johri, M., Miron, M. J., Roussin, A., Desmarais, S., Joyal, F., Kassis, J., Solymoss, S., Ginsberg, J. S., Lamping, D. L., Shrier, I., Kahn, S. R.. Economic burden and cost determinants of deep vein thrombosis during 2 years following diagnosis: a prospective evaluation. J Thromb Haemost; Dec 2011.
24. Medicare, . 2017 ASP Drug Pricing files. available in: www.cms.gov/apps/physician-fee-schedule/overview.aspx [last accessed March 2018]; 2017.
25. IMPPG, . International Medical Products Price Guide. [Internet]; 2016.
26. NADAC, . National Average Drug Acquisition Cost. Available in: https://data.medicaid.gov/Drug-Pricing-and-Payment/NADAC-National-Average-Drug-Acquisition-Cost-/a4y5-998d [last accessed: March 2018]; 2017.

## QUESTION

| Should Thrombolysis + Anticoagulation vs. Anticoagulation alone be used for patients with renal vein thrombosis? | |
|---|---|
| **POPULATION:** | patients with renal vein thrombosis |
| **INTERVENTION:** | Thrombolysis + Anticoagulation |
| **COMPARISON:** | Anticoagulation alone |
| **MAIN OUTCOMES:** | Mortality; Bleeding; Thrombus recurrence ; Thrombus progression; Proteinuria; Chronic kidney disease; High blood pressure; Long-term pathological kidney features; Atrophic non-functioning kidney; Clot resolution ; Complete clot resolution; |
| **SETTING:** | In-patient |
| **PERSPECTIVE:** | |
| **BACKGROUND:** | |
| **CONFLICT OF INTEREST:** | |

## ASSESSMENT

### Problem
Is the problem a priority?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ No<br>○ Probably no<br>○ Probably yes<br>● Yes<br>○ Varies<br>○ Don't know | Treatment of neonates with renal vein thrombosis include supportive measures, anticoagulation, and thrombolysis. The effect of each of these strategies is still debated as the evidence is scarce. | |

### Desirable Effects
How substantial are the desirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ Trivial<br>○ Small<br>○ Moderate<br>○ Large<br>○ Varies | | There is a limited number of studies addressing thrombolysis use in pediatric renal vein thrombosis. We dont know the desirabl effects of thrombolysis in pediatrics with RVT. |

● Don't know

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Thrombolysis + Anticoagulation | Anticoagulation alone | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality (follow-up: range 6 months to 5.7 years; assessed with: all-cause mortality )** | | | | | | | | | | | | |
| 1[1] | observational studies | serious[a] | not serious | not serious | very serious[b] | none | 0/4 (0.0%) | 1/3 (33.3%) | not estimable | | ⨁◯◯◯ Very low | |
| **Thrombus recurrence (follow-up: mean 5.7 years)** | | | | | | | | | | | | |
| 1[1] | observational studies | serious[a] | not serious | not serious | very serious[b] | none | 0/4 (0.0%) | 0/3 (0.0%) | not estimable | | ⨁◯◯◯ Very low | |
| **Thrombus progression (follow-up: mean 6 months)** | | | | | | | | | | | | |
| 1[1] | observational studies | serious[a] | not serious | not serious | very serious[b] | none | 1/3 (33.3%) | - | - | - | ⨁◯◯◯ Very low | |
| **Proteinuria (follow-up: median 5.7 years)** | | | | | | | | | | | | |
| 1[1] | observational studies | serious[a] | not serious | not serious | very serious[b] | none | 1/4 (25.0%) | 0/3 (0.0%) | not estimable | | ⨁◯◯◯ Very low | |
| **Chronic kidney disease (follow-up: range 6 months to 5.7 years)** | | | | | | | | | | | | |
| 2[1,2] | observational studies | serious[a] | not serious | not serious | very serious[b] | none | 1/7 (14.3%) | 0/3 (0.0%) | not estimable | | ⨁◯◯◯ Very low | |

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Thrombolysis + Anticoagulation | Anticoagulation alone | Relative (95% CI) | Absolute (95% CI) | | |
| **High blood pressure (follow-up: range 6 months to 5.7 years)** | | | | | | | | | | | | |
| 2[1,2] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 1/7 (14.3%) | 0/3 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Long-term pathological kidney features (follow-up: median 5.7 years; assessed with: Pathological kidney features: defined as proteinuria or kidney atrophy or hypertension or CKD)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 3/4 (75.0%) | 2/3 (66.7%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Atrophic non-functioning kidney (follow-up: mean 6 months; assessed with: renal scintigraphy)** | | | | | | | | | | | | |
| 1[2] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 3/3 (100.0%) | - | - | - | ⨁◯◯◯ Very low | CRITICAL |
| **Clot resolution (follow-up: range 6 months to 5.7 years; assessed with: complete or partial clot resolution)** | | | | | | | | | | | | |
| 2[1,2] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 5/7 (71.4%) | 3/3 (100.0%) | not estimable | | ⨁◯◯◯ Very low | IMPORTANT |
| **Complete clot resolution (follow-up: range 6 months to 5.7 years)** | | | | | | | | | | | | |
| 2[1,2] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 1/7 (14.3%) | 1/3 (33.3%) | not estimable | | ⨁◯◯◯ Very low | IMPORTANT |

**CI:** confidence interval

## Explanations

a. risk of bias was assessed using ROBINSI, we have concerns due to selection bias and confounding

b. we downgraded twice for imprecision due to small sample size and small number of

events.

## References

1.Bellaure Ndoudi Likoho 1 , Romain Berthaud 2 ,Claire Dossier 3 ,Jean-Daniel Delbet 4 ,Olivia Boyer 2 ,Véronique Baudouin 3 ,Marianne Alison 5 ,Valérie Biran 6 ,Marie-Françoise Hurtaud 7 ,Julien Hogan 3 ,Theresa Kwon 3 ,Anne Couderc 3. Renal vein thrombosis in neonates: a case series of diagnosis, treatment and childhood kidney function follow-up. Pediatric Nephrology ; 2023.

2.Fran¸cois Niada a, b,Rene´ Tabin a,Simon Kayemba-Kay'ş. Spontaneous neonatal renal vein thromboses: Should we treat them all? A report of five cases and a literature review. 2017.

# Undesirable Effects

How substantial are the undesirable anticipated effects?

**JUDGEMENT**

○ Large
● Moderate
○ Small
○ Trivial
○ Varies
○ Don't know

**RESEARCH EVIDENCE**

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Thrombolysis + Anticoagulation | Anticoagulation alone | Relative (95% CI) | Absolute (95% CI) | | |
| Bleeding (follow-up: median 5.7 years; assessed with: not specified) | | | | | | | | | | | | |
| 2[1] | observational studies | serious[a] | not serious | not serious | very serious[b] | none | 3/4 (75.0%) | 0/3 (0.0%) | not estimable | | ⨁◯◯◯ Very low[c] | |

**CI:** confidence interval

## Explanations

a. risk of bias was assessed using ROBINsI, we have concerns due to selection bias and confounding

b. we downgraded twice for imprecision due to small sample size and small number of events.

c. Niada et al; Dilated lateral ventricles on F/U: 1/3 Probably secondary to an intraventricular hemorrhage.

## References

1.Bellaure Ndoudi Likoho 1 , Romain Berthaud 2 ,Claire Dossier 3 ,Jean-Daniel Delbet 4 ,Olivia Boyer 2 ,Véronique Baudouin 3 ,Marianne Alison 5 ,Valérie Biran 6 ,Marie-Françoise

**ADDITIONAL CONSIDERATIONS**

The bleeding rates were higher in the thrombolysis arm, that's why we judged the undesirable effects as moderate.

| | | |
|---|---|---|
| | Hurtaud 7 ,Julien Hogan 3 ,Theresa Kwon 3 ,Anne Couderc 3. Renal vein thrombosis in neonates: a case series of diagnosis, treatment and childhood kidney function follow-up. Pediatric Nephrology ; 2023. | |

## Certainty of evidence

What is the overall certainty of the evidence of effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | Certainty of the evidence of effects was judged as 'very low' due to serious risk of bias, and imprecision. These were small studies with serious risk of bias and very small sample size with very small number of events. | |

## Values

Is there important uncertainty about or variability in how much people value the main outcomes?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ Important uncertainty or variability<br>○ Possibly important uncertainty or variability<br>● Probably no important uncertainty or variability<br>○ No important uncertainty or variability | **We did not identify utility related information or non-utility information for the outcomes of interest specific to the pediatric population in the literature.**<br><br>**<u>Additional information from the adult population:</u>**<br><br>**Our systematic review for the adult population found that the relative importance of the outcomes is as follows:** | |

| | | |
|---|---|---|
| | Pulmonary embolism: 0.63-0.93 (different methods) (Hogg et al., 2014, Hogg et al., 2013, Locadia et al., 2004)<br><br>Deep vein thrombosis: 0.64-0.99 (different methods) (Marvig et al., 2015, Utne et al., 2016, Hogg et al., 2013, Hogg et al., 2014, Locadia et al., 2004)<br><br>Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off)<br><br>Muscular bleeding: 0.76 (time trade off) (Locadia et al., 2004)<br><br>Minor intracranial bleeding event: 0.75 (standard gamble) (Hogg et al., 2013)<br><br>Major intracranial bleeding event: 0.15 (standard gamble) (Hogg et al., 2013)<br><br>Central nervous system bleeding: 0.29-0.60 (standard gamble) (Lenert et al., 1997)(O'Meara et al., 1994)<br><br>Treatment with LMWH: 0.993 (time trade off) (Marchetti et al., 2001)<br><br>Treatment with warfarin (as a surrogate): 0.989 (time trade off) (Marchetti et al., 2001)<br><br>**A systematic review was identified with the following non-utility information from the adult population:**<br><br>**Anticoagulant therapy**<br><br>Adult patients highly value the benefits of risk reduction in VTE recurrence and post-thrombosis syndrome (Locadia et al., 2004). Patients would favor efficacy and safety over convenience of route of administration (Noble et al., 2015). Further, patients would like to avoid adverse events but most of them are “not afraid of” the adverse events(Barcellona et al., 2000, Noble et al., 2015, O'Meara et al., 1994). For anticoagulant therapy in general, most patients would prefer the oral doses compared with injections, this is mainly because of treatment burden due to injection. For patients with venographically proven deep venous thrombosis, 15 of the 19 patients expressed a preference for the subcutaneous route for administration of heparin over intravenous administration. (Robinson et al., 1993) | |
| **Balance of effects**<br>Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | |
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |

| | | |
|---|---|---|
| ○ Favors the comparison<br>● Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>○ Don't know | | The balance of effects probably favors the using anticogulation alone, as we are not certain about the desirable effects of thrombolysis but we have certain about the harms assocaited with the use thrombolysis. Taking this into account we estimated the balance of effects as favoring not using thrombolysis. |

## Resources required

How large are the resource requirements (costs)?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ● Large costs<br>○ Moderate costs<br>○ Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br>○ Varies<br>○ Don't know | No direct research evidence was identified for costs of anticoagulation as compared to anticoagulation plus systemic thrombolysis for treatment in pediatric patients with symptomatic DVT or PE. Two studies reported the costs of disease from pediatric patients with any VTE. One reported for 834 pediatric patients with VTE a median annual expenditure of $25,258 and $24,934 USD in Medicaid and private insurance patients respectively.(2) Another study found that patients with VTE had an increased 8.1 inpatient days and excess average costs of $27,686 USD. (3)Additional information from adult population: In the adult population the cost of urokinase and equipment cost for the catheter directed thrombolysis is estimated to around $10,127 USD (4) In adult patients receiving stroke treatment, thrombolysis has been deemed as a cost-effective strategy, with direct cost of $2750 USD per dose. (5) For costs of anticoagulation in adult patients, the direct cost per week with warfarin in adults ranges from $3.54 to $11.44 USD while this number in Canada decreases to 0.49 to 0.84 CAD per week. (6)(7)(8) With heparin, the costs per unit ranges from $0.18 per 10 units, to $0.212 per 1000 units (9) with a Cost per week: $37.00 USD and $11.14 CAD per day in Canada. (7)(8) LMWH (enoxaparin) cost varies. The wholesale cost in the low and middle income economies is about $13 to $75 USD per week. (10) In the United States the wholesale cost is about $98.91 USD per day as of 2016.(1) | |

## Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|

| | | |
|---|---|---|
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | No direct research evidence was identified for costs of anticoagulation as compared to anticoagulation plus systemic thrombolysis for treatment in pediatric patients with symptomatic DVT or PE. the certainty of evidence was judged as very low. | |

## Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>● No included studies | No research evidence about cost effectiveness was identified. | |

## Equity

What would be the impact on health equity?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ Reduced<br>● Probably reduced<br>○ Probably no impact<br>○ Probably increased<br>○ Increased<br>○ Varies<br>○ Don't know | No research evidence was identified. | Taking into account the cost and avialability of thrombolysis, we considered that it would reduce equity. |

## Acceptability

Is the intervention acceptable to key stakeholders?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ No<br>○ Probably no<br>● Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | Survey and observational research suggests the following regarding acceptability and barriers associated with anticoagulation and thrombolysis in the pediatric population:<br><br>One survey of American Society of Pediatric Hematology/Oncology members demonstrates the wide variation in treatment approaches between practitioners, in this case with respect to thrombolytic therapy of pediatric VTE. With respect to the preferred agent, the survey results confirm that tPA has become the thrombolytic drug of choice in pediatric patients, although a small percentage of respondents stated a preference for others, such as urokinase. In contrast, responses varied widely regarding the preferred mode of tPA delivery (systemic vs. catheter-directed vs. use of catheter-directed therapy on a salvage basis) without clear majority preference for any single modality. Since the overwhelming majority of respondents (95%) reported having access to pediatric interventional radiology services, preferences for a given mode of tPA administration clearly could not be ascribed to IR availability and were not associated with any of the other queried professional demographic data. (Yee 2009).<br><br>Observational research suggests the following regarding acceptability and barriers associated with the intervention: In Australia a prospective chart audit in a tertiary paediatric centre assessed the level of compliance of antithrombotic medication use in current practice with guidelines across a 100-day prospective chart audit in 2008-2009. The study showed that the level of compliance for use of antithrombotic medications for the indications of DVT and PE was 98.8% and 61.5%, respectively. High compliance was correlated with strong recommendations, with low compliance found especially in areas where recommendations were based on 'weak' evidence. This reflects clinician confidence in the strength of evidence currently available for paediatric antithrombotic therapy where there may be barriers associated with the use of the intervention where only low-quality, inconsistent, or indirect evidence extrapolated from adult data is available. (Peng et al., 2011) | We judged that thrombolysis is probably acceptable by stakeholders. |

## Feasibility

Is the intervention feasible to implement?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ No<br>○ Probably no<br>○ Probably yes | No research evidence was identified. | Thrombolysis availability varies across the world. Feasible in some countries and not in |

| | | |
|---|---|---|
| ○ Yes<br>● Varies<br>○ Don't know | | other countries. |

## SUMMARY OF JUDGEMENTS

| | JUDGEMENT | | | | | | |
|---|---|---|---|---|---|---|---|
| **PROBLEM** | No | Probably no | Probably yes | **Yes** | | Varies | Don't know |
| **DESIRABLE EFFECTS** | Trivial | Small | Moderate | Large | | Varies | **Don't know** |
| **UNDESIRABLE EFFECTS** | Large | **Moderate** | Small | Trivial | | Varies | Don't know |
| **CERTAINTY OF EVIDENCE** | **Very low** | Low | Moderate | High | | | No included studies |
| **VALUES** | Important uncertainty or variability | Possibly important uncertainty or variability | **Probably no important uncertainty or variability** | No important uncertainty or variability | | | |
| **BALANCE OF EFFECTS** | Favors the comparison | **Probably favors the comparison** | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | Don't know |
| **RESOURCES REQUIRED** | **Large costs** | Moderate costs | Negligible costs and savings | Moderate savings | Large savings | Varies | Don't know |
| **CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES** | **Very low** | Low | Moderate | High | | | No included studies |
| **COST EFFECTIVENESS** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **EQUITY** | Reduced | **Probably reduced** | Probably no impact | Probably increased | Increased | Varies | Don't know |
| **ACCEPTABILITY** | No | Probably no | **Probably yes** | Yes | | Varies | Don't know |
| **FEASIBILITY** | No | Probably no | Probably yes | Yes | | **Varies** | Don't know |

## TYPE OF RECOMMENDATION

| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | Strong recommendation for the intervention |
|---|---|---|---|---|
| ● | ○ | ○ | ○ | ○ |

## CONCLUSIONS

### Recommendation

**Patietns with Unilateral RVT:**

**The ASH/ISTH guideline panel suggests/recommends using anticoagulation alone rather using thrombolysis followed by anticoagulation in pediatric patients with unilateral RVT (conditional recommendation based on very low certainty in the evidence about effects).**

**Patietns with Bilateral RVT:**

**The ASH/ISTH guideline panel suggests using thrombolyis followed by anticoagulation rather usinganticoagultion alone in pediatric patients with bilateral RVT (conditional recommendation based on very low certainty in the evidence about effects).**

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**Previous iteration gradepro:**

**Recommendation A. The ASH guideline panel recommends against using thrombolysis followed by standard anticoagulation, and rather use anticoagulation alone in neonates with non-life-threatening renal vein thrombosis (strong recommendation based on very low certainty in the evidence about effects).**

**Recommendation B. The ASH guideline panel suggests using thrombolysis followed by standard anticoagulation rather than anticoagulation alone in neonates with life-threatening renal vein thrombosis (conditional recommendation based on very low certainty in the evidence about effects).**

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**Published guideline:**

**The ASH guideline panel suggests using thrombolysis followed by standard anticoagulation rather than anticoagulation alone in neonates with life-threatening RVT**

**(conditional recommendation based on very low certainty in the evidence of effects ⨁◯◯◯). Remarks: When the condition is life-threatening (ie, bilateral thrombosis), the panel considered that the beneficial effects of thrombolysis would outweigh the undesirable consequences of the intervention.**

## Justification

## Subgroup considerations

## Implementation considerations

## Monitoring and evaluation

## Research priorities

# REFERENCES SUMMARY


1. NADAC, . National Average Drug Acquisition Cost. Available in: https://data.medicaid.gov/Drug-Pricing-and-Payment/NADAC-National-Average-Drug-Acquisition-Cost-/a4y5-998d [last accessed: March 2018]; 2017.
2. Boulet, S. L., Amendah, D., Grosse, S. D., Hooper, W. C.. Health care expenditures associated with venous thromboembolism among children. Thromb Res; May 2012.
3. Goudie, A., Dynan, L., Brady, P. W., Fieldston, E., Brilli, R. J., Walsh, K. E.. Costs of Venous Thromboembolism, Catheter-Associated Urinary Tract Infection, and Pressure Ulcer. Pediatrics; Sep 2015.
4. Karthikesalingam A, Young EL,Hinchliffe RJ,Loftus IM,Thompson MM,Holt PJ. A systematic review of percutaneous mechanical thrombectomy in the treatment of deep venous thrombosis. Eur J Vasc Endovasc Surg; 2011.
5. Kazley AS, Simpson KN,Simpson A,Jauch E,Adams RJ. Optimizing the Economic Impact of rtPA Use in a Stroke Belt State: The Case of South Carolina. Am Health Drug Benefits; 2013.
6. Biskupiak, J., Ghate, S. R., Jiao, T., Brixner, D.. Cost implications of formulary decisions on oral anticoagulants in nonvalvular atrial fibrillation. J Manag Care Pharm; Nov-Dec 2013.
7. Klarenbach, S., Lee, K., Boucher, M., So, H., Manns, B., Tonelli, M.. Direct Oral Anticoagulants for the Treatment of Venous Thromboembolic Events: Economic Evaluation. 2016.
8. Guanella, R., Ducruet, T., Johri, M., Miron, M. J., Roussin, A., Desmarais, S., Joyal, F., Kassis, J., Solymoss, S., Ginsberg, J. S., Lamping, D. L., Shrier, I., Kahn, S. R.. Economic burden and cost determinants of deep vein thrombosis during 2 years following diagnosis: a prospective evaluation. J Thromb Haemost; Dec 2011.
9. Medicare, . 2017 ASP Drug Pricing files. available in: www.cms.gov/apps/physician-fee-schedule/overview.aspx [last accessed March 2018]; 2017.
10. IMPPG, . International Medical Products Price Guide. [Internet]; 2016.

**Author(s):**
**Question:** Anticoagulation compared to no anticoagulation in pediatric patients with portal vein thrombosis
**Setting:** Inpatient
**Bibliography:** ASH/ISTH 2024 Guidelines for Management of Venous Thromboembolism: Treatment of Pediatric Venous Thromboembolism

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | anticoagulation | no anticoagulation | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | very serious[a] | not serious | not serious | very serious[b] | none | 0/2 (0.0%) | 0/5 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Portal Vein Thrombosis Resolution (Complete and Partial Resolution)[c]** | | | | | | | | | | | | |
| 3[1,2,3] | non-randomised studies | very serious[a] | not serious | not serious[d,e] | very serious[b] | none | 40/56 (71.4%) | 44/72 (61.1%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Portal Vein Progression** | | | | | | | | | | | | |
| 3[1,2,3] | non-randomised studies | very serious[a] | not serious | not serious[d] | very serious[b] | none | 0/56 (0.0%) | 2/73 (2.7%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Portal Hypertension** | | | | | | | | | | | | |
| 1[2] | non-randomised studies | very serious[a] | not serious | not serious[d] | very serious[b] | none | 0/19 (0.0%) | 0/55 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Recurrence of thrombus** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | very serious[a] | not serious | not serious | very serious[b] | none | 0/2 (0.0%) | 0/5 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Bleeding ( not defined)[f]** | | | | | | | | | | | | |
| 3[1,2,3] | non-randomised studies | very serious[a] | not serious | not serious[d] | very serious[b] | none | 1/56 (1.8%) | 0/73 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |

**CI:** confidence interval

**Explanations**

a. We assessed ROB, using ROBINsI. We downgraded for risk of bias due to concerns about selection bias without adjustment for known confounders.
b. We downgraded for imprecision because of small sample size and sample number of patients.
c. Solgun et al 2023 reports the mean duration for thrombus resolution (38.6 days in AC and 12.6 in no AC)
d. Observational studies performed in Argentina and Turkey
e. Cervio et al 2021 reported portal vein thrombosis while Bhatt et al 2018 reported complete and partial resolution
f. No definition for bleeding

**References**

1.CH, van,Ommen, KA, Bergman, M, Boerma, HA, Bouma, AE, Donker, M, Gouvernante, CV, Hulzebos, D, Khandour, R, Knol, MA, Raets, KD, Liem, RA, van,Lingen, M, van,de,Loo, E, Lopriore, M, van,der,Putten, JJ, Sol, MH, Suijker, DC, Vijlbrief, R, Visser, MM, van,Weissenbruch. NEOnatal Central-venous Line Observational study on Thrombosis (NEOCLOT): . Journal of thrombosis and haemostasis : JTH; 2023.
2.Mihir D. Bhatt, Vishal Patel,Michelle L. Butt,Anthony K.C. Chan,Bosco Paes,. Outcomes following neonatal portal vein thrombosis: A descriptive, single-center study and review of anticoagulant therapy. Pediatr Blood Cancer; 2018.
3.Cervio C, Hepner M,Bianco B,Pieroni G,Annetta E,Frontroth JP,Sciuccati G.. Portal Vein Thrombosis(PVT) in Neonates and Children: A Ten-year Prospective Registry of a Tertiary Care Single-centre in Argentina [abstract]. Res Pract Thromb Haemost.; 2021.

# QUESTION

| Should anticoagulation vs. no anticoagulation be used for pediatric patients with portal vein thrombosis? | |
|---|---|
| **POPULATION:** | pediatric patients with portal vein thrombosis |
| **INTERVENTION:** | anticoagulation |
| **COMPARISON:** | no anticoagulation |
| **MAIN OUTCOMES:** | Portal Vein Thrombosis Resolution (Complete and Partial Resolution); Portal Vein Progression; Portal Hypertension; Bleeding; Mortality (In studies data was requested for); |
| **SETTING:** | Inpatient |
| **PERSPECTIVE:** | Clinical recommendation – population perspective |
| **BACKGROUND:** | Portal vein thrombosis (PVT) is a clinical condition usually described as rare, but it is being more commonly recognized and detected with rates ranging from 1 in 100,000 live births to 36 per 1,000 neonatal intensive care unit admissions. (1) Its etiology is different if the affected population includes neonates, children or adults. In neonates PVT is usually secondary to umbilical vein catheters (UVC) and infection (2) (3) associated with other possible factors such as low birth weight, hypoxia, hypercoagulability, low flow state, congenital malformations, among others. In children, PVT is associated with liver transplantation, splenectomy, sickle cell disease, and abdominal sepsis, (1) while in adults it is related to cirrhosis from several causes. |

# ASSESSMENT

## Problem

Is the problem a priority?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ No<br>○ Probably no<br>○ Probably yes<br>● Yes<br>○ Varies<br>○ Don't know | Associated with the increasing use of intensive care units and UVCs in neonates, the use of better diagnostic techniques and awareness might be leading to an increase PVT detection rate. If PVT is not resolved, there may be long-term complications like portal hypertension (PHTN) and lobar atrophy.<br>There is currently no agreement and scarce evidence on the use of anticoagulants (AC) for the treatment of PVT and prevention of these long-term complications. | |
| | Adolopment | |
| ○ No<br>○ Probably no<br>○ Probably yes<br>● Yes<br>○ Varies<br>○ Don't know | Associated with the increasing use of intensive care units and UVCs in neonates, the use of better diagnostic techniques and awareness might be leading to an increase PVT detection rate. If PVT is not resolved there may be long term complications such as portal hypertension (PHTN), variceal bleeding and lobar atrophy. There is currently no agreement and scarce evidence on the use of anticoagulants (AC) for the treatment of PVT and prevention of these long-term complications. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Desirable Effects

How substantial are the desirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Trivial<br>○ Small<br>○ Moderate<br>○ Large<br>○ Varies<br>● Don't know | | The panel noted that in this condition it is important to consider the degree of occlusive thrombosis (prognosis differs among occlusive vs non-occlusive PVTs), and whether the desired outcomes may favor treatment with anticoagulant therapy compared to no treatment with anticoagulant therapy. |

| Outcomes | № of participants (studies) Follow up | Quality of the evidence (GRADE) | Impact |
|---|---|---|---|
| Mortality follow up: range 1 week to 5 years | (3 observational studies) | ⨁◯◯◯ VERY LOW[a,b] | Studies reported only 16% overall risk of death with no information for each group separately. In patients with no AC, spontaneous resolution of PVT is reported from 70% to 77% of patients with non-occlusive clots, and 31% to 48% with occlusive clots. One study [Morag 2006] describes 'no association' between AC and poor outcomes. |
| Neonatal Bleeding –Severe (reported as 'major bleeding') assessed with clinical assessment follow up: range 1 week to 12 weeks | (5 observational studies) | ⨁◯◯◯ VERY LOW[b,c,d] | The rate of major bleedings in all patients with PVT varies from 4.5% to 80%, and it's mostly related to esophageal varices and portal hypertension. Studies did not report bleeding events separately in those receiving and not receiving anticoagulation. [Morag 2006, Alvares 1983, Peter 2003] The rate of bleeding (from other pediatric populations) ranges from 3% to 5% with LMWH, UFH or VKA. [Ignjatovic 2010, Massicotte 2003] |

Experts from the panel expressed (in an online survey) that they have managed in total around 800 patients during their years of practice. Of these, about 50% are treated without anticoagulation; of these less than 5% have a progression of the thrombuss, and <1% die.

| | | | |
|---|---|---|---|
| Portal vein thrombosis (described as any VTE or 'no resolution' of the PVT) assessed with clinical diagnosis and imaging follow up: range 1 week to 12 weeks | (1 observational study) | ⊕◯◯◯ VERY LOW[b,c] | The rate of thrombotic events on each group of study is unknown. There is no distinction between groups on thrombotic outcomes. [Morag 2006] In patients with no AC, spontaneous resolution of PVT occurs in 70% to 77% of patients with non-occlusive clots, and 31% to 48% in those with occlusive clots. The same study describes 'no association' between AC and poor outcomes. |
| Heparin induced thrombocytopenia | (2 observational studies) | ⊕◯◯◯ VERY LOW[e] | Two observational studies reported the risk of HIT varies for pediatric patients. The risk is estimated to be close to 0% in children receiving standard heparin or LMWH. The risk of HIT is 2.3% (14/612) in children receiving heparin in the PICU. [f] |

a. These are all case series of retrospective nature obtained from one systematic review [Williams 2011]
b. No confidence intervals reported but with low absolute numbers of participants and events.
c. All case series with no comparison group.
d. The rate of bleeding in the anticoagulation group is obtained indirectly from other pediatric populations [Massicotte 2003]
e. Single arm study with no comparison to detect an effect

| | | |
|---|---|---|
| | f. Newall 2003; Schmugge 2002<br><br>NOTE: For a complete assessment see the EVIDENCE PROFILE.<br>**Undesirable consequences (additional information)**<br>Anticoagulation carries the risk of bleeding/hemorrhagic episodes. There are no studies assessing the risk of major or minor bleeding in patients with PVT. We assessed the usual risk of major bleeding from anticoagulants (LMWH, VKA, UFH) from one randomized trial (Massicotte et al., 2003) of LMWH (reviparin) for the prevention of thrombosis against UFH/VKA. The study was closed prematurely for poor accrual. The study included 186 patients and had a 15% rate of lost to follow up. One patient in the UFH/VKA group had a major bleeding (1.1%) with zero in the LMWH group. Minor bleeding occured in 53% of the LMWH group vs 44.7% in the UFH/VKA group. Others report the frequency of bleeding with LMWH from 0.7% to 3% (Ignjatovic et al., 2010). | |
| | Adolopment | |
| ○ Trivial<br>○ Small<br>○ Moderate<br>○ Large<br>○ Varies<br>● Don't know | *See Appendix 1*<br>**Explanations**<br><br>a. Solgun et al 2023 reports the mean duration for thrombus resolution (38.6 days in AC and 12.6 in no AC)<br>b. According to Robins I, the studies were found to have serious or critical risk of bias<br>c. Observational studies performed in Argentina and Turkey<br>d. Cervio et al 2021 reported portal vein thrombosis while Bhatt et al 2018 reported complete and partial resolution<br>e. Small number of patients with event<br>For Bhatt et al. mean follow-up time was 16.6 months, while for Cervio et al median follow up time for neonates was 4.4 years and 2.7 years for older children.<br><br>**References**<br><br>1.Mihir D. Bhatt, Vishal Patel,Michelle L. Butt,Anthony K.C. Chan,Bosco Paes,. Outcomes following neonatal portal vein thrombosis: A descriptive, single-center study and review of anticoagulant therapy. Pediatr Blood Cancer; 2018.<br>2.Cervio C, Hepner M,Bianco B,Pieroni G,Annetta E,Frontroth JP,Sciuccati G.. Portal Vein Thrombosis(PVT) in Neonates and Children: A Ten-year Prospective Registry of a Tertiary Care Single-centre in Argentina [abstract]. Res Pract Thromb Haemost.; 2021. | • Panel was unsure of the magnitude on patient clinical outcomes; however, panel also thinks there may be a likely small desirable effect on decreasing the progression of the clot which is an imaging/clot related outcomes.<br>• Selection for which patients took anticoagulation and which did not take anticoagulation may have occurred in the studies.<br>• Clot resolution and progression are imaging outcomes and not clinical outcomes.<br>• Spontaneous resolution does occur in portal vein thrombosis. The conditions such as occlusive help determine whether we anticoagulated or not.<br>• Not enough data, high risk of bias, small sample size, may not allow us to change the judgment from the previous guideline.<br>• High certainty of evidence.<br>• The limited data existing for portal hypertension and other long term effects, for which indirect evidence can be used, was argued to support "Don't Know"<br>• Although data were imprecise with small numbers of patients, panel agrees that preventing portal hypertension is of importance. |

## Undesirable Effects

How substantial are the undesirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

| | | |
|---|---|---|
| ○ Large<br>○ Moderate<br>● Small<br>○ Trivial<br>○ Varies<br>○ Don't know | <table><tr><th>Outcomes</th><th>№ of participants (studies) Follow up</th><th>Quality of the evidence (GRADE)</th><th>Impact</th></tr><tr><td>Mortality<br>follow up: range 1 week to 5 years</td><td>(3 observational studies)</td><td>⨁◯◯◯<br>VERY LOW[a,b]</td><td>Studies reported only 16% overall risk of death with no information for each group separately. In patients with no AC, spontaneous resolution of PVT is reported from 70% to 77% of patients with non-occlusive clots, and 31% to 48% with occlusive clots. One study [Morag 2006] describes 'no association' between AC and poor outcomes.</td></tr><tr><td>Neonatal Bleeding –Severe (reported as 'major bleeding')<br>assessed with: clinical assessment<br>follow up: range 1 week to 12 weeks</td><td>(5 observational studies)</td><td>⨁◯◯◯<br>VERY LOW[b,c,d]</td><td>The rate of major bleedings in all patients with PVT varies from 4.5% to 80%, and it's mostly related to esophageal varices and portal hypertension. Studies did not report bleeding events separately in those receiving and not receiving anticoagulation. [Morag 2006, Alvares 1983, Peter 2003] The rate of bleeding (from other pediatric populations) ranges from 3% to 5% with LMWH, UFH or VKA. [Ignjatovic 2010, Massicotte 2003]</td></tr></table> | Bleeding risks are important to consider in the anticipated undesirable effects. If the condition is accompanied by portal hypertension, the risk increases; and the risk also can be influenced by age (neonates vs children). |

| | | | |
|---|---|---|---|
| Portal vein thrombosis (described as any VTE or 'no resolution' of the PVT)<br>assessed with: clinical diagnosis and imaging<br>follow up: range 1 weeks to 12 weeks | (1 observational study) | ⊕◯◯◯<br>VERY LOW[b,c] | The rate of thrombotic events on each group of study is unknown. There is no distinction between groups on thrombotic outcomes. [Morag 2006] In patients with no AC, spontaneous resolution of PVT occurs in 70% to 77% of patients with non-occlusive clots, and 31% to 48% in those with occlusive clots. The same study describes 'no association' between AC and poor outcomes. |
| Heparin induced thrombocytopenia | (2 observational studies) | ⊕◯◯◯<br>VERY LOW[e] | Two observational studies reported the risk of HIT varies for pediatric patients. The risk is estimated to be close to 0% in children receiving standard heparin or LMWH. The risk of HIT is 2.3% (14/612) in children receiving heparin in the PICU. [f] |

a. These are all case series of retrospective nature obtained from one systematic review [Williams 2011]
b. No confidence intervals reported but with low absolute numbers of participants and events.
c. All case series with no comparison group.
d. The rate of bleeding in the anticoagulation group is obtained indirectly from other pediatric populations [Massicotte 2003]
e. Single arm study with no comparison to detect an effect

| | | |
|---|---|---|
| | f. Newall 2003; Schmugge 2002<br><br>NOTE: For a complete assessment see the EVIDENCE PROFILE.<br>**Undesirable consequences (additional information)**<br>Anticoagulation carries the risk of bleeding/hemorrhagic episodes. There are no studies assessing the risk of major or minor bleeding in patients with PVT. We assessed the usual risk of major bleeding from anticoagulants (LMWH, VKA, UFH) from one randomized trial (Massicotte et al., 2003) of LMWH (reviparin) for the prevention of thrombosis against UFH/VKA. The study was closed prematurely for poor accrual. The study included 186 patients and had a 15% rate of lost to follow up. One patient in the UFH/VKA group had a major bleeding (1.1%) with zero in the LMWH group. Minor bleeding occured in 53% of the LMWH group vs 44.7% in the UFH/VKA group. Others report the frequency of bleeding with LMWH from 0.7% to 3% (Ignjatovic et al., 2010). | |
| | Adolopment | |
| ○ Large<br>○ Moderate<br>● Small<br>○ Trivial<br>○ Varies<br>○ Don't know | *See Appendix 2*<br><br>**Explanations**<br><br>a. According to Robins I, the studies were found to have serious or critical risk of bias<br>b. Observational studies performed in Argentina and Turkey<br>c. Small number of patients with event<br>d. No definition for bleeding<br>For Bhatt et al. mean follow-up time was 16.6 months, while for Cervio et al median follow up time for neonates was 4.4 years and 2.7 years for older children.<br><br>**References**<br><br>1.Mihir D. Bhatt, Vishal Patel,Michelle L. Butt,Anthony K.C. Chan,Bosco Paes,. Outcomes following neonatal portal vein thrombosis: A descriptive, single-center study and review of anticoagulant therapy. Pediatr Blood Cancer; 2018.<br>2.Cervio C, Hepner M,Bianco B,Pieroni G,Annetta E,Frontroth JP,Sciuccati G.. Portal Vein Thrombosis(PVT) in Neonates and Children: A Ten-year Prospective Registry of a Tertiary Care Single-centre in Argentina [abstract]. Res Pract Thromb Haemost.; 2021.<br><br>**Undesirable consequences (additional information)**There are no studies assessing the risk of mortality in patients with PVT. Scarce data was found assessing the risk of major or minor bleeding in patients with PVT. No data was found on incidence of heparin induced thrombocytopenia (HIT) for patients with portal vein thrombosis. A systematic review (4) found 0 cases of HIT among 335 neonates reported by 6 studies taking heparin for various reasons. HIT among older children ( more than 6 months to 16 years of age) was found in 1 patients among 414 reported by 5 studies. | • The reason for having no bleeding events may be due to the small sample size.<br>• No intraventricular bleeding reported. This may indicate an underreporting of data reported to bleeding.<br>• Only anticoagulation related bleeding may have been considered in the studies.<br>• May have missed portal hypertension and variceal bleeding due to not following them up long enough.<br>• Bleeding due to anticoagulation versus anticoagulation due to portal hypertension should not be lumped.<br>• Use of data available for other thromboses. (indirect data) For desirable effects, the indirectness may not be as informative.<br>• Decision on whether to look at data specific for PVT versus indirect data from other studies. Although the data from PVT studies may lead to trivial effect, but considering the strength of the indirect data, the panel agrees that this would push the decision to small. |

## Certainty of evidence

What is the overall certainty of the evidence of effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

| | | |
|---|---|---|
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | Certainty of the evidence of effects was judged as 'very low'. All studies are case series with no comparison arm (high risk of bias), with indirectness for the bleeding outcome. | |
| | Adolopment | |
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | Certainty of the evidence of effects was judged as 'very low'. Although the studies were comparative studies, they had high risk of bias, with imprecision due to small number of events in all outcomes. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Values

Is there important uncertainty about or variability in how much people value the main outcomes?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Important uncertainty or variability<br>● Possibly important uncertainty or variability<br>○ Probably no important uncertainty or variability<br>○ No important uncertainty or variability | **<u>Utility related information:</u>**<br>**The relative importance of outcomes:**<br>**<u>Results from Panel Members' Utility Rating Survey</u>**:<br>Utilities rated on the visual analog scale, where 0 represents death and 1 represents full health, were as follows.<br>Pulmonary embolism – Severe marker state: 0.31<br>Pulmonary embolism – Moderate marker state: 0.49<br>Deep vein thrombosis (proximal) – Severe marker state: 0.49<br>Deep vein thrombosis (proximal) – Moderate marker state: 0.61<br>Deep vein thrombosis (distal) – Severe marker state: 0.56<br>Deep vein thrombosis (distal) – Moderate marker state: 0.68<br>Major bleeding: 0.30<br>Neonatal Bleeding – Severe: 0.30<br>Infant Bleeding – Severe: 0.26<br>Portal vein thrombosis in a child: 0.50<br>Heparin-induced thrombocytopenia: 0.59<br>**We did not identify utility related information or non-utility information for the outcomes of interest specific to the pediatric population in the literature.**<br><br>**<u>Additional information from the adult population:</u>**<br>**Our systematic review for the adult population found that the relative importance of the outcomes is as follows:**<br>Pulmonary embolism: 0.63-0.93 (different methods) (14, 15, 16)<br>Deep vein thrombosis: 0.64-0.99 (different methods) (15, 14, 16, 17, 18)<br>Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) (14, 16)<br>Muscular bleeding: 0.76 (time trade off) (16)<br>Minor intracranial bleeding event: 0.75 (standard gamble) (14) | Consideration about the variability in the significance of the portal vein thrombosis, depending on age and clinical circumstance. For example, portal vein thrombosis in a liver transplant patient as compared to a non-occlusive CVC related PVT in a neonate. Althgough the latter is more the focus of this guideline question. |

| | | |
|---|---|---|
| | Major intracranial bleeding event: 0.15 (standard gamble) (14)<br>Central nervous system bleeding: 0.29-0.60 (standard gamble) (19, 7)<br>Treatment with LMWH: 0.993 (time trade off) (20)<br>Treatment with warfarin (as a surrogate): 0.989 (time trade off)(20)<br><br>**<u>We also identified in the systematic review the following non-utility information from the adult population:</u>**<br>**Anticoagulant therapy**<br>Adult patients highly value the benefits of risk reduction in VTE recurrence and post-thrombosis syndrome(16). Patients would favor efficacy and safety over convenience of route of administration (6). Further, patients would like to avoid adverse events but most of them are "not afraid of" the adverse events (5, 6, 7). For anticoagulant therapy in general, most patients would prefer the oral doses compared with injections, this is mainly because of treatment burden due to injection(5, 6). For patients with venographically proven deep venous thrombosis, 15 of the 19 patients expressed a preference for the subcutaneous route for administration of heparin over intravenous administration (8).<br>**Warfarin**<br>Adult patients would like to switch to another anticoagulant if it is as effective as warfarin; this is mainly due to the treatment burden associated with monitoring, injection and dietary change due to warfarin use (9). In another study approximately half of the patients did not consider VKA therapy particularly difficult to manage (10).<br>**LMWH**<br>For adult patients receiving low molecular weight heparin, patients placed a high score on "importance of ease of use", "expectations of symptom relief", and "confidence in the treatment to prevent blood clots" while they had a low score of treatment-related side effects (bruise, bleeding). (11, 12). | |
| | Adolopment | |
| ○ Important uncertainty or variability<br>● Possibly important uncertainty or variability<br>○ Probably no important uncertainty or variability<br>○ No important uncertainty or variability | **<u>Utility related information:</u>**<br>**The relative importance of outcomes:**<br>**<u>Results from Panel Members' Utility Rating Survey</u>**:<br>Utilities rated on the visual analog scale, where 0 represents death and 1 represents full health, were as follows.<br>Pulmonary embolism – Severe marker state: 0.31<br>Pulmonary embolism – Moderate marker state: 0.49<br>Deep vein thrombosis (proximal) – Severe marker state: 0.49<br>Deep vein thrombosis (proximal) – Moderate marker state: 0.61<br>Deep vein thrombosis (distal) – Severe marker state: 0.56<br>Deep vein thrombosis (distal) – Moderate marker state: 0.68<br>Major bleeding: 0.30<br>Neonatal Bleeding – Severe: 0.30<br>Infant Bleeding – Severe: 0.26<br>Portal vein thrombosis in a child: 0.50<br>Heparin-induced thrombocytopenia: 0.59<br>**We did not identify utility related information or non-utility information for the outcomes of interest specific to the pediatric population in the literature.**<br><br>**<u>Additional information from the adult population:</u>Our systematic review for the adult population found that the relative importance of the outcomes is as follows:** Pulmonary embolism: 0.63-0.93 (different methods) (14, 15, 16)Deep vein thrombosis: 0.64-0.99 (different methods) (15, 14, 16, 17, 18) Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) (14, 16)Muscular bleeding: 0.76 (time trade off) (16) Minor intracranial bleeding event: 0.75 (standard gamble) (14) Major intracranial bleeding event: 0.15 (standard gamble) (14) Central nervous system bleeding: 0.29-0.60 (standard gamble) (19, 7) Treatment with LMWH: 0.993 (time trade off) (20)( Treatment with warfarin (as a surrogate): 0.989 (time trade off)(20) | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

| | | |
|---|---|---|
| | **<u>We also identified in the systematic review the following non-utility information from the adult population:</u>** **Anticoagulant therapy** Adult patients highly value the benefits of risk reduction in VTE recurrence and post-thrombosis syndrome(16). Patients would favor efficacy and safety over convenience of route of administration (6). Further, patients would like to avoid adverse events but most of them are "not afraid of" the adverse events (5, 6, 7). For anticoagulant therapy in general, most patients would prefer the oral doses compared with injections, this is mainly because of treatment burden due to injection(5, 6). For patients with venographically proven deep venous thrombosis, 15 of the 19 patients expressed a preference for the subcutaneous route for administration of heparin over intravenous administration (8). **Warfarin** Adult patients would like to switch to another anticoagulant if it is as effective as warfarin; this is mainly due to the treatment burden associated with monitoring, injection and dietary change due to warfarin use (9). In another study approximately half of the patients did not consider VKA therapy particularly difficult to manage (10). **LMWH** For adult patients receiving low molecular weight heparin, patients placed a high score on "importance of ease of use", "expectations of symptom relief", and "confidence in the treatment to prevent blood clots" while they had a low score of treatment-related side effects (bruise, bleeding). (11, 12).<br>**Information from the pediatric population:**<br>A qualitiative study recognized that at home enoxaparin therapy in infants was found to be "a traumatizing experience" by the parents (13). | |

## Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>● Varies<br>○ Don't know | | This decision depends on several factors:<br><br>**The balance probably favours anticoagulation if:**<br>> it is an occlusive PVT<br>> it is present in a liver transplant patient<br>> it is an idiopathic PVT<br><br>**The balance probably favours NO anticoagulation if:**<br>> it is a non-occlusive PVT<br>> presence of portal hypertension presumably due to an old clot<br><br>Also, consider that the limited evidence may preclude the ability to identify those at greater risk of PVT sequelae who may have a variable profile in terms of intervention benefits. |
| | Adolopment | |

| | | |
|---|---|---|
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>● Varies<br>○ Don't know | In (21) 9/32 (28%) patients with occlusive PVT developed portal hypertension, 9/32 (28%) developed cavernous transformation and 6/32 (18.7%) died. In non- occlusive PVT 1/25 (4%) developed portal hypertension, 2/25 (8%) developed cavernous transformation, 2/25 (8%) died. | This decision depends on several factors:<br><br>**The balance probably favours anticoagulation if:**<br>> it is an occlusive PVT<br>> it is present in a liver transplant patient<br>> it is an idiopathic PVT<br>>it is **non-neonatal** non-occlusive PVT<br><br>**The balance probably favours NO anticoagulation if:**<br>> it is a **neonatal** non-occlusive PVT<br>> presence of portal hypertension presumably due to an old clot<br><br>Also, consider that the limited evidence may preclude the ability to identify those at greater risk of PVT sequelae who may have a variable profile in terms of intervention benefits. |

## Resources required

How large are the resource requirements (costs)?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Large costs<br>● Moderate costs<br>○ Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br>○ Varies<br>○ Don't know | No research evidence was identified on anticoagulation costs for portal vein thrombosis.<br>Two studies reported the costs of disease from pediatric patients with any VTE. One reported for 834 pediatric patients with VTE a median annual expenditure of $25,258 and $24,934 USD in Medicaid and private insurance patients respectively. (22) Another study found that patients with VTE had an increased 8.1 inpatient days and excess average costs of $27,686 USD. (23)<br>**Additional information from adult population:**<br>In relation to the reported costs of anticoagulation, the direct cost per week with warfarin in adults ranges from $3.54 to $11.44 USD while this number in Canada decreases to $0.49 to $0.84 CAD per week. (24, 25, 26, 27) With heparin, the costs per unit range from $0.18 per 10 units, to $0.212 per 1000 units (28) with a cost per week of $37.00 USD and $11.14 CAD per day in Canada. (26, 27) LMWH (enoxaparin) cost varies. The wholesale cost in low and middle income economies is reported at about $13 to $75 USD per week. (29) In the United States the wholesale cost is about $98.91 USD per day as of 2016 (30). | Consideration about differentiation in costs among subgroups (e.g., occlusive vs non-occlusive) |
| | Adolopment | |
| ○ Large costs<br>● Moderate costs<br>○ Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br>○ Varies<br>○ Don't know | No research evidence was identified on anticoagulation costs for portal vein thrombosis.<br><br>Two studies reported the costs of disease from pediatric patients with any VTE. One reported for 834 pediatric patients with VTE a median annual expenditure of $25,258 and $24,934 USD in Medicaid and private insurance patients respectively. (22) Another study found that patients with VTE had an increased 8.1 inpatient days and excess average costs of $27,686 USD. (23)<br>**Additional information from adult population:**In relation to the reported costs of anticoagulation, the direct cost per week with warfarin in adults ranges from $3.54 to $11.44 USD while this number in Canada decreases to $0.49 to $0.84 CAD per week. (24, 25, 26, 27) With heparin, the costs per unit range from $0.18 per 10 units, to $0.212 per 1000 units (28) with a cost per week of $37.00 USD and $11.14 CAD per day in Canada. (26, 27) LMWH (enoxaparin) cost varies. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

| | | |
|---|---|---|
| | The wholesale cost in low and middle income economies is reported at about $13 to $75 USD per week. (29) In the United States the wholesale cost is about $98.91 USD per day as of 2016 (30). | |

## Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | No evidence research identified. | |
| | Adolopment | |
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | No evidence research identified. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

| | | |
|---|---|---|
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>● Varies<br>○ No included studies | No research evidence was identified. | |
| | Adolopment | |
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>● Varies<br>○ No included studies | No research evidence was identified. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Equity

What would be the impact on health equity?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Reduced<br>○ Probably reduced<br>● Probably no impact<br>○ Probably increased<br>○ Increased<br>○ Varies<br>○ Don't know | No research evidence was identified. | |
| | Adolopment | |
| ○ Reduced<br>○ Probably reduced<br>● Probably no impact<br>○ Probably increased<br>○ Increased<br>○ Varies<br>○ Don't know | No research evidence was identified.<br>One study conducted in Neatherlands found that neighborhoods with higher social economic status had lower incidence of VTE (31) | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Acceptability

Is the intervention acceptable to key stakeholders?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ No<br>○ Probably no<br>● Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | Observational research suggests the following regarding acceptability and barriers associated with the intervention:<br><br>In Australia a prospective chart audit in a tertiary paediatric centre assessed the level of compliance of antithrombotic medication use in | |

| | | |
|---|---|---|
| | current practice with guidelines across a 100-day prospective chart audit in 2008-2009. The study showed that the level of compliance for use of antithrombotic medications for the indications of DVT and PE was 98.8% and 61.5%, respectively. High compliance was correlated with strong recommendations, with low compliance found especially in areas where recommendations were based on 'weak' evidence. This reflects clinician confidence in the strength of evidence currently available for paediatric antithrombotic therapy where there may be barriers associated with the use of the intervention where only low-quality, inconsistent, or indirect evidence extrapolated from adult data is available. (Peng et al., 2011)<br><br>A key area where there was disagreement between clinical practice and guidelines was the routine use of unfractionated heparin infusions in children with central venous lines (Peng et al., 2011). | |
| | Adolopment | |
| ○ No<br>○ Probably no<br>● Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Feasibility

Is the intervention feasible to implement?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ No<br>○ Probably no<br>● Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | No research evidence identified. | |
| | Adolopment | |
| ○ No<br>○ Probably no<br>● Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | No research evidence identified. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

# SUMMARY OF JUDGEMENTS

| CRITERIA | ORIGINAL | IMPORTANCE FOR DECISION | ADOLOPMENT | IMPORTANCE FOR DECISION |
|---|---|---|---|---|
| PROBLEM | Yes | | Yes | |
| DESIRABLE EFFECTS | Don't know | | Don't know | |
| UNDESIRABLE EFFECTS | Small | | Small | |
| CERTAINTY OF EVIDENCE | Very low | | Very low | |
| VALUES | Possibly important uncertainty or variability | | Possibly important uncertainty or variability | |

| CRITERIA | ORIGINAL | IMPORTANCE FOR DECISION | ADOLOPMENT | IMPORTANCE FOR DECISION |
|---|---|---|---|---|
| BALANCE OF EFFECTS | Varies | | Varies | |
| RESOURCES REQUIRED | Moderate costs | | Moderate costs | |
| CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES | Very low | | Very low | |
| COST EFFECTIVENESS | Varies | | Varies | |
| EQUITY | Probably no impact | | Probably no impact | |
| ACCEPTABILITY | Probably yes | | Probably yes | |
| FEASIBILITY | Probably yes | | Probably yes | |

## TYPE OF RECOMMENDATION

Original

| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | **Conditional recommendation for the intervention** | Strong recommendation for the intervention |
|---|---|---|---|---|
| ○ | ○ | ○ | ● | ○ |

Adolopment

| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | **Conditional recommendation for the intervention** | Strong recommendation for the intervention |
|---|---|---|---|---|
| ○ | ○ | ○ | ● | ○ |

## CONCLUSIONS

Original

### Recommendation

**Recommendation A. The ASH guideline panel suggests using anticoagulation rather than no anticoagulation in pediatric patients with portal vein thrombosis (PVT) with occlusive thrombus, post liver transplant and idiopathic PVT (conditional recommendation based on very low certainty in the evidence about effects).**

***Recommendation B. The ASH guideline panel suggests against using anticoagulation, and rather use no anticoagulation, in pediatric patients with portal vein thrombosis with non-occlusive thrombus or portal hypertension (conditional recommendation based on very low certainty in the evidence about effects).***

### Justification

The balance probably favors anticoagulation for occlusive PVT; present in a liver transplant patient; or idiopathic PVT. The balance probably favors NO anticoagulation for non-occlusive PVT or in the presence of portal hypertension suggesting the thrombosis is old. In addition, the panel considered that the limited evidence may preclude the ability to identify those at greater risk of PVT sequelae who may have a variable profile in terms of intervention benefits.

Adolopment

## Recommendation

**Recommendation A. The ASH/ISTH guideline panel suggests using anticoagulation rather than no anticoagulation in neonates and children with occlusive portal vein thrombosis (PVT), and in children with non-occlusive PVT, post liver transplant PVT, and idiopathic PVT, (conditional recommendation based on very low certainty in the evidence about effects).**

***Recommendation B. The ASH/ISTH guideline panel suggests against using anticoagulation rather than using anticoagulation, in neonates with non-occlusive PVT and in children who have already developed portal hypertension (conditional recommendation based on very low certainty in the evidence about effects).***

## Justification

The balance probably favors anticoagulation for occlusive PVT; present in a liver transplant patient; or idiopathic PVT. The balance probably favors NO anticoagulation for non-occlusive PVT or in the presence of portal hypertension suggesting the thrombosis is old. In addition, the panel considered that the limited evidence may preclude the ability to identify those at greater risk of PVT sequelae who may have a variable profile in terms of intervention benefits.

## Subgroup considerations

Original

Adolopment

## Implementation considerations

Original

In children who will not be anticoagulated, follow up monitoring is important as extension of clot or organ disfunction may require reconsideration of treatment options.

Adolopment

## Monitoring and evaluation

Original

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Adolopment

## Research priorities

Original

More research needed from randomized or non-randomized studies providing information on the effects of anticoagulation in patients with PVT in different subgroups.

Adolopment

# REFERENCES SUMMARY


1. Williams, S., Chan, A. K.. Neonatal portal vein thrombosis: diagnosis and management. Semin Fetal Neonatal Med; Dec 2011.
2. Schwartz, DS, Gettner, PA, Konstantino, MM, Bartley, CL, Keller, MS, Ehrenkranz, RA. Umbilical venous catheterization and the risk of portal vein thrombosis. J Pediatr; 1997.
3. Rehan, V., Seshia, M. M.. Complications of umbilical vein catheter. Eur J Pediatr; Feb 1994.
4. Avila, M, Shah, V., Brandao, L.,R.. Systematic review on heparin-induced thrombocytopenia in children: a call to action. Thromb Haemost; 2013.
5. Barcellona, D., Contu, P., Sorano, G. G., Pengo, V., Marongiu, F.. The management of oral anticoagulant therapy: the patient's point of view. Thromb Haemost; Jan 2000.
6. Noble, S., Matzdorff, A., Maraveyas, A., Holm, M. V., Pisa, G.. Assessing patients' anticoagulation preferences for the treatment of cancer-associated thrombosis using conjoint methodology. Haematologica; Nov 2015.
7. O'Meara, J. J.,3rd, McNutt, R. A., Evans, A. T., Moore, S. W., Downs, S. M.. A decision analysis of streptokinase plus heparin as compared with heparin alone for deep-vein thrombosis. N Engl J Med; Jun 30 1994.
8. Robinson, A. M., McLean, K. A., Greaves, M., Channer, K. S.. Subcutaneous versus intravenous administration of heparin in the treatment of deep vein thrombosis; which do patients prefer? A randomized cross-over study. Postgrad Med J; Feb 1993.
9. Attaya, S., Bornstein, T., Ronquillo, N., Volgman, R., Braun, L. T., Trohman, R., Volgman, A.. Study of warfarin patients investigating attitudes toward therapy change (SWITCH Survey). Am J Ther; Nov 2012.
10. Wild, D., Murray, M., Donatti, C.. Patient perspectives on taking vitamin K antagonists: a qualitative study in the UK, USA and Spain. Expert Rev Pharmacoecon Outcomes Res; Oct 2009.
11. Baba, M., Al-Masri, M., Salhab, M., El-Ghanem, M.. Patient's Compliance on the Use of Extended Low Molecular Weight Heparin Post Major Pelvic Surgeries in Cancer Patients at King Hussein Cancer Center. Gulf J Oncolog; Jan 2015.
12. Cajfinger, F, Debourdeau, P, Lamblin, A, Benatar, V, Falvo, N, Benhamou, Y. Low-molecular-weight heparins for cancer-associated thrombosis: Adherence to clinical practice guidelines and patient perception in TROPIQUE, a 409-patient prospective observational study. Thromb Res; 2016.
13. Gilmore, H., Jones, S., Monagle, P., Monagle, S., Newall, F.. Investigating the experience of parents who have given their infants enoxaparin at home. Thrombosis Research; 2022.
14. Hogg, K., Kimpton, M., Carrier, M., Coyle, D., Forgie, M., Wells, P.. Estimating quality of life in acute venous thrombosis. JAMA Intern Med; Jun 24 2013.
15. Hogg, K., Shaw, J., Coyle, D., Fallah, P., Carrier, M., Wells, P.. Validity of standard gamble estimated quality of life in acute venous thrombosis. Thromb Res; Oct 2014.
16. Locadia, M., Bossuyt, P. M., Stalmeier, P. F., Sprangers, M. A., van Dongen, C. J., Middeldorp, S., Bank, I., van der Meer, J., Hamulyak, K., Prins, M. H.. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. Thromb Haemost; Dec 2004.
17. Marvig, C. L., Verhoef, T. I., de Boer, A., Kamali, F., Redekop, K., Pirmohamed, M., Daly, A. K., Manolopoulos, V. G., Wadelius, M., Bouvy, M., Maitland-van der Zee, A. H., consortium, Eu-Pact. Quality of life in patients with venous thromboembolism and atrial fibrillation treated with coumarin anticoagulants. Thromb Res; Jul 2015.
18. Utne, K. K., Tavoly, M., Wik, H. S., Jelsness-Jorgensen, L. P., Holst, R., Sandset, P. M., Ghanima, W.. Health-related quality of life after deep vein thrombosis. Springerplus; 2016.
19. Lenert, L. A., Soetikno, R. M.. Automated computer interviews to elicit utilities: potential applications in the treatment of deep venous thrombosis. J Am Med Inform Assoc; Jan-Feb 1997.
20. Marchetti, M., Pistorio, A., Barone, M., Serafini, S., Barosi, G.. Low-molecular-weight heparin versus warfarin for secondary prophylaxis of venous thromboembolism: a cost-effectiveness analysis. Am J Med; Aug 2001.
21. Cervio C, Hepner M,Bianco B,Pieroni G,Annetta E,Frontroth JP,Sciuccati G.. Portal Vein Thrombosis(PVT) in Neonates and Children: A Ten-year Prospective Registry of a Tertiary Care Single-centre in Argentina [abstract]. Res Pract Thromb Haemost.; 2021.
22. Boulet, S. L., Amendah, D., Grosse, S. D., Hooper, W. C.. Health care expenditures associated with venous thromboembolism among children. Thromb Res; May 2012.
23. Goudie, A., Dynan, L., Brady, P. W., Fieldston, E., Brilli, R. J., Walsh, K. E.. Costs of Venous Thromboembolism, Catheter-Associated Urinary Tract Infection, and Pressure Ulcer. Pediatrics; Sep 2015.
24. Biskupiak, J., Ghate, S. R., Jiao, T., Brixner, D.. Cost implications of formulary decisions on oral anticoagulants in nonvalvular atrial fibrillation. J Manag Care Pharm; Nov-Dec 2013.
25. Kearon C, Akl E. Duration of anticoagulant therapy for deep vein thrombosis and pulmonary embolism. Blood; 2014.
26. Klarenbach, S., Lee, K., Boucher, M., So, H., Manns, B., Tonelli, M.. Direct Oral Anticoagulants for the Treatment of Venous Thromboembolic Events: Economic Evaluation. 2016.
27. Guanella, R., Ducruet, T., Johri, M., Miron, M. J., Roussin, A., Desmarais, S., Joyal, F., Kassis, J., Solymoss, S., Ginsberg, J. S., Lamping, D. L., Shrier, I., Kahn, S. R.. Economic burden and cost determinants of deep vein thrombosis during 2 years following diagnosis: a prospective evaluation. J Thromb Haemost; Dec 2011.
28. Medicare, . 2017 ASP Drug Pricing files. available in: www.cms.gov/apps/physician-fee-schedule/overview.aspx [last accessed March 2018]; 2017.
29. IMPPG, . International Medical Products Price Guide. [Internet]; 2016.
30. NADAC, . National Average Drug Acquisition Cost. Available in: https://data.medicaid.gov/Drug-Pricing-and-Payment/NADAC-National-Average-Drug-Acquisition-Cost-/a4y5-998d [last accessed: March 2018]; 2017.
31. Kort, D., van Rein, N., van der Meer, F.J.M., Vermaas, H.W., Wiersma, N., Cannegieter, S.C., Lijfering, W.M.. Relationship between neighborhood socioeconomic status and venous thromboembolism: results from a population‐based study. Journal of Thrombosis and Haemostasis; 2017.

# APPENDICES

Appendix 1

**Author(s):**
**Question:** Anticoagulation compared to no anticoagulation in pediatric patients with portal vein thrombosis
**Setting:** Inpatient
**Bibliography:** ASH/ISTH 2024 Guidelines for Management of Venous Thromboembolism: Treatment of Pediatric Venous Thromboembolism

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | anticoagulation | no anticoagulation | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | very serious[a] | not serious | not serious | very serious[b] | none | 0/2 (0.0%) | 0/5 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Portal Vein Thrombosis Resolution (Complete and Partial Resolution)[c]** | | | | | | | | | | | | |
| 3[1,2,3] | non-randomised studies | very serious[a] | not serious | not serious[d,e] | very serious[b] | none | 40/56 (71.4%) | 44/72 (61.1%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Portal Vein Progression** | | | | | | | | | | | | |
| 3[1,2,3] | non-randomised studies | very serious[a] | not serious | not serious[d] | very serious[b] | none | 0/56 (0.0%) | 2/73 (2.7%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Portal Hypertension** | | | | | | | | | | | | |
| 1[2] | non-randomised studies | very serious[a] | not serious | not serious[d] | very serious[b] | none | 0/19 (0.0%) | 0/55 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Recurrence of thrombus** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | very serious[a] | not serious | not serious | very serious[b] | none | 0/2 (0.0%) | 0/5 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |

**CI:** confidence interval

**Explanations**

a. We assessed ROB, using ROBINsI. We downgraded for risk of bias due to concerns about selection bias without adjustment for known confounders.
b. We downgraded for imprecision because of small sample size and sample number of patients.
c. Solgun et al 2023 reports the mean duration for thrombus resolution (38.6 days in AC and 12.6 in no AC)
d. Observational studies performed in Argentina and Turkey
e. Cervio et al 2021 reported portal vein thrombosis while Bhatt et al 2018 reported complete and partial resolution

**References**

1.CH, van,Ommen, KA, Bergman, M, Boerma, HA, Bouma, AE, Donker, M, Gouvernante, CV, Hulzebos, D, Khandour, R, Knol, MA, Raets, KD, Liem, RA, van,Lingen, M, van,de,Loo, E, Lopriore, M, van,der,Putten, JJ, Sol, MH, Suijker, DC, Vijlbrief, R, Visser, MM, van,Weissenbruch. NEOnatal Central-venous Line Observational study on Thrombosis (NEOCLOT): . Journal of thrombosis and haemostasis : JTH; 2023.
2.Mihir D. Bhatt, Vishal Patel,Michelle L. Butt,Anthony K.C. Chan,Bosco Paes,. Outcomes following neonatal portal vein thrombosis: A descriptive, single-center study and review of anticoagulant therapy. Pediatr Blood Cancer; 2018.
3.Cervio C, Hepner M,Bianco B,Pieroni G,Annetta E,Frontroth JP,Sciuccati G.. Portal Vein Thrombosis(PVT) in Neonates and Children: A Ten-year Prospective Registry of a Tertiary Care Single-centre in Argentina [abstract]. Res Pract Thromb Haemost.; 2021.

Appendix 2

**Author(s):**
**Question:** Anticoagulation compared to no anticoagulation in pediatric patients with portal vein thrombosis
**Setting:** Inpatient
**Bibliography:** ASH/ISTH 2024 Guidelines for Management of Venous Thromboembolism: Treatment of Pediatric Venous Thromboembolism

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | anticoagulation | no anticoagulation | Relative (95% CI) | Absolute (95% CI) | | |
| **Bleeding ( not defined)[d]** | | | | | | | | | | | | |
| 3[1,2,3] | non-randomised studies | very serious[a] | not serious | not serious[c] | very serious[b] | none | 1/56 (1.8%) | 0/73 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |

**CI:** confidence interval

**Explanations**

a. We assessed ROB, using ROBINsI. We downgraded for risk of bias due to concerns about selection bias without adjustment for known confounders.
b. We downgraded for imprecision because of small sample size and sample number of patients.
c. Observational studies performed in Argentina and Turkey
d. No definition for bleeding

**References**

1.CH, van,Ommen, KA, Bergman, M, Boerma, HA, Bouma, AE, Donker, M, Gouvernante, CV, Hulzebos, D, Khandour, R, Knol, MA, Raets, KD, Liem, RA, van,Lingen, M, van,de,Loo, E, Lopriore, M, van,der,Putten, JJ, Sol, MH, Suijker, DC, Vijlbrief, R, Visser, MM, van,Weissenbruch. NEOnatal Central-venous Line Observational study on Thrombosis (NEOCLOT): . Journal of thrombosis and haemostasis : JTH; 2023.
2.Mihir D. Bhatt, Vishal Patel,Michelle L. Butt,Anthony K.C. Chan,Bosco Paes,. Outcomes following neonatal portal vein thrombosis: A descriptive, single-center study and review of anticoagulant therapy. Pediatr Blood Cancer; 2018.
3.Cervio C, Hepner M,Bianco B,Pieroni G,Annetta E,Frontroth JP,Sciuccati G.. Portal Vein Thrombosis(PVT) in Neonates and Children: A Ten-year Prospective Registry of a Tertiary Care Single-centre in Argentina [abstract]. Res Pract Thromb Haemost.; 2021.

**Author(s):**
**Question:** Anticoagulation compared to no anticoagulation in pediatric patients with superficial vein thrombosis
**Setting:** Inpatient
**Bibliography:** ASH/ISTH 2024 Guidelines for Management of Venous Thromboembolism: Treatment of Pediatric Venous Thromboembolism

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | anticoagulation | no anticoagulation | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality (follow-up: 3 months)** | | | | | | | | | | | | |
| 2[1,2] | randomised trials | not serious | not serious | very serious[a] | very serious[b] | none | 2/1718 (0.1%) | 1/1612 (0.1%) | **RR 1.88** (0.17 to 20.70) | **1 more per 1,000** (from 1 fewer to 12 more) | ⨁◯◯◯ Very low | CRITICAL |
| **Mortality (follow-up: 3 months)** | | | | | | | | | | | | |
| 1[3] | randomised trials | not serious | not serious | very serious[a] | serious[b] | none | No deaths occured in either arm. Rivaroxaban: 0/211, Fondaparinux: 0/224, Total: 0/435 | | | | ⨁◯◯◯ Very low | CRITICAL |
| **Pulmonary Embolism (follow-up: 3 months)** | | | | | | | | | | | | |
| 2[1,2] | randomised trials | not serious | not serious | very serious[a] | very serious[b] | none | 2/1718 (0.1%) | 6/1612 (0.4%) | **RR 0.31** (0.06 to 1.54) | **3 fewer per 1,000** (from 3 fewer to 2 more) | ⨁◯◯◯ Very low | CRITICAL |
| **Pulmonary Embolism (follow-up: 3 months)** | | | | | | | | | | | | |
| 1[3] | randomised trials | not serious | not serious | very serious[a] | serious[b] | none | No events of PE developed in either arm. Rivaroxaban: 0/211, Fondaparinux: 0/224, Total: 0/435 | | | | ⨁◯◯◯ Very low | CRITICAL |
| **Deep Vein Thrombosis (follow-up: 3 months)** | | | | | | | | | | | | |
| 2[1,2] | randomised trials | not serious | not serious | very serious[a] | serious[b] | none | 13/1718 (0.8%) | 24/1612 (1.5%) | **RR 0.54** (0.26 to 1.04) | **7 fewer per 1,000** (from 11 fewer to 1 more) | ⨁◯◯◯ Very low | CRITICAL |
| **Deep Vein Thrombosis (follow-up: 3 months)** | | | | | | | | | | | | |
| 1[3] | randomised trials | not serious | not serious | very serious[a] | serious[b] | none | In the rivaroxaban group, 6 patients out of 211 (2.8%) develped DVT while 2 out of 224 (0.8%) in the Fondaparinux group developed DVT | | | | ⨁◯◯◯ Very low | CRITICAL |
| **Deep Vein Thrombosis** | | | | | | | | | | | | |
| 1[4] | non-randomised studies | serious[c] | not serious | not serious | serious[b] | none | Among 209 patients who developed a superficial vein thrombosis and no previous or concurrent DVT, 12 (5.7%) developed a deep vein thrombosis. | | | | ⨁◯◯◯ Very low | CRITICAL |
| **SVT Extension (follow-up: 3 months)** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[1] | randomised trials | not serious | not serious | very serious[a] | not serious | none | 5/1502 (0.3%) | 54/1500 (3.6%) | **RR 0.08** (0.03 to 0.22) | **33 fewer per 1,000** (from 35 fewer to 28 fewer) | ⨁⨁◯◯ Low | CRITICAL |

**SVT Extension (follow-up: 3 months)**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[3] | randomised trials | not serious | not serious | very serious[d] | very serious[b] | none | In the rivaroxaban group, 2 patients out of 211 (0.9%) had SVT extension while 1 out of 224 (0.4%) in the Fondaparinux group had SVT extension | | | | ⨁◯◯◯ Very low | CRITICAL |

**SVT Recurrence (follow-up: 3 months)**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[1] | randomised trials | not serious | not serious | very serious[a] | not serious | none | 8/1502 (0.5%) | 28/1500 (1.9%) | **RR 0.27** (0.12 to 0.59) | **14 fewer per 1,000** (from 16 fewer to 8 fewer) | ⨁⨁◯◯ Low | CRITICAL |

**SVT Reccurence (follow-up: 3 months)**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[3] | randomised trials | not serious | not serious | very serious[a] | serious[b] | none | In the rivaroxaban group, 8 patients out of 211 (3.7%) had SVT Recurrence while 12 out of 224 (5.3%) in the Fondaparinux group had SVT Recurrence | | | | ⨁◯◯◯ Very low | CRITICAL |

**Major Bleeding**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2[1,2] | randomised trials | not serious | not serious | very serious[a] | very serious[b] | none | 1/1715 (0.1%) | 1/1600 (0.1%) | **RR 0.93** (0.05 to 14.90) | **0 fewer per 1,000** (from 1 fewer to 9 more) | ⨁◯◯◯ Very low | CRITICAL |

**Major Bleeding (follow-up: 3 months)**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[3] | randomised trials | not serious | not serious | very serious[a] | serious[b] | none | No events of major bleeding occured in either arm. | | | | ⨁◯◯◯ Very low | CRITICAL |

**Clinically Relevant Non-Major Bleed**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[1] | randomised trials | not serious | not serious | very serious[a] | serious[b] | none | 5/1499 (0.3%) | 8/1488 (0.5%) | **RR 0.62** (0.20 to 1.89) | **2 fewer per 1,000** (from 4 fewer to 5 more) | ⨁◯◯◯ Very low | CRITICAL |

**Clinically Relevant Non-Major Bleed (follow-up: 3 months)**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[3] | randomised trials | not serious | not serious | very serious[a] | serious[b] | none | In the rivaroxaban group, 6 patients out of 236 (2.5%) had CRNMB while 1 out of 235 (0.9%) in the Fondaparinux group had CRNMB | | | | ⨁◯◯◯ Very low | CRITICAL |

**CI:** confidence interval; **RR:** risk ratio

**Explanations**

a. Based on adult data
b. Imprecision due to small number of included patients and patients with events in the included studies.

c. Doan et al was assessed to have selection bias
d. One study [Beyer-Westendorf 2017] assesses outcomes comparing Rivaroxaban versus Fondaparinux in adult population with superficial vein thrombosis

**References**


1.Decousus, Hervé, Prandoni, Paolo, Mismetti, Patrick, Bauersachs, Rupert M., Boda, Zoltán, Brenner, Benjamin, Laporte, Silvy, Matyas, Lajos, Middeldorp, Saskia, Sokurenko, German, Leizorovicz, Alain. Fondaparinux for the Treatment of Superficial-Vein Thrombosis in the Legs. New England Journal of Medicine; 2010.
2.Group, Superficial,Thrombophlebitis,Treated,By,Enoxaparin,Study. A pilot randomized double-blind comparison of a low-molecular-weight heparin, a . Archives of internal medicine; 2003.
3.J, Beyer-Westendorf, SM, Schellong, H, Gerlach, E, Rabe, JI, Weitz, K, Jersemann, K, Sahin, R, Bauersachs, investigators, SURPRISE. Prevention of thromboembolic complications in patients with superficial-vein . The Lancet. Haematology; 2017.
4.P, Doan, A, Cox, E, Rao, B, Branchford. Temporal and anatomic relationship between superficial and deep vein thromboses . Thrombosis research; 2021.

## QUESTION

| Should anticoagulation vs. no anticoagulation be used for pediatric patients with superficial vein thrombosis? | |
|---|---|
| **POPULATION:** | pediatric patients with superficial vein thrombosis |
| **INTERVENTION:** | anticoagulation |
| **COMPARISON:** | no anticoagulation |
| **MAIN OUTCOMES:** | Death; CVC related thrombosis in infants; Infant bleeding -severe; Pulmonary embolism; Deep venous thrombosis; Heparin induced thrombocytopenia |
| **SETTING:** | Inpatient |
| **PERSPECTIVE:** | Clinical recommendation - Population perspective |
| **BACKGROUND:** | Central venous access devices (CVAD) or central venous lines (CVL) are an important part of treatment in many pediatric conditions (e.g. cancer and other critical illnesses). They are, however, an important risk factor for venous thromboembolism (VTE) with a rising in incidence, most likely secondary to increase use, detection, better care, and clinical awareness.(1)The incidence of CVL related thrombosis in children varies significantly from 4% to 13% when identified by clinical diagnosis, to up to 50% depending on imaging modality, the affected population, CVL type, and study design.(2) |
| **CONFLICT OF INTEREST:** | |

## ASSESSMENT

**Problem**
Is the problem a priority?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ No<br>○ Probably no<br>○ Probably yes<br>● Yes<br>○ Varies<br>○ Don't know | CVL related thrombosis is an important factor to consider treatment with anticoagulants in children. Current guidelines suggest that CVADs associated with confirmed thrombosis be removed after 3 to 5 days of therapeutic anticoagulation rather than left in situ.(Monagle et al., 2012) Both strategies have risks involved and should be considered in the decision making process. Current guidelines recommend AC with UFH or LMWH based on adult data adapted to expert consensus. | |
| | Adolopment | |
| ○ No<br>○ Probably no | Example:'no additional research evidence, local or global considered': or 'additional local | Add considerations made be the adoloping panel, including the justification for any change |

| | | |
|---|---|---|
| ○ Probably yes<br>● Yes<br>○ Varies<br>○ Don't know | evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | in judgment. |

## Desirable Effects

How substantial are the desirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

○ Trivial
○ Small
○ Moderate
○ Large
○ Varies
● Don't know

| Outcomes | № of participants (studies) Follow up | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects* (95% CI) | |
|---|---|---|---|---|---|
| | | | | Risk with no anticoagulation | Risk difference with anticoagulation |
| Death<br>follow up: mean 3 months | 3002<br>(1 RCT) | ⨁◯◯◯<br>VERY LOW[a,b,c] | **RR 2.00**<br>(0.18 to 22.00) | Study population | |
| | | | | 1 per 1,000 | **1 more per 1,000**<br>(1 fewer to 14 more) |
| CVC related thrombosis in infants assessed with: ADULT outcome "deep vein thrombosis"<br>follow up: mean 3 months | 218<br>(1 RCT) | ⨁◯◯◯<br>VERY LOW[d,e,f] | **RR 0.85**<br>(0.23 to 3.06) | Study population | |
| | | | | 45 per 1,000 | **7 fewer per 1,000**<br>(34 fewer to 92 more) |
| Infant bleeding -severe assessed with: ADULT outcome 'major bleeding'<br>follow up: range 1 weeks to 12 weeks | 218<br>(1 RCT) | ⨁◯◯◯<br>VERY LOW[d,e,f] | not estimable | Study population | |
| | | | | 0 per 1,000 | **0 fewer per 1,000**<br>(0 fewer to 0 fewer) |

Only indirect data from adult populations was identified that assessed the effect of anticoagulants for superficial vein thrombosis.

Based on surveyed panelists, out of 700 patients with CVAD superficial vein thrombosis the majority of patients (~50%) didn't get treatment with anticoagulation.

| | | | | | | |
|---|---|---|---|---|---|---|
| Pulmonary embolism - not reported | - | - | - | - | - | |
| Deep venous thrombosis - not reported | - | - | - | - | - | |
| Heparin induced thrombocytopenia - not reported[g] | - | - | - | - | - | |

a. One study [Decousus 2012] assesses outcomes comparing fondaparinux vs placebo in adult population with superficial vein thrombosis
b. No studies were found evaluating superficial vein thrombosis in children, this study evaluates adult population with superficial vein thrombosis treated with fondaparinux, a drug that is not yet approved for use in children.
c. Two events in intervention and 1 event on control arm, with wide confidence intervals.
d. One study [Stenox group 2003] evaluating LMWH vs placebo in adults with superficial vein thrombosis of the leg.
e. One study [Stenox group 2003] that evaluates adults with superficial vein thrombosis of the leg. We considered the use of LMWH as more direct intervention than fondaparinux as the latter is not yet approved for use in children.
f. Confidence interval is wide and include null and thresholds for plausible benefit / harm
g. Rates of HIT in children vary from almost zero in unselected heparinized children to 2.3% in the PICU. [Monagle 2012]

NOTE: For a complete assessment see the EVIDENCE PROFILE.



| | | |
|---|---|---|
| | Adolopment | |
| ○ Trivial<br>● Small<br>○ Moderate<br>○ Large<br>○ Varies<br>○ Don't know | | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

**Author(s):**
**Question:** Anticoagulation compared to no anticoagulation in pediatric patients with superficial vein thrombosis
**Setting:** Inpatient
**Bibliography:** ASH/ISTH 2024 Guidelines for Management of Venous Thromboembolism: Treatment of Pediatric Venous Thromboembolism

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | anticoagulation | no anticoagulation | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality (follow-up: 3 months)** | | | | | | | | | | | | |
| 2[1,2] | randomised trials | not serious | not serious | very serious[a] | very serious[b] | none | 2/1718 (0.1%) | 1/1612 (0.1%) | **RR 1.88** (0.17 to 20.70) | **1 more per 1,000** (from 1 fewer to 12 more) | ⨁◯◯◯ Very low | CRITICAL |
| **Mortality (follow-up: 3 months)** | | | | | | | | | | | | |
| 1[3] | randomised trials | not serious | not serious | very serious[a] | serious[b] | none | No deaths occured in either arm. Rivaroxaban: 0/211, Fondaparinux: 0/224, Total: 0/435 | | | | ⨁◯◯◯ Very low | CRITICAL |
| **Pulmonary Embolism (follow-up: 3 months)** | | | | | | | | | | | | |
| 2[1,2] | randomised trials | not serious | not serious | very serious[a] | very serious[b] | none | 2/1718 (0.1%) | 6/1612 (0.4%) | **RR 0.31** (0.06 to 1.54) | **3 fewer per 1,000** (from 3 fewer to 2 more) | ⨁◯◯◯ Very low | CRITICAL |
| **Pulmonary Embolism (follow-up: 3 months)** | | | | | | | | | | | | |
| 1[3] | randomised trials | not serious | not serious | very serious[a] | serious[b] | none | No events of PE developed in either arm. Rivaroxaban: 0/211, Fondaparinux: 0/224, Total: 0/435 | | | | ⨁◯◯◯ Very low | CRITICAL |
| **Deep Vein Thrombosis (follow-up: 3 months)** | | | | | | | | | | | | |
| 2[1,2] | randomised trials | not serious | not serious | very serious[a] | serious[b] | none | 13/1718 (0.8%) | 24/1612 (1.5%) | **RR 0.54** (0.26 to 1.04) | **7 fewer per 1,000** (from 11 fewer to 1 more) | ⨁◯◯◯ Very low | CRITICAL |
| **Deep Vein Thrombosis (follow-up: 3 months)** | | | | | | | | | | | | |
| 1[3] | randomised trials | not serious | not serious | very serious[a] | serious[b] | none | In the rivaroxaban group, 6 patients out of 211 (2.8%) develped DVT while 2 out of 224 (0.8%) in the Fondaparinux group developed DVT | | | | ⨁◯◯◯ Very low | CRITICAL |
| **Deep Vein Thrombosis** | | | | | | | | | | | | |
| 1[4] | non-randomised studies | serious[c] | not serious | not serious | serious[b] | none | Among 209 patients who developed a superficial vein thrombosis and no previous or concurrent DVT, 12 (5.7%) developed a deep vein thrombosis. | | | | ⨁◯◯◯ Very low | CRITICAL |
| **SVT Extension (follow-up: 3 months)** | | | | | | | | | | | | |
| 1[1] | randomised trials | not serious | not serious | very serious[a] | not serious | none | 5/1502 (0.3%) | 54/1500 (3.6%) | **RR 0.08** (0.03 to 0.22) | **33 fewer per 1,000** (from 35 fewer to 28 fewer) | ⨁⨁◯◯ Low | CRITICAL |
| **SVT Extension (follow-up: 3 months)** | | | | | | | | | | | | |
| 1[3] | randomised trials | not serious | not serious | very serious[d] | very serious[b] | none | In the rivaroxaban group, 2 patients out of 211 (0.9%) had SVT extension while 1 out of 224 (0.4%) in the Fondaparinux group had SVT extension | | | | ⨁◯◯◯ Very low | CRITICAL |
| **SVT Recurrence (follow-up: 3 months)** | | | | | | | | | | | | |
| 1[1] | randomised trials | not serious | not serious | very serious[a] | not serious | none | 8/1502 (0.5%) | 28/1500 (1.9%) | **RR 0.27** (0.12 to 0.59) | **14 fewer per 1,000** (from 16 fewer to 8 fewer) | ⨁⨁◯◯ Low | CRITICAL |
| **SVT Reccurence (follow-up: 3 months)** | | | | | | | | | | | | |
| 1[3] | randomised trials | not serious | not serious | very serious[a] | serious[b] | none | In the rivaroxaban group, 8 patients out of 211 (3.7%) had SVT Recurrence while 12 out of 224 (5.3%) in the Fondaparinux group had SVT Recurrence | | | | ⨁◯◯◯ Very low | CRITICAL |

**CI:** confidence interval; **RR:** risk ratio

**Explanations**

a. Based on adult data
b. Imprecision due to small number of included patients and patients with events in the included studies.
c. Doan et al was assessed to have selection bias
d. One study [Beyer-Westendorf 2017] assesses outcomes comparing Rivaroxaban versus Fondaparinux in adult population with superficial vein thrombosis

**References**

1.Decousus, Hervé, Prandoni, Paolo, Mismetti, Patrick, Bauersachs, Rupert M., Boda, Zoltán, Brenner, Benjamin, Laporte, Silvy, Matyas, Lajos, Middeldorp, Saskia, Sokurenko, German, Leizorovicz, Alain. Fondaparinux for the Treatment of Superficial-Vein Thrombosis in the Legs. New England Journal of Medicine; 2010.
2.Group, Superficial,Thrombophlebitis,Treated,By,Enoxaparin,Study. A pilot randomized double-blind comparison of a low-molecular-weight heparin, a . Archives of internal medicine; 2003.
3.J, Beyer-Westendorf, SM, Schellong, H, Gerlach, E, Rabe, JI, Weitz, K, Jersemann, K, Sahin, R, Bauersachs, investigators, SURPRISE. Prevention of thromboembolic complications in patients with superficial-vein . The Lancet. Haematology; 2017.
4.P, Doan, A, Cox, E, Rao, B, Branchford. Temporal and anatomic relationship between superficial and deep vein thromboses . Thrombosis research; 2021.



## Undesirable Effects

How substantial are the undesirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|

| | Original | |
|---|---|---|
| ○ Large<br>○ Moderate<br>● Small<br>○ Trivial<br>○ Varies<br>○ Don't know | | Panel considered that undesirable effects would be small.<br><br>based on survey results from the panel collective experience, progression when untreated is very low (recurrence) and 0 to few bleeds and 0 to low mortality with no anticoagulation. |

| Outcomes | № of participants (studies) Follow up | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects* (95% CI) | |
|---|---|---|---|---|---|
| | | | | Risk with no anticoagulation | Risk difference with anticoagulation |
| Death<br>follow up: mean 3 months | 3002<br>(1 RCT) | ⨁◯◯◯<br>VERY LOW[a,b,c] | **RR 2.00**<br>(0.18 to 22.00) | Study population | |
| | | | | 1 per 1,000 | **1 more per 1,000**<br>(1 fewer to 14 more) |
| CVC related thrombosis in infants<br>assessed with: ADULT outcome "deep vein thrombosis"<br>follow up: mean 3 months | 218<br>(1 RCT) | ⨁◯◯◯<br>VERY LOW[d,e,f] | **RR 0.85**<br>(0.23 to 3.06) | Study population | |
| | | | | 45 per 1,000 | **7 fewer per 1,000**<br>(34 fewer to 92 more) |
| Infant bleeding -severe<br>assessed with: ADULT outcome 'major bleeding'<br>follow up: range 1 weeks to 12 weeks | 218<br>(1 RCT) | ⨁◯◯◯<br>VERY LOW[d,e,f] | not estimable | Study population | |
| | | | | 0 per 1,000 | **0 fewer per 1,000**<br>(0 fewer to 0 fewer) |
| Pulmonary embolism - not reported | - | - | - | - | - |
| Deep venous thrombosis - not reported | - | - | - | - | - |
| Heparin induced thrombocytopenia - not | - | - | - | - | - |

| | | | | | | |
|---|---|---|---|---|---|---|
| reported[g] | | | | | | |

a. One study [Decousus 2012] assesses outcomes comparing fondaparinux vs placebo in adult population with superficial vein thrombosis
b. No studies were found evaluating superficial vein thrombosis in children, this study evaluates adult population with superficial vein thrombosis treated with fondaparinux, a drug that is not yet approved for use in children.
c. Two events in intervention and 1 event on control arm, with wide confidence intervals.
d. One study [Stenox group 2003] evaluating LMWH vs placebo in adults with superficial vein thrombosis of the leg.
e. One study [Stenox group 2003] that evaluates adults with superficial vein thrombosis of the leg. We considered the use of LMWH as more direct intervention than fondaparinux as the latter is not yet approved for use in children.
f. Confidence interval is wide and include null and thresholds for plausible benefit / harm
g. Rates of HIT in children vary from almost zero in unselected heparinized children to 2.3% in the PICU. [Monagle 2012]

NOTE: For a complete assessment see the EVIDENCE PROFILE.

Adolopment

○ Large
○ Moderate
● Small
○ Trivial
○ Varies
○ Don't know

Add considerations made be the adoloping panel, including the justification for any change in judgment.

**Author(s):**
**Question:** Anticoagulation compared to no anticoagulation in pediatric patients with superficial vein thrombosis
**Setting:** Inpatient
**Bibliography:** ASH/ISTH 2024 Guidelines for Management of Venous Thromboembolism: Treatment of Pediatric Venous Thromboembolism

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | anticoagulation | no anticoagulation | Relative (95% CI) | Absolute (95% CI) | | |
| **Major Bleeding** | | | | | | | | | | | | |
| 2[1,2] | randomised trials | not serious | not serious | very serious[a] | very serious[b] | none | 1/1715 (0.1%) | 1/1600 (0.1%) | **RR 0.93** (0.05 to 14.90) | **0 fewer per 1,000** (from 1 fewer to 9 more) | ⨁◯◯◯ Very low | CRITICAL |
| **Major Bleeding (follow-up: 3 months)** | | | | | | | | | | | | |
| 1[3] | randomised trials | not serious | not serious | very serious[a] | serious[b] | none | No events of major bleeding occured in either arm. | | | | ⨁◯◯◯ Very low | CRITICAL |
| **Clinically Relevant Non-Major Bleed** | | | | | | | | | | | | |
| 1[1] | randomised trials | not serious | not serious | very serious[a] | serious[b] | none | 5/1499 (0.3%) | 8/1488 (0.5%) | **RR 0.62** (0.20 to 1.89) | **2 fewer per 1,000** (from 4 fewer to 5 more) | ⨁◯◯◯ Very low | CRITICAL |
| **Clinically Relevant Non-Major Bleed (follow-up: 3 months)** | | | | | | | | | | | | |
| 1[3] | randomised trials | not serious | not serious | very serious[a] | serious[b] | none | In the rivaroxaban group, 6 patients out of 236 (2.5%) had CRNMB while 1 out of 235 (0.9%) in the Fondaparinux group had CRNMB | | | | ⨁◯◯◯ Very low | CRITICAL |

**CI:** confidence interval; **RR:** risk ratio

**Explanations**

a. Based on adult data
b. Imprecision due to small number of included patients and patients with events in the included studies.

**References**

1.Decousus, Hervé, Prandoni, Paolo, Mismetti, Patrick, Bauersachs, Rupert M., Boda, Zoltán, Brenner, Benjamin, Laporte, Silvy, Matyas, Lajos, Middeldorp, Saskia, Sokurenko, German, Leizorovicz, Alain. Fondaparinux for the Treatment of Superficial-Vein Thrombosis in the Legs. New England Journal of Medicine; 2010.
2.Group, Superficial,Thrombophlebitis,Treated,By,Enoxaparin,Study. A pilot randomized double-blind comparison of a low-molecular-weight heparin, a . Archives of internal medicine; 2003.
3.J, Beyer-Westendorf, SM, Schellong, H, Gerlach, E, Rabe, JI, Weitz, K, Jersemann, K, Sahin, R, Bauersachs, investigators, SURPRISE. Prevention of thromboembolic complications in patients with superficial-vein . The Lancet. Haematology; 2017.

## Certainty of evidence

What is the overall certainty of the evidence of effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Very low<br>○ Low<br>○ Moderate<br>○ High<br>● No included studies | Certainty of the evidence of effects was judged as very low certainty due to very serious indirectness and imprecision. | |
| | Adolopment | |

| | | |
|---|---|---|
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Values

Is there important uncertainty about or variability in how much people value the main outcomes?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Important uncertainty or variability<br>● Possibly important uncertainty or variability<br>○ Probably no important uncertainty or variability<br>○ No important uncertainty or variability | **Utility related information:**<br><br>**The relative importance of outcomes:**<br><br>**Results from Panel Members' Utility Rating Survey**:<br><br>Utilities rated on the visual analog scale, where 0 represents death and 1 represents full health, were as follows.<br><br>Pulmonary embolism – Severe marker state: 0.31<br><br>Pulmonary embolism – Moderate marker state: 0.49<br><br>Deep vein thrombosis (proximal) – Severe marker state: 0.49<br><br>Deep vein thrombosis (proximal) – Moderate marker state: 0.61<br><br>Deep vein thrombosis (distal) – Severe marker state: 0.56<br><br>Deep vein thrombosis (distal) – Moderate marker state: 0.68<br><br>Major bleeding: 0.30<br><br>Neonatal Bleeding – Severe: 0.30<br><br>Infant Bleeding – Severe: 0.26 | Variation in the perceived importance of superficial vein thrombosis will exist among patients and clinicians. |

CVC-related thrombosis: 0.53

Heparin-induced thrombocytopenia: 0.59

**We did not identify utility related information or non-utility information for the outcomes of interest specific to the pediatric population in the literature.**

**Additional information from the adult population:**

**Our systematic review for the adult population found that the relative importance of the outcomes is as follows:**

Pulmonary embolism: 0.63-0.93 (different methods) (Hogg et al., 2014, Hogg et al., 2013, Locadia et al., 2004)

Deep vein thrombosis: 0.64-0.99 (different methods)(Hogg et al., 2013, Hogg et al., 2014, Locadia et al., 2004, Marvig et al., 2015, Utne et al., 2016)

Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) (Hogg et al., 2013, Locadia et al., 2004)

Muscular bleeding: 0.76 (time trade off)(Locadia et al., 2004)

Minor intracranial bleeding event: 0.75 (standard gamble) (Hogg et al., 2013)

Major intracranial bleeding event: 0.15 (standard gamble) (Hogg et al., 2013)

Central nervous system bleeding: 0.29-0.60 (standard gamble)(Lenert et al., 1997, O'Meara et al., 1994)

Treatment with LMWH: 0.993 (time trade off) (Marchetti et al., 2001)

Treatment with warfarin (as a surrogate): 0.989 (time trade off) (Marchetti et al., 2001)

**We also identified in the systematic review the following non-utility information from the adult population:**

**Anticoagulant therapy**

Adult patients highly value the benefits of risk reduction in VTE recurrence and post-thrombosis syndrome (Locadia et al., 2004). Patients would favor efficacy and safety over convenience of route of administration (Noble et al., 2015). Further, patients would like to avoid adverse events but most of them are “not afraid of” the adverse events (Barcellona et

| | | |
|---|---|---|
| | al., 2000, Noble et al., 2015, O'Meara et al., 1994). For anticoagulant therapy in general, most patients would prefer the oral doses compared with injections, this is mainly because of treatment burden due to injection (Barcellona et al., 2000, Noble et al., 2015). For patients with venographically proven deep venous thrombosis, 15 of the 19 patients expressed a preference for the subcutaneous route for administration of heparin over intravenous administration(Robinson et al., 1993).<br><br>**Warfarin**<br><br>Adult patients would like to switch to another anticoagulant if it is as effective as warfarin; this is mainly due to the treatment burden associated with monitoring, injection and dietary change due to warfarin use (Attaya et al., 2012). In another study approximately half of the patients did not consider VKA therapy particularly difficult to manage (Wild et al., 2009).<br><br>**LMWH**<br><br>For adult patients receiving low molecular weight heparin, patients placed a high score on “importance of ease of use”, “expectations of symptom relief”, and “confidence in the treatment to prevent blood clots” while they had a low score of treatment-related side effects (bruise, bleeding).(Baba et al., 2015) (Cajfinger et al., 2016) | |
| | Adolopment | |
| ○ Important uncertainty or variability<br>● Possibly important uncertainty or variability<br>○ Probably no important uncertainty or variability<br>○ No important uncertainty or variability | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

| | | |
|---|---|---|
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>● Don't know | | There is very scarce information on this topic to judge a balance. |
| | Adolopment | |
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>● Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Most data on lower limb (above the knee)<br><br>No evidence to distinguish between CVAD vs spontanous |

## Resources required

How large are the resource requirements (costs)?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Large costs<br>● Moderate costs<br>○ Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br>○ Varies<br>○ Don't know | No research evidence was identified for anticoagulation costs for CVAD related superfician vein thrombosis in pediatric patients.<br><br>Two studies reported the costs of disease from pediatric patients with any VTE. One reported for 834 pediatric patients with VTE a median annual expenditure of $25,258 and $24,934 USD in Medicaid and private insurance patients respectively. (Boulet et al., 2012)Another study found that patients with VTE had an increased 8.1 inpatient days and excess average costs of $27,686 USD. (Goudie et al., 2015) **Additional information from adult population:**<br><br>In relation to the reported costs of anticoagulation, the direct cost per week with warfarin in adults ranges from 3.54 to $11.44 USD while this number in Canada decreases to $0.49 to $0.84 CAD per week. (Biskupiak et al., 2013, Kearon C, 2014, Klarenbach et al., 2016, | Children will present with VTE in hospital, and the costs will be added to the whole inpatient costs when offering anticoagulation as treatment. Also important to consider the duration of treatment |

| | | |
|---|---|---|
| | Guanella et al., 2011) With heparin, the costs per unit range from $0.18 per 10 units, to $0.212 per 1000 units [ASP] with a cost per week of $37.00 USD and $11.14 CAD per day in Canada. (Klarenbach et al., 2016, Guanella et al., 2011) LMWH (enoxaparin) cost varies. The wholesale cost in low and middle income economies is reported at about $13 to $75 USD per week. (IMPPG, 2016) In the United States the wholesale cost is about $98.91 USD per day as of 2016 (NADAC, 2017). | |
| | Adolopment | |
| ○ Large costs<br>● Moderate costs<br>○ Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | No research evidence found. | |

| | | |
|---|---|---|
| | Adolopment | |
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>● No included studies | No research on cost-effectiveness | |
| | Adolopment | |

| | | |
|---|---|---|
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>● No included studies | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Equity

What would be the impact on health equity?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Reduced<br>○ Probably reduced<br>● Probably no impact<br>○ Probably increased<br>○ Increased<br>○ Varies<br>○ Don't know | No research evidence was identified. | Panel noted that there should be a consideration that CVAD related events will occur in hospital. |
| | Adolopment | |
| ○ Reduced<br>○ Probably reduced<br>● Probably no impact<br>○ Probably increased<br>○ Increased<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Acceptability

Is the intervention acceptable to key stakeholders?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

| | | |
|---|---|---|
| ○ No<br>○ Probably no<br>● Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | Observational research suggests the following regarding acceptability and barriers associated with the intervention:<br><br>In Australia a prospective chart audit in a tertiary paediatric centre assessed the level of compliance of antithrombotic medication use in current practice with guidelines across a 100-day prospective chart audit in 2008-2009. The study showed that the level of compliance for use of antithrombotic medications for the indications of DVT and PE was 98.8% and 61.5%, respectively. High compliance was correlated with strong recommendations, with low compliance found especially in areas where recommendations were based on 'weak' evidence. This reflects clinician confidence in the strength of evidence currently available for paediatric antithrombotic therapy where there may be barriers associated with the use of the intervention where only low-quality, inconsistent, or indirect evidence extrapolated from adult data is available. (Peng et al., 2011) Another study conducted at a large pediatric tertiary care hospital in the United States showed that implementation of a patient-care policy helped to improve compliance with guidelines, specifically for VTE prophylaxis, from a baseline compliance rate of 22% to an average rate of 83% during the 4-year study period (Raffini et al., 2011). While assessed for VTE prophylaxis similar patient-care policies may help to address acceptability concerns for VTE treatment in the pediatric population. | Probably acceptable. |
| | Adolopment | |
| ○ No<br>○ Probably no<br>● Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Feasibility

Is the intervention feasible to implement?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ No<br>○ Probably no<br>● Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | The views and clinical practice of children's cancer units were surveyed regarding management of central venous catheter (CVC) occlusion (CVC-occlusion), CVC-related thrombosis (CVC-thrombosis) and thromboembolism (CVC-thromboembolism). All centres used heparinised saline flushes as prophylaxis against CVCocclusion, with little variation (_30% centres) in frequency, volume and heparin concentration. Symptoms or signs suggesting partial CVC-occlusion, total CVC-occlusion, or CVC-thrombosis/thromboembolism were always investigated in 20%, 55% and 85% of centres, respectively, but with | The panel considered that the intervention is probably feasible to implement. |

| | | |
|---|---|---|
| | considerable variability in the nature and sequence of investigations performed. The clinical practice of different centres regarding prevention, investigation and treatment of CVC-occlusion/thrombosis varies greatly. (Skinner et al., 2008) | |
| | Adolopment | |
| ○ No<br>○ Probably no<br>○ Probably yes<br>● Yes<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## SUMMARY OF JUDGEMENTS

| CRITERIA | ORIGINAL | IMPORTANCE FOR DECISION | ADOLOPMENT | IMPORTANCE FOR DECISION |
|---|---|---|---|---|
| PROBLEM | Yes | | Yes | |
| DESIRABLE EFFECTS | Don't know | | Small | |
| UNDESIRABLE EFFECTS | Small | | Small | |
| CERTAINTY OF EVIDENCE | No included studies | | Very low | |
| VALUES | Possibly important uncertainty or variability | | Possibly important uncertainty or variability | |
| BALANCE OF EFFECTS | Don't know | | Probably favors the intervention | |
| RESOURCES REQUIRED | Moderate costs | | Moderate costs | |
| CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES | Very low | | Very low | |
| COST EFFECTIVENESS | No included studies | | No included studies | |

| CRITERIA | ORIGINAL | IMPORTANCE FOR DECISION | ADOLOPMENT | IMPORTANCE FOR DECISION |
|---|---|---|---|---|
| EQUITY | Probably no impact | | Probably no impact | |
| ACCEPTABILITY | Probably yes | | Probably yes | |
| FEASIBILITY | Probably yes | | Yes | |

## TYPE OF RECOMMENDATION

Original

| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | Strong recommendation for the intervention |
|---|---|---|---|---|
| ○ | ○ | ● | ○ | ○ |

Adolopment

| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | Strong recommendation for the intervention |
|---|---|---|---|---|
| ○ | ○ | ○ | ● | ○ |

## CONCLUSIONS

Original

**Recommendation**

**The ASH guideline panel suggests using either anticoagulation or no anticoagulation in pediatric patients with central venous access device (CVAD)-related superficial vein thrombosis (conditional recommendation based on very low certainty in the evidence about effects).**

**Justification**

There was very little direct or indirect data on which to base this recommendation. The collective experience of the panel suggested that in most patients, no anticoagulation will be appropriate. However, in patients who have a CVAD line that is still functioning, and they continue to need venous access, or in those whose symptoms progress,

anticoagulation seems appropriate.

Adolopment

## Recommendation

**The ASH/ISTH guideline panel suggests using anticoagulation over no anticoagulation in pediatric patients with superficial vein thrombosis (conditional recommendation based on very low certainty in the evidence about effects).**

## Justification

Based on lower limb adult data

Variability in dosage and optimal intesity and duration varies (Prophylactic versus theraputic dosing)

## Subgroup considerations

Original

Adolopment

Concerns about extrapolation to pediatric population concerning central line, PIV, Upper extremeity?

## Implementation considerations

Original

Adolopment

## Monitoring and evaluation

Original

Adolopment

## Research priorities

Original

Adolopment

## REFERENCES SUMMARY

1. Raffini, L, Huang, YS, Witmer, C, Feudtner, C. Dramatic increase in venous thromboembolism in children's hospitals in the United States from 2001 to 2007. Pediatrics; 2009.
2. Jaffray, J, Bauman, M, Massicotte, P. The Impact of Central Venous Catheters on Pediatric Venous Thromboembolism. Frontiers in Pediatrics; 2017.

**Author(s):**
**Question:** Thrombolysis followed by anticoagulation compared to anticoagulation alone in pediatric patients with proximal DVT
**Setting:** Inpatient
**Bibliography:** ASH/ISTH 2024 Guidelines for Management of Venous Thromboembolism: Treatment of Pediatric Venous Thromboembolism

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | thrombolysis followed by anticoagulation | anticoagulation alone | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality** | | | | | | | | | | | | |
| 4[1,2,3,4] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 5/54 (9.3%) | 2/21 (9.5%) | **RR 0.97** (0.20 to 4.63) | **3 fewer per 1,000** (from 76 fewer to 346 more) | ⨁◯◯◯ Very low | CRITICAL |
| **Mortality** | | | | | | | | | | | | |
| 4[5,6,7,8] | non-randomised studies | serious[c] | not serious | not serious | very serious[b] | none | 6/72 (8.3%) | - | - | - | ⨁◯◯◯ Very low | CRITICAL |
| **Resolution (assessed with: Complete and Partial Resolution)** | | | | | | | | | | | | |
| 4[1,3,4,9,10] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 49/55 (89.1%) | 20/29 (69.0%) | **RR 1.29** (0.99 to 1.68) | **200 more per 1,000** (from 7 fewer to 469 more) | ⨁◯◯◯ Very low | CRITICAL |
| **Resolution (assessed with: Complete or Partial Resolution)** | | | | | | | | | | | | |
| 5[5,6,7,8,11] | non-randomised studies | serious[c] | not serious | not serious | very serious[b] | none | 56/75 (74.7%) | - | - | - | ⨁◯◯◯ Very low | CRITICAL |
| **Reccurence** | | | | | | | | | | | | |
| 4[1,2,3,4] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 5/54 (9.3%) | 2/21 (9.5%) | **RR 0.97** (0.20 to 4.63) | **3 fewer per 1,000** (from 76 fewer to 346 more) | ⨁◯◯◯ Very low | CRITICAL |
| **Recurrence** | | | | | | | | | | | | |
| 2[6,12] | non-randomised studies | serious[c] | not serious | not serious | very serious[b] | none | 12/54 (22.2%) | - | - | - | ⨁◯◯◯ Very low | CRITICAL |
| **Post-Thrombotic Syndrome** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 4[1,2,4,9,10] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 13/36 (36.1%) | 13/34 (38.2%) | **RR 1.87** (0.77 to 4.40) | **333 more per 1,000** (from 88 fewer to 1,000 more) | ⨁◯◯◯ Very low | CRITICAL |
| **Post-Thrombotic Syndrome** | | | | | | | | | | | | |
| 3[6,7,12] | non-randomised studies | serious[c] | not serious | not serious | very serious[b] | none | 9/61 (14.8%) | - | - | - | ⨁◯◯◯ Very low | CRITICAL |
| **Major Bleeding** | | | | | | | | | | | | |
| 2[1,3,10] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 2/20 (10.0%) | 5/55 (9.1%) | **RR 0.76** (0.10 to 5.88) | **22 fewer per 1,000** (from 82 fewer to 444 more) | ⨁◯◯◯ Very low | CRITICAL |
| **CRNMB** | | | | | | | | | | | | |
| 2[1,3] | non-randomised studies | serious[b] | not serious | not serious | very serious[b] | none | 0/11 (0.0%) | 1/42 (2.4%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Bleeding (Unspecified)** | | | | | | | | | | | | |
| 6[5,6,7,8,11,12] | non-randomised studies | serious[c] | not serious | not serious | very serious[b] | none | 11/100 (11.0%) | - | - | - | ⨁◯◯◯ Very low | CRITICAL |

**CI:** confidence interval; **RR:** risk ratio

**Explanations**

a. Risk of bias, assessed using ROBINS-I, was judged to be serious due to selection bias.
b. Imprecision due to small number of included patients and patients with events in the included studies.
c. Risk of bias was judged to be serious due to selection bias.

**References**


1.R, Kumar, K, Harsh, S, Saini, SH, O'Brien, J, Stanek, P, Warren, J, Giver, MR, Go, BA, Kerlin. Treatment-Related Outcomes in Paget-Schroetter Syndrome-A Cross-Sectional . The Journal of pediatrics; 2019.
2.C, Tarango, R, Kumar, M, Patel, A, Blackmore, P, Warren, JS, Palumbo. Inferior vena cava atresia predisposing to acute lower extremity deep vein . Pediatric blood & cancer; 2018.
3.CH, van,Ommen, KA, Bergman, M, Boerma, HA, Bouma, AE, Donker, M, Gouvernante, CV, Hulzebos, D, Khandour, R, Knol, MA, Raets, KD, Liem, RA, van,Lingen, M, van,de,Loo, E, Lopriore, M, van,der,Putten, JJ, Sol, MH, Suijker, DC, Vijlbrief, R, Visser, MM, van,Weissenbruch. NEOnatal Central-venous Line Observational study on Thrombosis (NEOCLOT): . Journal of thrombosis and haemostasis : JTH; 2023.
4., , Warad, . Clinical Outcomes of May-Thurner Syndrome in Pediatric Patients: A Single Institutional Experience.
5.P, Grizante-Lopes, MP, Garanito, DM, Celeste, VLJ, Krebs, JDA, Carneiro. Thrombolytic therapy in preterm infants: Fifteen-year experience.. Pediatric blood & cancer; 2020.
6.CT, Cohen, SE, Sartain, H, Sangi-Haghpeykar, KU, Kukreja, SB, Desai. Clinical characteristics and outcomes of combined thrombolysis and . Pediatric hematology and oncology; 2021.
7.E, Zengin, N, Sarper, A, Yazal,Erdem, I, Odaman,Al, M, Sezgin,Evim, N, Yaralı, B, Belen, A, Akçay, A, Türedi,Yıldırım, TH, Karapınar, AM, Güneş, S, Aylan,Gelen, H, Ören, L, Olcay, B, Baytan, H, Gülen, G, Öztürk, MF, Orhan, Y, Oymak, S, Akpınar, Ö, Tüfekçi, M, Albayrak, B, Tatlı,Güneş, A, Canpolat, N, Özbek. Thrombolysis with Systemic Recombinant Tissue Plasminogen Activator in Children: . Turkish journal of haematology : official journal of Turkish Society of ; 2021.
8., , Cervio, . Thrombolytic therapy in neonates and children: A twelve-year prospective registry of a single tertiary pediatric center in Argentina.
9.CT, Cohen, S, Kirk, SB, Desai, KU, Kukreja, L, Srivaths. Diagnosis, Clinical Characteristics, and Treatment Modalities of Adolescent . Journal of pediatric hematology/oncology; 2021.
10.NA, Goldenberg, JD, Durham, R, Knapp-Clevenger, MJ, Manco-Johnson. A thrombolytic regimen for high-risk deep venous thrombosis may substantially . Blood; 2007.
11.E, Pekpak, E, İnce, M, Ertem, E, Tutar, T, İleri, T, Ucar, ST, Tiras, HF, Cakmakli, Z, Uysal. Tissue Plasminogen Activator Use in Pediatric Patients: A Single Center . Journal of pediatric hematology/oncology; 2021.
12., , Brauner, . Retrospective case series study of patients with may-Thurner syndrome in a single tertiary pediatric center.

**Author(s):**
**Question:** Thrombolysis followed by anticoagulation compared to anticoagulation alone in pediatric patients with PE with hemodynamic compromise
**Setting:** Inpatient
**Bibliography:** ASH/ISTH 2024 Guidelines for Management of Venous Thromboembolism: Treatment of Pediatric Venous Thromboembolism

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | thrombolysis followed by anticoagulation | anticoagulation alone | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortalty (assessed with: All Cause Mortality)** | | | | | | | | | | | | |
| 3[1,2,3] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 6/15 (40.0%) | 8/16 (50.0%) | **RR 0.88** (0.42 to 1.85) | **60 fewer per 1,000** (from 290 fewer to 425 more) | ⨁◯◯◯ Very low | CRITICAL |
| **Recurrence** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 3/7 (42.9%) | 3/15 (20.0%) | **RR 2.14** (0.57 to 8.09) | **228 more per 1,000** (from 86 fewer to 1,000 more) | ⨁◯◯◯ Very low | CRITICAL |
| **Neurological Outcomes** | | | | | | | | | | | | |
| 1[2] | non-randomised studies | serious[c] | not serious | not serious | very serious[b] | none | 1/5 (20.0%) [d] | - | - | - | ⨁◯◯◯ Very low | NOT IMPORTANT |
| **Bleeding (assessed with: Unspecified Bleed (Intracranial/Extracranial))** | | | | | | | | | | | | |
| 1[3] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 1/7 (14.3%) | 0/1 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |

**CI:** confidence interval; **RR:** risk ratio

**Explanations**

a. Risk of bias, assessed using ROBINS-I, was judged to be serious due to selection bias.
b. Imprecision due to small number of included patients and patients with events in the included studies.
c. Non-comparative study
d. Hypoxic ischemic brain injury

**References**

1.MC, Pelland-Marcotte, C, Tucker, A, Klaassen, ML, Avila, A, Amid, N, Amiri, S, Williams, J, Halton, LR, Brandão. Outcomes and risk factors of massive and submassive pulmonary embolism in . The Lancet. Haematology; 2019.
2.RW, Morgan, HR, Stinson, H, Wolfe, RB, Lindell, AA, Topjian, VM, Nadkarni, RM, Sutton, RA, Berg, TJ, Kilbaugh. Pediatric In-Hospital Cardiac Arrest Secondary to Acute Pulmonary Embolism.. Critical care medicine; 2018.
3.CE, Ross, JA, Shih, ME, Kleinman, MW, Donnino. Pediatric Massive and Submassive Pulmonary Embolism: A Single-Center Experience.. Hospital pediatrics; 2020.

**Author(s):**
**Question:** Thrombolysis followed by anticoagulation compared to anticoagulation alone in pediatric patients with sub-massive PE
**Setting:** Inpatient
**Bibliography:** ASH/ISTH 2024 Guidelines for Management of Venous Thromboembolism: Treatment of Pediatric Venous Thromboembolism

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | thrombolysis followed by anticoagulation | anticoagulation alone | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality (assessed with: All-Cause Mortality)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 0/14 (0.0%) | 1/9 (11.1%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Resolution (follow-up: 6 months; assessed with: Complete or Partial Resolution)** | | | | | | | | | | | | |
| 1[2] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 5/5 (100.0%) | 3/3 (100.0%) | **RR 1.00** (0.64 to 1.56) | **0 fewer per 1,000** (from 360 fewer to 560 more) | ⨁◯◯◯ Very low | CRITICAL |
| **Progression (Submassive to Massive)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 1/14 (7.1%) | 1/9 (11.1%) | **RR 0.64** (0.05 to 9.03) | **40 fewer per 1,000** (from 106 fewer to 892 more) | ⨁◯◯◯ Very low | IMPORTANT |
| **Chronic thromboembolic pulmonary hypertension (follow-up: 6 months)** | | | | | | | | | | | | |
| 1[2] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 0/5 (0.0%) | 0/2 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Bleeding (assessed with: Unspecified)** | | | | | | | | | | | | |
| 2[1,2] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 0/19 (0.0%) | 0/9 (0.0%) | not pooled | see comment | ⨁◯◯◯ Very low | CRITICAL |

**CI:** confidence interval; **RR:** risk ratio

**Explanations**

a. Risk of bias, assessed using ROBINS-I, was judged to be serious due to selection bias.
b. Imprecision due to small number of included patients and patients with events in the included studies.

**References**

1.CE, Ross, JA, Shih, ME, Kleinman, MW, Donnino. Pediatric Massive and Submassive Pulmonary Embolism: A Single-Center Experience.. Hospital pediatrics; 2020.
2.J, Belsky, P, Warren, J, Stanek, R, Kumar. Catheter-directed thrombolysis for submassive pulmonary embolism in children: A . Pediatric blood & cancer; 2020.

## QUESTION

| Should thrombolysis followed by anticoagulation vs. anticoagulation alone be used for pediatric patients with proximal DVT? | |
|---|---|
| **POPULATION:** | pediatric patients with proximal DVT |
| **INTERVENTION:** | thrombolysis followed by anticoagulation |
| **COMPARISON:** | anticoagulation alone |
| **MAIN OUTCOMES:** | Mortality; Non-fatal pulmonary embolism -representing the moderate marker state; Deep vein thrombosis; Major bleeding; Post-thrombotic syndrome. |
| **SETTING:** | Inpatient |
| **PERSPECTIVE:** | Clinical recommendation - Population perspective |
| **BACKGROUND:** | The first line of treatment of venous thromboembolism in the pediatric populations includes anticoagulation, although in some instances, it might require the use of thrombolytics and/or invasive vascular procedures. The infusion of thrombolytics, such as tissue plasminogen activator (tPA) either systemically or directed by catheter are more commonly being used in adults. In the pediatric field, however, there still is need for evidence to ascertain the risks and benefits of such therapy.(1) |
| **CONFLICT OF INTEREST:** | |

## ASSESSMENT

**Problem**
Is the problem a priority?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ No<br>○ Probably no<br>○ Probably yes<br>● Yes<br>○ Varies<br>○ Don't know | In patients with symptomatic DVT or PE, the use of anticoagulation is the first line of therapy. In some instances, the use of thrombolytic drugs such as tissue plasminogen activator (tPA) might be warranted. The lack of evidence on this topic frequently precludes clinicians to be confident on the decision-making process. | |
| | Adolopment | |

| | | |
|---|---|---|
| ○ No<br>○ Probably no<br>○ Probably yes<br>● Yes<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Desirable Effects

How substantial are the desirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ● Trivial<br>○ Small<br>○ Moderate<br>○ Large<br>○ Varies<br>○ Don't know | <table><tr><th>Outcomes</th><th>№ of participants (studies) Follow up</th><th>Certainty of the evidence (GRADE)</th><th>Relative effect (95% CI)</th><th colspan="2">Anticipated absolute effects* (95% CI)</th></tr><tr><th></th><th></th><th></th><th></th><th>Risk with anticoagulation alone</th><th>Risk difference with thrombolysis followed by anticoagulation</th></tr><tr><td>Mortality assessed with: as all-cause mortality follow up: range 1 days to 6 years</td><td>320 (15 observational studies)</td><td>⨁◯◯◯ VERY LOW[a,b]</td><td>not pooled</td><td colspan="2">Study population</td></tr><tr><td></td><td></td><td></td><td></td><td>not pooled</td><td>not pooled</td></tr><tr><td>Mortality assessed with: in ADULTS with massive PE as</td><td>2526 (22 RCTs)[c]</td><td>⨁◯◯◯ VERY LOW[d,e]</td><td>RR 0.61 (0.40 to 0.94)</td><td colspan="2">Study population</td></tr><tr><td></td><td></td><td></td><td></td><td>45 per 1,000</td><td>18 fewer per 1,000</td></tr></table> | The panel considers the desirable effects as trivial. |

| | | | | | |
|---|---|---|---|---|---|
| all-cause mortality | | | | | (27 fewer to 3 fewer) |
| Non-fatal pulmonary embolism - representing the moderate marker state assessed with: any PE in ADULTS with PE and hemodynamic compromise follow up: range 7 days to 90 days | 2288 (16 RCTs)[c] | ⨁◯◯◯ VERY LOW[d,e] | **RR 0.56** (0.35 to 0.91) | Study population | |
| | | | | 40 per 1,000 | **18 fewer per 1,000** (26 fewer to 4 fewer) |
| Deep vein thrombosis assessed with: in children as NO clot resolution or progression (early) follow up: range 1 days to 2 weeks | 320 (15 observational studies) | ⨁◯◯◯ VERY LOW[a,b] | not pooled | Study population | |
| | | | | not pooled | not pooled |
| Deep vein thrombosis assessed with: in ADULTS as NO clot resolution or progression (early) | 462 (8 RCTs)[f] | ⨁◯◯◯ VERY LOW[d,g,h] | **RR 0.40** (0.21 to 0.74) | Study population | |
| | | | | 632 per 1,000 | **379 fewer per 1,000** (499 fewer to 164 fewer) |
| | | | | Study population | |

| | | | | | |
|---|---|---|---|---|---|
| Major bleeding assessed with: any major bleeding follow up: range 1 days to 2 weeks | 297 (15 observational studies) | ⨁◯◯◯ VERY LOW[a,b] | not pooled | not pooled | not pooled |
| Major bleeding assessed with: in ADULTS as any major bleeding (early) | 1103 (17 RCTs)[f] | ⨁◯◯◯ VERY LOW[d,g] | **RR 2.23** (1.41 to 3.52) | Study population | |
| | | | | 43 per 1,000 | **53 more per 1,000** (18 more to 109 more) |
| Post-thrombotic syndrome assessed with: PTS with pediatric adapted scale (moderate or severe) follow up: median 4.5 years | 183 (7 observational studies) | ⨁◯◯◯ VERY LOW[a,b] | not pooled | Study population | |
| | | | | not pooled | not pooled |
| Post-thrombotic syndrome assessed with: in ADULTS | 306 (3 RCTs)[f] | ⨁◯◯◯ VERY LOW[d,h] | **RR 0.66** (0.53 to 0.81) | Study population | |
| | | | | 658 per 1,000 | **224 fewer per 1,000** (309 fewer to 125 fewer) |

a. Case series and only one comparative study.
b. Low rates of events and few participants.
c. Data from Chattarje 2014 and updated in ASH guideline on treatment of PE in adults.

| | | |
|---|---|---|
| | d. From adult data<br>e. Low event rates with confidence intervals not excluding plausible benefit or harm<br>f. From Watson 2016 Cochrane systematic review<br>g. All studies with concerns about randomization list generation and adequate concealment<br>h. Heterogeneity at the study level.<br><br>NOTE: See also the evidence profile for complete evidence assessments. | |
| | Adolopment | |
| ● Trivial<br>○ Small<br>○ Moderate<br>○ Large<br>○ Varies<br>○ Don't know | *See Appendix 2*<br><br>*See Appendix 3See Appendix 4* | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Undesirable Effects

How substantial are the undesirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

● Large
○ Moderate
○ Small
○ Trivial
○ Varies
○ Don't know

| Outcomes | № of participants (studies) Follow up | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects* (95% CI) | |
|---|---|---|---|---|---|
| | | | | Risk with anticoagulation alone | Risk difference with thrombolysis followed by anticoagulation |
| Mortality assessed with: as all-cause mortality follow up: range 1 days to 6 years | 320 (15 observational studies) | ⨁◯◯◯ VERY LOW[a,b] | not pooled | Study population | |
| | | | | not pooled | not pooled |
| Mortality assessed with: in ADULTS with massive PE as all-cause mortality | 2526 (22 RCTs)[c] | ⨁◯◯◯ VERY LOW[d,e] | **RR 0.61** (0.40 to 0.94) | Study population | |
| | | | | 45 per 1,000 | **18 fewer per 1,000** (27 fewer to 3 fewer) |
| Non-fatal pulmonary embolism - representing the moderate marker state assessed with: any PE in ADULTS with PE and hemodynamic compromise | 2288 (16 RCTs)[c] | ⨁◯◯◯ VERY LOW[d,e] | **RR 0.56** (0.35 to 0.91) | Study population | |
| | | | | 40 per 1,000 | **18 fewer per 1,000** (26 fewer to 4 fewer) |

Panel considered undesirable effects as large.

Undesirable effects might be considered large for systemic therapy but moderate for catheter directed therapy.

| | | | | | |
|---|---|---|---|---|---|
| follow up: range 7 days to 90 days | | | | | |
| Deep vein thrombosis assessed with: in children as NO clot resolution or progression (early) follow up: range 1 days to 2 weeks | 320 (15 observational studies) | ⨁◯◯◯ VERY LOW[a,b] | not pooled | Study population | |
| | | | | not pooled | not pooled |
| Deep vein thrombosis assessed with: in ADULTS as NO clot resolution or progression (early) | 462 (8 RCTs)[f] | ⨁◯◯◯ VERY LOW[d,g,h] | **RR 0.40** (0.21 to 0.74) | Study population | |
| | | | | 632 per 1,000 | **379 fewer per 1,000** (499 fewer to 164 fewer) |
| Major bleeding assessed with: any major bleeding follow up: range 1 days to 2 weeks | 297 (15 observational studies) | ⨁◯◯◯ VERY LOW[a,b] | not pooled | Study population | |
| | | | | not pooled | not pooled |
| Major bleeding assessed with: in ADULTS as any major | 1103 (17 RCTs)[f] | ⨁◯◯◯ VERY LOW[d,g] | **RR 2.23** (1.41 to 3.52) | Study population | |
| | | | | 43 per 1,000 | **53 more per 1,000** (18 more to 109 more) |

| | | | | | |
|---|---|---|---|---|---|
| bleeding (early) | | | | | |
| Post-thrombotic syndrome assessed with: PTS with pediatric adapted scale (moderate or severe) follow up: median 4.5 years | 183 (7 observational studies) | ⨁◯◯◯ VERY LOW[a,b] | not pooled | Study population | |
| | | | | not pooled | not pooled |
| Post-thrombotic syndrome assessed with: in ADULTS | 306 (3 RCTs)[f] | ⨁◯◯◯ VERY LOW[d,h] | **RR 0.66** (0.53 to 0.81) | Study population | |
| | | | | 658 per 1,000 | **224 fewer per 1,000** (309 fewer to 125 fewer) |

a. Case series and only one comparative study.
b. Low rates of events and few participants.
c. Data from Chattarje 2014 and updated in ASH guideline on treatment of PE in adults.
d. From adult data
e. Low event rates with confidence intervals not excluding plausible benefit or harm
f. From Watson 2016 Cochrane systematic review
g. All studies with concerns about randomization list generation and adequate concealment
h. Heterogeneity at the study level.

NOTE: See also the evidence profile for complete evidence assessments.

| | | |
|---|---|---|
| | | |
| | Adolopment | |
| ● Large<br>○ Moderate<br>○ Small<br>○ Trivial<br>○ Varies<br>○ Don't know | *See Appendix 1* | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Certainty of evidence

What is the overall certainty of the evidence of effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | Certainty of the evidence of effects was judged as 'very low' due to imprecision, indirecntess, risk of bias. | Panel members noted that when the condition is a sub-massive or massive PE, the uncertainty is very low. However, when other conditions are considered, the uncertainty in the evidence could be higher. |
| | Adolopment | |

| | | |
|---|---|---|
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | Certainty of the evidence of effects was judged as 'very low' due to imprecision, and risk of bias. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Values

Is there important uncertainty about or variability in how much people value the main outcomes?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Important uncertainty or variability<br>● Possibly important uncertainty or variability<br>○ Probably no important uncertainty or variability<br>○ No important uncertainty or variability | **<u>Utility related information:</u>**<br><br>**The relative importance of outcomes:**<br><br>**<u>Results from Panel Members' Utility Rating Survey</u>**:<br>Utilities rated on the visual analog scale, where 0 represents death and 1 represents full health, were as follows.<br>Pulmonary embolism – Severe marker state: 0.31<br>Pulmonary embolism – Moderate marker state: 0.49<br>Deep vein thrombosis (proximal) – Severe marker state: 0.49<br>Deep vein thrombosis (proximal) – Moderate marker state: 0.61<br>Deep vein thrombosis (distal) – Severe marker state: 0.56<br>Deep vein thrombosis (distal) – Moderate marker state: 0.68<br>Major bleeding: 0.30 | Panel members noted a possibly important uncertainty, as some patients might prefer the risks of thrombolysis over anticoagulation for conditions with higher risks (e.g., submassive or massive PE) |

| | | |
|---|---|---|
| | Neonatal Bleeding – Severe: 0.30<br><br>Infant Bleeding – Severe: 0.26<br><br>Post-thrombotic syndrome – Long term marker state: 0.60<br><br>**We did not identify utility related information or non-utility information for the outcomes of interest specific to the pediatric population in the literature.**<br><br>**<u>Additional information from the adult population:</u>**<br><br>**Our systematic review for the adult population found that the relative importance of the outcomes is as follows:**<br><br>Pulmonary embolism: 0.63-0.93 (different methods) (Hogg et al., 2014, Hogg et al., 2013, Locadia et al., 2004)<br><br>Deep vein thrombosis: 0.64-0.99 (different methods) (Marvig et al., 2015, Utne et al., 2016, Hogg et al., 2013, Hogg et al., 2014, Locadia et al., 2004)<br><br>Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off)<br><br>Muscular bleeding: 0.76 (time trade off) (Locadia et al., 2004)<br><br>Minor intracranial bleeding event: 0.75 (standard gamble) (Hogg et al., 2013)<br><br>Major intracranial bleeding event: 0.15 (standard gamble) (Hogg et al., 2013)<br><br>Central nervous system bleeding: 0.29-0.60 (standard gamble) (Lenert et al., 1997)(O'Meara et al., 1994)<br><br>Treatment with LMWH: 0.993 (time trade off) (Marchetti et al., 2001)<br><br>Treatment with warfarin (as a surrogate): 0.989 (time trade off) (Marchetti et al., 2001)<br><br>**<u>A systematic review was identified with the following non-utility information from the adult population:</u>** | |

| | | |
|---|---|---|
| | **Anticoagulant therapy**<br><br>Adult patients highly value the benefits of risk reduction in VTE recurrence and post-thrombosis syndrome (Locadia et al., 2004). Patients would favor efficacy and safety over convenience of route of administration (Noble et al., 2015). Further, patients would like to avoid adverse events but most of them are "not afraid of" the adverse events(Barcellona et al., 2000, Noble et al., 2015, O'Meara et al., 1994). For anticoagulant therapy in general, most patients would prefer the oral doses compared with injections, this is mainly because of treatment burden due to injection. For patients with venographically proven deep venous thrombosis, 15 of the 19 patients expressed a preference for the subcutaneous route for administration of heparin over intravenous administration. (Robinson et al., 1993) | |
| | Adolopment | |
| ○ Important uncertainty or variability<br>○ Possibly important uncertainty or variability<br>○ Probably no important uncertainty or variability<br>○ No important uncertainty or variability | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |
| **Balance of effects**<br>Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | |
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| | Original | |

| | | |
|---|---|---|
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>● Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>○ Don't know | | The panel mentioned that balance probably favors thrombolysis.<br><br>Panel members noted that studies using fibrinolytics may have patients with more severe associated VTE/PE with expected worse outcomes, e.g., fibrinolytics for VTE associated with major organ dysfunction where timely reperfusion is needed.<br><br>The patient representative noted that patients usually are unaware of the implications of such therapies and rely on their physicians for making this decision. |
| | Adolopment | |
| ○ Favors the comparison<br>● Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Resources required

How large are the resource requirements (costs)?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

| | | |
|---|---|---|
| ● Large costs<br>○ Moderate costs<br>○ Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br>○ Varies<br>○ Don't know | No direct research evidence was identified for costs of anticoagulation as compared to anticoagulation plus systemic thrombolysis for treatment in pediatric patients with symptomatic DVT or PE.<br><br>Two studies reported the costs of disease from pediatric patients with any VTE. One reported for 834 pediatric patients with VTE a median annual expenditure of $25,258 and $24,934 USD in Medicaid and private insurance patients respectively.(Boulet et al., 2012) Another study found that patients with VTE had an increased 8.1 inpatient days and excess average costs of $27,686 USD. (Goudie et al., 2015)<br><br>**Additional information from adult population:** In the adult population the cost of urokinase and equipment cost for the catheter directed thrombolysis is estimated to around $10,127 USD (Karthikesalingam A, 2011) In adult patients receiving stroke treatment, thrombolysis has been deemed as a cost-effective strategy, with direct cost of $2750 USD per dose. (Kazley AS, 2013)<br><br>For costs of anticoagulation in adult patients, the direct cost per week with warfarin in adults ranges from $3.54 to $11.44 USD while this number in Canada decreases to 0.49 to 0.84 CAD per week. (Biskupiak et al., 2013)(Klarenbach et al., 2016)(Guanella et al., 2011) With heparin, the costs per unit ranges from $0.18 per 10 units, to $0.212 per 1000 units (Medicare, 2017) with a Cost per week: $37.00 USD and $11.14 CAD per day in Canada. (Klarenbach et al., 2016)(Guanella et al., 2011) LMWH (enoxaparin) cost varies. The wholesale cost in the low and middle income economies is about $13 to $75 USD per week. (IMPPG, 2016) In the United States the wholesale cost is about $98.91 USD per day as of 2016.(NADAC, 2017) | Although no direct evidence was found, the panel considered that the cost of tPA varies depending on forms of administration (e.g., IV vs. interventional procedure). Overall, the thrombolysis was considered to have higher costs. |
| | Adolopment | |
| ○ Large costs<br>○ Moderate costs<br>○ Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | No research evidence found. | |
| | Adolopment | |
| ○ Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

| | | |
|---|---|---|
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>● No included studies | No research evidence was identified about cost-effectiveness. | |
| | Adolopment | |
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>● No included studies | **Information from adult population:**<br><br>In ATTRACT (Acute Venous Thrombosis: Thrombus Removal With Adjunctive Catheter-Directed Thrombolysis), which looked at direct costs (treatment and hospitalizations) an incremental cost-effectiveness ratio for PCDT of $222 041/QALY gained for proximal DVT. For iliofemoral DVT, QALY gains with PCDT were greater, yielding an incremental cost-effectiveness ratio of $137 526/QALY. The analysis assumed a healthcare system perspective and estimated direct healthcare costs and QALYs over a lifetime horizon; productivity costs were not included in the model. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Equity

What would be the impact on health equity?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Reduced<br>● Probably reduced<br>○ Probably no impact<br>○ Probably increased<br>○ Increased<br>○ Varies<br>○ Don't know | No research evidence identified. | The panel considers that equity would probably be reduced if thrombolysis is implemented in the indicated situations with high risks and in low resource settings. |
| | Adolopment | |

| | | |
|---|---|---|
| ○ Reduced<br>○ Probably reduced<br>○ Probably no impact<br>○ Probably increased<br>○ Increased<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Acceptability

Is the intervention acceptable to key stakeholders?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br>● Varies<br>○ Don't know | Survey and observational research suggests the following regarding acceptability and barriers associated with anticoagulation and thrombolysis in the pediatric population:<br><br>One survey of American Society of Pediatric Hematology/Oncology members demonstrates the wide variation in treatment approaches between practitioners, in this case with respect to thrombolytic therapy of pediatric VTE. With respect to the preferred agent, the survey results confirm that tPA has become the thrombolytic drug of choice in pediatric patients, although a small percentage of respondents stated a preference for others, such as urokinase. In contrast, responses varied widely regarding the preferred mode of tPA delivery (systemic vs. catheter-directed vs. use of catheter-directed therapy on a salvage basis) without clear majority preference for any single modality. Since the overwhelming majority of respondents (95%) reported having access to pediatric interventional radiology services, preferences for a given mode of tPA administration clearly could not be ascribed to IR availability and were not associated with any of the other queried professional demographic data. (Yee 2009).<br><br>Observational research suggests the following regarding acceptability and barriers associated with the intervention: In Australia a prospective chart audit in a tertiary paediatric centre assessed the level of compliance of antithrombotic medication use in current practice with guidelines across a 100-day prospective chart audit in 2008-2009. The study showed that the level of compliance for use | |

| | | |
|---|---|---|
| | of antithrombotic medications for the indications of DVT and PE was 98.8% and 61.5%, respectively. High compliance was correlated with strong recommendations, with low compliance found especially in areas where recommendations were based on 'weak' evidence. This reflects clinician confidence in the strength of evidence currently available for paediatric antithrombotic therapy where there may be barriers associated with the use of the intervention where only low-quality, inconsistent, or indirect evidence extrapolated from adult data is available. (Peng et al., 2011) | |
| | Adolopment | |
| ○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Feasibility

Is the intervention feasible to implement?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br>● Varies<br>○ Don't know | No research evidence was identified. | The panel discuss how availability of interventional radiology equipment and personnel in certain settings, and availability of thrombolytic drugs might hamper the feasibilty of implementing the intervention. |
| | Adolopment | |
| ○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |



## SUMMARY OF JUDGEMENTS

| CRITERIA | ORIGINAL | IMPORTANCE FOR DECISION | ADOLOPMENT | IMPORTANCE FOR DECISION |
|---|---|---|---|---|
| PROBLEM | Yes | | Yes | |
| DESIRABLE EFFECTS | Trivial | | Trivial | |
| UNDESIRABLE EFFECTS | Large | | Large | |
| CERTAINTY OF EVIDENCE | Very low | | Very low | |
| VALUES | Possibly important uncertainty or variability | | | |
| BALANCE OF EFFECTS | Probably favors the intervention | | Probably favors the comparison | |
| RESOURCES REQUIRED | Large costs | | | |
| CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES | Very low | | | |
| COST EFFECTIVENESS | No included studies | | No included studies | |
| EQUITY | Probably reduced | | | |
| ACCEPTABILITY | Varies | | | |
| FEASIBILITY | Varies | | | |



## TYPE OF RECOMMENDATION

Original

| Strong recommendation against the intervention | **Conditional recommendation against the intervention** | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | Strong recommendation for the intervention |
|---|---|---|---|---|
| ○ | ● | ○ | ○ | ○ |

Adolopment

| Strong recommendation against the intervention | **Conditional recommendation against the intervention** | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | Strong recommendation for the intervention |
|---|---|---|---|---|
| ○ | ● | ○ | ○ | ○ |

## CONCLUSIONS

Original

### Recommendation

**The ASH guideline panel suggests against using thrombolysis followed by anticoagulation, and rather use anticoagulation alone in pediatric patients with proximal DVT (conditional recommendation based on very low certainty in the evidence about effects).**

### Justification

The panel considered issues such as the size and clinical impact of VTE as important in deciding the relative risk/benefit ratio of thrombolysis. In most cases the risks seem too high for the potential benefit however there may be individuals in whom the opposite is true. Extrapolation of adult data was difficult. There is insufficient data to address the relative risk benefit of local thrombolysis via interventional radiology compared to systemic thrombolysis and the panel noted the centers with access to pediatric interventional radiology were often stronger advocates of thrombolysis.

Adolopment

### Recommendation

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

### Justification

### Subgroup considerations

## Implementation considerations

It is important to consider if the interventional radiology services are available in locations it should be implemented.

## Monitoring and evaluation

## Research priorities

## REFERENCES SUMMARY

1. Ansah DA, Patel KN Montegna L Nicholson GT Ehrlich AC Petit CJ. Tissue Plasminogen Activator Use in Children: Bleeding Complications and Thrombus Resolution. J Pediatr; 2016.

# APPENDICES

Appendix 1

**Author(s):**
**Question:** Thrombolysis followed by anticoagulation compared to anticoagulation alone in pediatric patients with proximal DVT
**Setting:** Inpatient
**Bibliography:** ASH/ISTH 2024 Guidelines for Management of Venous Thromboembolism: Treatment of Pediatric Venous Thromboembolism

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | thrombolysis followed by anticoagulation | anticoagulation alone | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality** | | | | | | | | | | | | |
| 4[1,2,3,4] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 5/54 (9.3%) | 2/21 (9.5%) | **RR 0.97** (0.20 to 4.63) | **3 fewer per 1,000** (from 76 fewer to 346 more) | ⨁◯◯◯ Very low | CRITICAL |
| **Mortality** | | | | | | | | | | | | |
| 4[5,6,7,8] | non-randomised studies | serious[c] | not serious | not serious | very serious[b] | none | 6/72 (8.3%) | - | - | - | ⨁◯◯◯ Very low | CRITICAL |
| **Resolution (assessed with: Complete and Partial Resolution)** | | | | | | | | | | | | |
| 4[1,3,4,9,10] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 49/55 (89.1%) | 20/29 (69.0%) | **RR 1.29** (0.99 to 1.68) | **200 more per 1,000** (from 7 fewer to 469 more) | ⨁◯◯◯ Very low | CRITICAL |
| **Resolution (assessed with: Complete or Partial Resolution)** | | | | | | | | | | | | |
| 5[5,6,7,8,11] | non-randomised studies | serious[c] | not serious | not serious | very serious[b] | none | 56/75 (74.7%) | - | - | - | ⨁◯◯◯ Very low | CRITICAL |
| **Reccurence** | | | | | | | | | | | | |
| 4[1,2,3,4] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 5/54 (9.3%) | 2/21 (9.5%) | **RR 0.97** (0.20 to 4.63) | **3 fewer per 1,000** (from 76 fewer to 346 more) | ⨁◯◯◯ Very low | CRITICAL |
| **Recurrence** | | | | | | | | | | | | |
| 2[6,12] | non-randomised studies | serious[c] | not serious | not serious | very serious[b] | none | 12/54 (22.2%) | - | - | - | ⨁◯◯◯ Very low | CRITICAL |
| **Post-Thrombotic Syndrome** | | | | | | | | | | | | |
| 4[1,2,4,9,10] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 13/36 (36.1%) | 13/34 (38.2%) | **RR 1.87** (0.77 to 4.40) | **333 more per 1,000** (from 88 fewer to 1,000 more) | ⨁◯◯◯ Very low | CRITICAL |
| **Post-Thrombotic Syndrome** | | | | | | | | | | | | |
| 3[6,7,12] | non-randomised studies | serious[c] | not serious | not serious | very serious[b] | none | 9/61 (14.8%) | - | - | - | ⨁◯◯◯ Very low | CRITICAL |

**CI:** confidence interval; **RR:** risk ratio

**Explanations**

a. Risk of bias, assessed using ROBINS-I, was judged to be serious due to selection bias.
b. Imprecision due to small number of included patients and patients with events in the included studies.
c. Risk of bias was judged to be serious due to selection bias.

**References**


1.R, Kumar, K, Harsh, S, Saini, SH, O'Brien, J, Stanek, P, Warren, J, Giver, MR, Go, BA, Kerlin. Treatment-Related Outcomes in Paget-Schroetter Syndrome-A Cross-Sectional . The Journal of pediatrics; 2019.
2.C, Tarango, R, Kumar, M, Patel, A, Blackmore, P, Warren, JS, Palumbo. Inferior vena cava atresia predisposing to acute lower extremity deep vein . Pediatric blood & cancer; 2018.
3.CH, van,Ommen, KA, Bergman, M, Boerma, HA, Bouma, AE, Donker, M, Gouvernante, CV, Hulzebos, D, Khandour, R, Knol, MA, Raets, KD, Liem, RA, van,Lingen, M, van,de,Loo, E, Lopriore, M, van,der,Putten, JJ, Sol, MH, Suijker, DC, Vijlbrief, R, Visser, MM, van,Weissenbruch. NEOnatal Central-venous Line Observational study on Thrombosis (NEOCLOT): . Journal of thrombosis and haemostasis : JTH; 2023.
4., , Warad, . Clinical Outcomes of May-Thurner Syndrome in Pediatric Patients: A Single Institutional Experience.
5.P, Grizante-Lopes, MP, Garanito, DM, Celeste, VLJ, Krebs, JDA, Carneiro. Thrombolytic therapy in preterm infants: Fifteen-year experience.. Pediatric blood & cancer; 2020.
6.CT, Cohen, SE, Sartain, H, Sangi-Haghpeykar, KU, Kukreja, SB, Desai. Clinical characteristics and outcomes of combined thrombolysis and . Pediatric hematology and oncology; 2021.
7.E, Zengin, N, Sarper, A, Yazal,Erdem, I, Odaman,Al, M, Sezgin,Evim, N, Yarali, B, Belen, A, Akçay, A, Türedi,Yildirim, TH, Karapinar, AM, Güneş, S, Aylan,Gelen, H, Ören, L, Olcay, B, Baytan, H, Gülen, G, Öztürk, MF, Orhan, Y, Oymak, S, Akpınar, Ö, Tüfekçi, M, Albayrak, B, Tatlı,Güneş, A, Canpolat, N, Özbek. Thrombolysis with Systemic Recombinant Tissue Plasminogen Activator in Children: . Turkish journal of haematology : official journal of Turkish Society of ; 2021.
8., , Cervio, . Thrombolytic therapy in neonates and children: A twelve-year prospective registry of a single tertiary pediatric center in Argentina.
9.CT, Cohen, S, Kirk, SB, Desai, KU, Kukreja, L, Srivaths. Diagnosis, Clinical Characteristics, and Treatment Modalities of Adolescent . Journal of pediatric hematology/oncology; 2021.
10.NA, Goldenberg, JD, Durham, R, Knapp-Clevenger, MJ, Manco-Johnson. A thrombolytic regimen for high-risk deep venous thrombosis may substantially . Blood; 2007.
11.E, Pekpak, E, Ince, M, Ertem, E, Tutar, T, Ileri, T, Ucar, ST, Tiras, HF, Cakmakli, Z, Uysal. Tissue Plasminogen Activator Use in Pediatric Patients: A Single Center . Journal of pediatric hematology/oncology; 2021.
12., , Brauner, . Retrospective case series study of patients with may-Thurner syndrome in a single tertiary pediatric center.

Appendix 2

**Author(s):**
**Question:** Thrombolysis followed by anticoagulation compared to anticoagulation alone in pediatric patients with proximal DVT
**Setting:** Inpatient
**Bibliography:** ASH/ISTH 2024 Guidelines for Management of Venous Thromboembolism: Treatment of Pediatric Venous Thromboembolism

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | thrombolysis followed by anticoagulation | anticoagulation alone | Relative (95% CI) | Absolute (95% CI) | | |
| **Major Bleeding** | | | | | | | | | | | | |
| 2[1,2,7] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 2/20 (10.0%) | 5/55 (9.1%) | **RR 0.76** (0.10 to 5.88) | **22 fewer per 1,000** (from 82 fewer to 444 more) | ⨁◯◯◯ Very low | CRITICAL |
| **CRNMB** | | | | | | | | | | | | |
| 2[1,2] | non-randomised studies | serious[b] | not serious | not serious | very serious[b] | none | 0/11 (0.0%) | 1/42 (2.4%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Bleeding (Unspecified)** | | | | | | | | | | | | |
| 6[3,4,5,6,8,9] | non-randomised studies | serious[c] | not serious | not serious | very serious[b] | none | 11/100 (11.0%) | - | - | - | ⨁◯◯◯ Very low | CRITICAL |

**CI:** confidence interval; **RR:** risk ratio

**Explanations**

a. Risk of bias, assessed using ROBINS-I, was judged to be serious due to selection bias.
b. Imprecision due to small number of included patients and patients with events in the included studies.
c. Risk of bias was judged to be serious due to selection bias.

**References**


1.R, Kumar, K, Harsh, S, Saini, SH, O'Brien, J, Stanek, P, Warren, J, Giver, MR, Go, BA, Kerlin. Treatment-Related Outcomes in Paget-Schroetter Syndrome-A Cross-Sectional . The Journal of pediatrics; 2019.
2.CH, van,Ommen, KA, Bergman, M, Boerma, HA, Bouma, AE, Donker, M, Gouvernante, CV, Hulzebos, D, Khandour, R, Knol, MA, Raets, KD, Liem, RA, van,Lingen, M, van,de,Loo, E, Lopriore, M, van,der,Putten, JJ, Sol, MH, Suijker, DC, Vijlbrief, R, Visser, MM, van,Weissenbruch. NEOnatal Central-venous Line Observational study on Thrombosis (NEOCLOT) : . Journal of thrombosis and haemostasis : JTH; 2023.
3.P, Grizante-Lopes, MP, Garanito, DM, Celeste, VLJ, Krebs, JDA, Carneiro. Thrombolytic therapy in preterm infants: Fifteen-year experience.. Pediatric blood & cancer; 2020.
4.CT, Cohen, SE, Sartain, H, Sangi-Haghpeykar, KU, Kukreja, SB, Desai. Clinical characteristics and outcomes of combined thrombolysis and . Pediatric hematology and oncology; 2021.
5.E, Zengin, N, Sarper, A, Yazal,Erdem, I, Odaman,Ai, M, Sezgin,Evim, N, Yarali, B, Belen, A, Akçay, A, Türedi,Yildirim, TH, Karapinar, AM, Güneş, S, Aylan,Gelen, H, Ören, L, Olcay, B, Baytan, H, Gülen, G, Öztürk, MF, Orhan, Y, Oymak, S, Akpınar, Ö, Tüfekçi, M, Albayrak, B, Tatlı,Güneş, A, Canpolat, N, Özbek. Thrombolysis with Systemic Recombinant Tissue Plasminogen Activator in Children: . Turkish journal of haematology : official journal of Turkish Society of ; 2021.
6., , Cervio, . Thrombolytic therapy in neonates and children: A twelve-year prospective registry of a single tertiary pediatric center in Argentina.
7.NA, Goldenberg, JD, Durham, R, Knapp-Clevenger, MJ, Manco-Johnson. A thrombolytic regimen for high-risk deep venous thrombosis may substantially . Blood; 2007.
8.E, Pekpak, E, Ince, M, Ertem, E, Tutar, T, Ileri, T, Ucar, ST, Tiras, HF, Cakmakli, Z, Uysal. Tissue Plasminogen Activator Use in Pediatric Patients: A Single Center . Journal of pediatric hematology/oncology; 2021.
9., , Brauner, . Retrospective case series study of patients with may-Thurner syndrome in a single tertiary pediatric center.

## QUESTION

| Should thrombolysis followed by anticoagulation vs. anticoagulation alone be used for pediatric patients with PE with hemodynamic compromise? | |
|---|---|
| **POPULATION:** | pediatric patients with PE with hemodynamic compromise |
| **INTERVENTION:** | thrombolysis followed by anticoagulation |
| **COMPARISON:** | anticoagulation alone |
| **MAIN OUTCOMES:** | Mortality; Non-fatal pulmonary embolism -representing the moderate marker state; Deep vein thrombosi; Major bleeding; Post-thrombotic syndrome. |
| **SETTING:** | Inpatient |
| **PERSPECTIVE:** | Clinical recommendation - Population perspective |
| **BACKGROUND:** | The first line of treatment of venous thromboembolism in the pediatric populations includes anticoagulation, although in some instances, it might require the use of thrombolytics and/or invasive vascular procedures. The infusion of thrombolytics, such as tissue plasminogen activator (tPA) either systemically or directed by catheter are more commonly being used in adults. In the pediatric field, however, there still is need for evidence to ascertain the risks and benefits of such therapy. (1) |
| **CONFLICT OF INTEREST:** | |

## ASSESSMENT

**Problem**
Is the problem a priority?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ No<br>○ Probably no<br>○ Probably yes<br>● Yes<br>○ Varies<br>○ Don't know | In patients with symptomatic DVT or PE, the use of anticoagulation is the first line of therapy. In some instances, the use of thrombolytic drugs such as tissue plasminogen activator (tPA) might be warranted. The lack of evidence on this topic frequently precludes clinicians to be confident on the decision-making process. | |
| | Adolopment | |

| | | |
|---|---|---|
| ○ No<br>○ Probably no<br>○ Probably yes<br>● Yes<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Desirable Effects

How substantial are the desirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

● Trivial
○ Small
○ Moderate
○ Large
○ Varies
○ Don't know

| Outcomes | № of participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects* (95% CI) | |
|---|---|---|---|---|---|
| | | | | Risk with anticoagulation alone | Risk difference with thrombolysis followed by anticoagulation |
| Mortality assessed with: as all-cause mortality follow up: range 1 days to 6 years | 320 (15 observational studies) | ⨁◯◯◯ VERY LOW[a,b] | not pooled | Study population | |
| | | | | not pooled | not pooled |
| Deep vein thrombosis assessed with: in children as NO clot resolution or progression (early) | 320 (15 observational studies) | ⨁◯◯◯ VERY LOW[a,b] | not pooled | Study population | |
| | | | | not pooled | not pooled |

The consideration is different for patients with DVT/PE versus patients with massive PE, where desirable effects are considered to be larger.

** in notes the judgment is 'moderate' but here it was as 'trivial'**

| | | | | | |
|---|---|---|---|---|---|
| follow up: range 1 days to 2 weeks | | | | | |
| Major bleeding assessed with: any major bleeding follow up: range 1 days to 2 weeks | 297 (15 observational studies) | ⨁◯◯◯ VERY LOW[a,b] | not pooled | Study population | |
| | | | | not pooled | not pooled |
| Post-thrombotic syndrome assessed with: PTS with pediatric adapted scale (moderate or severe) follow up: median 4.5 years | 183 (7 observational studies) | ⨁◯◯◯ VERY LOW[a,b] | not pooled | Study population | |
| | | | | not pooled | not pooled |

a. Case series and only one comparative study.
b. Low rates of events and few participants.

| | | |
|---|---|---|
| | Adolopment | |
| ● Trivial<br>○ Small<br>○ Moderate<br>○ Large<br>○ Varies<br>○ Don't know | *See Appendix 2* | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Undesirable Effects

How substantial are the undesirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

● Large
○ Moderate
○ Small
○ Trivial
○ Varies
○ Don't know

| Outcomes | № of participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects* (95% CI) | |
|---|---|---|---|---|---|
| | | | | Risk with anticoagulation alone | Risk difference with thrombolysis followed by anticoagulation |
| Mortality assessed with: as all-cause mortality follow up: range 1 days to 6 years | 320 (15 observational studies) | ⨁◯◯◯ VERY LOW[a,b] | not pooled | Study population | |
| | | | | not pooled | not pooled |
| Deep vein thrombosis assessed with: in | 320 (15 observational studies) | ⨁◯◯◯ VERY LOW[a,b] | not pooled | Study population | |
| | | | | not pooled | not pooled |

Rates of bleeding 1-2% vs 10-30%

Consideration of rate of bleeding with combined therapy versus anticoagulation alone.

Undesirable effects might be considered large for systemic therapy but moderate for catheter directed therapy.

| | | | | | |
|---|---|---|---|---|---|
| children as NO clot resolution or progression (early) follow up: range 1 days to 2 weeks | | | | | |
| Major bleeding assessed with: any major bleeding follow up: range 1 days to 2 weeks | 297 (15 observational studies) | ⨁◯◯◯ VERY LOW[a,b] | not pooled | Study population | |
| | | | | not pooled | not pooled |
| Post-thrombotic syndrome assessed with: PTS with pediatric adapted scale (moderate or severe) follow up: median 4.5 years | 183 (7 observational studies) | ⨁◯◯◯ VERY LOW[a,b] | not pooled | Study population | |
| | | | | not pooled | not pooled |

a. Case series and only one comparative study.
b. Low rates of events and few participants.

| | | |
|---|---|---|
| | | |
| | Adolopment | |
| ● Large<br>○ Moderate<br>○ Small<br>○ Trivial<br>○ Varies<br>○ Don't know | *See Appendix 1* | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Certainty of evidence

What is the overall certainty of the evidence of effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | Certainty of the evidence of effects was judged as 'very low' due to imprecision, indirecntess, risk of bias. | When the condition is a sub-massive or massive PE the uncertainty is very low. However, when other conditions are considered there might be more uncertainty on the evidence. |
| | Adolopment | |

| | | |
|---|---|---|
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | Certainty of the evidence of effects was judged as 'very low' due to imprecision and risk of bias. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Values

Is there important uncertainty about or variability in how much people value the main outcomes?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Important uncertainty or variability<br>● Possibly important uncertainty or variability<br>○ Probably no important uncertainty or variability<br>○ No important uncertainty or variability | **<u>Utility related information:</u>**<br><br>**The relative importance of outcomes:**<br><br>**<u>Results from Panel Members' Utility Rating Survey</u>**:<br>Utilities rated on the visual analog scale, where 0 represents death and 1 represents full health, were as follows.<br>Pulmonary embolism – Severe marker state: 0.31<br>Pulmonary embolism – Moderate marker state: 0.49<br>Deep vein thrombosis (proximal) – Severe marker state: 0.49<br>Deep vein thrombosis (proximal) – Moderate marker state: 0.61<br>Deep vein thrombosis (distal) – Severe marker state: 0.56<br>Deep vein thrombosis (distal) – Moderate marker state: 0.68<br>Major bleeding: 0.30 | Panel members noted a possibly important uncertainty in patients with less severe conditions (e.g., DVT) but might prefere the risks of thrombolytic treatment over anticoagulation for conditions with different risks (e.g., massive PE) |

| | | |
|---|---|---|
| | Neonatal Bleeding – Severe: 0.30<br><br>Infant Bleeding – Severe: 0.26<br><br>Post-thrombotic syndrome – Long term marker state: 0.60<br><br>**We did not identify utility related information or non-utility information for the outcomes of interest specific to the pediatric population in the literature.**<br><br>**<u>Additional information from the adult population:</u>**<br><br>**Our systematic review for the adult population found that the relative importance of the outcomes is as follows:**<br><br>Pulmonary embolism: 0.63-0.93 (different methods) (Hogg 2013, Hogg 2014, Locadia 2004)<br><br>Deep vein thrombosis: 0.64-0.99 (different methods) (Hogg 2013, Hogg 2014, Locadia 2004, Marvig 2015, Utne 2016)<br><br>Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) (Hogg 2013, Locadia 2004)<br><br>Muscular bleeding: 0.76 (time trade off) (Locadia 2004)<br><br>Minor intracranial bleeding event: 0.75 (standard gamble) (Hogg 2013)<br><br>Major intracranial bleeding event: 0.15 (standard gamble) (Hogg 2013)<br><br>Central nervous system bleeding: 0.29-0.60 (standard gamble) (Lenert 1997, O'Meara 1994)<br><br>Treatment with LMWH: 0.993 (time trade off) (Marchetti 2001)<br><br>Treatment with warfarin (as a surrogate): 0.989 (time trade off) (Marchetti 2001) | |

| | | |
|---|---|---|
| | **<u>We also identified in the systematic review the following non-utility information from the adult population:</u>**<br><br>**Anticoagulant therapy**<br><br>Adult patients highly value the benefits of risk reduction in VTE recurrence and post-thrombosis syndrome (Locadia 2004). Patients would favor efficacy and safety over convenience of route of administration (Noble 2015). Further, patients would like to avoid adverse events but most of them are "not afraid of" the adverse events (Barcellona 2000, Noble 2015, O'Meara 1994). For anticoagulant therapy in general, most patients would prefer the oral doses compared with injections, this is mainly because of treatment burden due to injection (Barcellona 2000, Noble 2015). For patients with venographically proven deep venous thrombosis, 15 of the 19 patients expressed a preference for the subcutaneous route for administration of heparin over intravenous administration (Robinson 1993). | |
| | Adolopment | |
| ○ Important uncertainty or variability<br>● Possibly important uncertainty or variability<br>○ Probably no important uncertainty or variability<br>○ No important uncertainty or variability | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

| | | |
|---|---|---|
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>● Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>○ Don't know | | > Studies using fibrinolytics may have patients with more severe VTE/PE with expected worse outcomes.<br><br>> Fibrinolytics for VTE associated with major organ dysfunction where timely reperfusion is needed. |
| | Adolopment | |
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>● Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Resources required

How large are the resource requirements (costs)?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ● Large costs<br>○ Moderate costs<br>○ Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br>○ Varies<br>○ Don't know | No direct research evidence was identified for costs of anticoagulation as compared to anticoagulation plus systemic thrombolysis for treatment in pediatric patients with symptomatic DVT or PE.<br><br>Two studies reported the costs of disease from pediatric patients with any VTE. One reported for 834 pediatric patients with VTE a median annual expenditure of $25,258 and $24,934 USD in Medicaid and private insurance patients respectively. [Boulet 2012] Another study found that patients with VTE had an increased 8.1 inpatient days and excess average costs of $27,686 USD. [Goudie 2015] | Additional considerations for discussion:<br><br>> Consideration about cost of tPA, and administration (IV vs. interventional procedure) which could change the cost. |

| | | |
|---|---|---|
| | **Additional information from adult population:** In the adult population the cost of urokinase and equipment cost for the catheter directed thrombolysis is estimated to around $10,127 USD [Karthikesalingam 2011] In adult patients receiving stroke treatment, thrombolysis has been deemed as a cost-effective strategy, with direct cost of $2750 USD per dose. [Kazley 2013]<br><br>For costs of anticoagulation in adult patients, the direct cost per week with warfarin in adults ranges from $3.54 to $11.44 USD while this number in Canada decreases to 0.49 to 0.84 CAD per week. [Biskupiak Lyman, Kearon, Klarenbach, Guanella] With heparin, the costs per unit ranges from $0.18 per 10 units, to $0.212 per 1000 units [ASP] with a Cost per week: $37.00 USD and $11.14 CAD per day in Canada. [Klarenbach, Guanella] LMWH (enoxaparin) cost varies. The wholesale cost in the low and middle income economies is about $13 to $75 USD per week. [IMPPG] In the United States the wholesale cost is about $98.91 USD per day as of 2016 [NADAC 2016] | |
| | Adolopment | |
| ● Large costs<br>○ Moderate costs<br>○ Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

| | | |
|---|---|---|
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | No research evidence found. | |
| | Adolopment | |
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

| | | |
|---|---|---|
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>● No included studies | No research evidence was identified. | |
| | Adolopment | |
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>● No included studies | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Equity

What would be the impact on health equity?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Reduced<br>● Probably reduced<br>○ Probably no impact<br>○ Probably increased<br>○ Increased<br>○ Varies<br>○ Don't know | No research evidence identified. | |
| | Adolopment | |

| | | |
|---|---|---|
| ○ Reduced<br>● Probably reduced<br>○ Probably no impact<br>○ Probably increased<br>○ Increased<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Acceptability

Is the intervention acceptable to key stakeholders?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br>● Varies<br>○ Don't know | Survey and observational research suggests the following regarding acceptability and barriers associated with anticoagulation and thrombolysis in the pediatric population:<br><br>One survey of American Society of Pediatric Hematology/Oncology members demonstrates the wide variation in treatment approaches between practitioners, in this case with respect to thrombolytic therapy of pediatric VTE. With respect to the preferred agent, the survey results confirm that tPA has become the thrombolytic drug of choice in pediatric patients, although a small percentage of respondents stated a preference for others, such as urokinase. In contrast, responses varied widely regarding the preferred mode of tPA delivery (systemic vs. catheter-directed vs. use of catheter-directed therapy on a salvage basis) without clear majority preference for any single modality. Since the overwhelming majority of respondents (95%) reported having access to pediatric interventional radiology services, preferences for a given mode of tPA administration clearly could not be ascribed to IR availability and were not associated with any of the other queried professional demographic data (Yee 2009).<br><br>Observational research suggests the following regarding acceptability and barriers associated with the intervention: In Australia a prospective chart audit in a tertiary paediatric centre assessed the level of compliance of antithrombotic medication use in current practice with guidelines across a 100-day prospective chart audit in 2008-2009. The study showed that the level of compliance for use | |

| | | |
|---|---|---|
| | of antithrombotic medications for the indications of DVT and PE was 98.8% and 61.5%, respectively. High compliance was correlated with strong recommendations, with low compliance found especially in areas where recommendations were based on 'weak' evidence. This reflects clinician confidence in the strength of evidence currently available for paediatric antithrombotic therapy where there may be barriers associated with the use of the intervention where only low-quality, inconsistent, or indirect evidence extrapolated from adult data is available. (Peng 2011) | |
| | Adolopment | |
| ○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br>● Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Feasibility

Is the intervention feasible to implement?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br>● Varies<br>○ Don't know | No research evidence was identified. | > Consideration about availability of interventional radiology in setting.<br><br>> Availability of thrombolytic drugs. |
| | Adolopment | |
| ○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br>● Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |



## SUMMARY OF JUDGEMENTS

| CRITERIA | ORIGINAL | IMPORTANCE FOR DECISION | ADOLOPMENT | IMPORTANCE FOR DECISION |
|---|---|---|---|---|
| **PROBLEM** | Yes | | Yes | |
| **DESIRABLE EFFECTS** | Trivial | | Trivial | |
| **UNDESIRABLE EFFECTS** | Large | | Large | |
| **CERTAINTY OF EVIDENCE** | Very low | | Very low | |
| **VALUES** | Possibly important uncertainty or variability | | Possibly important uncertainty or variability | |
| **BALANCE OF EFFECTS** | Probably favors the intervention | | Probably favors the intervention | |
| **RESOURCES REQUIRED** | Large costs | | Large costs | |
| **CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES** | Very low | | Very low | |
| **COST EFFECTIVENESS** | No included studies | | No included studies | |
| **EQUITY** | Probably reduced | | Probably reduced | |
| **ACCEPTABILITY** | Varies | | Varies | |
| **FEASIBILITY** | Varies | | Varies | |



## TYPE OF RECOMMENDATION

Original

| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | **Conditional recommendation for the intervention** | Strong recommendation for the intervention |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| ○ | ○ | ○ | ● | ○ |

Adolopment

| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | **Conditional recommendation for the intervention** | Strong recommendation for the intervention |
|---|---|---|---|---|
| ○ | ○ | ○ | ● | ○ |

## CONCLUSIONS

Original

**Recommendation**

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

**Justification**

The panel considered PE with hemodynamic compromise to be life threatening with limited time to respond to standard anticoagulation, and so conditionally recommended thrombolysis in addition to anticoagulation based predominantly on extrapolation of adult data

Adolopment

**Recommendation**

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

**Justification**

**Subgroup considerations**

There is no current evidence available about further subgroups in pediatric patients with PE with hemodynamic compromise.

## Implementation considerations

Consider if the interventional radiology services are available in locations it should be implemented.

## Monitoring and evaluation

--

## Research priorities

Further research is needed on the use of thrombolytics vs anticoagulation alone in patients with PE with hemodynamic compromise, with comparisons also between the use of systemtic versus catheter directed therapy.

## REFERENCES SUMMARY

1. Ansah DA, Patel KN Montegna L Nicholson GT Ehrlich AC Petit CJ. Tissue Plasminogen Activator Use in Children: Bleeding Complications and Thrombus Resolution. J Pediatr; 2016.

# APPENDICES

Appendix 1

**Author(s):**
**Question:** Thrombolysis followed by anticoagulation compared to anticoagulation alone in pediatric patients with PE with hemodynamic compromise
**Setting:** Inpatient
**Bibliography:** ASH/ISTH 2024 Guidelines for Management of Venous Thromboembolism: Treatment of Pediatric Venous Thromboembolism

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | thrombolysis followed by anticoagulation | anticoagulation alone | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortalty (assessed with: All Cause Mortality)** | | | | | | | | | | | | |
| 3[1,2,3] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 6/15 (40.0%) | 8/16 (50.0%) | **RR 0.88** (0.42 to 1.85) | **60 fewer per 1,000** (from 290 fewer to 425 more) | ⨁◯◯◯ Very low | CRITICAL |
| **Recurrence** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 3/7 (42.9%) | 3/15 (20.0%) | **RR 2.14** (0.57 to 8.09) | **228 more per 1,000** (from 86 fewer to 1,000 more) | ⨁◯◯◯ Very low | CRITICAL |
| **Neurological Outcomes** | | | | | | | | | | | | |
| 1[2] | non-randomised studies | serious[c] | not serious | not serious | very serious[b] | none | 1/5 (20.0%) [d] | - | - | - | ⨁◯◯◯ Very low | NOT IMPORTANT |

**CI:** confidence interval; **RR:** risk ratio

**Explanations**

a. Risk of bias, assessed using ROBINS-I, was judged to be serious due to selection bias.
b. Imprecision due to small number of included patients and patients with events in the included studies.
c. Non-comparative study
d. Hypoxic ischemic brain injury

**References**

1.MC, Pelland-Marcotte, C, Tucker, A, Klaassen, ML, Avila, A, Amid, N, Amiri, S, Williams, J, Halton, LR, Brandão. Outcomes and risk factors of massive and submassive pulmonary embolism in . The Lancet. Haematology; 2019.
2.RW, Morgan, HR, Stinson, H, Wolfe, RB, Lindell, AA, Topjian, VM, Nadkarni, RM, Sutton, RA, Berg, TJ, Kilbaugh. Pediatric In-Hospital Cardiac Arrest Secondary to Acute Pulmonary Embolism.. Critical care medicine; 2018.
3.CE, Ross, JA, Shih, ME, Kleinman, MW, Donnino. Pediatric Massive and Submassive Pulmonary Embolism: A Single-Center Experience.. Hospital pediatrics; 2020.

Appendix 2

**Author(s):**
**Question:** Thrombolysis followed by anticoagulation compared to anticoagulation alone in pediatric patients with PE with hemodynamic compromise
**Setting:** Inpatient
**Bibliography:** ASH/ISTH 2024 Guidelines for Management of Venous Thromboembolism: Treatment of Pediatric Venous Thromboembolism

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | thrombolysis followed by anticoagulation | anticoagulation alone | Relative (95% CI) | Absolute (95% CI) | | |
| **Bleeding (assessed with: Unspecified Bleed (Intracranial/Extracranial))** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 1/7 (14.3%) | 0/1 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |

**CI:** confidence interval; **RR:** risk ratio

**Explanations**

a. Risk of bias, assessed using ROBINS-I, was judged to be serious due to selection bias.
b. Imprecision due to small number of included patients and patients with events in the included studies.

**References**

1.CE, Ross, JA, Shih, ME, Kleinman, MW, Donnino. Pediatric Massive and Submassive Pulmonary Embolism: A Single-Center Experience.. Hospital pediatrics; 2020.

## QUESTION

| Should thrombolysis followed by anticoagulation vs. anticoagulation alone be used for pediatric patients with sub-massive PE? | |
|---|---|
| **POPULATION:** | pediatric patients with sub-massive PE |
| **INTERVENTION:** | thrombolysis followed by anticoagulation |
| **COMPARISON:** | anticoagulation alone |
| **MAIN OUTCOMES:** | Mortality; Non-fatal pulmonary embolism -representing the moderate marker state; Deep vein thrombosis; Deep vein thrombosis; Major bleeding; Major bleeding; Post-thrombotic syndrome; Post-thrombotic syndrome. |
| **SETTING:** | Inpatient |
| **PERSPECTIVE:** | Clinical recommendation - Population perspective |
| **BACKGROUND:** | The first line of treatment of venous thromboembolism in the pediatric populations includes anticoagulation, although in some instances, it might require the use of thrombolytics and/or invasive vascular procedures. The infusion of thrombolytics, such as tissue plasminogen activator (tPA) either systemically or directed by catheter are more commonly being used in adults. In the pediatric field, however, there still is need for evidence to ascertain the risks and benefits of such therapy. (1) |
| **CONFLICT OF INTEREST:** | |

## ASSESSMENT

### Problem

Is the problem a priority?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ No<br>○ Probably no<br>○ Probably yes<br>● Yes<br>○ Varies<br>○ Don't know | In patients with symptomatic DVT or PE, the use of anticoagulation is the first line of therapy. In some instances, the use of thrombolytic drugs such as tissue plasminogen activator (tPA) might be warranted. The lack of evidence on this topic frequently precludes clinicians to be confident on the decision-making process. | |
| | Adolopment | |

| | | |
|---|---|---|
| ○ No<br>○ Probably no<br>○ Probably yes<br>● Yes<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Desirable Effects

How substantial are the desirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

● Trivial
○ Small
○ Moderate
○ Large
○ Varies
○ Don't know

| Outcomes | Nº of participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects* (95% CI) | |
|---|---|---|---|---|---|
| | | | | Risk with anticoagulation alone | Risk difference with thrombolysis followed by anticoagulation |
| Mortality assessed with: as all-cause mortality follow up: range 1 days to 6 years | 320 (15 observational studies) | ⨁◯◯◯ VERY LOW[a,b] | not pooled | Study population | |
| | | | | not pooled | not pooled |
| Deep vein thrombosis assessed with: in children as NO clot resolution or progression (early) | 320 (15 observational studies) | ⨁◯◯◯ VERY LOW[a,b] | not pooled | Study population | |
| | | | | not pooled | not pooled |

The consideration is different for patients with DVT/PE versus patients with massive PE, where desirable effects are considered to be larger.

** in notes the judgment is 'moderate' but here it was as 'trivial'**

| | | | | | |
|---|---|---|---|---|---|
| follow up: range 1 days to 2 weeks | | | | | |
| Major bleeding assessed with: any major bleeding follow up: range 1 days to 2 weeks | 297 (15 observational studies) | ⨁◯◯◯ VERY LOW[a,b] | not pooled | Study population | |
| | | | | not pooled | not pooled |
| Post-thrombotic syndrome assessed with: PTS with pediatric adapted scale (moderate or severe) follow up: median 4.5 years | 183 (7 observational studies) | ⨁◯◯◯ VERY LOW[a,b] | not pooled | Study population | |
| | | | | not pooled | not pooled |

a. Case series and only one comparative study.
b. Low rates of events and few participants.

| | | |
|---|---|---|
| | | |
| | Adolopment | |
| ● Trivial<br>○ Small<br>○ Moderate<br>○ Large<br>○ Varies<br>○ Don't know | *See Appendix 2* | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Undesirable Effects

How substantial are the undesirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

● Large
○ Moderate
○ Small
○ Trivial
○ Varies
○ Don't know

| Outcomes | № of participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects* (95% CI) | |
|---|---|---|---|---|---|
| | | | | Risk with anticoagulation alone | Risk difference with thrombolysis followed by anticoagulation |
| Mortality assessed with: as all-cause mortality follow up: range 1 days to 6 years | 320 (15 observational studies) | ⨁◯◯◯ VERY LOW[a,b] | not pooled | Study population | |
| | | | | not pooled | not pooled |
| Deep vein thrombosis assessed with: in | 320 (15 observational studies) | ⨁◯◯◯ VERY LOW[a,b] | not pooled | Study population | |
| | | | | not pooled | not pooled |

Rates of bleeding 1-2% vs 10-30%

Consideration of rate of bleeding with combined therapy versus anticoagulation alone.

Undesirable effects might be considered large for systemic therapy but moderate for catheter directed therapy.

| | | | | | |
|---|---|---|---|---|---|
| children as NO clot resolution or progression (early) follow up: range 1 days to 2 weeks | | | | | |
| Major bleeding assessed with: any major bleeding follow up: range 1 days to 2 weeks | 297 (15 observational studies) | ⨁◯◯◯ VERY LOW[a,b] | not pooled | Study population | |
| | | | | not pooled | not pooled |
| Post-thrombotic syndrome assessed with: PTS with pediatric adapted scale (moderate or severe) follow up: median 4.5 years | 183 (7 observational studies) | ⨁◯◯◯ VERY LOW[a,b] | not pooled | Study population | |
| | | | | not pooled | not pooled |

a. Case series and only one comparative study.
b. Low rates of events and few participants.

| | | |
|---|---|---|
| | | |
| | Adolopment | |
| ● Large<br>○ Moderate<br>○ Small<br>○ Trivial<br>○ Varies<br>○ Don't know | *See Appendix 1* | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Certainty of evidence

What is the overall certainty of the evidence of effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | Certainty of the evidence of effects was judged as 'very low' due to imprecision, indirecntess, risk of bias. | When the condition is a sub-massive or massive PE the uncertainty is very low. However, when other conditions are considered there might be more uncertainty on the evidence. |
| | Adolopment | |

| | | |
|---|---|---|
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Values

Is there important uncertainty about or variability in how much people value the main outcomes?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Important uncertainty or variability<br>● Possibly important uncertainty or variability<br>○ Probably no important uncertainty or variability<br>○ No important uncertainty or variability | **Utility related information:**<br><br>**The relative importance of outcomes:**<br><br>**Results from Panel Members' Utility Rating Survey**:<br>Utilities rated on the visual analog scale, where 0 represents death and 1 represents full health, were as follows.<br>Pulmonary embolism – Severe marker state: 0.31<br>Pulmonary embolism – Moderate marker state: 0.49<br>Deep vein thrombosis (proximal) – Severe marker state: 0.49<br>Deep vein thrombosis (proximal) – Moderate marker state: 0.61<br>Deep vein thrombosis (distal) – Severe marker state: 0.56<br>Deep vein thrombosis (distal) – Moderate marker state: 0.68<br>Major bleeding: 0.30 | Panel members consider a possibly important uncertainty, but note that some patients might prefer the risks of thrombolysis over anticoagulation for conditions with higher risk of poor outcome (e.g., sub-massive or PE with hemodynamic compromise). |

| | | |
|---|---|---|
| | Neonatal Bleeding – Severe: 0.30<br><br>Infant Bleeding – Severe: 0.26<br><br>Post-thrombotic syndrome – Long term marker state: 0.60<br><br>**We did not identify utility related information or non-utility information for the outcomes of interest specific to the pediatric population in the literature.**<br><br>**<u>Additional information from the adult population:</u>**<br><br>**Our systematic review for the adult population found that the relative importance of the outcomes is as follows:**<br><br>Pulmonary embolism: 0.63-0.93 (different methods) (Hogg 2013, Hogg 2014, Locadia 2004)<br><br>Deep vein thrombosis: 0.64-0.99 (different methods) (Hogg 2013, Hogg 2014, Locadia 2004, Marvig 2015, Utne 2016)<br><br>Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) (Hogg 2013, Locadia 2004)<br><br>Muscular bleeding: 0.76 (time trade off) (Locadia 2004)<br><br>Minor intracranial bleeding event: 0.75 (standard gamble) (Hogg 2013)<br><br>Major intracranial bleeding event: 0.15 (standard gamble) (Hogg 2013)<br><br>Central nervous system bleeding: 0.29-0.60 (standard gamble) (Lenert 1997, O'Meara 1994)<br><br>Treatment with LMWH: 0.993 (time trade off) (Marchetti 2001)<br><br>Treatment with warfarin (as a surrogate): 0.989 (time trade off) (Marchetti 2001) | |

| | | |
|---|---|---|
| | **<u>We also identified in the systematic review the following non-utility information from the adult population:</u>**<br><br>**Anticoagulant therapy**<br><br>Adult patients highly value the benefits of risk reduction in VTE recurrence and post-thrombosis syndrome (Locadia 2004). Patients would favor efficacy and safety over convenience of route of administration (Noble 2015). Further, patients would like to avoid adverse events but most of them are "not afraid of" the adverse events (Barcellona 2000, Noble 2015, O'Meara 1994). For anticoagulant therapy in general, most patients would prefer the oral doses compared with injections, this is mainly because of treatment burden due to injection (Barcellona 2000, Noble 2015). For patients with venographically proven deep venous thrombosis, 15 of the 19 patients expressed a preference for the subcutaneous route for administration of heparin over intravenous administration (Robinson 1993). | |
| | Adolopment | |
| ○ Important uncertainty or variability<br>● Possibly important uncertainty or variability<br>○ Probably no important uncertainty or variability<br>○ No important uncertainty or variability | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

| | | |
|---|---|---|
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>● Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>○ Don't know | | > Studies using fibrinolytics may have patients with more severe VTE/PE with expected worse outcomes.<br><br>> Fibrinolytics for VTE associated with major organ dysfunction where timely reperfusion is needed. |
| | Adolopment | |
| ○ Favors the comparison<br>● Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Discussion between probably favors the intervention and does not favor either |

## Resources required

How large are the resource requirements (costs)?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ● Large costs<br>○ Moderate costs<br>○ Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br>○ Varies<br>○ Don't know | No direct research evidence was identified for costs of anticoagulation as compared to anticoagulation plus systemic thrombolysis for treatment in pediatric patients with symptomatic DVT or PE.<br><br>Two studies reported the costs of disease from pediatric patients with any VTE. One reported for 834 pediatric patients with VTE a median annual expenditure of $25,258 and $24,934 USD in Medicaid and private insurance patients respectively. [Boulet 2012] Another study found that patients with VTE had an increased 8.1 inpatient days and excess average costs of $27,686 USD. [Goudie 2015] | Additional considerations for discussion:<br><br>> Consideration about cost of tPA, and administration (IV vs. interventional procedure) which could change the cost. |

| | | |
|---|---|---|
| | **Additional information from adult population:** In the adult population the cost of urokinase and equipment cost for the catheter directed thrombolysis is estimated to around $10,127 USD [Karthikesalingam 2011] In adult patients receiving stroke treatment, thrombolysis has been deemed as a cost-effective strategy, with direct cost of $2750 USD per dose. [Kazley 2013]<br><br>For costs of anticoagulation in adult patients, the direct cost per week with warfarin in adults ranges from $3.54 to $11.44 USD while this number in Canada decreases to 0.49 to 0.84 CAD per week. [Biskupiak Lyman, Kearon, Klarenbach, Guanella] With heparin, the costs per unit ranges from $0.18 per 10 units, to $0.212 per 1000 units [ASP] with a Cost per week: $37.00 USD and $11.14 CAD per day in Canada. [Klarenbach, Guanella] LMWH (enoxaparin) cost varies. The wholesale cost in the low and middle income economies is about $13 to $75 USD per week. [IMPPG] In the United States the wholesale cost is about $98.91 USD per day as of 2016 [NADAC 2016] | |
| | Adolopment | |
| ● Large costs<br>○ Moderate costs<br>○ Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

| | | |
|---|---|---|
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | No research evidence was found. | |
| | Adolopment | |
| ○ Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

| | | |
|---|---|---|
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>● No included studies | No research evidence was identified. | |
| | Adolopment | |
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>● No included studies | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Equity

What would be the impact on health equity?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Reduced<br>● Probably reduced<br>○ Probably no impact<br>○ Probably increased<br>○ Increased<br>○ Varies<br>○ Don't know | No research evidence identified. | |
| | Adolopment | |

| | | |
|---|---|---|
| ○ Reduced<br>○ Probably reduced<br>○ Probably no impact<br>○ Probably increased<br>○ Increased<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Acceptability

Is the intervention acceptable to key stakeholders?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br>● Varies<br>○ Don't know | Survey and observational research suggests the following regarding acceptability and barriers associated with anticoagulation and thrombolysis in the pediatric population:<br><br>One survey of American Society of Pediatric Hematology/Oncology members demonstrates the wide variation in treatment approaches between practitioners, in this case with respect to thrombolytic therapy of pediatric VTE. With respect to the preferred agent, the survey results confirm that tPA has become the thrombolytic drug of choice in pediatric patients, although a small percentage of respondents stated a preference for others, such as urokinase. In contrast, responses varied widely regarding the preferred mode of tPA delivery (systemic vs. catheter-directed vs. use of catheter-directed therapy on a salvage basis) without clear majority preference for any single modality. Since the overwhelming majority of respondents (95%) reported having access to pediatric interventional radiology services, preferences for a given mode of tPA administration clearly could not be ascribed to IR availability and were not associated with any of the other queried professional demographic data (Yee 2009).<br><br>Observational research suggests the following regarding acceptability and barriers associated with the intervention: In Australia a prospective chart audit in a tertiary paediatric centre assessed the level of compliance of antithrombotic medication use in current practice with guidelines across a 100-day prospective chart audit in 2008-2009. The study showed that the level of compliance for use | |

| | | |
|---|---|---|
| | of antithrombotic medications for the indications of DVT and PE was 98.8% and 61.5%, respectively. High compliance was correlated with strong recommendations, with low compliance found especially in areas where recommendations were based on 'weak' evidence. This reflects clinician confidence in the strength of evidence currently available for paediatric antithrombotic therapy where there may be barriers associated with the use of the intervention where only low-quality, inconsistent, or indirect evidence extrapolated from adult data is available. (Peng 2011) | |
| | Adolopment | |
| ○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Feasibility

Is the intervention feasible to implement?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br>● Varies<br>○ Don't know | No research evidence was identified. | > Consideration about availability of interventional radiology in setting.<br><br>> Availability of thrombolytic drugs. |
| | Adolopment | |
| ○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |



## SUMMARY OF JUDGEMENTS

| CRITERIA | ORIGINAL | IMPORTANCE FOR DECISION | ADOLOPMENT | IMPORTANCE FOR DECISION |
|---|---|---|---|---|
| PROBLEM | Yes | | Yes | |
| DESIRABLE EFFECTS | Trivial | | Trivial | |
| UNDESIRABLE EFFECTS | Large | | Large | |
| CERTAINTY OF EVIDENCE | Very low | | Very low | |
| VALUES | Possibly important uncertainty or variability | | Possibly important uncertainty or variability | |
| BALANCE OF EFFECTS | Probably favors the intervention | | Probably favors the comparison | |
| RESOURCES REQUIRED | Large costs | | Large costs | |
| CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES | Very low | | | |
| COST EFFECTIVENESS | No included studies | | No included studies | |
| EQUITY | Probably reduced | | | |
| ACCEPTABILITY | Varies | | | |
| FEASIBILITY | Varies | | | |



## TYPE OF RECOMMENDATION

Original

| Strong recommendation against the intervention | **Conditional recommendation against the intervention** | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | Strong recommendation for the intervention |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| ○ | ● | ○ | ○ | ○ |

Adolopment

| Strong recommendation against the intervention | **Conditional recommendation against the intervention** | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | Strong recommendation for the intervention |
|---|---|---|---|---|
| ○ | ● | ○ | ○ | ○ |

## CONCLUSIONS

Original

**Recommendation**

**The ASH guideline panel suggests against using thrombolysis followed by anticoagulation, and rather use anticoagulation alone in pediatric patients with sub-massive pulmonary embolism (PE) (conditional recommendation based on very low certainty in the evidence about effects).**

**Justification**

The panel considered sub-massive PE to represent children with PE who did not have haemodynamic instability. There were minimal pediatric data and review of adult data revealed considerable uncertainty, that was complicated by limitations in ability to extrapolate. The panel concluded the risks outweighed the benefits in most cases, hence a conditional recommendation against thrombolysis.

Adolopment

**Recommendation**

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

**Justification**

**Subgroup considerations**

There is no currently evidence available about further subgroups in pediatric patients with sub-massive PE.

## Implementation considerations

Consider if the interventional radiology services are available in locations it should be implemented.

## Monitoring and evaluation

--

## Research priorities

Further research about thrombolysis vs anticoagulation is needed with emphasis in patients with DVT, sub-massive, and PE with hemodynamic compromise.

## REFERENCES SUMMARY

1. Ansah DA, Patel KN Montegna L Nicholson GT Ehrlich AC Petit CJ. Tissue Plasminogen Activator Use in Children: Bleeding Complications and Thrombus Resolution. J Pediatr; 2016.

# APPENDICES

Appendix 1

**Author(s):**
**Question:** Thrombolysis followed by anticoagulation compared to anticoagulation alone in pediatric patients with sub-massive PE
**Setting:** Inpatient
**Bibliography:** ASH/ISTH 2024 Guidelines for Management of Venous Thromboembolism: Treatment of Pediatric Venous Thromboembolism

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | thrombolysis followed by anticoagulation | anticoagulation alone | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality (assessed with: All-Cause Mortality)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 0/14 (0.0%) | 1/9 (11.1%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Resolution (follow-up: 6 months; assessed with: Complete or Partial Resolution)** | | | | | | | | | | | | |
| 1[2] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 5/5 (100.0%) | 3/3 (100.0%) | **RR 1.00** (0.64 to 1.56) | **0 fewer per 1,000** (from 360 fewer to 560 more) | ⨁◯◯◯ Very low | CRITICAL |
| **Progression (Submassive to Massive)** | | | | | | | | | | | | |
| 1[1] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 1/14 (7.1%) | 1/9 (11.1%) | **RR 0.64** (0.05 to 9.03) | **40 fewer per 1,000** (from 106 fewer to 892 more) | ⨁◯◯◯ Very low | IMPORTANT |
| **Chronic thromboembolic pulmonary hypertension (follow-up: 6 months)** | | | | | | | | | | | | |
| 1[2] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 0/5 (0.0%) | 0/2 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |

**CI:** confidence interval; **RR:** risk ratio

**Explanations**

a. Risk of bias, assessed using ROBINS-I, was judged to be serious due to selection bias.
b. Imprecision due to small number of included patients and patients with events in the included studies.

**References**

1.CE, Ross, JA, Shih, ME, Kleinman, MW, Donnino. Pediatric Massive and Submassive Pulmonary Embolism: A Single-Center Experience.. Hospital pediatrics; 2020.
2.J, Belsky, P, Warren, J, Stanek, R, Kumar. Catheter-directed thrombolysis for submassive pulmonary embolism in children: A . Pediatric blood & cancer; 2020.

# Appendix 2

**Author(s):**
**Question:** Thrombolysis followed by anticoagulation compared to anticoagulation alone in pediatric patients with sub-massive PE
**Setting:** Inpatient
**Bibliography:** ASH/ISTH 2024 Guidelines for Management of Venous Thromboembolism: Treatment of Pediatric Venous Thromboembolism

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | thrombolysis followed by anticoagulation | anticoagulation alone | Relative (95% CI) | Absolute (95% CI) | | |
| **Bleeding (assessed with: Unspecified)** | | | | | | | | | | | | |
| 2[1,2] | non-randomised studies | serious[a] | not serious | not serious | very serious[b] | none | 0/19 (0.0%) | 0/9 (0.0%) | not pooled | see comment | ⨁◯◯◯ Very low | CRITICAL |

**CI:** confidence interval; **RR:** risk ratio

**Explanations**

a. Risk of bias, assessed using ROBINS-I, was judged to be serious due to selection bias.
b. Imprecision due to small number of included patients and patients with events in the included studies.

**References**

1.CE, Ross, JA, Shih, ME, Kleinman, MW, Donnino. Pediatric Massive and Submassive Pulmonary Embolism: A Single-Center Experience.. Hospital pediatrics; 2020.
2.J, Belsky, P, Warren, J, Stanek, R, Kumar. Catheter-directed thrombolysis for submassive pulmonary embolism in children: A . Pediatric blood & cancer; 2020.

**Author(s):**
**Question:** Immediate removal of a non-functioning or unneeded central venous access device (CVAD) compared to delayed removal in pediatric patients with symptomatic CVAD related thrombosis
**Setting:** Inpatient
**Bibliography:** ASH/ISTH 2024 Guidelines for Management of Venous Thromboembolism: Treatment of Pediatric Venous Thromboembolism

| Certainty assessment | | | | | | | № of patients | | Effect | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | immediate removal of a non-functioning or unneeded central venous access device (CVAD) | delayed removal | Relative (95% CI) | Absolute (95% CI) | Certainty | Importance |
| **Symptomatic pulmonary embolism (immediate removal < 48 hours, delayed removal >48 hours, we used the 48 hours cutoff regardless of AC status)** | | | | | | | | | | | | |
| 2[1,2] | non-randomised studies | serious[a] | not serious | not serious | serious[b] | none | 1/485 (0.2%) | 0/241 (0.0%) | not estimable | | ⨁⨁◯◯ Low | CRITICAL |

**CI:** confidence interval

**Explanations**

a. Risk of bias was assessed using ROBINs-I, we downgraded for ROB because these are observational studies with selection bias and without any adjustment for known confounders.
b. We downgraded for imprecision, because there was only 1 event in the immediate removal arm and no events in the delayed removal arm. The relative risk and absolute risk are not estimable.

**References**

1.Julie Jaffray, Lisa Baumann Kreuziger,Brian Branchford ,Choo Phei Wee ,E Vincent S Faustino,Neil A Zakai 5 ,Stacy E Croteau,Michael Silvey,John H Fargo,James D Cooper,Nihal Bakeer,Amy Stillings ,Emily Krava,Guy Young,Neil A Goldenberg. Symptomatic pulmonary embolus after catheter removal in children with catheter related thrombosis: A report from the CHAT Consortium. J Thromb Haemost; 2022.
2.CH, van,Ommen, KA, Bergman, M, Boerma, HA, Bouma, AE, Donker, M, Gouvernante, CV, Hulzebos, D, Khandour, R, Knol, MA, Raets, KD, Liem, RA, van,Lingen, M, van,de,Loo, E, Lopriore, M, van,der,Putten, JJ, Sol, MH, Suijker, DC, Vijlbrief, R, Visser, MM, van,Weissenbruch. NEOnatal Central-venous Line Observational study on Thrombosis (NEOCLOT): . Journal of thrombosis and haemostasis : JTH; 2023.

## QUESTION

| Should immediate removal of a non-functioning or unneeded central venous access device (CVAD) vs. delayed removal be used for pediatric patients with symptomatic CVAD related thrombosis? | |
|---|---|
| **POPULATION:** | pediatric patients with symptomatic CVAD related thrombosis |
| **INTERVENTION:** | immediate removal of a non-functioning or unneeded central venous access device (CVAD) |
| **COMPARISON:** | delayed removal |
| **MAIN OUTCOMES:** | Mortality; CVC related thrombosis in infants (stated as 'no resolution' of the CVC); Infant Bleeding – Severe; Pulmonary embolism - Severe; Deep venous thrombosis - Severe |
| **SETTING:** | Inpatient |
| **PERSPECTIVE:** | Clinical recommendation – population perspective |
| **BACKGROUND:** | Central venous access devices (CVAD) or central venous lines (CVL) are an important part of treatment in many pediatric conditions (e.g. cancer and other critical illnesses). They are, however, an important risk factor for venous thromboembolism (VTE) with a rising in incidence, most likely secondary to increase use, detection, better care, and clinical awareness.(1) The incidence of CVAD related thrombosis in children varies significantly from 4% to 13% when identified by clinical diagnosis, to up to 50% depending on imaging modality, the affected population, CVAD type, and study design. (2) |
| **CONFLICT OF INTEREST:** | |

## ASSESSMENT

**Problem**
Is the problem a priority?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ No<br>○ Probably no<br>○ Probably yes<br>● Yes<br>○ Varies<br>○ Don't know | CVL related thrombosis is an important factor to consider the removal or treatment with anticoagulants in children. Current guidelines suggest that CVADs associated with confirmed thrombosis be removed after 3 to 5 days of therapeutic anticoagulation rather than left in situ.(3) Both strategies have risks involved. | |
| | Adolopment | |

| | | |
|---|---|---|
| ○ No<br>○ Probably no<br>○ Probably yes<br>● Yes<br>○ Varies<br>○ Don't know | CVL related thrombosis is an important factor to consider the removal or treatment with anticoagulants in children. Current guidelines suggest that CVADs associated with confirmed thrombosis be removed after 3 to 5 days of therapeutic anticoagulation rather than left in situ.(3) Both strategies have risks involved.<br><br>CVL related thrombosis is an important factor to consider the removal or treatment with anticoagulants in children. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Desirable Effects

How substantial are the desirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

○ Trivial
○ Small
○ Moderate
○ Large
○ Varies
● Don't know

| Outcomes | Nº of participants (studies) Follow up | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects* (95% CI) | |
|---|---|---|---|---|---|
| | | | | Risk with delayed removal | Risk difference with immediate removal of a non-functioning or unneeded central venous access device (CVAD) |
| Mortality<br>follow up: range 1 days to 12 weeks | 0<br>(3 observational studies) | ⨁◯◯◯<br>VERY LOW[a,b,c,d] | - | One observational study (Kenney 1996) with 17 pediatric patients assessed removal (n=8) vs no removal (n=9). Only one patient (in the no removal group) died. Two single arm studies from adults with cancer states a risk of death in the no removal group ranging from 1.4 to 9%. | |
| CVC related thrombosis in infants (stated as 'no resolution' of the CVC)<br>assessed with: imaging and clinical assessment<br>follow up: range 1 weeks to 12 weeks | 0<br>(3 observational studies) | ⨁◯◯◯<br>VERY LOW[a,b,c,d] | - | One observational study (Kenney 1996) with 17 pediatric patients assessed removal (n=8) vs no removal (n=9). Two patients (in the no removal group) had CVC thrombosis considered as 'no resolution'. Indirect evidence from two one-arm studies on adult patients with cancer states a risk of VTE in the no removal group ranging from 0% to 1.4%. | |
| Infant Bleeding – Severe<br>assessed with: clinical evaluation | 0<br>(3 observational studies) | ⨁◯◯◯<br>VERY LOW[a,b,c,d] | - | One observational study (Kenney 1996) with 17 pediatric patients assessed removal (n=8) vs no removal (n=9). No bleeding events were reported. Indirect evidence from two one-arm studies on adult patients with cancer states a risk of bleeding in the no removal group ranging from | |

Although the panel members feel that there would be potentially decreased risk of infection and clot progression with removal, the judgement was stated as 'don't know'.

| | | | | | | |
|---|---|---|---|---|---|---|
| follow up: range 1 weeks to 12 weeks | | | | 5.4% to 12.8%. | | |
| Pulmonary embolism - Severe - not reported | - | - | - | - | - | |
| Deep venous thrombosis - Severe - not reported | - | - | - | - | - | |

a. All case series and case reports without comparison groups. Only one assesses this question in children. (Kenney 1996)
b. All studies vary in inclusion criteria and different populations with or without cancer
c. Only one study (Kenney 1996) assesses children, the other two evaluate adult patients with malignancies and critical illnesses.
d. All case series report few patients and few cases

NOTE: For a complete assessment see the EVIDENCE PROFILE.

**Potential undesirable effects of the intervention (removing the catheter)**

Most clinicans and guidelines advocate for a course of 3 to 5 days of anticoagulation before removing a CVAD, due to a concern over the risk of paradoxical emboli at the time of the CVAD removal. (Biermayr et al., 2016, Filippi et al., 2004) Although no specific numbers were found in any population, (Bleker et al., 2016) case reports and case series suggest clinicians should delay CVAD removal until 3 to 5 days of anticoagulant therapy. (3)



| | | |
|---|---|---|
| | Adolopment | |
| ○ Trivial<br>○ Small<br>○ Moderate<br>○ Large<br>○ Varies<br>● Don't know | | We dont know how substantial are the desirable effects of immedaite versus late removal in the case of the catheter related thrombus. |

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | immediate removal of a non-functioning or unneeded central venous access device (CVAD) | delayed removal | Relative (95% CI) | Absolute (95% CI) | | |
| Symptomatic pulmonary embolism (immediate removal < 48 hours, delayed removal >48 hours, we used the 48 hours cutoff regardless of AC status) | | | | | | | | | | | | |
| 2[1,2] | observational studies | serious[a] | not serious | not serious | serious[b] | none | 1/485 (0.2%) | 0/241 (0.0%) | not estimable | | ⨁⨁◯◯ Low | CRITICAL |

**CI:** confidence interval

## Explanations

a. Risk of bias was assessed using ROBINs-I, we downgraded for ROB because these are observational studies with selection bias and without adjustment for known confounders.

b. We downgraded for imprecision, because there was only 1 event in the immediate removal arm and no events in the delayed removal arm. The relative risk and absolute risk are not estimable.

## References


1.Julie Jaffray, Lisa Baumann Kreuziger,Brian Branchford ,Choo Phei Wee ,E Vincent S Faustino,Neil A Zakai 5 ,Stacy E Croteau,Michael Silvey,John H Fargo,James D Cooper,Nihal Bakeer,Amy Stillings ,Emily Krava,Guy Young,Neil A Goldenberg. Symptomatic pulmonary embolus after catheter removal in children with catheter related thrombosis: A report from the CHAT Consortium. J Thromb Haemost; 2022.

2.CH, van,Ommen, KA, Bergman, M, Boerma, HA, Bouma, AE, Donker, M, Gouvernante, CV, Hulzebos, D, Khandour, R, Knol, MA, Raets, KD, Liem, RA, van,Lingen, M, van,de,Loo, E, Lopriore, M, van,der,Putten, JJ, Sol, MH, Suijker, DC, Vijlbrief, R, Visser, MM, van,Weissenbruch. NEOnatal Central-venous Line Observational study on Thrombosis (NEOCLOT): . Journal of thrombosis and haemostasis : JTH; 2023.




## Undesirable Effects

How substantial are the undesirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

○ Large
○ Moderate
○ Small
○ Trivial
○ Varies
● Don't know

| Outcomes | № of participants (studies) Follow up | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects* (95% CI) | |
|---|---|---|---|---|---|
| | | | | Risk with delayed removal | Risk difference with immediate removal of a non-functioning or unneeded central venous access device (CVAD) |
| Mortality<br>follow up: range 1 days to 12 weeks | 0<br>(3 observational studies) | ⨁◯◯◯<br>VERY LOW[a,b,c,d] | - | One observational study (Kenney 1996) with 17 pediatric patients assessed removal (n=8) vs no removal (n=9). Only one patient (in the no removal group) died. Two single arm studies from adults with cancer states a risk of death in the no removal group ranging from 1.4 to 9%. | |
| CVC related thrombosis in infants (stated as 'no resolution' of the CVC)<br>assessed with: imaging and clinical assessment<br>follow up: range 1 weeks to 12 weeks | 0<br>(3 observational studies) | ⨁◯◯◯<br>VERY LOW[a,b,c,d] | - | One observational study (Kenney 1996) with 17 pediatric patients assessed removal (n=8) vs no removal (n=9). Two patients (in the no removal group) had CVC thrombosis considered as 'no resolution'. Indirect evidence from two one-arm studies on adult patients with cancer states a risk of VTE in the no removal group ranging from 0% to 1.4%. | |
| Infant Bleeding – Severe<br>assessed with: clinical evaluation<br>follow up: range 1 weeks to 12 weeks | 0<br>(3 observational studies) | ⨁◯◯◯<br>VERY LOW[a,b,c,d] | - | One observational study (Kenney 1996) with 17 pediatric patients assessed removal (n=8) vs no removal (n=9). No bleeding events were reported. Indirect evidence from two one-arm studies on adult patients with cancer states a risk of bleeding in the no removal group ranging from 5.4% to 12.8%. | |
| Pulmonary embolism - Severe - not reported | - | - | - | - | - |
| Deep venous thrombosis - Severe - not reported | - | - | - | - | - |

a. All case series and case reports without comparison groups. Only one assesses this question in children. (Kenney 1996)

Removal of a non-functioning line could increase risk of PE and cerebrovascular accident (CVA).

As the line is non-functioning, there is already no access through the existing line.

| | | |
|---|---|---|
| | b. All studies vary in inclusion criteria and different populations with or without cancer<br>c. Only one study (Kenney 1996) assesses children, the other two evaluate adult patients with malignancies and critical illnesses.<br>d. All case series report few patients and few cases<br><br>NOTE: For a complete assessment see the EVIDENCE PROFILE.<br><br>**Potential undesirable effects of the intervention (removing the catheter)**<br><br>Most clinicans and guidelines advocate for a course of 3 to 5 days of anticoagulation before removing a CVAD, due to a concern over the risk of paradoxical emboli at the time of the CVAD removal. (Biermayr et al., 2016, Filippi et al., 2004) Although no specific numbers were found in any population, (Bleker et al., 2016) case reports and case series suggest clinicians should delay CVAD removal until 3 to 5 days of anticoagulant therapy. (3) | |
| | Adolopment | |
| ○ Large<br>○ Moderate<br>○ Small<br>○ Trivial<br>○ Varies<br>● Don't know | No research evidence. | We dont know the undesirable effects and we dont have any data about adverse events of anticogulation. |

## Certainty of evidence

What is the overall certainty of the evidence of effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

| | | |
|---|---|---|
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | Certainty of the evidence of effects was judged as 'very low' due to risk of bias, imprecision, indirectness. All evidence is from observational studies (with only one direct study) from adult populations with malignancies and with low number of participants and events. | |
| | Adolopment | |
| ○ Very low<br>● Low<br>○ Moderate<br>○ High<br>○ No included studies | Even though we have new evidence addresing this question, the certainty of the evidence of effects was judged as 'low' due to risk of bias, imprecision. All evidence is from observational studies and we had only one event in the immediate removal group | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Values

Is there important uncertainty about or variability in how much people value the main outcomes?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Important uncertainty or variability<br>● Possibly important uncertainty or variability<br>○ Probably no important uncertainty or variability<br>○ No important uncertainty or variability | **<u>Utility related information:</u>**<br><br>**The relative importance of outcomes:**<br><br>**<u>Results from Panel Members' Utility Rating Survey</u>**:<br><br>Utilities rated on the visual analog scale, where 0 represents death and 1 represents full health, were as follows.<br><br>Pulmonary embolism – Severe marker state: 0.31<br><br>Pulmonary embolism – Moderate marker state: 0.49<br><br>Deep vein thrombosis (proximal) – Severe marker state: 0.49 | The panel noted possible important uncertainty or variability in how much people value the main outcomes, considering different values placed on CVC related thrombosis and value placed on the outcomes such as stroke and PE. |

| | | |
|---|---|---|
| | Deep vein thrombosis (proximal) – Moderate marker state: 0.61<br>Deep vein thrombosis (distal) – Severe marker state: 0.56<br>Deep vein thrombosis (distal) – Moderate marker state: 0.68<br>Major bleeding: 0.30<br>Neonatal Bleeding – Severe: 0.30<br>Infant Bleeding – Severe: 0.26<br>CVC-Related Thrombosis in Infants: 0.53<br><br>**We did not identify utility related information or non-utility information for the outcomes of interest specific to the pediatric population in the literature.**<br>**<u>Additional information from the adult population:</u>**<br>**Our systematic review for the adult population found that the relative importance of the outcomes is as follows:**<br>Pulmonary embolism: 0.63-0.93 (different methods)(4, 5, 6)<br>Deep vein thrombosis: 0.64-0.99 (different methods) (5, 4, 6, 7, 8)<br>Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) (5, 6)<br>Muscular bleeding: 0.76 (time trade off) (6)<br>Minor intracranial bleeding event: 0.75 (standard gamble) (5)<br>Major intracranial bleeding event: 0.15 (standard gamble) (5)<br>Central nervous system bleeding: 0.29-0.60 (standard gamble) (9, 10) | |
| | Adolopment | |
| ○ Important uncertainty or variability<br>● Possibly important uncertainty or variability<br>○ Probably no important | Utility related information: The relative importance of outcomes: Results from Panel Members' Utility Rating Survey: Utilities rated on the visual analog scale, where 0 represents death and 1 represents full health, were as follows. Pulmonary embolism – Severe marker state: 0.31 Pulmonary embolism – Moderate marker state: 0.49 Deep vein thrombosis (proximal) – Severe marker state: 0.49 Deep vein thrombosis (proximal) – Moderate marker state: 0.61 Deep vein thrombosis (distal) – Severe marker state: 0.56 Deep vein thrombosis (distal) – Moderate marker state: 0.68 Major bleeding: 0.30 Neonatal Bleeding – Severe: 0.30 Infant Bleeding – Severe: 0.26 CVC-Related Thrombosis in Infants: 0.53We did not identify utility related information or non-utility information for the outcomes of interest specific to the pediatric population in the literature.Additional information from the adult population:Our systematic review for the adult | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

| | | |
|---|---|---|
| uncertainty or variability<br>○ No important uncertainty or variability | population found that the relative importance of the outcomes is as follows: Pulmonary embolism: 0.63-0.93 (different methods)(4, 5, 6) Deep vein thrombosis: 0.64-0.99 (different methods) (5, 4, 6, 7, 8)Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) (5, 6)Muscular bleeding: 0.76 (time trade off) (6) Minor intracranial bleeding event: 0.75 (standard gamble) (5) Major intracranial bleeding event: 0.15 (standard gamble) (5) Central nervous system bleeding: 0.29-0.60 (standard gamble) (9, 10) | |

## Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Favors the comparison<br>● Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>○ Don't know | | The panel noted that the balance probably favours the comparison given a high value on avoiding potential risk of emboli leading to PE or cerebrovascular accident (CVA). |
| | Adolopment | |
| ○ Favors the comparison<br>○ Probably favors the comparison<br>● Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Based on the new evidence, we noted that the balance of effects dont favor the intervention nor the comparison. |

| | | |
|---|---|---|
| ○ Don't know | | |

## Resources required

How large are the resource requirements (costs)?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Large costs<br>○ Moderate costs<br>● Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br>○ Varies<br>○ Don't know | No research evidence was identified regarding the resource use associated with CVAD removal as compared to delayed removal. | The panel considered that the line would require removal eventually for both groups (immediate and delayed removal groups), therefore immediate removal would result in negligible costs or savings. |
| | Adolopment | |
| ○ Large costs<br>○ Moderate costs<br>● Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Immediate removal of the line will result in only negligible costs. |

## Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Very low<br>○ Low<br>○ Moderate<br>○ High<br>● No included studies | | |
| | Adolopment | |
| ○ Very low<br>○ Low<br>○ Moderate<br>○ High<br>● No included studies | No included studies about resources required. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |

| | | |
|---|---|---|
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>● No included studies | No research evidence was identified. | |
| | Adolopment | |
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>● No included studies | No included studies addressing cost effectiveness of immediate catheter removal in pedaitrics. | Add considerations made be the adoloping panel, including the justification for any change in judgment. |

## Equity

What would be the impact on health equity?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ Reduced<br>○ Probably reduced | No research evidence was identified. | |

| | | |
|---|---|---|
| ● Probably no impact<br>○ Probably increased<br>○ Increased<br>○ Varies<br>○ Don't know | | |
| | Adolopment | |
| ○ Reduced<br>○ Probably reduced<br>● Probably no impact<br>○ Probably increased<br>○ Increased<br>○ Varies<br>○ Don't know | No research evidence about equity. | Althought there is no research evidence, but immediate catheter removal will not impact equity. |

## Acceptability

Is the intervention acceptable to key stakeholders?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Original | |
| ○ No<br>○ Probably no<br>● Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | A survey study suggests the following regarding acceptability and barriers associated with the intervention:<br><br>A UK survey has identified nonconformity of approach in terms of the timing of CVAD insertion in relation to induction therapy. Almost half of UK centers defer CVAD insertion until after completion of induction therapy due to concerns that the risk of thrombosis during induction therapy, as a result of administration of 2 doses of asparaginase during induction, may be increased by early CVAD placement. (Biss et al., 2016) | The panel discussed variability in what is perceived as the best option by clinicians. |
| | Adolopment | |
| ○ No<br>○ Probably no<br>● Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Immediate catheter removal is probably acceptable intervention by the stakeholders. |

| **Feasibility**<br>Is the intervention feasible to implement? | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| | Original | |
| ○ No<br>○ Probably no<br>● Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | Survey research suggests the following regarding feasibility of the intervention option:<br><br>The views and clinical practice of children's cancer units were surveyed regarding management of central venous catheter (CVC) occlusion (CVC-occlusion), CVC-related thrombosis (CVC-thrombosis) and thromboembolism (CVC-thromboembolism). All centres used heparinised saline flushes as prophylaxis against CVC occlusion, with little variation (30% centres) in frequency, volume and heparin concentration. Symptoms or signs suggesting partial CVC-occlusion, total CVC-occlusion, or CVC-thrombosis/thromboembolism were always investigated in 20%, 55% and 85% of centres, respectively, but with considerable variability in the nature and sequence of investigations performed. The clinical practice of different centres regarding prevention, investigation and treatment of CVC-occlusion/thrombosis varies greatly. (Skinner et al., 2008) | The panel noted availabilty of a surgeon to remove the CVAD and/or place another line is important. |
| | Adolopment | |
| ○ No<br>○ Probably no<br>● Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | Example:'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or'additional global evidence indentified: xxx'. | Immediate catheter removal is easy and feasible Intervention to implement. |

## SUMMARY OF JUDGEMENTS

| CRITERIA | ORIGINAL | IMPORTANCE FOR DECISION | ADOLOPMENT | IMPORTANCE FOR DECISION |
|---|---|---|---|---|
| **PROBLEM** | Yes | | Yes | |
| **DESIRABLE EFFECTS** | Don't know | | Don't know | |
| **UNDESIRABLE EFFECTS** | Don't know | | Don't know | |

| CRITERIA | ORIGINAL | IMPORTANCE FOR DECISION | ADOLOPMENT | IMPORTANCE FOR DECISION |
|---|---|---|---|---|
| CERTAINTY OF EVIDENCE | Very low | | Low | |
| VALUES | Possibly important uncertainty or variability | | Possibly important uncertainty or variability | |
| BALANCE OF EFFECTS | Probably favors the comparison | | Does not favor either the intervention or the comparison | |
| RESOURCES REQUIRED | Negligible costs and savings | | Negligible costs and savings | |
| CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES | No included studies | | No included studies | |
| COST EFFECTIVENESS | No included studies | | No included studies | |
| EQUITY | Probably no impact | | Probably no impact | |
| ACCEPTABILITY | Probably yes | | Probably yes | |
| FEASIBILITY | Probably yes | | Probably yes | |

## TYPE OF RECOMMENDATION

Original

| Strong recommendation against the intervention | **Conditional recommendation against the intervention** | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | Strong recommendation for the intervention |
|---|---|---|---|---|
| ○ | ● | ○ | ○ | ○ |

Adolopment

| Strong recommendation against the intervention | Conditional recommendation against the intervention | **Conditional recommendation for either the intervention or the comparison** | Conditional recommendation for the intervention | Strong recommendation for the intervention |
|---|---|---|---|---|
| ○ | ○ | ● | ○ | ○ |

## CONCLUSIONS

Original

### Recommendation

**The ASH guideline panel suggests delayed removal of a central venous access device (CVAD) until after initiation of anticoagulation (days) rather than immediate removal in pediatric patients with symptomatic central venous line related thrombosis who no longer require venous access or their CVAD is non-functioning (conditional recommendation based on very low certainty in the evidence about effects).**

### Justification

Not enough published evidence was identified to inform this recommendation.

The panel placed high value on avoiding potential risk of emboli leading to PE or paradoxical stroke and this was thought to be achieved by a few days of anticoagulation. The risk of infection and bleeding with anticoagulation before removing the CVAD was considered to be small. The panel recognised that surgical availability was often a pragmatic determinant of CVAD removal.

Adolopment

### Recommendation

**The ASH/ISTH guideline panel suggests either delayed removal of a central venous access device (CVAD) or immediate removal in pediatric patients with symptomatic central venous line related thrombosis who no longer require venous access or their CVAD is non-functioning (conditional recommendation based on low certainty in the evidence about effects).**

### Justification

### Subgroup considerations

Original

--

Adolopment

Special consideration to patients with right to left shunts (atrial septal defects).

The size of the thrombus would affect the approach also.

## Implementation considerations

Original

--

Adolopment

## Monitoring and evaluation

Original

–

Adolopment

## Research priorities

Original

–

Adolopment

# REFERENCES SUMMARY


1. Raffini, L, Huang, YS, Witmer, C, Feudtner, C. Dramatic increase in venous thromboembolism in children's hospitals in the United States from 2001 to 2007. Pediatrics; 2009.
2. Jaffray, J, Bauman, M, Massicotte, P. The Impact of Central Venous Catheters on Pediatric Venous Thromboembolism. Frontiers in Pediatrics; 2017.
3. Monagle, P, Chan, AK, Goldenberg, NA, Ichord, RN, Journeycake, JM, Nowak-Gottl, U. Antithrombotic therapy in neonates and children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest; 2012.
4. Hogg, K., Shaw, J., Coyle, D., Fallah, P., Carrier, M., Wells, P.. Validity of standard gamble estimated quality of life in acute venous thrombosis. Thromb Res; Oct 2014.
5. Hogg, K., Kimpton, M., Carrier, M., Coyle, D., Forgie, M., Wells, P.. Estimating quality of life in acute venous thrombosis. JAMA Intern Med; Jun 24 2013.
6. Locadia, M., Bossuyt, P. M., Stalmeier, P. F., Sprangers, M. A., van Dongen, C. J., Middeldorp, S., Bank, I., van der Meer, J., Hamulyak, K., Prins, M. H.. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. Thromb Haemost; Dec 2004.
7. Marvig, C. L., Verhoef, T. I., de Boer, A., Kamali, F., Redekop, K., Pirmohamed, M., Daly, A. K., Manolopoulos, V. G., Wadelius, M., Bouvy, M., Maitland-van der Zee, A. H., consortium, Eu-Pact. Quality of life in patients with venous thromboembolism and atrial fibrillation treated with coumarin anticoagulants. Thromb Res; Jul 2015.
8. Utne, K. K., Tavoly, M., Wik, H. S., Jelsness-Jorgensen, L. P., Holst, R., Sandset, P. M., Ghanima, W.. Health-related quality of life after deep vein thrombosis. Springerplus; 2016.
9. Lenert, L. A., Soetikno, R. M.. Automated computer interviews to elicit utilities: potential applications in the treatment of deep venous thrombosis. J Am Med Inform Assoc; Jan-Feb 1997.
10. O'Meara, J. J.,3rd, McNutt, R. A., Evans, A. T., Moore, S. W., Downs, S. M.. A decision analysis of streptokinase plus heparin as compared with heparin alone for deep-vein thrombosis. N Engl J Med; Jun 30 1994.

**Author(s):**
**Question:** DOAC compared to Standard of Care for Venous Thromboembolism in Pediatric Patients
**Setting:** In-Patient
**Bibliography:**

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | DOAC | Standard of Care | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality (follow-up: 3 months)** | | | | | | | | | | | | |
| 3[1,2,3] | randomised trials | serious[a] | not serious | not serious | serious[b] | none | 3/522 (0.6%) | 2/267 (0.7%) | **RR 0.71** (0.14 to 3.56) | **2 fewer per 1,000** (from 6 fewer to 19 more) | ⨁⨁◯◯ Low | CRITICAL |
| **Recurrence (follow-up: 3 months)** | | | | | | | | | | | | |
| 3[1,2,3] | randomised trials | not serious | not serious | serious[c] | serious[b] | none | 11/523 (2.1%) | 14/267 (5.2%) | **RR 0.43** (0.20 to 0.93) | **30 fewer per 1,000** (from 42 fewer to 4 fewer) | ⨁⨁◯◯ Low | CRITICAL |
| **Resolution (assessed with: Complete and Partial Resolution)** | | | | | | | | | | | | |
| 2[2,3] | randomised trials | not serious | not serious | not serious | serious[d] | none | 395/512 (77.1%) | 181/255 (71.0%) | **RR 1.09** (0.99 to 1.19) | **64 more per 1,000** (from 7 fewer to 135 more) | ⨁⨁⨁◯ Moderate | CRITICAL |
| **Post-thrombotic Syndrome (follow-up: 3 months)** | | | | | | | | | | | | |
| 2[2,3] | randomised trials | serious[a] | not serious | serious[c] | very serious[b] | none | 4/511 (0.8%) | 0/255 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Major Bleeding (follow-up: 3 months)** | | | | | | | | | | | | |
| 3[1,2,3] | randomised trials | not serious | not serious | not serious | very serious[b] | none | 4/517 (0.8%) | 5/264 (1.9%) | **RR 0.48** (0.14 to 1.57) | **10 fewer per 1,000** (from 16 fewer to 11 more) | ⨁⨁◯◯ Low | CRITICAL |
| **CRNMB (follow-up: 3 months)** | | | | | | | | | | | | |
| 2[2,3] | randomised trials | not serious | not serious | not serious | serious[b] | none | 12/506 (2.4%) | 2/252 (0.8%) | **RR 2.98** (0.67 to 13.27) | **16 more per 1,000** (from 3 fewer to 97 more) | ⨁⨁⨁◯ Moderate | CRITICAL |

**CI:** confidence interval; **RR:** risk ratio

**Explanations**

a. Reporting Bias

b. Small number of events
c. Outcomes assessed at 3 months
d. Wide absolute CI

**References**

1.Eghbali, Aziz, Rahimi Afzal, Roghayyeh, Sheikhbeygloo, Roya, Eghbali, Aygin, Taherkhanchi, Bahar, Bagheri, Bahador. Dabigatran <em>versus</em> Warfarin for the Treatment of Pediatric Thromboembolism: A Pilot Randomized Trial. Pharm Sci; 2020.
2.C, Male, AWA, Lensing, JS, Palumbo, R, Kumar, I, Nurmeev, K, Hege, D, Bonnet, P, Connor, HL, Hooimeijer, M, Torres, AKC, Chan, G, Kenet, S, Holzhauer, A, Santamaría, P, Amedro, E, Chalmers, P, Simioni, RV, Bhat, DL, Yee, O, Lvova, J, Beyer-Westendorf, TT, Biss, I, Martinelli, P, Saracco, M, Peters, K, Kállay, CA, Gauger, MP, Massicotte, G, Young, AF, Pap, M, Majumder, WT, Smith, JF, Heubach, SD, Berkowitz, K, Thelen, D, Kubitza, M, Crowther, MH, Prins, P, Monagle, Investigators, EINSTEIN-Jr,Phase,3. Rivaroxaban compared with standard anticoagulants for the treatment of acute . The Lancet. Haematology; 2020.
3.J, Halton, LR, Brandão, M, Luciani, L, Bomgaars, E, Chalmers, LG, Mitchell, I, Nurmeev, A, Sharathkumar, P, Svirin, K, Gorbatikov, I, Tartakovsky, M, Simetzberger, F, Huang, Z, Sun, J, Kreuzer, S, Gropper, P, Reilly, M, Brueckmann, M, Albisetti, Investigators, DIVERSITY,Trial. Dabigatran etexilate for the treatment of acute venous thromboembolism in . The Lancet. Haematology; 2021.

**Author(s):**
**Question:** Rivaroxaban compared to Standard of Care for Venous Thromboembolism in Pediatric Patients
**Setting:** In-Patient
**Bibliography:** American Society of Hematology 2024 Guidelines for Management of Venous Thromboembolism: Treatment of Pediatric Venous Thromboembolism

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Rivaroxaban | Standard of Care | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality - Rivaroxaban (follow-up: 3 months; assessed with: All Cause Mortality)** | | | | | | | | | | | | |
| 1[1] | randomised trials | not serious | not serious | not serious | very serious[a] | none | 1/335 (0.3%) [b] | 0/165 (0.0%) | not estimable | | ⨁⨁◯◯ Low | CRITICAL |
| **Recurrence of VTE - Rivaroxaban (follow-up: 3 months)** | | | | | | | | | | | | |
| 1[1] | randomised trials | not serious | not serious | serious[c] | serious[a] | none | 4/335 (1.2%) | 5/165 (3.0%) | **RR 0.39** (0.11 to 1.45) | **18 fewer per 1,000** (from 27 fewer to 14 more) | ⨁⨁◯◯ Low | CRITICAL |
| **Resolution - Rivaroxaban (follow-up: 3 months; assessed with: Complete and Partial Resolution)** | | | | | | | | | | | | |
| 1[1] | randomised trials | not serious | not serious | not serious | serious[d] | none | 257/335 (76.7%) | 118/165 (71.5%) | **RR 1.07** (0.96 to 1.20) | **50 more per 1,000** (from 29 fewer to 143 more) | ⨁⨁⨁◯ Moderate | CRITICAL |
| **Post-thrombotic Syndrome - Rivaroxaban (follow-up: 3 months)** | | | | | | | | | | | | |
| 1[1] | randomised trials | not serious | not serious | serious[e] | very serious[a] | none | 2/335 (0.6%) | 0/165 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Major Bleeding - Rivaroxaban (follow-up: 3 months)** | | | | | | | | | | | | |
| 1[1] | randomised trials | not serious | not serious | not serious | very serious[a] | none | 0/329 (0.0%) | 2/162 (1.2%) | not estimable | | ⨁⨁◯◯ Low | CRITICAL |
| **Clinically Relevant Non-Major Bleed - Rivaroxaban (follow-up: 3 months)** | | | | | | | | | | | | |
| 1[1] | randomised trials | not serious | not serious | not serious | serious[a] | none | 10/329 (3.0%) | 1/162 (0.6%) | **RR 4.92** (0.64 to 38.13) | **24 more per 1,000** (from 2 fewer to 229 more) | ⨁⨁⨁◯ Moderate | CRITICAL |

**CI:** confidence interval; **RR:** risk ratio

**Explanations**

a. Imprecision due to small number of patients with events in the included studies.
b. The patient that died were was not due to therapy or VTE related causes.
c. Recurrence of venous thromboembolisms may occur after long term follow-up. Indirectness was judged to be serious since the outcome (recurrence) was evaluated at 3 months.
d. Wide Absolute 95% Confidence Interval, ranging from an effect to an effect
e. Post-thrombotic syndrome may occur after long term follow-up. Indirectness was judged to be serious since the outcome (PTS) was evaluated at 3 months.

**References**

1.C, Male, AWA, Lensing, JS, Palumbo, R, Kumar, I, Nurmeev, K, Hege, D, Bonnet, P, Connor, HL, Hooimeijer, M, Torres, AKC, Chan, G, Kenet, S, Holzhauer, A, Santamaría, P, Amedro, E, Chalmers, P, Simioni, RV, Bhat, DL, Yee, O, Lvova, J, Beyer-Westendorf, TT, Biss, I, Martinelli, P, Saracco, M, Peters, K, Kállay, CA, Gauger, MP, Massicotte, G, Young, AF, Pap, M, Majumder, WT, Smith, JF, Heubach, SD, Berkowitz, K, Thelen, D, Kubitza, M, Crowther, MH, Prins, P, Monagle, Investigators, EINSTEIN-Jr,Phase,3. Rivaroxaban compared with standard anticoagulants for the treatment of acute . The Lancet. Haematology; 2020.

**Author(s):**
**Question:** Dabigatran compared to Standard of Care for Venous Thromboembolism in Pediatric Patients
**Setting:** In-Patient
**Bibliography:**

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Dabigatran | Standard of Care | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality - Dabigatran (follow-up: 3 months; assessed with: All Cause Mortality)** | | | | | | | | | | | | |
| 2[1,2] | randomised trials | serious[a] | not serious | serious[b] | very serious[c] | none | 2/187 (1.1%) [d] | 2/102 (2.0%) [e] | **RR 0.51** (0.07 to 3.51) | **10 fewer per 1,000** (from 18 fewer to 49 more) | ⨁◯◯◯ Very low | CRITICAL |
| **Recurrence of VTE - Dabigatran (follow-up: 3 months)** | | | | | | | | | | | | |
| 2[1,2] | randomised trials | not serious | not serious | serious[b] | serious[c] | none | 7/188 (3.7%) | 9/102 (8.8%) | **RR 0.45** (0.17 to 1.17) | **49 fewer per 1,000** (from 73 fewer to 15 more) | ⨁⨁◯◯ Low | CRITICAL |
| **Resolution - Dabigatran (follow-up: 3 months; assessed with: Complete and Partial Resolution)** | | | | | | | | | | | | |
| 1[1] | randomised trials | not serious | not serious | serious[b] | serious[f] | none | 138/177 (78.0%) | 63/90 (70.0%) | **RR 1.11** (0.95 to 1.30) | **77 more per 1,000** (from 35 fewer to 210 more) | ⨁⨁◯◯ Low | CRITICAL |
| **Post-thrombotic Syndrome - Dabigatran (follow-up: 3 months)** | | | | | | | | | | | | |
| 1[1] | randomised trials | serious[a] | not serious | serious[g] | serious[c] | none | 1/176 (0.6%) | 0/90 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Major Bleeding - Dabigatran (follow-up: 3 months)** | | | | | | | | | | | | |
| 2[1,2] | randomised trials | not serious | not serious | serious[b] | very serious[c] | none | 4/188 (2.1%) | 3/102 (2.9%) | **RR 0.79** (0.19 to 3.32) | **6 fewer per 1,000** (from 24 fewer to 68 more) | ⨁◯◯◯ Very low | CRITICAL |
| **Clinically Relevant Non-Major Bleed- Dabigatran (follow-up: 3 months)** | | | | | | | | | | | | |
| 1[1] | randomised trials | not serious | not serious | serious[b] | serious[c] | none | 2/177 (1.1%) | 1/90 (1.1%) | **RR 1.02** (0.09 to 11.07) | **0 fewer per 1,000** (from 10 fewer to 112 more) | ⨁⨁◯◯ Low | CRITICAL |

**CI:** confidence interval; **RR:** risk ratio

**Explanations**

a. Risk of bias, assessed using ROB-2 was judged to be serious due to reporting bias.
b. Indirectness due to drug monitoring that occurred when giving Dabigatran
c. Imprecision due to small number of included patients and patients with events in the included studies.
d. A 14- year-old male with stage IV adenocarcinoma of the lung, died during follow-up due to cardio respiratory failure 22 days after stopping dabigatran. Another adolescent, a 17-year-old male with a history of cancer (metastatic osteosarcoma, bilateral lung metastases), died 241 days after the study ended
e. One due to retroperitoneal bleeding (not therapy related). One on-treatment adverse event leading to death 10 days after stopping standard of care
f. Wide Absolute CI
g. Indirectness due to drug monitoring that occurred when giving Dabigatran and outcome assessed at 3 months despite usually

**References**

1.J, Halton, LR, Brandão, M, Luciani, L, Bomgaars, E, Chalmers, LG, Mitchell, I, Nurmeev, A, Sharathkumar, P, Svirin, K, Gorbatikov, I, Tartakovsky, M, Simetzberger, F, Huang, Z, Sun, J, Kreuzer, S, Gropper, P, Reilly, M, Brueckmann, M, Albisetti, Investigators, DIVERSITY,Trial. Dabigatran etexilate for the treatment of acute venous thromboembolism in . The Lancet. Haematology; 2021.
2.Eghbali, Aziz, Rahimi Afzal, Roghayyeh, Sheikhbeygloo, Roya, Eghbali, Aygin, Taherkhanchi, Bahar, Bagheri, Bahador. Dabigatran <em>versus</em> Warfarin for the Treatment of Pediatric Thromboembolism: A Pilot Randomized Trial. Pharm Sci; 2020.

**Author(s):**
**Question:** Rivaroxaban compared to Standard of Care for Venous Thromboembolism in Pediatric Patients
**Setting:** In-Patient
**Bibliography:** American Society of Hematology 2024 Guidelines for Management of Venous Thromboembolism: Treatment of Pediatric Venous Thromboembolism

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Rivaroxaban | Standard of Care | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality - Rivaroxaban (follow-up: 3 months; assessed with: All Cause Mortality)** | | | | | | | | | | | | |
| 1[1] | randomised trials | not serious | not serious | not serious | very serious[a] | none | 1/335 (0.3%) [b] | 0/165 (0.0%) | not estimable | | ⨁⨁◯◯ Low | CRITICAL |
| **Recurrence of VTE - Rivaroxaban (follow-up: 3 months)** | | | | | | | | | | | | |
| 1[1] | randomised trials | not serious | not serious | serious[c] | serious[a] | none | 4/335 (1.2%) | 5/165 (3.0%) | **RR 0.39** (0.11 to 1.45) | **18 fewer per 1,000** (from 27 fewer to 14 more) | ⨁⨁◯◯ Low | CRITICAL |
| **Resolution - Rivaroxaban (follow-up: 3 months; assessed with: Complete and Partial Resolution)** | | | | | | | | | | | | |
| 1[1] | randomised trials | not serious | not serious | not serious | serious[d] | none | 257/335 (76.7%) | 118/165 (71.5%) | **RR 1.07** (0.96 to 1.20) | **50 more per 1,000** (from 29 fewer to 143 more) | ⨁⨁⨁◯ Moderate | CRITICAL |
| **Post-thrombotic Syndrome - Rivaroxaban (follow-up: 3 months)** | | | | | | | | | | | | |
| 1[1] | randomised trials | not serious | not serious | serious[e] | very serious[a] | none | 2/335 (0.6%) | 0/165 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |
| **Major Bleeding - Rivaroxaban (follow-up: 3 months)** | | | | | | | | | | | | |
| 1[1] | randomised trials | not serious | not serious | not serious | very serious[a] | none | 0/329 (0.0%) | 2/162 (1.2%) | not estimable | | ⨁⨁◯◯ Low | CRITICAL |
| **Clinically Relevant Non-Major Bleed - Rivaroxaban (follow-up: 3 months)** | | | | | | | | | | | | |
| 1[1] | randomised trials | not serious | not serious | not serious | serious[a] | none | 10/329 (3.0%) | 1/162 (0.6%) | **RR 4.92** (0.64 to 38.13) | **24 more per 1,000** (from 2 fewer to 229 more) | ⨁⨁⨁◯ Moderate | CRITICAL |

**CI:** confidence interval; **RR:** risk ratio

**Explanations**

a. Imprecision due to small number of patients with events in the included studies.
b. The patient that died were was not due to therapy or VTE related causes.
c. Recurrence of venous thromboembolisms may occur after long term follow-up. Indirectness was judged to be serious since the outcome (recurrence) was evaluated at 3 months.
d. Wide Absolute CI
e. Post-thrombotic syndrome may occur after long term follow-up. Indirectness was judged to be serious since the outcome (PTS) was evaluated at 3 months.

**References**

1.C, Male, AWA, Lensing, JS, Palumbo, R, Kumar, I, Nurmeev, K, Hege, D, Bonnet, P, Connor, HL, Hooimeijer, M, Torres, AKC, Chan, G, Kenet, S, Holzhauer, A, Santamaría, P, Amedro, E, Chalmers, P, Simioni, RV, Bhat, DL, Yee, O, Lvova, J, Beyer-Westendorf, TT, Biss, I, Martinelli, P, Saracco, M, Peters, K, Kállay, CA, Gauger, MP, Massicotte, G, Young, AF, Pap, M, Majumder, WT, Smith, JF, Heubach, SD, Berkowitz, K, Thelen, D, Kubitza, M, Crowther, MH, Prins, P, Monagle, Investigators, EINSTEIN-Jr,Phase,3. Rivaroxaban compared with standard anticoagulants for the treatment of acute . The Lancet. Haematology; 2020.

## QUESTION

| Should Dabigatran vs. Standard of Care be used for Venous Thromboembolism in Pediatric Patients? | |
|---|---|
| **POPULATION:** | Venous Thromboembolism in Pediatric Patients |
| **INTERVENTION:** | Dabigatran |
| **COMPARISON:** | Standard of Care |
| **MAIN OUTCOMES:** | Mortality - Dabigatran; Recurrence of VTE - Dabigatran; Resolution - Dabigatran; Post-thrombotic Syndrome - Dabigatran; Major Bleeding - Dabigatran; Clinically Relevant Non-Major Bleed- Dabigatran; |
| **SETTING:** | In-Patient |
| **PERSPECTIVE:** | |
| **BACKGROUND:** | |
| **CONFLICT OF INTEREST:** | |

## ASSESSMENT

### Problem
Is the problem a priority?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ No<br>○ Probably no<br>○ Probably yes<br>● Yes<br>○ Varies<br>○ Don't know | Direct Oral Anticoagulants (DOACs) have become the preferred choice of oral anticoagulation in adults due to multiple trials showing higher efficacy, less bleeding and no required monitoring (1)(2). In the ASH 2018 guideline for pediatric VTE, an a priori decisionwas made to not address the use of DOACs over other treatment modalities due to the limited evidence at the time. However, with the emergence of numerous studies comparing the use of DOACs versus other anticoagulants in the pediatric population, the comparison between these medications is of importance. | |

### Desirable Effects
How substantial are the desirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ Trivial<br>● Small<br>○ Moderate | | |

| | | |
|---|---|---|
| ○ Large<br>○ Varies<br>○ Don't know | *See Appendix 2* | |

## Undesirable Effects

How substantial are the undesirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ Large<br>○ Moderate<br>○ Small<br>● Trivial<br>○ Varies<br>○ Don't know | *See Appendix 1* | |

## Certainty of evidence

What is the overall certainty of the evidence of effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | Certainty of the evidence of effects was judged as 'Very Low ' due to risk of bias and Imprecision. | |

## Values

Is there important uncertainty about or variability in how much people value the main outcomes?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ Important uncertainty or variability<br>○ Possibly important uncertainty or variability<br>● Probably no important uncertainty | We did not identify utility related information or non-utility information for the outcomes of interest specific to the pediatric population in the literature. **Results from Panel Members' Utility Rating Survey:**<br><br>Utilities rated on the visual analog scale, where 0 represents death and 1 | |

| | | |
|---|---|---|
| or variability<br>○ No important uncertainty or variability | represents full health, were as follows: Pulmonary embolism – Severe marker state: 0.31 Pulmonary embolism – Moderate marker state: 0.49 Deep vein thrombosis (proximal) – Severe marker state: 0.49 Deep vein thrombosis (proximal) – Moderate marker state: 0.61 Deep vein thrombosis (distal) – Severe marker state: 0.56 Deep vein thrombosis (distal) – Moderate marker state: 0.68 Major bleeding: 0.30 Neonatal Bleeding – Severe: 0.30 Infant Bleeding – Severe: 0.26 Our systematic review for the adult population found that the relative importance of the outcomes is as follows: Pulmonary embolism: 0.63-0.93 (different methods) (Hogg et al., 2014, Hogg et al., 2013, Locadia et al., 2004) Deep vein thrombosis: 0.64-0.99 (different methods) (Hogg et al., 2014, Hogg et al., 2013, Locadia et al., 2004)(Marvig et al., 2015)(Utne et al., 2016) Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) (Hogg et al., 2013, Locadia et al., 2004) Muscular bleeding: 0.76 (time trade off) (Locadia et al., 2004) Minor intracranial bleeding event: 0.75 (standard gamble) (Hogg et al., 2013) Major intracranial bleeding event: 0.15 (standard gamble) (Hogg et al., 2013) Central nervous system bleeding: 0.29-0.60 (standard gamble) (Lenert et al., 1997)(O'Meara et al., 1994) Treatment with LMWH: 0.993 (time trade off) (Marchetti et al., 2001) Treatment with warfarin (as a surrogate): 0.989 (time trade off) (Marchetti et al., 2001)**Anticoagulant therapy** In an cross-sectional study utilizing online support groups for Adult VTE patients, out of 521 patients, extreme concern was mostly expressed for recurrent VTE (33%) and mortality (29%), followed by major bleeding (21%), moderate bleeding (16%) (3) Adult patients highly value the benefits of risk reduction in VTE recurrence and post-thrombosis syndrome (4). Patients would favor efficacy and safety over convenience of route of administration (5). Further, patients would like to avoid adverse events but most of them are “not afraid of” the adverse events (6)(5)(7). For anticoagulant therapy in general, most patients would prefer the oral doses compared with injections, this is mainly because of treatment burden due to injection. For patients with venographically proven deep venous thrombosis, 15 of the 19 patients expressed a preference for the subcutaneous route for administration of heparin over intravenous administration(8). **Warfarin** Adult patients would like to switch to another anticoagulant if it is as effective as warfarin; this is mainly due to the treatment burden associated with monitoring, injection and dietary change due to warfarin use. In another study approximately half of the patients did not consider VKA therapy particularly difficult to manage. (9)(10) **LMWH** For adult patients receiving low molecular weight heparin, patients placed a high score on “importance of ease of use”, “expectations of symptom relief”, and “confidence in the treatment to prevent blood clots” while they had a low score of treatment-related side effects (bruise, bleeding). (11)**DOAC**According to a systematic review for adult patients comparing DOACs to LMWH, DOACs was found to have a better effect in preventing thromboembolism, and less bleeding (2). Similar findings were seen comparing DOACs to Warfarin. | |

## Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>● Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>○ Don't know | | Desirable effects were judged to be:<br><br>Undesirable effects were judged to be: |

## Resources required

How large are the resource requirements (costs)?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ Large costs<br>○ Moderate costs<br>○ Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br>● Varies<br>○ Don't know | Found in table | No monitoring required |

## Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|

| | | |
|---|---|---|
| ○ Very low<br>○ Low<br>○ Moderate<br>○ High<br>● No included studies | No research evidence was found (based on database estimates) | |

## Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>● No included studies | We did not identify cost effectiveness studies for pediatric VTE.<br><br><u>Adult Cost effectiveness studies:</u><br><br>In Spain, for patients with cancer associated thrombosis, DOACs including Dabigatran were found to be cost-effective and cost-saving as compared to LMWH. **(Muñoz, 2022)** Similar findings were found by Amin et al for patients with VTE in comparison to both enoxaparin and VKA. **(Amin,2014)(Amin,2015)** In Netherlands, Dabigatran resulted in cost saving compared with VKAs for treatment of DVT. **(van Leent, 2015)** Similar findings in China were found by Sun et al. **(Sun, 2021)**<br><br>In Thailand, at a willing-to-pay of $5003, DOACs were found to be not cost-effective in comparison to warfarin in VTE. **(Niyomsri,2023)** | |

## Equity

What would be the impact on health equity?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ Reduced<br>○ Probably reduced | Various studies have shown a difference in prescription patterns for DOACs versus other anticoagulants in VTE and Atrial Fibrillation based on Ethnicity and | |

| | | |
|---|---|---|
| ○ Probably no impact<br>○ Probably increased<br>○ Increased<br>○ Varies<br>● Don't know | Socioeconomic Status. **(Nathan, 2019)(Essien,2021)** However these differences could not be explained cost or insurance coverage. | |

## Acceptability

Is the intervention acceptable to key stakeholders?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ No<br>○ Probably no<br>○ Probably yes<br>● Yes<br>○ Varies<br>○ Don't know | In 167 adult patients with DVT/SVT 81.5% patients preferred oral treatment over injectable treatment mainly due to ease of administration. 8.4% preferred injectable treatments over oral treatmnt mostly due to being more efficent than oral(42.8%). 10.1% had no preference. No difference was found in anticoagulant preference between duration of anticoagulation. (12)In the Netherlands, a study including 135 patients on Warfarin for VTE was carried out. The study employed the "trade-offtechnique" methodology to ask the patients if they would switch from warfarin dependent on each of the four distinct advantages of DOACs. 65% would switch to DOACs if it resulted in less drug/food interations, 57% for decreased bleeding risk and 36% for no need for laboratory control. (3) | Dyspepsia was noted in some pts in the trial, may impact acceptability. (Summary of AE in the undesirable effects, mennoragia) |

## Feasibility

Is the intervention feasible to implement?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ No<br>○ Probably no<br>● Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | No research evidence | Oral medication Versus injectable<br><br>Suspension formula avaliable for infants<br><br>Not all countries have DOACs approved for pediatric use |



## SUMMARY OF JUDGEMENTS

| | JUDGEMENT | | | | | | |
|---|---|---|---|---|---|---|---|
| **PROBLEM** | No | Probably no | Probably yes | **Yes** | | Varies | Don't know |
| **DESIRABLE EFFECTS** | Trivial | **Small** | Moderate | Large | | Varies | Don't know |
| **UNDESIRABLE EFFECTS** | Large | Moderate | Small | **Trivial** | | Varies | Don't know |

| | JUDGEMENT | | | | | | |
|---|---|---|---|---|---|---|---|
| **CERTAINTY OF EVIDENCE** | **Very low** | Low | Moderate | High | | | No included studies |
| **VALUES** | Important uncertainty or variability | Possibly important uncertainty or variability | **Probably no important uncertainty or variability** | No important uncertainty or variability | | | |
| **BALANCE OF EFFECTS** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | **Probably favors the intervention** | Favors the intervention | Varies | Don't know |
| **RESOURCES REQUIRED** | Large costs | Moderate costs | Negligible costs and savings | Moderate savings | Large savings | **Varies** | Don't know |
| **CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES** | Very low | Low | Moderate | High | | | **No included studies** |
| **COST EFFECTIVENESS** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **EQUITY** | Reduced | Probably reduced | Probably no impact | Probably increased | Increased | Varies | **Don't know** |
| **ACCEPTABILITY** | No | Probably no | Probably yes | **Yes** | | Varies | Don't know |
| **FEASIBILITY** | No | Probably no | **Probably yes** | Yes | | Varies | Don't know |

## TYPE OF RECOMMENDATION

| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | **Conditional recommendation for the intervention** | Strong recommendation for the intervention |
|---|---|---|---|---|
| ○ | ○ | ○ | ● | ○ |

## CONCLUSIONS

## Recommendation

**The ASH/ISTH guideline panel suggests using Dabigatran over Standard of Care (LMWH, UFH, VKA, Fodaparinux) in pediatric patients with Venous Thromboembolism (VTE) (conditional recommendation based on very low certainty in the evidence about effects).**

## Justification

## Subgroup considerations

## Implementation considerations

## Monitoring and evaluation

## Research priorities

# REFERENCES SUMMARY


1. H, Whitworth, L, Raffini. Practical Considerations for Use of Direct Oral Anticoagulants in Children.. Frontiers in pediatrics; 2022.
2. Y, Tian, T, Pan, X, Wen, G, Ao, Y, Ma, X, Liu, R, Liu, H, Ran. Efficacy and Safety of Direct Oral Anticoagulants Compared With Heparin for . Clinical and applied thrombosis/hemostasis : official journal of the ; 2023.
3. PL, Lutsey, KJ, Horvath, L, Fullam, S, Moll, MR, Rooney, M, Cushman, NA, Zakai. Anticoagulant Preferences and Concerns among Venous Thromboembolism Patients.. Thrombosis and haemostasis; 2018.
4. Locadia, M., Bossuyt, P. M., Stalmeier, P. F., Sprangers, M. A., van Dongen, C. J., Middeldorp, S., Bank, I., van der Meer, J., Hamulyak, K., Prins, M. H.. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. Thromb Haemost; Dec 2004.
5. Noble, S., Matzdorff, A., Maraveyas, A., Holm, M. V., Pisa, G.. Assessing patients' anticoagulation preferences for the treatment of cancer-associated thrombosis using conjoint methodology. Haematologica; Nov 2015.
6. Barcellona, D., Contu, P., Sorano, G. G., Pengo, V., Marongiu, F.. The management of oral anticoagulant therapy: the patient's point of view. Thromb Haemost; Jan 2000.
7. O'Meara, J. J.,3rd, McNutt, R. A., Evans, A. T., Moore, S. W., Downs, S. M.. A decision analysis of streptokinase plus heparin as compared with heparin alone for deep-vein thrombosis. N Engl J Med; Jun 30 1994.
8. Robinson, A. M., McLean, K. A., Greaves, M., Channer, K. S.. Subcutaneous versus intravenous administration of heparin in the treatment of deep vein thrombosis; which do patients prefer? A randomized cross-over study. Postgrad Med J; Feb 1993.
9. Attaya, S., Bornstein, T., Ronquillo, N., Volgman, R., Braun, L. T., Trohman, R., Volgman, A.. Study of warfarin patients investigating attitudes toward therapy change (SWITCH Survey). Am J Ther; Nov 2012.
10. Wild, D., Murray, M., Donatti, C.. Patient perspectives on taking vitamin K antagonists: a qualitative study in the UK, USA and Spain. Expert Rev Pharmacoecon Outcomes Res; Oct 2009.
11. Baba, M., Al-Masri, M., Salhab, M., El-Ghanem, M.. Patient's Compliance on the Use of Extended Low Molecular Weight Heparin Post Major Pelvic Surgeries in Cancer Patients at King Hussein Cancer Center. Gulf J Oncolog; Jan 2015.
12. D, Lanéelle, C, Le,Brun, C, Mauger, J, Guillaumat, E, Le,Pabic, L, Omarjee, G, Mahé, Group, SFMV,VTE,Study. Patient Characteristics and Preferences Regarding Anticoagulant Treatment in . Frontiers in cardiovascular medicine; 2021.

# APPENDICES

Appendix 1

**Author(s):**
**Question:** Dabigatran compared to Standard of Care for Venous Thromboembolism in Pediatric Patients
**Setting:** In-Patient
**Bibliography:**

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Dabigatran | Standard of Care | Relative (95% CI) | Absolute (95% CI) | | |
| **Major Bleeding - Dabigatran (follow-up: 3 months)** | | | | | | | | | | | | |
| 2[1,2] | randomised trials | not serious | not serious | serious[a] | very serious[b] | none | 4/188 (2.1%) | 3/102 (2.9%) | **RR 0.79** (0.19 to 3.32) | **6 fewer per 1,000** (from 24 fewer to 68 more) | ⨁◯◯◯ Very low | CRITICAL |
| **Clinically Relevant Non-Major Bleed- Dabigatran (follow-up: 3 months)** | | | | | | | | | | | | |
| 1[1] | randomised trials | not serious | not serious | serious[a] | serious[b] | none | 2/177 (1.1%) | 1/90 (1.1%) | **RR 1.02** (0.09 to 11.07) | **0 fewer per 1,000** (from 10 fewer to 112 more) | ⨁⨁◯◯ Low | CRITICAL |

**CI:** confidence interval; **RR:** risk ratio

**Explanations**

a. Indirectness due to drug monitoring that occurred when giving Dabigatran
b. Imprecision due to small number of included patients and patients with events in the included studies.

**References**

1.J, Halton, LR, Brandão, M, Luciani, L, Bomgaars, E, Chalmers, LG, Mitchell, I, Nurmeev, A, Sharathkumar, P, Svirin, K, Gorbatikov, I, Tartakovsky, M, Simetzberger, F, Huang, Z, Sun, J, Kreuzer, S, Gropper, P, Reilly, M, Brueckmann, M, Albisetti, Investigators, DIVERSITY,Trial. Dabigatran etexilate for the treatment of acute venous thromboembolism in . The Lancet. Haematology; 2021.
2.Eghbali, Aziz , Rahimi Afzal, Roghayyeh, Sheikhbeygloo, Roya, Eghbali, Aygin, Taherkhanchi, Bahar, Bagheri, Bahador. Dabigatran <em>versus</em> Warfarin for the Treatment of Pediatric Thromboembolism: A Pilot Randomized Trial. Pharm Sci; 2020.

Appendix 2

**Author(s):**
**Question:** Dabigatran compared to Standard of Care for Venous Thromboembolism in Pediatric Patients
**Setting:** In-Patient
**Bibliography:**

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Dabigatran | Standard of Care | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality - Dabigatran (follow-up: 3 months; assessed with: All Cause Mortality)** | | | | | | | | | | | | |
| 2[1,2] | randomised trials | serious[a] | not serious | serious[b] | very serious[c] | none | 2/187 (1.1%) [d] | 2/102 (2.0%) [e] | **RR 0.51** (0.07 to 3.51) | **10 fewer per 1,000** (from 18 fewer to 49 more) | ⨁◯◯◯ Very low | CRITICAL |
| **Recurrence of VTE - Dabigatran (follow-up: 3 months)** | | | | | | | | | | | | |
| 2[1,2] | randomised trials | not serious | not serious | serious[b] | serious[c] | none | 7/188 (3.7%) | 9/102 (8.8%) | **RR 0.45** (0.17 to 1.17) | **49 fewer per 1,000** (from 73 fewer to 15 more) | ⨁⨁◯◯ Low | CRITICAL |
| **Resolution - Dabigatran (follow-up: 3 months; assessed with: Complete and Partial Resolution)** | | | | | | | | | | | | |
| 1[1] | randomised trials | not serious | not serious | serious[b] | serious[f] | none | 138/177 (78.0%) | 63/90 (70.0%) | **RR 1.11** (0.95 to 1.30) | **77 more per 1,000** (from 35 fewer to 210 more) | ⨁⨁◯◯ Low | CRITICAL |
| **Post-thrombotic Syndrome - Dabigatran (follow-up: 3 months)** | | | | | | | | | | | | |
| 1[1] | randomised trials | serious[a] | not serious | serious[g] | serious[c] | none | 1/176 (0.6%) | 0/90 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |

**CI:** confidence interval; **RR:** risk ratio

**Explanations**

a. Risk of bias, assessed using ROB-2 was judged to be serious due to reporting bias.
b. Indirectness due to drug monitoring that occurred when giving Dabigatran
c. Imprecision due to small number of included patients and patients with events in the included studies.
d. A 14- year-old male with stage IV adenocarcinoma of the lung, died during follow-up due to cardio respiratory failure 22 days after stopping dabigatran. Another adolescent, a 17-year-old male with a history of cancer (metastatic osteosarcoma, bilateral lung metastases), died 241 days after the study ended
e. One due to retroperitoneal bleeding (not therapy related). One on-treatment adverse event leading to death 10 days after stopping standard of care
f. Wide Absolute CI
g. Indirectness due to drug monitoring that occurred when giving Dabigatran and outcome assessed at 3 months despite usually

**References**

1.J, Halton, LR, Brandão, M, Luciani, L, Bomgaars, E, Chalmers, LG, Mitchell, I, Nurmeev, A, Sharathkumar, P, Svirin, K, Gorbatikov, I, Tartakovsky, M, Simetzberger, F, Huang, Z, Sun, J, Kreuzer, S, Gropper, P, Reilly, M, Brueckmann, M, Albisetti, Investigators, DIVERSITY,Trial. Dabigatran etexilate for the treatment of acute venous thromboembolism in . The Lancet. Haematology; 2021.
2.Eghbali, Aziz, Rahimi Afzal, Roghayyeh, Sheikhbeygloo, Roya, Eghbali, Aygin, Taherkhanchi, Bahar, Bagheri, Bahador. Dabigatran <em>versus</em> Warfarin for the Treatment of Pediatric Thromboembolism: A Pilot Randomized Trial. Pharm Sci; 2020.

## QUESTION

| Should DOAC vs. Standard of Care be used for Venous Thromboembolism in Pediatric Patients? | |
|---|---|
| **POPULATION:** | Venous Thromboembolism in Pediatric Patients |
| **INTERVENTION:** | DOAC |
| **COMPARISON:** | Standard of Care |
| **MAIN OUTCOMES:** | Mortality; Recurrence; Resolution; Post-thrombotic Syndrome; Major Bleeding; CRNMB; |
| **SETTING:** | In-Patient |
| **PERSPECTIVE:** | |
| **BACKGROUND:** | |
| **CONFLICT OF INTEREST:** | |

## ASSESSMENT

### Problem
Is the problem a priority?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ No<br>○ Probably no<br>○ Probably yes<br>● Yes<br>○ Varies<br>○ Don't know | Direct Oral Anticoagulants (DOACs) have become the preferred choice of oral anticoagulation in adults due to multiple trials showing higher efficacy, less bleeding and no required monitoring (1)(2). In the ASH 2018 guideline for pediatric VTE, an a priori decision was made to not address the use of DOACs over other treatment modalities due to the limited evidence at the time. However, with the emergence of numerous studies comparing the use of DOACs versus other anticoagulants in the pediatric population, the comparison between these medications is of importance. | |

### Desirable Effects
How substantial are the desirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ Trivial<br>● Small<br>○ Moderate | | Small to Moderate<br><br>Follow-up may be too short to evaluate reccurence |

| | | |
|---|---|---|
| ○ Large<br>○ Varies<br>○ Don't know | *See Appendix 2* | accurtly<br><br>Reccurence and PTS downgrade for Indirectness<br><br>Population in RCTs limited to low-risk patients |

## Undesirable Effects

How substantial are the undesirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ Large<br>○ Moderate<br>● Small<br>○ Trivial<br>○ Varies<br>○ Don't know | *See Appendix 1* | Trvial to small<br><br>Higher weight for MB |

## Certainty of evidence

What is the overall certainty of the evidence of effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ Very low<br>● Low<br>○ Moderate<br>○ High<br>○ No included studies | Certainty of the evidence of effects was judged as 'Low ' due to risk of bias and imprecision. | |

## Values

Is there important uncertainty about or variability in how much people value the main outcomes?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ Important uncertainty or variability<br>○ Possibly important uncertainty or variability<br>● Probably no important uncertainty or variability<br>○ No important uncertainty or variability | We did not identify utility related information or non-utility information for the outcomes of interest specific to the pediatric population in the literature. **Results from Panel Members' Utility Rating Survey:**<br><br>Utilities rated on the visual analog scale, where 0 represents death and 1 represents full health, were as follows: Pulmonary embolism – Severe marker state: 0.31 Pulmonary embolism – Moderate marker state: 0.49 Deep vein thrombosis (proximal) – Severe marker state: 0.49 Deep vein thrombosis (proximal) – Moderate marker state: 0.61 Deep vein thrombosis (distal) – Severe marker state: 0.56 Deep vein thrombosis (distal) – Moderate marker state: 0.68 Major bleeding: 0.30 Neonatal Bleeding – Severe: 0.30 Infant Bleeding – Severe: 0.26 Our systematic review for the adult population found that the relative importance of the outcomes is as follows: Pulmonary embolism: 0.63-0.93 (different methods) (Hogg et al., 2014, Hogg et al., 2013, Locadia et al., 2004) Deep vein thrombosis: 0.64-0.99 (different methods) (Hogg et al., 2014, Hogg et al., 2013, Locadia et al., 2004)(Marvig et al., 2015)(Utne et al., 2016) Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) (Hogg et al., 2013, Locadia et al., 2004) Muscular bleeding: 0.76 (time trade off) (Locadia et al., 2004) Minor intracranial bleeding event: 0.75 (standard gamble) (Hogg et al., 2013) Major intracranial bleeding event: 0.15 (standard gamble) (Hogg et al., 2013) Central nervous system bleeding: 0.29-0.60 (standard gamble) (Lenert et al., 1997)(O'Meara et al., 1994) Treatment with LMWH: 0.993 (time trade off) (Marchetti et al., 2001) Treatment with warfarin (as a surrogate): 0.989 (time trade off) (Marchetti et al., 2001)**Anticoagulant therapy** In an cross-sectional study utilizing online support groups for Adult VTE patients, out of 521 patients, extreme concern was mostly expressed for recurrent VTE (33%) and mortality (29%), followed by major bleeding (21%), moderate bleeding (16%) (3) Adult patients highly value the benefits of risk reduction in VTE recurrence and post-thrombosis syndrome (4). Patients would favor efficacy and safety over convenience of route of administration (5). Further, patients would like to avoid adverse events but most of them are “not afraid of” the adverse events (6)(5)(7). For anticoagulant therapy in general, most patients would prefer the oral doses compared with injections, this is mainly because of treatment burden due to injection. For patients with venographically proven deep venous thrombosis, 15 of the 19 patients expressed a preference for the subcutaneous route for administration of heparin over intravenous administration(8). **Warfarin** Adult patients would like to switch to another anticoagulant if it is as effective as warfarin; this is mainly due to the treatment burden associated with monitoring, injection and dietary change due to warfarin use. In another study approximately half of the patients did not consider VKA therapy particularly difficult to manage. | |

| | | |
|---|---|---|
| | (9)(10) **LMWH** For adult patients receiving low molecular weight heparin, patients placed a high score on “importance of ease of use”, “expectations of symptom relief”, and “confidence in the treatment to prevent blood clots” while they had a low score of treatment-related side effects (bruise, bleeding). (11)**DOAC**According to a systematic review for adult patients comparing DOACs to LMWH, DOACs was found to have a better effect in preventing thromboembolism, and less bleeding (2). Similar findings were seen comparing DOACs to Warfarin. | |

## Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>● Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>○ Don't know | Desirable effects were judged to be: Small<br><br>Undesirable effects were judged to be: Small | Desirable effects were judged to be: Small<br><br>Undesirable effects were judged to be: Small |

## Resources required

How large are the resource requirements (costs)?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ Large costs<br>○ Moderate costs<br>○ Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br>● Varies<br>○ Don't know | Found in Table | Cost of drugs, monitoring<br><br>Varies considered |

## Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|

| | | |
|---|---|---|
| ○ Very low<br>○ Low<br>○ Moderate<br>○ High<br>● No included studies | No research evidence was found (based on database estimates) | |

## Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>● No included studies | We did not identify cost effectiveness studies for pediatric VTE.<br><br><u>Adult Cost effectiveness studies:</u><br><br>In a study investigating the cost effectiveness of rivaroxaban as compared to enoxaparin + VKA for the treatment of DVT/PE at 3, 6, or 12 month durations from a US payer perspective; Rivaroxaban was shown to be dominant (less costly, more effective) **(Lefebvre, 2014)**. Peacock et al. showed Rivaroxaban to have a lower total cost as compared to low-molecular-weight heparin, unfractionated heparin, warfarin in low risk PE. **(Peacock,2019)** Based on a cost effectiveness study from the REMOTEV Registry, rivaroxaban was found to be an effective, safe and less costly alternative for warfain. **(Kepka,2023)**<br><br>Similarly, a study in greece comparing the cost of Rivaroxaban in comparison to SOC "enoxaparin followed by dose-adjusted vitamin-K antagonists" for DVT and PE. For 3 and 6 month duration, rivaroxaban was found to be less costly and more effective in DVT and cost effective in PE **(Gourzoulidis, 2017)**.In Spain, for patients with cancer associated thrombosis, DOACs including Rivaroxaban and Dabigatran was found to be cost-effective and cost-saving as compared to LMWH in VTE. **(Muñoz, 2022)** In China, Rivaroxaban resulted in cost saving compared with enoxaparin/warfarin for treatment of acute DVT. **(Yang, 2020)** Similar findings in | Small group to elaborate |

| | | |
|---|---|---|
| | China were found by Sun et al. **(Sun, 2021)** Amin et al found that for patients with VTE in comparison to both enoxaparin and VKA. **(Amin,2014)(Amin,2015)** In Netherlands, Dabigatran resulted in cost saving compared with VKAs for treatment of DVT. **(van Leent, 2015)**<br><br>In Thailand, at a willing-to-pay of $5003, DOACs were found to be not cost-effective in comparison to warfarin in VTE. **(Niyomsri,2023)** | |

## Equity
What would be the impact on health equity?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ Reduced<br>○ Probably reduced<br>○ Probably no impact<br>○ Probably increased<br>○ Increased<br>○ Varies<br>● Don't know | Various studies have shown a difference in prescription patterns for DOACs versus other anticoagulants in VTE and Atrial Fibrillation based on Ethnicity and Socioeconomic Status. **(Nathan, 2019)(Essien,2021)** However these differences could not be explained cost or insurance coverage. | |

## Acceptability
Is the intervention acceptable to key stakeholders?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ No<br>○ Probably no<br>○ Probably yes<br>● Yes<br>○ Varies<br>○ Don't know | <u>Adult Data:</u><br><br>In 167 adult patients with DVT/SVT 81.5% patients preferred oral treatment over injectable treatment mainly due to ease of administration. 8.4% preferred injectable treatments over oral treatmnt mostly due to being more efficent than oral (42.8%). 10.1% had no preference. No difference was found in anticoagulant preference between duration of anticoagulation. (12) In the Netherlands, a study including 135 patients on Warfarin for VTE was carried out. The study employed the "trade-off technique" methodology to ask the patients if they would switch from warfarin dependent on each of the four distinct advantages of DOACs. 65% would switch to DOACs if it resulted in less drug/food interations, 57% for decreased bleeding risk and 36% for no need for laboratory control. (3) | |

## Feasibility
Is the intervention feasible to implement?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ No<br>○ Probably no<br>● Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | No research evidence | Oral medication Versus injectable<br><br>Suspension formula avaliable for infants<br><br>Not all countries have DOACs/or SOC approved for pediatric use |

## SUMMARY OF JUDGEMENTS

| | JUDGEMENT | | | | | | |
|---|---|---|---|---|---|---|---|
| **PROBLEM** | No | Probably no | Probably yes | **Yes** | | Varies | Don't know |
| **DESIRABLE EFFECTS** | Trivial | **Small** | Moderate | Large | | Varies | Don't know |
| **UNDESIRABLE EFFECTS** | Large | Moderate | **Small** | Trivial | | Varies | Don't know |
| **CERTAINTY OF EVIDENCE** | Very low | **Low** | Moderate | High | | | No included studies |
| **VALUES** | Important uncertainty or variability | Possibly important uncertainty or variability | **Probably no important uncertainty or variability** | No important uncertainty or variability | | | |
| **BALANCE OF EFFECTS** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | **Probably favors the intervention** | Favors the intervention | Varies | Don't know |
| **RESOURCES REQUIRED** | Large costs | Moderate costs | Negligible costs and savings | Moderate savings | Large savings | **Varies** | Don't know |
| **CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES** | Very low | Low | Moderate | High | | | **No included studies** |
| **COST EFFECTIVENESS** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **EQUITY** | Reduced | Probably reduced | Probably no impact | Probably increased | Increased | Varies | **Don't know** |
| **ACCEPTABILITY** | No | Probably no | Probably yes | **Yes** | | Varies | Don't know |

| | JUDGEMENT | | | | | | |
|---|---|---|---|---|---|---|---|
| **FEASIBILITY** | No | Probably no | **Probably yes** | Yes | | Varies | Don't know |

## TYPE OF RECOMMENDATION

| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | **Conditional recommendation for the intervention** | Strong recommendation for the intervention |
|---|---|---|---|---|
| ○ | ○ | ○ | ● | ○ |

## CONCLUSIONS

### Recommendation

**The ASH/ISTH guideline panel suggests using DOACs (Rivaroxaban/Dabigatran) over Standard of Care (LMWH, UFH, VKA, Fodaparinux) in pediatric patients with Venous Thromboembolism (VTE) (conditional recommendation based on low certainty in the evidence about effects).**

### Justification

### Subgroup considerations

## Implementation considerations

## Monitoring and evaluation

## Research priorities

# REFERENCES SUMMARY


1. H, Whitworth, L, Raffini. Practical Considerations for Use of Direct Oral Anticoagulants in Children.. Frontiers in pediatrics; 2022.
2. Y, Tian, T, Pan, X, Wen, G, Ao, Y, Ma, X, Liu, R, Liu, H, Ran. Efficacy and Safety of Direct Oral Anticoagulants Compared With Heparin for . Clinical and applied thrombosis/hemostasis : official journal of the ; 2023.
3. PL, Lutsey, KJ, Horvath, L, Fullam, S, Moll, MR, Rooney, M, Cushman, NA, Zakai. Anticoagulant Preferences and Concerns among Venous Thromboembolism Patients.. Thrombosis and haemostasis; 2018.
4. Locadia, M., Bossuyt, P. M., Stalmeier, P. F., Sprangers, M. A., van Dongen, C. J., Middeldorp, S., Bank, I., van der Meer, J., Hamulyak, K., Prins, M. H.. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. Thromb Haemost; Dec 2004.
5. Noble, S., Matzdorff, A., Maraveyas, A., Holm, M. V., Pisa, G.. Assessing patients' anticoagulation preferences for the treatment of cancer-associated thrombosis using conjoint methodology. Haematologica; Nov 2015.
6. Barcellona, D., Contu, P., Sorano, G. G., Pengo, V., Marongiu, F.. The management of oral anticoagulant therapy: the patient's point of view. Thromb Haemost; Jan 2000.
7. O'Meara, J. J.,3rd, McNutt, R. A., Evans, A. T., Moore, S. W., Downs, S. M.. A decision analysis of streptokinase plus heparin as compared with heparin alone for deep-vein thrombosis. N Engl J Med; Jun 30 1994.
8. Robinson, A. M., McLean, K. A., Greaves, M., Channer, K. S.. Subcutaneous versus intravenous administration of heparin in the treatment of deep vein thrombosis; which do patients prefer? A randomized cross-over study. Postgrad Med J; Feb 1993.
9. Attaya, S., Bornstein, T., Ronquillo, N., Volgman, R., Braun, L. T., Trohman, R., Volgman, A.. Study of warfarin patients investigating attitudes toward therapy change (SWITCH Survey). Am J Ther; Nov 2012.
10. Wild, D., Murray, M., Donatti, C.. Patient perspectives on taking vitamin K antagonists: a qualitative study in the UK, USA and Spain. Expert Rev Pharmacoecon Outcomes Res; Oct 2009.
11. Baba, M., Al-Masri, M., Salhab, M., El-Ghanem, M.. Patient's Compliance on the Use of Extended Low Molecular Weight Heparin Post Major Pelvic Surgeries in Cancer Patients at King Hussein Cancer Center. Gulf J Oncolog; Jan 2015.
12. D, Lanéelle, C, Le,Brun, C, Mauger, J, Guillaumat, E, Le,Pabic, L, Omarjee, G, Mahé, Group, SFMV,VTE,Study. Patient Characteristics and Preferences Regarding Anticoagulant Treatment in . Frontiers in cardiovascular medicine; 2021.

# APPENDICES

Appendix 1

**Author(s):**
**Question:** DOAC compared to Standard of Care for Venous Thromboembolism in Pediatric Patients
**Setting:** In-Patient
**Bibliography:**

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | DOAC | Standard of Care | Relative (95% CI) | Absolute (95% CI) | | |
| **Major Bleeding (follow-up: 3 months)** | | | | | | | | | | | | |
| 3[1,2,3] | randomised trials | not serious | not serious | not serious | very serious[a] | none | 4/517 (0.8%) | 5/264 (1.9%) | **RR 0.48** (0.14 to 1.57) | **10 fewer per 1,000** (from 16 fewer to 11 more) | ⨁◯◯◯ Low | CRITICAL |
| **CRNMB (follow-up: 3 months)** | | | | | | | | | | | | |
| 2[2,3] | randomised trials | not serious | not serious | not serious | serious[a] | none | 12/506 (2.4%) | 2/252 (0.8%) | **RR 2.98** (0.67 to 13.27) | **16 more per 1,000** (from 3 fewer to 97 more) | ⨁⨁◯◯ Moderate | CRITICAL |

**CI:** confidence interval; **RR:** risk ratio

**Explanations**

a. Small number of events

**References**


1.Eghbali, Aziz, Rahimi Afzal, Roghayyeh, Sheikhbeygloo, Roya, Eghbali, Aygin, Taherkhanchi, Bahar, Bagheri, Bahador. Dabigatran <em>versus</em> Warfarin for the Treatment of Pediatric Thromboembolism: A Pilot Randomized Trial. Pharm Sci; 2020.
2.C, Male, AWA, Lensing, JS, Palumbo, R, Kumar, I, Nurmeev, K, Hege, D, Bonnet, P, Connor, HL, Hooimeijer, M, Torres, AKC, Chan, G, Kenet, S, Holzhauer, A, Santamaría, P, Amedro, E, Chalmers, P, Simioni, RV, Bhat, DL, Yee, O, Lvova, J, Beyer-Westendorf, TT, Biss, I, Martinelli, P, Saracco, M, Peters, K, Kállay, CA, Gauger, MP, Massicotte, G, Young, AF, Pap, M, Majumder, WT, Smith, JF, Heubach, SD, Berkowitz, K, Thelen, D, Kubitza, M, Crowther, MH, Prins, P, Monagle, Investigators, EINSTEIN-Jr,Phase,3. Rivaroxaban compared with standard anticoagulants for the treatment of acute . The Lancet. Haematology; 2020.
3.J, Halton, LR, Brandão, M, Luciani, L, Bomgaars, E, Chalmers, LG, Mitchell, I, Nurmeev, A, Sharathkumar, P, Svirin, K, Gorbatikov, I, Tartakovsky, M, Simetzberger, F, Huang, Z, Sun, J, Kreuzer, S, Gropper, P, Reilly, M, Brueckmann, M, Albisetti, Investigators, DIVERSITY,Trial. Dabigatran etexilate for the treatment of acute venous thromboembolism in . The Lancet. Haematology; 2021.

Appendix 2

**Author(s):**
**Question:** DOAC compared to Standard of Care for Venous Thromboembolism in Pediatric Patients
**Setting:** In-Patient
**Bibliography:**

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | DOAC | Standard of Care | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality (follow-up: 3 months)** | | | | | | | | | | | | |
| 3[1,2,3] | randomised trials | serious[a] | not serious | not serious | serious[b] | none | 3/522 (0.6%) | 2/267 (0.7%) | **RR 0.71** (0.14 to 3.56) | **2 fewer per 1,000** (from 6 fewer to 19 more) | ⨁◯◯◯ Low | CRITICAL |
| **Recurrence (follow-up: 3 months)** | | | | | | | | | | | | |
| 3[1,2,3] | randomised trials | not serious | not serious | serious[c] | serious[b] | none | 11/523 (2.1%) | 14/267 (5.2%) | **RR 0.43** (0.20 to 0.93) | **30 fewer per 1,000** (from 42 fewer to 4 fewer) | ⨁⨁◯◯ Low | CRITICAL |
| **Resolution (assessed with: Complete and Partial Resolution)** | | | | | | | | | | | | |
| 2[2,3] | randomised trials | not serious | not serious | not serious | serious[d] | none | 395/512 (77.1%) | 181/255 (71.0%) | **RR 1.09** (0.99 to 1.19) | **64 more per 1,000** (from 7 fewer to 135 more) | ⨁⨁⨁◯ Moderate | CRITICAL |
| **Post-thrombotic Syndrome (follow-up: 3 months)** | | | | | | | | | | | | |
| 2[2,3] | randomised trials | serious[a] | not serious | serious[c] | very serious[b] | none | 4/511 (0.8%) | 0/255 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |

**CI:** confidence interval; **RR:** risk ratio

**Explanations**

a. Reporting Bias
b. Small number of events
c. Outcomes assessed at 3 months
d. Wide absolute CI

**References**


1.Eghbali, Aziz, Rahimi Afzal, Roghayyeh, Sheikhbeygloo, Roya, Eghbali, Aygin, Taherkhanchi, Bahar, Bagheri, Bahador. Dabigatran <em>versus</em> Warfarin for the Treatment of Pediatric Thromboembolism: A Pilot Randomized Trial. Pharm Sci; 2020.
2.C, Male, AWA, Lensing, JS, Palumbo, R, Kumar, I, Nurmeev, K, Hege, D, Bonnet, P, Connor, HL, Hooimeijer, M, Torres, AKC, Chan, G, Kenet, S, Holzhauer, A, Santamaría, P, Amedro, E, Chalmers, P, Simioni, RV, Bhat, DL, Yee, O, Lvova, J, Beyer-Westendorf, TT, Biss, I, Martinelli, P, Saracco, M, Peters, K, Kállay, CA, Gauger, MP, Massicotte, G, Young, AF, Pap, M, Majumder, WT, Smith, JF, Heubach, SD, Berkowitz, K, Thelen, D, Kubitza, M, Crowther, MH, Prins, P, Monagle, Investigators, EINSTEIN-Jr,Phase,3. Rivaroxaban compared with standard anticoagulants for the treatment of acute . The Lancet. Haematology; 2020.
3.J, Halton, LR, Brandão, M, Luciani, L, Bomgaars, E, Chalmers, LG, Mitchell, I, Nurmeev, A, Sharathkumar, P, Svirin, K, Gorbatikov, I, Tartakovsky, M, Simetzberger, F, Huang, Z, Sun, J, Kreuzer, S, Gropper, P, Reilly, M, Brueckmann, M, Albisetti, Investigators, DIVERSITY,Trial. Dabigatran etexilate for the treatment of acute venous thromboembolism in . The Lancet. Haematology; 2021.

## QUESTION

| Should Rivaroxaban vs. Standard of Care be used for Venous Thromboembolism in Pediatric Patients? | |
|---|---|
| **POPULATION:** | Venous Thromboembolism in Pediatric Patients |
| **INTERVENTION:** | Rivaroxaban |
| **COMPARISON:** | Standard of Care |
| **MAIN OUTCOMES:** | Mortality - Rivaroxaban; Recurrence of VTE - Rivaroxaban; Resolution - Rivaroxaban; Post-thrombotic Syndrome - Rivaroxaban; Major Bleeding - Rivaroxaban; Clinically Relevant Non-Major Bleed - Rivaroxaban; |
| **SETTING:** | In-Patient |
| **PERSPECTIVE:** | |
| **BACKGROUND:** | |
| **CONFLICT OF INTEREST:** | Anthony Chan<br>Christoph Male<br>Paul Monagle<br>Leonardo Brandao |

## ASSESSMENT

### Problem
Is the problem a priority?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ No<br>○ Probably no<br>○ Probably yes<br>● Yes<br>○ Varies<br>○ Don't know | Direct Oral Anticoagulants (DOACs) have become the preferred choice of oral anticoagulation in adults due to multiple trials showing higher efficacy, less bleeding and no required monitoring (1)(2). In the ASH 2018 guideline for pediatric VTE, an a priori decision was made to not address the use of DOACs over other treatment modalities due to the limited evidence at the time. However, with the emergence of numerous studies comparing the use of DOACs versus other anticoagulants in the pediatric population, the comparison between these medications is of importance. | |

### Desirable Effects
How substantial are the desirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ Trivial<br>● Small<br>○ Moderate<br>○ Large<br>○ Varies<br>○ Don't know | *See Appendix 2* | |

## Undesirable Effects

How substantial are the undesirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ Large<br>○ Moderate<br>● Small<br>○ Trivial<br>○ Varies<br>○ Don't know | *See Appendix 1* | |

## Certainty of evidence

What is the overall certainty of the evidence of effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ Very low<br>● Low<br>○ Moderate<br>○ High<br>○ No included studies | Certainty of the evidence of effects was judged as 'Low - Moderate' due to imprecision. | |

## Values

Is there important uncertainty about or variability in how much people value the main outcomes?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|

| | | |
|---|---|---|
| ○ Important uncertainty or variability<br>○ Possibly important uncertainty or variability<br>● Probably no important uncertainty or variability<br>○ No important uncertainty or variability | We did not identify utility related information or non-utility information for the outcomes of interest specific to the pediatric population in the literature.<br><br>**Results from Panel Members' Utility Rating Survey:** Utilities rated on the visual analog scale, where 0 represents death and 1 represents full health, were as follows:<br><br>Pulmonary embolism – Severe marker state: 0.31 Pulmonary embolism – Moderate marker state: 0.49 Deep vein thrombosis (proximal) – Severe marker state: 0.49<br><br>Deep vein thrombosis (proximal) – Moderate marker state: 0.61<br><br>Deep vein thrombosis (distal) – Severe marker state: 0.56<br><br>Deep vein thrombosis (distal) – Moderate marker state: 0.68<br><br>Major bleeding: 0.30 Neonatal Bleeding – Severe: 0.30<br><br>Infant Bleeding – Severe: 0.26<br><br>Our systematic review for the adult population found that the relative importance of the outcomes is as follows: Pulmonary embolism: 0.63-0.93 (different methods) (Hogg et al., 2014, Hogg et al., 2013, Locadia et al., 2004) Deep vein thrombosis: 0.64-0.99 (different methods) (Hogg et al., 2014, Hogg et al., 2013, Locadia et al., 2004)(Marvig et al., 2015)(Utne et al., 2016) Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) (Hogg et al., 2013, Locadia et al., 2004) Muscular bleeding: 0.76 (time trade off) (Locadia et al., 2004) Minor intracranial bleeding event: 0.75 (standard gamble) (Hogg et al., 2013) Major intracranial bleeding event: 0.15 (standard gamble) (Hogg et al., 2013) Central nervous system bleeding: 0.29-0.60 (standard gamble) (Lenert et al., 1997)(O'Meara et al., 1994) Treatment with LMWH: 0.993 (time trade off) (Marchetti et al., 2001) Treatment with warfarin (as a surrogate): 0.989 (time trade off) (Marchetti et al., 2001)<br><br>**Anticoagulant therapy**<br><br>In an cross-sectional study utilizing online support groups for Adult VTE patients, out of 521 patients, extreme concern was mostly expressed for recurrent VTE (33%) and mortality (29%), followed by major bleeding (21%), moderate bleeding (16%) (3)<br><br>Adult patients highly value the benefits of risk reduction in VTE recurrence and post-thrombosis syndrome (4). Patients would favor efficacy and safety over convenience of route of administration (5). Further, patients would like to avoid adverse events but most of them are “not afraid of” the adverse events (6)(5)(7). For anticoagulant therapy in general, most patients would prefer the oral doses compared with injections, this is mainly because of treatment burden due to injection. For patients with venographically proven deep venous thrombosis, 15 of | |

| | | |
|---|---|---|
| | the 19 patients expressed a preference for the subcutaneous route for administration of heparin over intravenous administration(8).<br><br>**Warfarin** Adult patients would like to switch to another anticoagulant if it is as effective as warfarin; this is mainly due to the treatment burden associated with monitoring, injection and dietary change due to warfarin use. In another study approximately half of the patients did not consider VKA therapy particularly difficult to manage. (9)(10) **LMWH** For adult patients receiving low molecular weight heparin, patients placed a high score on "importance of ease of use", "expectations of symptom relief", and "confidence in the treatment to prevent blood clots" while they had a low score of treatment-related side effects (bruise, bleeding). (11)<br><br>**DOAC**<br><br>According to a systematic review for adult patients comparing DOACs to LMWH, DOACs was found to have a better effect in preventing thromboembolism, and less bleeding (2). Similar findings were seen comparing DOACs to Warfarin. | |

## Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>● Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>○ Don't know | | Desirable effects were judged to be:<br><br>Undesirable effects were judged to be: |

## Resources required

How large are the resource requirements (costs)?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|

| | | |
|---|---|---|
| ○ Large costs<br>○ Moderate costs<br>○ Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br>● Varies<br>○ Don't know | Found in Table | |

## Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ Very low<br>○ Low<br>○ Moderate<br>○ High<br>● No included studies | No research evidence was found (based on database estimates) | |

## Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>● No included studies | We did not identify cost effectiveness studies for pediatric VTE.<br><br><u>Adult Cost effectiveness studies:</u><br><br>In a study investigating the cost effectiveness of rivaroxaban as compared to enoxaparin + VKA for the treatment of DVT/PE at 3, 6, or 12 month durations from a | |

| | | |
|---|---|---|
| | US payer perspective; Rivaroxaban was shown to be dominant (less costly, more effective) **(Lefebvre, 2014)**. Peacock et al. showed Rivaroxaban to have a lower total cost as compared to low-molecular-weight heparin, unfractionated heparin, warfarin in low risk PE. **(Peacock,2019)** Based on a cost effectiveness study from the REMOTEV Registry, rivaroxaban was found to be an effective, safe and less costly alternative for warfain. **(Kepka,2023)**<br><br>Similarly, a study in greece comparing the cost of Rivaroxaban in comparison to SOC "enoxaparin followed by dose-adjusted vitamin-K antagonists" for DVT and PE. For 3 and 6 month duration, rivaroxaban was found to be less costly and more effective in DVT and cost effective in PE **(Gourzoulidis, 2017)**.In Spain, for patients with cancer associated thrombosis, DOACs including Rivaroxaban was found to be cost-effective and cost-saving as compared to LMWH in VTE. **(Muñoz, 2022)** In China, Rivaroxaban resulted in cost saving compared with enoxaparin/warfarin for treatment of acute DVT. **(Yang, 2020)** Similar findings in China were found by Sun et al. **(Sun, 2021)**<br><br>In Thailand, at a willing-to-pay of $5003, DOACs were found to be not cost-effective in comparison to warfarin in VTE. **(Niyomsri,2023)** | |

## Equity
What would be the impact on health equity?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ Reduced<br>○ Probably reduced<br>○ Probably no impact<br>○ Probably increased<br>○ Increased<br>○ Varies<br>● Don't know | Various studies have shown a difference in prescription patterns for DOACs versus other anticoagulants in VTE and Atrial Fibrillation based on Ethnicity and Socioeconomic Status. **(Nathan, 2019)(Essien,2021)** However these differences could not be explained cost or insurance coverage. | |

## Acceptability
Is the intervention acceptable to key stakeholders?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ No | In 167 adult patients with DVT/SVT 81.5% patients preferred oral treatment over | |

| | | |
|---|---|---|
| ○ Probably no<br>○ Probably yes<br>● Yes<br>○ Varies<br>○ Don't know | injectable treatment mainly due to ease of administration. 8.4% preferred injectable treatments over oral treatmnt mostly due to being more efficent than oral (42.8%). 10.1% had no preference. No difference was found in anticoagulant preference between duration of anticoagulation. (12)<br><br>In the Netherlands, a study including 135 patients on Warfarin for VTE was carried out. The study employed the "trade-off technique" methodology to ask the patients if they would switch from warfarin dependent on each of the four distinct advantages of DOACs. 65% would switch to DOACs if it resulted in less drug/food interations, 57% for decreased bleeding risk and 36% for no need for laboratory control. (3) | |

## Feasibility

Is the intervention feasible to implement?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ No<br>○ Probably no<br>● Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | No research evidence | Oral medication Versus injectable<br><br>Suspension formula avaliable for infants<br><br>Not all countries have DOACs approved for pediatric use |

## SUMMARY OF JUDGEMENTS

| | JUDGEMENT | | | | | | |
|---|---|---|---|---|---|---|---|
| **PROBLEM** | No | Probably no | Probably yes | **Yes** | | Varies | Don't know |
| **DESIRABLE EFFECTS** | Trivial | **Small** | Moderate | Large | | Varies | Don't know |
| **UNDESIRABLE EFFECTS** | Large | Moderate | **Small** | Trivial | | Varies | Don't know |
| **CERTAINTY OF EVIDENCE** | Very low | **Low** | Moderate | High | | | No included studies |
| **VALUES** | Important uncertainty or variability | Possibly important uncertainty or variability | **Probably no important uncertainty or** | No important uncertainty or variability | | | |

| | JUDGEMENT | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | **variability** | | | | |
| **BALANCE OF EFFECTS** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | **Probably favors the intervention** | Favors the intervention | Varies | Don't know |
| **RESOURCES REQUIRED** | Large costs | Moderate costs | Negligible costs and savings | Moderate savings | Large savings | **Varies** | Don't know |
| **CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES** | Very low | Low | Moderate | High | | | **No included studies** |
| **COST EFFECTIVENESS** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **EQUITY** | Reduced | Probably reduced | Probably no impact | Probably increased | Increased | Varies | **Don't know** |
| **ACCEPTABILITY** | No | Probably no | Probably yes | **Yes** | | Varies | Don't know |
| **FEASIBILITY** | No | Probably no | **Probably yes** | Yes | | Varies | Don't know |

## TYPE OF RECOMMENDATION

| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | **Conditional recommendation for the intervention** | Strong recommendation for the intervention |
|---|---|---|---|---|
| ○ | ○ | ○ | ● | ○ |



## CONCLUSIONS

**Recommendation**

**The ASH/ISTH guideline panel suggests using Rivaroxaban over Standard of Care (LMWH, UFH, VKA, Fodaparinux) in pediatric patients with Venous Thromboembolism (VTE) (conditional recommendation based on very low certainty in the evidence about effects).**

## Justification

## Subgroup considerations

## Implementation considerations

## Monitoring and evaluation

## Research priorities

# REFERENCES SUMMARY


1. H, Whitworth, L, Raffini. Practical Considerations for Use of Direct Oral Anticoagulants in Children.. Frontiers in pediatrics; 2022.
2. Y, Tian, T, Pan, X, Wen, G, Ao, Y, Ma, X, Liu, R, Liu, H, Ran. Efficacy and Safety of Direct Oral Anticoagulants Compared With Heparin for . Clinical and applied thrombosis/hemostasis : official journal of the ; 2023.
3. PL, Lutsey, KJ, Horvath, L, Fullam, S, Moll, MR, Rooney, M, Cushman, NA, Zakai. Anticoagulant Preferences and Concerns among Venous Thromboembolism Patients.. Thrombosis and haemostasis; 2018.
4. Locadia, M., Bossuyt, P. M., Stalmeier, P. F., Sprangers, M. A., van Dongen, C. J., Middeldorp, S., Bank, I., van der Meer, J., Hamulyak, K., Prins, M. H.. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. Thromb Haemost; Dec 2004.
5. Noble, S., Matzdorff, A., Maraveyas, A., Holm, M. V., Pisa, G.. Assessing patients' anticoagulation preferences for the treatment of cancer-associated thrombosis using conjoint methodology. Haematologica; Nov 2015.
6. Barcellona, D., Contu, P., Sorano, G. G., Pengo, V., Marongiu, F.. The management of oral anticoagulant therapy: the patient's point of view. Thromb Haemost; Jan 2000.
7. O'Meara, J. J.,3rd, McNutt, R. A., Evans, A. T., Moore, S. W., Downs, S. M.. A decision analysis of streptokinase plus heparin as compared with heparin alone for deep-vein thrombosis. N Engl J Med; Jun 30 1994.
8. Robinson, A. M., McLean, K. A., Greaves, M., Channer, K. S.. Subcutaneous versus intravenous administration of heparin in the treatment of deep vein thrombosis; which do patients prefer? A randomized cross-over study. Postgrad Med J; Feb 1993.
9. Attaya, S., Bornstein, T., Ronquillo, N., Volgman, R., Braun, L. T., Trohman, R., Volgman, A.. Study of warfarin patients investigating attitudes toward therapy change (SWITCH Survey). Am J Ther; Nov 2012.
10. Wild, D., Murray, M., Donatti, C.. Patient perspectives on taking vitamin K antagonists: a qualitative study in the UK, USA and Spain. Expert Rev Pharmacoecon Outcomes Res; Oct 2009.
11. Baba, M., Al-Masri, M., Salhab, M., El-Ghanem, M.. Patient's Compliance on the Use of Extended Low Molecular Weight Heparin Post Major Pelvic Surgeries in Cancer Patients at King Hussein Cancer Center. Gulf J Oncolog; Jan 2015.
12. D, Lanéelle, C, Le,Brun, C, Mauger, J, Guillaumat, E, Le,Pabic, L, Omarjee, G, Mahé, Group, SFMV,VTE,Study. Patient Characteristics and Preferences Regarding Anticoagulant Treatment in . Frontiers in cardiovascular medicine; 2021.

# APPENDICES

Appendix 1

**Author(s):**
**Question:** Rivaroxaban compared to Standard of Care for Venous Thromboembolism in Pediatric Patients
**Setting:** In-Patient
**Bibliography:** American Society of Hematology 2024 Guidelines for Management of Venous Thromboembolism: Treatment of Pediatric Venous Thromboembolism

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Rivaroxaban | Standard of Care | Relative (95% CI) | Absolute (95% CI) | | |
| **Major Bleeding - Rivaroxaban (follow-up: 3 months)** | | | | | | | | | | | | |
| 1[1] | randomised trials | not serious | not serious | not serious | very serious[a] | none | 0/329 (0.0%) | 2/162 (1.2%) | not estimable | | ⨁⨁◯◯ Low | CRITICAL |
| **Clinically Relevant Non-Major Bleed - Rivaroxaban (follow-up: 3 months)** | | | | | | | | | | | | |
| 1[1] | randomised trials | not serious | not serious | not serious | serious[a] | none | 10/329 (3.0%) | 1/162 (0.6%) | **RR 4.92** (0.64 to 38.13) | **24 more per 1,000** (from 2 fewer to 229 more) | ⨁⨁⨁◯ Moderate | CRITICAL |

**CI:** confidence interval; **RR:** risk ratio

**Explanations**

a. Imprecision due to small number of patients with events in the included studies.

**References**

1.C, Male, AWA, Lensing, JS, Palumbo, R, Kumar, I, Nurmeev, K, Hege, D, Bonnet, P, Connor, HL, Hooimeijer, M, Torres, AKC, Chan, G, Kenet, S, Holzhauer, A, Santamaría, P, Amedro, E, Chalmers, P, Simioni, RV, Bhat, DL, Yee, O, Lvova, J, Beyer-Westendorf, TT, Biss, I, Martinelli, P, Saracco, M, Peters, K, Kállay, CA, Gauger, MP, Massicotte, G, Young, AF, Pap, M, Majumder, WF, Smith, JF, Heubach, SD, Berkowitz, K, Thelen, D, Kubitza, M, Crowther, MH, Prins, P, Monagle, Investigators, EINSTEIN-Jr,Phase,3. Rivaroxaban compared with standard anticoagulants for the treatment of acute . The Lancet. Haematology; 2020.

Appendix 2

**Author(s):**
**Question:** Rivaroxaban compared to Standard of Care for Venous Thromboembolism in Pediatric Patients
**Setting:** In-Patient
**Bibliography:** American Society of Hematology 2024 Guidelines for Management of Venous Thromboembolism: Treatment of Pediatric Venous Thromboembolism

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Rivaroxaban | Standard of Care | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality - Rivaroxaban (follow-up: 3 months; assessed with: All Cause Mortality)** | | | | | | | | | | | | |
| 1[1] | randomised trials | not serious | not serious | not serious | very serious[a] | none | 1/335 (0.3%) [b] | 0/165 (0.0%) | not estimable | | ⨁⨁◯◯ Low | CRITICAL |
| **Recurrence of VTE - Rivaroxaban (follow-up: 3 months)** | | | | | | | | | | | | |
| 1[1] | randomised trials | not serious | not serious | serious[c] | serious[a] | none | 4/335 (1.2%) | 5/165 (3.0%) | **RR 0.39** (0.11 to 1.45) | **18 fewer per 1,000** (from 27 fewer to 14 more) | ⨁⨁◯◯ Low | CRITICAL |
| **Resolution - Rivaroxaban (follow-up: 3 months; assessed with: Complete and Partial Resolution)** | | | | | | | | | | | | |
| 1[1] | randomised trials | not serious | not serious | not serious | serious[d] | none | 257/335 (76.7%) | 118/165 (71.5%) | **RR 1.07** (0.96 to 1.20) | **50 more per 1,000** (from 29 fewer to 143 more) | ⨁⨁⨁◯ Moderate | CRITICAL |
| **Post-thrombotic Syndrome - Rivaroxaban (follow-up: 3 months)** | | | | | | | | | | | | |
| 1[1] | randomised trials | not serious | not serious | serious[e] | very serious[a] | none | 2/335 (0.6%) | 0/165 (0.0%) | not estimable | | ⨁◯◯◯ Very low | CRITICAL |

**CI:** confidence interval; **RR:** risk ratio

**Explanations**

a. Imprecision due to small number of patients with events in the included studies.
b. The patient that died were was not due to therapy or VTE related causes.
c. Recurrence of venous thromboembolisms may occur after long term follow-up. Indirectness was judged to be serious since the outcome (recurrence) was evaluated at 3 months.
d. Wide Absolute 95% Confidence Interval, ranging from an effect to an effect
e. Post-thrombotic syndrome may occur after long term follow-up. Indirectness was judged to be serious since the outcome (PTS) was evaluated at 3 months.

**References**

1.C, Male, AWA, Lensing, JS, Palumbo, R, Kumar, I, Nurmeev, K, Hege, D, Bonnet, P, Connor, HL, Hooimeijer, M, Torres, AKC, Chan, G, Kenet, S, Holzhauer, A, Santamaría, P, Amedro, E, Chalmers, P, Simioni, RV, Bhat, DL, Yee, O, Lvova, J, Beyer-Westendorf, TT, Biss, I, Martinelli, P, Saracco, M, Peters, K, Kállay, CA, Gauger, MP, Massicotte, G, Young, AF, Pap, M, Majumder, WF, Smith, JF, Heubach, SD, Berkowitz, K, Thelen, D, Kubitza, M, Crowther, MH, Prins, P, Monagle, Investigators, EINSTEIN-Jr,Phase,3. Rivaroxaban compared with standard anticoagulants for the treatment of acute . The Lancet. Haematology; 2020.

## Overarching question: Rivaroxaban Vs Dabigatran

**Question 1:**Should Rivaroxaban vs. Standard of Care be used for Venous Thromboembolism in Pediatric Patients?

**Question 2:**Should Dabigatran vs. Standard of Care be used for Venous Thromboembolism in Pediatric Patients?

## Summary of judgements

| | Rivaroxaban/Standard of Care | Dabigatran/Standard of Care | Importance for decision |
|---|---|---|---|
| **Balance of effects** | Probably favors the intervention | Probably favors the intervention | **high** |
| **Certainty of evidence** | Low | Very low | |
| **Resources required** | Varies | Varies | **moderate** |
| **Cost effectiveness** | No included studies | No included studies | **low** |
| **Equity** | Don't know | Don't know | **low** |
| **Acceptability** | Yes | Yes | **high** |
| **Feasibility** | Probably yes | Probably yes | **high** |

## Review

| | Rivaroxaban | Dabigatran | Importance for decision | Comment |
|---|---|---|---|---|
| **Balance of effects** | ★★★★ | ★★★ | **high** | |
| **Resources required** | ★★★★ | ★★★★ | **moderate** | |
| **Cost effectiveness** | ★★★★ | ★★★★ | **low** | |
| **Equity** | ★★★ | ★★★ | **low** | |
| **Acceptability** | ★★★★ | ★★★★ | **high** | |
| **Feasibility** | ★★★★ | ★★★★ | **high** | |

| | |
|---|---|
| **Recommendation** | The ASH/ISTH panel suggests using **either Rivaroxaban or Dabigatran** in pediatric patients with Venous Thromboembolism (VTE) there may be individual populations/co-morbidities or jurisdictional avalibility that would lead clinicans to choose one over the other (reference table). |
| **Strength of recommendation Conditional** | |
| **Justification** | |
| **Subgroup considerations** | |
| **Implementation considerations** | |
| **Monitoring and evaluation** | |

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|---|---|
| **Research priorities** | |