Effective Health Care

Antithrombotics in Children

Results of Topic Selection Process & Next Steps

The American College of Chest Physicians (ACCP) is interested in a new evidence review on prevention and treatment of thrombosis in neonates and children to inform an update of their 2012 clinical practice guideline.

Because limited original research addresses the nomination, a new review is not feasible at this time. No further activity on this nomination will be undertaken by the Effective Health Care (EHC) Program.

Topic Brief

Topic Name: Antithrombotics in Children

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Conflict of Interest: None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report

Summary

- This nomination meets the selection criteria of appropriateness and importance, and impact.
- The nomination partly meets duplication. Eleven relevant systematic reviews cover portions of the scope.
- A new review is not feasible. Ten studies were identified of a range of study types including RCT, case series and case studies.

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Background

A variety of conditions can increase risk of thrombosis in children, either as a result of the underlying medical issue or as an adverse effect of treatment.

For example, children when hospitalized often require vascular access to deliver medications intravenously and also for drawing blood.[1] Options include peripherally placed catheters, and central venous access devices such as peripherally inserted catheters (PICC) and umbilical artery catheters. Complications are infection and thrombosis More than 3.5 patients per 10,000 hospital admissions develop catheter-related deep vein thrombosis.[2] Catheter-related occlusions can occur in as many as 25% of lines placed in children.[3]

Management is aimed at prevention of thrombosis, and treatment when it occurs. Multiple options are available. Choice depends on a variety of factors such as benefits and harms, age, underlying condition, and duration of time of the condition. Preventive interventions include unfractionated heparin, low molecular weight heparin (LMWH), vitamin K antagonist (VKA), and antiplatelet drugs, such as aspirin. Treatment interventions include high dose heparin or low molecular weight heparin; thrombolytics; and thrombectomy.

Despite the range of available options, due to the limited evidence many recommendations about use of interventions in children are based on extrapolation from adults and which may be inappropriate.[4]

The American College of Chest Physicians nominated this topic to inform an update of their 2012 guideline.[4]

Nominator and Stakeholder Engagement: We reviewed the key questions and PICOTS with the nominator. After consultation, the questions related to infective endocarditis, cardiac catheterization, and use of intravenous immunoglobulin and aspirin for Kawasaki Disease were excluded from the scope.

The key questions for this nomination are:

KQ 1: In children with deep vein thrombosis (DVT) or pulmonary embolus (PE), what is the effectiveness and harms of treatments?

KQ 2: What is the effectiveness and harms of anticoagulants for

a. Neonates with acute ischemic stroke (AIS) and documented cardioembolic source?
b. Neonates with recurrent AIS
c. Children with AIS with undetermined cause
d. Children with AIS and in situ thrombosis
e. Children with AIS and thrombophilia
f. Children with AIS and documented cardioembolic source
g. Children with AIS and dissection
h. Children with AIS and vasculopathy
i. Children with AIS and moyamoya

KQ 3: In neonates with femoral artery thrombosis, what are the effectiveness and harms of anticoagulants to treat thrombosis?

KQ 4: In neonates with aortic thrombosis, what are the effectiveness and harms of anticoagulants?

KQ 5: what is the effectiveness of treatments for renal vein thrombosis in neonates?

KQ 6: what is the effectiveness of treatments for cerebral sinovenous thrombosis in children?

KQ 7. What is the effectiveness of treatments for right atrial thrombosis in children?

KQ 8: In neonates with purpura fulminans what is the effectiveness and harms of fresh frozen plasma compared to anticoagulation?

KQ 9 In children with Kawasaki disease what are the effectiveness and harms of interventions to
a. Prevent thrombosis?
b. Treat thrombosis?

KQ 10: In children with dilated cardiomyopathy what are the effectiveness and harms of anticoagulants to prevent thrombosis?

KQ 11: In children with primary pulmonary hypertension what are the effectiveness and harms of anticoagulants to prevent thrombosis?

KQ 12: In children with sickle cell disease what is the effectiveness of
a. Exchange transfusion to treat acute ischemic stroke?
b. Chronic transfusion program to prevent acute ischemic stroke?

KQ 13: In neonates with a Blalock-Taussig shunt, what is the effectiveness and harms of anticoagulants
a. To prevent thrombosis?
b. To treat thrombosis?

KQ 14: In neonates with Stage 1 Norwood, what are the effectiveness and harms of anticoagulants to prevent thrombosis?

KQ 15: In children with Glenn or bilateral cavo pulmonary shunt what are the effectiveness and harms of anticoagulants to prevent thrombosis?

KQ 16: In children with Fontan surgery what are the effectiveness and harms of anticoagulants to prevent thrombosis?

KQ 17: What is the effectiveness and harms of anticoagulants to prevent thrombosis in children with
a. Biologic prosthetic heart valve
b. Mechanical prosthetic heart valve

KQ 18: In children with endovascular stents what are the effectiveness and harms of anticoagulants to prevent thrombosis?

KQ 19: In children with ventricular assist devices what are the effectiveness and harms of anticoagulants to prevent thrombosis?

KQ 20: What are the effectiveness and harms of anticoagulants to prevent thrombosis in children with
a. Arteriovenous fistula for hemodialysis access
b. CVAD for hemodialysis access

KQ 21: In neonates with peripheral arterial catheters what are the effectiveness and harms of anticoagulants
a. To prevent thrombosis?
b. To treat thrombosis?

KQ 22: What is the effectiveness and harms of anticoagulants to prevent central venous access device (CVAD) thrombosis in
a. Neonates
b. Children
c. Children with short to medium term need for CVAD
d. Children with long-term need for CVAD

KQ 23: In neonates with umbilical artery catheters what are the effectiveness and harms of anticoagulants to prevent thrombosis?

See Appendix A for KQ and PICOTS.

Methods

We assessed nomination, Antithrombotics in Children, for priority for a systematic review or other AHRQ EHC report with a hierarchical process using established selection criteria (Appendix A). Assessment of each criteria determined the need for evaluation of the next one.

1. Determine the *appropriateness* of the nominated topic for inclusion in the EHC program.
2. Establish the overall *importance* of a potential topic as representing a health or healthcare issue in the United States.
3. Determine the *desirability of new evidence review* by examining whether a new systematic review or other AHRQ product would be duplicative.
4. Assess the *potential impact* a new systematic review or other AHRQ product.
5. Assess whether the *current state of the evidence* allows for a systematic review or other AHRQ product (feasibility).
6. Determine the *potential value* of a new systematic review or other AHRQ product.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

Desirability of New Review/Duplication

We searched for high-quality, completed or in-process evidence reviews published in the last three years on the key questions of the nomination. See Appendix B for sources searched.

Impact of a New Evidence Review

The impact of a new evidence review was qualitatively assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was possible for a review to influence the current practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.).

Feasibility of New Evidence Review

We conducted a literature search in PubMed from February 2013 to February 2018. See Appendix C for the PubMed search strategy and links to the ClinicalTrials.gov search.

Compilation of Findings

We constructed a table with the selection criteria and our assessments (Appendix A).

Results

Appropriateness and Importance

This is an appropriate and important topic.

Desirability of New Review/Duplication

A new evidence review would partly duplicate existing reviews (Table 2). Six systematic reviews cover:

- Renal vein thrombosis (KQ 5)[5, 6]
- Cerebral sinovenous thrombosis (KQ 6)[5, 6]
- Right atrial thrombosis (KQ 7)[6]
- Sickle cell disease (KQ 12)[7, 8]
- Norwood procedure (KQ 14)[9]
- Glenn or bilateral cavopulmonary shunt (KQ 15)[9]
- Fontan surgery (KQ 16)[9]
- Umbilical artery catheter (KQ 23), prevention of thrombosis with anticoagulants[10]

Eight systematic reviews are partially duplicative. These cover:

- Anticoagulation for DVT and PE treatment (KQ 1)[5]
- Acute ischemic stroke treatment (KQ 2) in children[11]
- Femoral artery thrombosis treatment (KQ 3) with heparin and low molecular weight heparin[6]
- Purpura fulminans (KQ 8) treatment with protein C[5]
- Central venous access device (KQ 22), prevention of thrombosis with anticoagulants[10, 12-15]

We identified one review potentially applicable to hemodialysis access (KQ 19)[16]; however due to limited detail about the scope, this was not considered duplicative.

Table 2. Key Questions and Duplication Results

Key Question	Duplication (2/2015-2/2018)
KQ 1: DVT or PE treatment	Total number of systematic reviews: 1 • In-process SR: 1[5]
KQ 2: Acute ischemic stroke, treatment	Total number of systematic reviews: 1 • SR:1[11]
KQ 3: Femoral artery thrombosis, treatment	Total number of systematic reviews: 1 • SR: 1[6]
KQ 4: Aortic thrombosis, treatment	Total number of systematic reviews: 0
KQ 5: Renal vein thrombosis, treatment	Total number of systematic reviews: 2 • In-process SR: 1[5] • SR: 1[6]
KQ 6: Cerebral sinovenous thrombosis, treatment	Total number of systematic reviews: 2 • In-process SR: 1[5] • SR: 1[6]
KQ 7: Right atrial thrombosis, treatment	Total number of systematic reviews: 1 • In-process SR: 1[5]
KQ 8: Purpura fulminans, treatment	Total number systematic reviews: 1 • In-process SR: 1[5]
KQ 9: Kawasaki disease, prevention and treatment	Total number of systematic reviews: 0
KQ 10: Dilated cardiomyopathy, prevention	Total number of systematic reviews: 0
KQ 11: Primary pulmonary hypertension, prevention	Total number of systematic reviews: 0
KQ 12: Sickle cell, prevention and treatment of acute ischemic stroke	Total number of systematic reviews: 1 • In-process SR: 1[7, 8]
KQ 13: Blalock-Taussig shunt: prevention and treatment of thrombosis	Total number of systematic reviews: 0
KQ 14: Norwood stage 1, prevention	Total number of systematic reviews: 1 • SR: 1[9]
KQ 15: Glenn or bilateral cavopulmonary shunt, prevention	Total number of systematic reviews: 1 • SR: 1[9]
KQ 16: Fontan surgery, prevention	Total number of systematic reviews: 1 • SR: 1[9]
KQ 17: Prosthetic valves, prevention	Total number of systematic reviews: 0
KQ 18: Endovascular stents, prevention	Total number of systematic reviews: 0
KQ 19: Ventricular assist device, prevention	Total number of systematic reviews: 0
KQ 20: Hemodialysis access, prevention	Total number of systematic reviews: 1 • SR: 1[16]
KQ 21: Peripheral arterial catheter, prevention and treatment	Total number of systematic reviews: 0
KQ 22: Central venous access device, prevention	Total number of systematic reviews: 5 • SR: 5[10, 12-15]

Key Question	Duplication (2/2015-2/2018)
KQ 23: Umbilical artery catheter, prevention	Total number of systematic reviews: 1 • SR: 1[10]

Abbreviations: AHRQ=Agency for Healthcare Research and Quality; KQ=Key Question; SR=systematic review; DVT=deep vein thrombosis; PE=pulmonary embolus;

Impact of a New Evidence Review

A new systematic review may have high impact. The guidance available for many areas of the nomination have limited evidence and are supported by consensus.

Feasibility of a New Evidence Review

A new evidence review examining is not feasible. For the remaining 14 KQ, we identified ten studies addressing five KQ (Table 3), and all but two were non-comparative studies. Study types included: case studies (3), case series (3), RCT (1), retrospective analysis (2), and cross-over study (1). At most two studies were identified for a single key question.

Table 3: Key Questions and Feasibility Results

Key Question	Feasibility (2/2013-2/2018)
KQ 1: DVT or PE treatment with interventional radiology and surgical procedures	Size/scope of review Relevant Studies Identified: 0 Clinicaltrials.gov: 0
KQ 2: Acute ischemic stroke, treatment in neonates	Size/scope of review Relevant Studies Identified: 0 Clinicaltrials.gov: 0
KQ 3: Femoral artery thrombosis, treatment with thrombectomy and thrombolysis	Size/scope of review Relevant Studies Identified: 0 Clinicaltrials.gov: 0
KQ 4: Aortic thrombosis, treatment	Size/scope of review Relevant Studies Identified: 2 • Case study, 2[17, 18] Clinicaltrials.gov: 0
KQ 8: Purpura fulminans, treatment with FFP	Size/scope of review Relevant Studies Identified: 0 Clinicaltrials.gov: 0
KQ 9: Kawasaki disease, prevention and treatment	Size/scope of review Relevant Studies Identified: 2 • Case study[19] • Case series[20, 21] Clinicaltrials.gov: 0
KQ 10: Dilated cardiomyopathy, prevention	Size/scope of review Relevant Studies Identified: 0 Clinicaltrials.gov: 0
KQ 11: Primary pulmonary hypertension, prevention	Size/scope of review Relevant Studies Identified: 0 Clinicaltrials.gov: 0
KQ 13: Blalock-Taussig shunt: prevention and treatment of thrombosis	Size/scope of review Relevant Studies Identified: 0 Clinicaltrials.gov: 0
KQ 17: Prosthetic valves, prevention	Size/scope of review Relevant Studies Identified: 0 Clinicaltrials.gov: 0

Key Question	Feasibility (2/2013-2/2018)
KQ 18: Endovascular stents, prevention	Size/scope of review Relevant Studies Identified: 0 Clinicaltrials.gov: 0
KQ 19: Ventricular assist device, prevention	Size/scope of review Relevant Studies Identified: 1 • Case series, 1[22] Clinicaltrials.gov: 0
KQ 20: Hemodialysis access, prevention	Size/scope of review Relevant Studies Identified: 2 • Cross-over, 1[23] • Case series, 1[24] Clinicaltrials.gov: 0
KQ 21: Peripheral arterial catheter, prevention and treatment	Size/scope of review Relevant Studies Identified: 2 • RCT, 1[25] • Case series, 1[26] Clinicaltrials.gov: 0
KQ 22: Central venous Access Device, prevention with thrombolysis	Size/scope of review Relevant Studies Identified: 0 Clinicaltrials.gov: 0

Abbreviations: AHRQ=Agency for Healthcare Research and Quality; KQ=Key Question; SR=systematic review; DVT=deep vein thrombosis; PE=pulmonary embolus;

Summary of Findings

- Appropriateness and importance: The topic is both appropriate and important.
- Duplication: A new review would be partly duplicative of an existing product. We found 11 reviews that covered portions of the nomination.
- Impact: A new systematic review has high potential. The guidance for many areas of the nomination have limited evidence and are supported by consensus.
- Feasibility: A new review is not feasible. The evidence base is likely small, with at most two studies identified for a KQ. In total we identified 10 studies across the remaining five of the 14 remaining KQ.

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Appendix A: KQ and PICOTS

KQ 1: In children with deep vein thrombosis (DVT) or pulmonary embolus (PE), what is the effectiveness and harms of treatments?

Population	Intervention	Comparator	Outcome
Children 28 days to 18 years with DVT or PE Subgroups: children with central venous access device (CVAD), children with central venous line (CVL)	• Anticoagulation • Interventional radiology • Surgical stenting, dilatation or bypass	• No therapy, • other included intervention	• Mortality • Extension of thrombus • Primary Pulmonary embolus • Paradoxical stroke • Postthrombotic syndrome • Recurrence (Deep Vein Thrombosis (DVT) or Pulmonary Embolism (PE)) • Hemorrhage (major and central nervous system (CNS)) • Harms of intervention
Children 28 days to 18 years with DVT or PE Subgroups: children with central venous access device (CVAD), children with central venous line (CVL)	• Systemic thrombolysis • Local thrombolysis • Thrombectomy • Inferior vena cava filter	• Anticoagulation	• Mortality • Extension of thrombus • Primary Pulmonary embolus • Paradoxical stroke • Postthrombotic syndrome • Recurrence (DVT or PE) • Hemorrhage (major and CNS) Harms of intervention
Children 28 days to 18 years with DVT or PE Subgroups: children with central venous access device (CVAD), children with central venous line (CVL)	• Anticoagulation with heparin or low-molecular weight heparin	• Vitamin K antagonist	• Mortality • Extension of thrombus • Primary Pulmonary embolus • Paradoxical stroke • Postthrombotic syndrome • Recurrence (DVT or PE) • Hemorrhage (major and CNS) Harms of intervention
Neonates up to 28 days Subgroups: neonates with CVAD, CVL	• Anticoagulation • Thrombolysis	• No therapy • Other intervention	• Mortality • Pulmonary embolus • Paradoxical stroke • Postthrombotic syndrome • Recurrence (DVT or PE) • Hemorrhage (major and CNS)

KQ 2: What is the effectiveness and harms of anticoagulants for

a. Neonates with acute ischemic stroke (AIS) and documented cardioembolic source?
b. Neonates with recurrent AIS
c. Children with AIS with undetermined cause
d. Children with AIS and in situ thrombosis
e. Children with AIS and thrombophilia
f. Children with AIS and documented cardioembolic source
g. Children with AIS and dissection
h. Children with AIS and vasculopathy
i. Children with AIS and moyamoya

Population	Intervention	Comparator	Outcome
2a. Neonates 0-28 days with AIS with documented cardioembolic source treatment	Anticoagulation	Antiplatelet therapy no therapy	• Mortality • Functional status • Hemorrhage (major and CNS) • Recurrent AIS

Population	Intervention	Comparator	Outcome
2b. Neonates 0-28 days with recurrent AIS	• Antiplatelet therapy • anticoagulation	No therapy	• Mortality • Functional status • Hemorrhage (major and CNS) • Recurrent AIS
2c. Children 28 days to 18 years with AIS due to undetermined cause	• Anticoagulation • aspirin • thrombolysis	No therapy Other treatment	• Mortality • Recurrent AIS • Functional status • Hemorrhage (major and CNS)
2d. Children 28 days to 18 years with AIS due to in situ thrombosis	• Anticoagulation • aspirin • thrombolysis	No therapy Other treatment	• Mortality • Recurrent AIS • Functional status • Hemorrhage (major and CNS)
2e. Children 28 days to 18 years with AIS due to thrombophilia	• Anticoagulation • Aspirin • thrombolysis	No therapy Other treatment	• Mortality • Recurrent AIS • Functional status • Hemorrhage (major and CNS)
2f. Children 28 days to 18 years with AIS and identified cardioembolic source	Anticoagulation	Aspirin	• Mortality • Recurrent AIS • Functional status • Hemorrhage (major and CNS)
2g. Children 28 days to 18 years with AIS and dissection	Anticoagulation	Aspirin	• Mortality • Recurrent AIS • Functional status • Intracranial hemorrhage
2h. Children 28 days to 18 years with AIS and vasculopathy other than dissection or moyamoya	• Anticoagulation • aspirin	No therapy	• Mortality • Recurrent AIS • Functional status • Hemorrhage (major and CNS)
2i. Children 28 days to 18 years with AIS and moyamoya	• Aspirin • Co-intervention: with/without neurosurgical direct/ indirect revascularization, surgical revascularization (direct/indirect)	No antithrombotic therapy Cointervention: with/without neurosurgical direct/ indirect surgical revascularization, each other	• Mortality • Recurrent AIS • Functional status • Hemorrhage (major and CNS)
2i. Children 28 days to 18 years with AIS and moyamoya	Surgical revascularization (direct/indirect)	Antiplatelet therapy without direct/ indirect surgical revascularization	• Mortality • Recurrent AIS • Functional status • Hemorrhage (major and CNS)

KQ 3: In neonates with femoral artery thrombosis, what are the effectiveness and harms of anticoagulants to treat thrombosis?

Population	Intervention	Comparator	Outcome
3. Neonates 0- 28 days with femoral artery thrombosis	Anticoagulation	• No therapy • Antiplatelet therapy	• Claudication • Leg shortening • Tissue loss • Hemorrhage (major and CNS)
3. Neonates 0- 28 days with femoral artery thrombosis	• Thrombolysis (followed by standard anticoagulation or antiplatelet therapy) • Thrombectomy followed by anticoagulation	• Anticoagulation alone • antiplatelet therapy alone • Other included intervention	• Claudication • Leg shortening • Tissue loss • Hemorrhage (major and CNS)

KQ 4: In neonates with aortic thrombosis, what are the effectiveness and harms of anticoagulants?

Population	Intervention	Comparator	Outcome
4. Neonates 0-28 days with aortic thrombosis. Subgroups: UAC related, spontaneous thrombosis	Thrombolysis	Anticoagulation	• Mortality • Tissue loss • Renal impairment • Hypertension • Necrotizing enterocolitis (NEC) • Embolization • Hemorrhage (major and CNS)

KQ 5: what is the effectiveness of treatments for renal vein thrombosis in neonates?

Population	Intervention	Comparator	Outcome
5. Neonates up to 28 days with unilateral renal vein thrombosis	Anticoagulation	No therapy	• Mortality • Renal failure • Renal atrophy • Hypertension • Extension • Recurrent venous thromboembolism (VTE) • Hemorrhage (major and CNS)
5. Neonates up to 28 days with renal vein thrombosis with bilateral or inferior vena cava involvement	• Anticoagulation • thrombolysis	No therapy, each other	• Mortality • Renal failure • Renal atrophy • Hypertension • Extension • Recurrent VTE • Hemorrhage (major and CNS)

KQ 6: what is the effectiveness of treatments for cerebral sinovenous thrombosis (CSVT) in children?

Population	Intervention	Comparator	Outcome
6. Neonates up to 28 days with cerebral sinovenous thrombosis	Anticoagulation	No therapy	• Mortality • Functional status • Extension • Recurrent CSVT • Hemorrhage (major and CNS) • Visual outcomes/need for surgical management of increased intracranial pressure (fenestration shunt)
6. Children 28 days to 18 years with cerebral sinovenous thrombosis	Anticoagulation, with thrombolysis (followed by standard anticoagulation)	• No therapy • Anticoagulation alone	• Mortality • Thrombus extension • Functional status • Hemorrhage (major and CNS)

KQ 7. What is the effectiveness of treatments for right atrial thrombosis in children?

Population	Intervention	Comparator	Outcome
7. Children 28 days to 18 years with right atrial thrombosis (with or without a central venous access device (CVAD)	Thrombolysis, with surgical thrombectomy (followed by standard anticoagulation or antiplatelet therapy)	Anticoagulation (without thrombolysis or surgical thrombectomy), each other	• Mortality • PE • Paradoxical stroke • Postthrombotic syndrome • Recurrent VTE • Hemorrhage (major and CNS)

KQ 8: In neonates with purpura fulminans what is the effectiveness and harms of fresh frozen plasma or protein C replacement compared to anticoagulation?

Population	Intervention	Comparator	Outcome
8. Neonates 0-28 days with purpura fulminans	• Fresh frozen plasma • Protein C replacement	Anticoagulation	• Mortality • Vision • Neurologic outcome • Primary thrombosis • Recurrent thrombosis (among those with major vessel thrombosis at presentation) • Harms of treatment

KQ 9: In children with Kawasaki disease what are the effectiveness and harms of anticoagulants to

a. Prevent thrombosis?
b. Treat thrombosis?

Population	Intervention	Comparator	Outcome
9a. Children 28 days to 18 years Kawasaki disease with coronary aneurysms	Anticoagulation	Antiplatelet therapy	• Myocardial infarction • Mortality • Hemorrhage (major and CNS)
9b. Children 28 days to 18 years Kawasaki disease with coronary aneurysms and acute thrombosis	Thrombolysis	Anticoagulation	• Myocardial infarction • Mortality • Hemorrhage (major and CNS)

KQ 10: In children with dilated cardiomyopathy what are the effectiveness and harms of anticoagulants to prevent thrombosis?

Population	Intervention	Comparator	Outcome
10. Children 28 days to 18 years with dilated cardiomyopathy	• Vitamin K antagonist (VKA) • Aspirin	No therapy	• Mortality • Thrombosis • Ischemic stroke • Hemorrhage (major and CNS)

KQ 11: In children with primary pulmonary hypertension what are the effectiveness and harms of anticoagulants to prevent thrombosis?

Population	Intervention	Comparator	Outcome
11. Children 28 days to 18 years with primary pulmonary hypertension	VKAs	No therapy	• Mortality • Thrombosis • Heart/lung transplantation • Hemorrhage (major and CNS)

KQ 12: In children with sickle cell disease what is the effectiveness of

a. Exchange transfusion to treat acute ischemic stroke?
b. Chronic transfusion program to prevent acute ischemic stroke?

Population	Intervention	Comparator	Outcome
12a. children 28 days to 18 years with sickle cell disease and acute ischemic stroke	Exchange transfusion	No treatment	• Mortality • Recurrent AIS • Functional status • Intracranial hemorrhage
12b. Children 28 days to 18 years with sickle cell disease	Chronic transfusion program	No treatment	• Mortality • Recurrent AIS • Functional status • Intracranial hemorrhage

KQ 13: In neonates with a Blalock-Taussig shunt, what is the effectiveness and harms of anticoagulants

a. To prevent thrombosis?
b. To treat thrombosis?

Population	Intervention	Comparator	Outcome
13a. Neonates 0-28 days with Blalock-Taussig shunt	• Heparin or LMWH • Aspirin • Clopidogrel	• None • Heparin or LMWH • Aspirin • Clopidogrel	• Intracardiac thrombosis (includes shunt thrombosis) • Mortality • Tissue loss • Hemorrhage (major and CNS)
13b. Neonates 0-28 days with Blalock-Taussig shunt thrombosis	Thrombolysis	Surgical intervention	• Intracardiac thrombosis (includes shunt thrombosis) • Mortality • Tissue loss • Hemorrhage (major and CNS)

KQ 14: In neonates with Stage 1 Norwood, what are the effectiveness and harms of anticoagulants to prevent thrombosis?

Population	Intervention	Comparator	Outcome
14. Neonates 0- 28 days with Stage 1 Norwood	Anticoagulation	Antiplatelet therapy	• Intracardiac thrombosis • Mortality • Tissue loss • Hemorrhage (major and CNS)

KQ 15: In children with Glenn or bilateral cavo pulmonary shunt what are the effectiveness and harms of anticoagulants to prevent thrombosis?

Population	Intervention	Comparator	outcome
15. Children 28 days to 18 years with Glenn or bilateral cavo pulmonary shunt	Anticoagulation	No therapy	• Intracardiac thrombosis • Mortality • Tissue loss • Hemorrhage (major and CNS) • Ischemic stroke • Fontan surgery

KQ 16: In children with Fontan surgery what are the effectiveness and harms of anticoagulants to prevent thrombosis?

Population	Intervention	Comparator	Outcome
16. Children 28 days to 18 years with Fontan surgery	• Anticoagulation • Antiplatelet therapy	No therapy	• Intracardiac thrombosis • Mortality • Fontan takedown • Ischemic stroke • Hemorrhage (major and CNS)

KQ 17: What is the effectiveness and harms of anticoagulants to prevent thrombosis in children with

a. Biologic prosthetic heart valve
b. Mechanical prosthetic heart valve

Population	Intervention	Comparator	Outcome
17a. Children 28 days to 18 years with biologic prosthetic heart valves	• VKAs • aspirin	No therapy	• Mortality • Valve replacement • Thrombosis • Ischemic stroke • Hemorrhage (major and CNS)
17b. Children 28 days to 18 years with mechanical prosthetic heart valves	• Antiplatelet agents • Anticoagulation • VKAs	No therapy	• Mortality • Valve replacement • Thrombosis • Ischemic stroke • Hemorrhage (major and CNS)
17b. Children 28 days to 18 years with mechanical prosthetic heart valves	• Antiplatelet agents • Antiplatelet with VKA	VKAs alone	• Mortality • Valve replacement • Thrombosis • Ischemic stroke • Hemorrhage (major and CNS)

KQ 18: In children with endovascular stents what are the effectiveness and harms of anticoagulants to prevent thrombosis?

Population	Intervention	Comparator	Outcome
18. Children 28 days to 18 years with endovascular stents	• Heparin or low molecular weight heparin (LMWH) • aspirin	No therapy	• Patency • Mortality • Pulmonary emboli • Ischemic stroke

KQ 19: In children with ventricular assist devices what are the effectiveness and harms of anticoagulants to prevent thrombosis?

Population	Intervention	Comparator	Outcome
18. Children 28 days to 18 years with ventricular assist devices	• Anticoagulation • Antiplatelet agents	No therapy	• Mortality • Thrombosis • Ischemic stroke • Blocked circuit requiring surgery • Hemorrhage (major and CNS)

KQ 20: what are the effectiveness and harms of anticoagulants to prevent thrombosis in children with

a. Arteriovenous fistula for hemodialysis access
b. Central venous access device (CVAD) for hemodialysis access

Population	Intervention	Comparator	Outcome
20a. Children 28 days to 18 years with arteriovenous fistula for hemodialysis access	• Continuous anticoagulation • Procedural unfractionated heparin (UFH) or LMWH	No therapy	• Mortality • Thrombosis • Shunt dysfunction • Shunt infection • Hemorrhage (major and CNS)
20b. Children 28 days to 18 years with central venous access device (CVAD) for hemodialysis access	• Continuous anticoagulation • Procedural UFH or LMWH	No therapy	• Mortality • Thrombosis • CVAD dysfunction • Sepsis/CVAD infection • Hemorrhage (major and CNS)

KQ 21: In neonates with peripheral arterial catheters what are the effectiveness and harms of anticoagulants

a. To prevent thrombosis?
b. To treat thrombosis?

Population	Intervention	Comparator	Outcome
21a. Neonates 0- 28 days with peripheral arterial catheters (excluding femoral artery)	Thrombolysis	No therapy	• Tissue loss • Growth failure • Hemorrhage (major and CNS)
21b. Neonates 0- 28 days with peripheral arterial catheter thrombosis (excluding femoral artery catheter thrombosis)	Thrombolysis	• No therapy, • Thrombectomy • Anticoagulation • Antiplatelet therapy	• Tissue loss • Growth failure • Hemorrhage (major and CNS)

KQ 22: What is the effectiveness and harms of anticoagulants to prevent central venous access device (CVAD) thrombosis in

a. Neonates
b. Children
c. Children with short to medium term need for CVAD
d. Children with long-term need for CVAD

Population	Intervention	Comparator	Outcome
22a. Neonates 0-28 days with CVAD	• Local heparin (1-2 units/mL infusion) • heparin lock, • intermittent local thrombolysis	• No therapy • Other included intervention	• Patency • Sepsis/CVAD infection • DVT • PE • Hemorrhage (major and CNS)
22a. Neonates 0-28 days with CVAD	• Systemic heparin • LMWH	• No therapy • Other included intervention	• Patency • Sepsis/CVAD infection • DVT • PE • Hemorrhage (major and CNS)
22b. Children 28 days to 18 years with CVAD	• Local heparin (1-2 units/mL infusion) • heparin lock, • intermittent local thrombolysis	No therapy	• Patency • CVAD dysfunction • Sepsis/CVAD infection • DVT • PE • Hemorrhage (major and CNS)

Population	Intervention	Comparator	Outcome
22c. Children 28 days to 18 years with short to medium-term CVAD	Systemic anticoagulation	No therapy	• Patency • CVAD dysfunction • Sepsis/CVAD infection • DVT • PE • Hemorrhage (major and CNS) mortality
22d. Children 28 days to 18 years long-term CVAD	Systemic anticoagulation	No therapy	• Patency • CVAD dysfunction • Sepsis/CVAD infection • DVT • PE • Major bleeding • Mortality

KQ 23: In neonates with umbilical artery catheters what are the effectiveness and harms of anticoagulants to prevent thrombosis?

Population	Intervention	Comparator	Outcome
23. Neonates 0-28 days with UAC	Heparin prophylaxis	No therapy	• Patency • Aortic thrombosis • Hemorrhage (major and CNS) • Necrotizing enterocolitis • Embolization (eg, digital artery) • Tissue loss • Mortality

Appendix B. Selection Criteria Summary

Selection Criteria	Assessment
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the U.S.?	Yes
1b. Is the nomination a request for a systematic review?	Yes
1c. Is the focus on effectiveness or comparative effectiveness?	Yes
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	A variety of conditions require the use of medications and interventions to prevent and treat thrombosis.
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the U.S. population or for a vulnerable population	Yes.
2c. Represents important uncertainty for decision makers	Yes
2d. Incorporates issues around both clinical benefits and potential clinical harms	Yes
2e. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Yes children who may need antithrombotic therapy often have serious medical conditions, such as stroke or cardiac disease; or have conditions that require shunts or vascular access that have risks for thrombosis or infection. These in turn impact long-term outcomes, as well as costs for patients, their families, and he health system.

Selection Criteria	Assessment
3. Desirability of a New Evidence Review/Duplication	
3. Would not be redundant (i.e., the proposed topic is not already covered by available or soon-to-be available high-quality systematic review by AHRQ or others)	A new evidence review would partly duplicate existing reviews. Six systematic reviews[5, 6, 8-10, 27] cover the scope of: Renal vein thrombosis (KQ 5); Cerebral sinovenous thrombosis (KQ 6); Right atrial thrombosis (KQ 7); Sickle cell disease (KQ 12); Norwood procedure (KQ 14); Glenn or bilateral cavopulmonary shunt (KQ 15); Fontan surgery (KQ 16); and Umbilical artery catheter (KQ 23), anticoagulation. Eight systematic reviews [5, 6, 10-15] partly cover the scope of: • DVT and PE treatment (KQ 1), anticoagulation. The in-process review for the American Society of Hematology guideline does not include interventional radiology procedures and stenting. • Acute ischemic stroke (KQ 2). The systematic review for the Royal College of Pediatric and Child Health guideline did not include neonates. • Femoral artery thrombosis treatment (KQ 3), heparin and low molecular weight heparin. The systematic review does not cover thrombolysis or thrombectomy. • Purpura fulminans (KQ 8), protein C treatment. The in-process review does not include fresh frozen plasma. • Central venous access device (KQ 22), anticoagulation. The reviews do not address local thrombolysis. We identified a review on hemodialysis access (KQ 20); though the review did not indicate an age restriction, no studies included children. Based on uncertainty about the scope of the review, this was not considered duplicative.
4. Impact of a New Evidence Review	
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	For many areas the evidence supporting guidelines is limited and the recommendations for children may be extrapolated from available evidence in adults.[4, 5, 28-32]
4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?	Practice variation is likely related to uncertainty in the evidence.
5. Primary Research	
5. Effectively utilizes existing research and knowledge by considering: - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies)	A new review is not feasible. Size/scope of review: 9 studies across 14 KQ, with at most 2 studies per KQ.

Abbreviations: AHRQ=Agency for Healthcare Research and Quality; KQ=Key Question;

Appendix C. Search for Evidence Reviews (Duplication)

Listed are the sources searched.

Search date: February 2015 to February, 2018
AHRQ: Evidence reports and technology assessments, USPSTF recommendations
VA Products: PBM, and HSR&D (ESP) publications, and VA/DoD EBCPG Program
Cochrane Systematic Reviews and Protocols http://www.cochranelibrary.com/
PubMed
PubMed Health http://www.ncbi.nlm.nih.gov/pubmedhealth/
HTA (CRD database): Health Technology Assessments http://www.crd.york.ac.uk/crdweb/
PROSPERO Database (international prospective register of systematic reviews and protocols) http://www.crd.york.ac.uk/prospero/
CADTH (Canadian Agency for Drugs and Technologies in Health) https://www.cadth.ca/
DoPHER (Database of promoting health effectiveness reviews) http://eppi.ioe.ac.uk/webdatabases4/Intro.aspx?ID=9
Systematic Reviews (Journal) : protocols and reviews http://systematicreviewsjournal.biomedcentral.com/

Appendix D. Search Strategy & Results (Feasibility)

Antithrombotics in Children MEDLINE(PubMed) March 14th, 2018	
Concept	Search String
0-28 days	**"Infant, Newborn"[Mesh]**
28 days to 18 years	**((("Infant"[Mesh:NoExp]) OR "Child, Preschool"[Mesh]) OR "Child"[Mesh]) OR "Adolescent"[Mesh]**
prevention	**"prevention and control" [Subheading] OR "Tertiary Prevention"[Mesh] OR "Secondary Prevention"[Mesh] OR "Primary Prevention"[Mesh]**
treatment	**(treatment[Title/Abstract]) OR ("Therapeutics"[Mesh] OR "therapy" [Subheading])**
anticoagulants	**"Anticoagulants"[Mesh] OR "Anticoagulants" [Pharmacological Action]**
aortic thrombosis	**Aortic thrombosis[Title/Abstract]**
Kawasaki disease	**(Kawasaki disease[Title/Abstract]) OR "Mucocutaneous Lymph Node Syndrome"[Mesh]**
dilated cardiomyopathy	**"Cardiomyopathy, Dilated"[Majr]**
Blalock-Taussig Shunt	**(Blalock-Taussig Shunt[Title/Abstract]) OR "Blalock-Taussig Procedure"[Mesh]**
prosthetic valves	**(Prosthetic valves[Title/Abstract]) OR "prosthetic heart valve"[Title/Abstract]**
endovascular stents	**(Endovascular stents[Title/Abstract]) OR endovascular aneurysm[Title/Abstract]**
ventricular assist device	**(Ventricular assist device[Title/Abstract]) OR "Heart-Assist Devices"[Mesh]**
peripheral arterial catheter	**(Peripheral arterial catheter[Title/Abstract]) OR ("Catheterization, Peripheral"[Mesh] OR "Vascular Access Devices"[Mesh])**
radiology or surgery	**("Venous Thromboembolism/radiotherapy"[Mesh] OR "Venous Thromboembolism/surgery"[Mesh])**
acute ischemic stroke	**"Acute ischemic stroke"[Title/Abstract]**
femoral artery thrombosis, treatment with thrombectomy and thrombolysis	**((("Thrombectomy"[Mesh]) OR ("Mechanical Thrombolysis"[Mesh] OR "Thrombolytic Therapy"[Mesh]))) AND "Femoral Artery"[Mesh]**
purpura fulminans, treatment with FFP	**("Purpura Fulminans"[Mesh]) AND "Plasma"[Mesh]**

primary pulmonary hypertension	**"Familial Primary Pulmonary Hypertension"[Mesh]**
Central venous Access Device	**"Vascular Access Devices"[Mesh]**
Not Editorials, etc.	**(((((letter[Publication Type]) OR news[Publication Type]) OR patient education handout[Publication Type]) OR comment[Publication Type]) OR editorial[Publication Type]) OR newspaper article[Publication Type]**
Limit to last 5 years ; human ; English	**Filters activated: published in the last 5 years, Humans, English**
Systematic Reviews	**"Systematic[sb]"**
Randomized Controlled Trials	**(((((((groups[tiab])) OR (trial[tiab])) OR (randomly[tiab])) OR (drug therapy[sh])) OR (placebo[tiab])) OR (randomized[tiab])) OR (controlled clinical trial[pt])) OR (randomized controlled trial[pt])**

ClinicalTrials.gov searched on March 14th, 2018

27 Studies found for: **Completed Studies | Anticoagulants | Child | Start date from 03/14/2013 to 03/14/2018**
https://clinicaltrials.gov/ct2/results?cond=&term=&type=&rslt=&recrs=e&age_v=&age=0&gndr=&intr=Anticoagulants&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&strd_s=03%2F14%2F2013&strd_e=03%2F14%2F2018&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&lupd_s=&lupd_e=

4 Studies found for**: Active, not recruiting Studies | Anticoagulants | Child | Start date from 03/14/2013 to 03/14/2018**
https://clinicaltrials.gov/ct2/results?cond=&term=&type=&rslt=&recrs=d&age_v=&age=0&gndr=&intr=Anticoagulants&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&strd_s=03%2F14%2F2013&strd_e=03%2F14%2F2018&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&lupd_s=&lupd_e=

46 Studies found for**: Recruiting Studies | Anticoagulants | Child | Start date from 03/14/2013 to 03/14/2018**
https://clinicaltrials.gov/ct2/results?cond=&term=&type=&rslt=&recrs=a&age_v=&age=0&gndr=&intr=Anticoagulants&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&strd_s=03%2F14%2F2013&strd_e=03%2F14%2F2018&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&lupd_s=&lupd_e=