Complete Summary

GUIDELINE TITLE

Antithrombotic therapy in children: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy.

BIBLIOGRAPHIC SOURCE(S)

Monagle P, Chan A, Massicotte P, Chalmers E, Michelson AD. Antithrombotic therapy in children: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004 Sep;126(3 Suppl):645S-87S. [487 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Monagle P, Michelson AD, Bovill E, Andrew M. Antithrombotic therapy in children. Chest 2001 Jan;119(1 Suppl):344S-370S.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- February 28, 2008, Heparin Sodium Injection: The U.S. Food and Drug Administration (FDA) informed the public that Baxter Healthcare Corporation has voluntarily recalled all of their multi-dose and single-use vials of heparin sodium for injection and their heparin lock flush solutions. Alternate heparin manufacturers are expected to be able to increase heparin production sufficiently to supply the U.S. market. There have been reports of serious adverse events including allergic or hypersensitivity-type reactions, with symptoms of oral swelling, nausea, vomiting, sweating, shortness of breath, and cases of severe hypotension.
- August 16, 2007, Coumadin (Warfarin): Updates to the labeling for Coumadin to include pharmacogenomics information to explain that people's genetic makeup may influence how they respond to the drug.

COMPLETE SUMMARY CONTENT

** REGULATORY ALERT **
SCOPE

METHODOLOGY - including Rating Scheme and Cost Analysis
RECOMMENDATIONS
EVIDENCE SUPPORTING THE RECOMMENDATIONS
BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS
CONTRAINDICATIONS
QUALIFYING STATEMENTS
IMPLEMENTATION OF THE GUIDELINE
INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES
IDENTIFYING INFORMATION AND AVAILABILITY
DISCLAIMER

SCOPE

DISEASE/CONDITION(S)

- Thromboembolic disorders, including the following:
  - Venous thromboembolic complications
  - Arterial thromboembolic complications
  - Myocardial infarction
  - Some forms of strokes
- Conditions, diseases, or interventions that predispose a patient to thromboembolism, including the following:
  - Mechanical or biological prosthetic heart valves
  - Cardiac catheterization
  - Central arterial catheters
  - Umbilical arterial catheterization (UAC)
  - Stage 1 Norwood procedure
  - Endovascular stents
  - Blalock-Taussig shunts
  - Fontan surgery
  - Central venous catheters
  - Atrial venous fibrillation
  - Kawasaki's disease
  - Cardiopulmonary bypass
  - Hemodialysis
  - Purpura fulminans
  - Dilated cardiomyopathy

GUIDELINE CATEGORY

Management
Prevention
Treatment

CLINICAL SPECIALTY

Cardiology
Critical Care
Emergency Medicine
Family Practice

Pediatrics
Pulmonary Medicine

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To detail the evidence showing that the interaction of antithrombotic agents with the hemostatic system of young patients differs from that of adult patients
- To describe the mechanisms of action, therapeutic ranges, dose regimes, monitoring requirements, factors influencing dose-response relationships, and side effects of antithrombotic, antiplatelet, and thrombolytic agents in neonates and children
- To discuss background information regarding the biological rationale related to specific antithrombotic agents, and evidence regarding appropriate administration and side effects, and to review evidence regarding thromboembolic markers
- To provide evidence-based clinical practice guidelines to assist clinicians in preventing and effectively treating thrombotic disorders in specific pediatric patient populations

TARGET POPULATION

Pediatric patients who are candidates for antithrombotic therapy

Note: Throughout this article, the term *pediatric patients* is used to refer to all neonates and children (i.e., from birth to 16 years of age). The term *neonates* refers to infants from birth to 28 days of age corrected for gestational age. The term *children* refers to patients 28 days to 16 years of age.

INTERVENTIONS AND PRACTICES CONSIDERED

Prevention or Treatment

Pharmacotherapy

1. Low-molecular-weight heparin (LMWH) such as, reviparin and enoxaparin
2. Unfractionated heparin (UFH)
3. Protamine sulfate to reverse heparin therapy
4. Vitamin K antagonists (VKAs)
5. Reversal of oral anticoagulation therapy with vitamin K1
6. Aspirin therapy
7. Oral anticoagulation therapy in combination with aspirin therapy and/or dipyridamole
8. Thrombolytic agents (tissue plasminogen activator (tPA), streptokinase, urokinase)

Note: The following antithrombotic and antiplatelet therapies are considered but not recommended: danaparoid (Orgaran), ticlopidine and clopidogrel, and glycoprotein (GP) IIb/IIIa antagonists (abciximab, tirofiban, and eptifibatide).

Other Related Treatment

1. Treatment of bleeding:
    - Transfusions of platelet concentrates and/or the use of products that enhance platelet adhesion
    - Stopping an infusion of the thrombolytic agent, followed by administering a cryoprecipitate, other blood products as indicated, or anti-fibrinolytic agent
2. Fresh frozen plasma (FFP) or protein C concentrate

Management

Oral Anticoagulation Monitoring

1. International normalized ratio (INR)
2. Activated partial thromboplastin time (aPTT)
3. Anti-factor Xa levels
4. Pediatric anticoagulation clinics
5. Whole-blood prothrombin time/international normalized ratio (INR) monitors for home use

MAJOR OUTCOMES CONSIDERED

Effectiveness and safety of treatments, as evidenced by the following:

- Rates of thromboembolic complications
- Rates of hemorrhagic complications
- Mortality
- Recurrence rates
- Patency

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Process of Searching for Evidence

Defining the clinical question provided the framework for formulating eligibility criteria that guided the search for relevant evidence. Prior to searching for the evidence, methodological experts and librarians reviewed each question to ensure that the librarians could derive a comprehensive search strategy.

In specifying eligibility criteria, authors not only identified patients, interventions, and outcomes, but also methodological criteria. For most therapeutic studies, authors restricted eligibility to randomized controlled trials (RCTs).

For many questions, RCTs did not provide sufficient data, and article authors also included observational studies. This was also true when randomized trials were not the most appropriate design to use for addressing the research question. In particular, randomized trials are not necessarily the best design to understand risk groups (e.g., the baseline or expected risk of a given event for certain subpopulations). Because there are no interventions examined in questions about prognosis, one replaces interventions by the exposure, which is time.

Identifying the Evidence

To identify the relevant evidence, a team of librarians at the University at Buffalo conducted comprehensive literature searches. For each question the authors provided, the librarians developed sensitive (but not specific) search strategies, including all languages, and conducted separate searches for systematic reviews, RCTs, and, if applicable, observational studies. The librarians searched the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effectiveness and Cochrane Register of Controlled Trial, the ACP Journal Club, MEDLINE, and Embase for studies published between 1966 and June 2002 in any language. To filter MEDLINE and Embase search results for RCT evidence, the librarians used the search strategy developed by the Cochrane Collaboration (full strategy available in Appendix online at: http://www.chestjournal.org/content/vol126/3_suppl_1).

For observational studies, they restricted their searches to human studies. Searches were not further restricted in terms of methodology. While increasing the probability of identifying all published studies, this sensitive approach resulted in large number of citations for many of the defined clinical questions. Therefore, trained research assistants screened the citation list developed from the search and removed any apparently irrelevant citations. These irrelevant citations included press news, editorials, narrative reviews, single case reports, animal studies (any nonhuman studies), and letters to the editor. Authors included data from abstracts of recent meetings if reporting was transparent and all necessary data for the formulation of a recommendation were available. The guideline developers did not explicitly use Internet sources to search for research data.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

The rating scheme framework captures the trade-off between benefits and risks (1 or 2) (and the methodological quality of the underlying evidence (A, B, C+, or C). See "Rating Scheme for the Strength of the Recommendations."

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Summarizing Evidence

The electronic searches also included searching for systematic reviews. If authors were satisfied with a recent high-quality systematic review, evidence from that review provided a foundation for the relevant recommendation.

Pooled analyses from high-quality systematic reviews formed, wherever possible, the evidence base of the recommendations. Pooling offers the advantage of obtaining more precise estimates of treatment effects and allows for a greater generalizability of results. However, pooling also bears the risk of spurious generalization. In general, the summary estimates of interest were the different types of outcomes conveying benefit and downsides (i.e., risk, burden, and cost).

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus (Consensus Development Conference)

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The strength of any recommendation depends on the following two factors: the trade-off between the benefits and the risks, burdens, and costs; and the strength of the methodology that leads to the treatment effect. The guideline developers grade the trade-off between benefits and risks in the two categories: 1, in which the trade-off is clear enough that most patients, despite differences in values, would make the same choice; and 2, in which the trade-off is less clear, and individual patients´ values will likely lead to different choices.

When randomized trials provide precise estimates suggesting large treatment effects, and the risks and costs of therapy are small, treatment for average patients with compatible values and preferences can be confidently recommended.

If the balance between benefits and risks is in doubt, methodologically rigorous studies providing **Grade A** evidence and recommendations may still be weak (**Grade 2**). Uncertainty may come from less precise estimates of benefit, harm, or costs, or from small effect sizes.

There is an independent impact of validity and consistency, and the balance of positive and negative impacts of treatment on the strength of recommendations.

In situations in which there is doubt about the value of the trade-off, any recommendation will be weaker, moving from **Grade 1** to **Grade 2**.

Grade 1 recommendations can only be made when there is a relatively clear picture of both the benefits and the risks, burdens, and costs, and when the balance between the two clearly favors recommending or not recommending the intervention for the typical patient with compatible values and preferences. A number of factors can reduce the strength of a recommendation, moving it from **Grade 1** to **Grade 2**. Uncertainty about a recommendation to treat may be introduced if the following conditions apply: (1) the target event that is trying to be prevented is less important (confident recommendations are more likely to be made to prevent death or stroke than asymptomatic deep vein thrombosis); (2) the magnitude of risk reduction in the overall group is small; (3) the probability of the target event is low in a particular subgroup of patients; (4) the estimate of the treatment effect is imprecise, as reflected in a wide confidence interval (CI) around the effect; (5) there is substantial potential harm associated with therapy; or (6) there is an expectation for a wide divergence in values even among average or typical patients. Higher costs would also lead to weaker recommendations to treat.

The more balanced the trade-off between benefits and risks, the greater the influence of individual patient values in decision making. Virtually all patients, if they understand the benefits and risks, will take aspirin after experiencing a myocardial infarction (MI) or will comply with prophylaxis to reduce the risk of thromboembolism after undergoing hip replacement. Thus, one way of thinking about a **Grade 1** recommendation is that variability in patient values is unlikely to influence treatment choice in average or typical patients.

When the trade-off between benefits and risks is less clear, individual patient values may influence treatment decisions even among patients with average or typical preferences.

Grade 2 recommendations are those in which variation in patient values or individual physician values will often mandate different treatment choices, even among average or typical patients. An alternative, but similar, interpretation is that a **Grade 2** recommendation suggests that clinicians conduct detailed conversations with patients to ensure that their ultimate recommendation is consistent with the patient's values.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Grade of Recommendation	Clarity of Risk/Benefit	Methodological Strength of Supporting Evidence	Implications
1A	Clear	Randomized controlled trials (RCTs) without important	Strong recommendation; can apply to most patients in most

Grade of Recommendation	Clarity of Risk/Benefit	Methodological Strength of Supporting Evidence	Implications
		limitations	circumstances without reservation
1C+	Clear	No RCTs, but strong RCT results can be unequivocally extrapolated, or overwhelming evidence from observational studies	Strong recommendation; can apply to most patients in most circumstances
1B	Clear	RCTs with important limitations (inconsistent results, methodological flaws*)	Strong recommendation; likely to apply to most patients
1C	Clear	Observational studies	Intermediate-strength recommendation; may change when stronger evidence is available
2A	Unclear	RCTs without important limitations	Intermediate-strength recommendation; best action may differ depending on circumstances or patients' or societal values
2C+	Unclear	No RCTs, but strong RCT results can be unequivocally extrapolated, or overwhelming evidence from observational	Weak recommendation; best action may differ depending on circumstances or patients' or societal values

Grade of Recommendation	Clarity of Risk/Benefit	Methodological Strength of Supporting Evidence	Implications
		studies	
2B	Unclear	RCTs with important limitations (inconsistent results, methodological flaws*)	Weak recommendation; alternative approaches likely to be better for some patients under some circumstances
2C	Unclear	Observational studies	Very weak recommendation; other alternatives may be equally reasonable

**These situations include RCTs with both lack of blinding and subjective outcomes, where the risk of bias in measurement of outcomes is high, or RCTs with large loss to follow-up.*

COST ANALYSIS

While conference participants agreed that recommendations should reflect economic considerations, incorporating costs is fraught with difficult challenges. For most recommendations, formal economic analyses are unavailable. Even when analyses are available, they may be methodologically weak or biased. Furthermore, costs differ radically across jurisdictions, and even sometimes across hospitals within jurisdictions.

Because of these challenges, the guideline developers consider economic factors only when the costs of one therapeutic option over another are substantially different within major jurisdictions in which clinicians make use of these recommendations. As a result, in jurisdictions in which resource constraints are severe, alternative allocations may serve the health of the public far better than some of the interventions that are designated as **Grade 1A**. This will likely be true for all less industrialized countries and, with the increasing promotion of expensive drugs with marginal benefits, may be increasingly true for wealthier nations. Furthermore, recommendations change (either in direction or with respect to grade) only when the guideline developers believe that costs are high in relation to benefits. Instances in which costs have influenced recommendations are labeled in the "values and preferences" statements associated with the recommendation.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The guideline authors formulated draft recommendations prior to the conference that served as the foundation for authors to work together and critique the recommendations. Drafts of all articles including draft recommendations were available for review during the conference. A representative of each article presented potentially controversial issues in their recommendations at plenary meetings. Article authors met to integrate feedback, to consider related recommendations in other articles, and to revise their own guidelines accordingly. Authors continued this process after the conference until they reached agreement within their groups and with other author groups who had provided critical feedback. Finally, the editors of this supplement harmonized the articles and resolved remaining disagreements through facilitated discussion.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The rating scheme is defined at the end of the "Major Recommendations" field.

Specific Indications for Antithrombotic Therapy

Venous Thromboembolism (VTE)

Neonates with VTE

1. The guideline developers suggest treatment with either unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH), or radiographic monitoring and anticoagulation therapy if extension occurs (**Grade 2C**).
2. The guideline developers suggest that if clinicians elect treatment with anticoagulation therapy, they administer UFH or LMWH, and subsequently administer LMWH for 10 days to 3 months (**Grade 2C**).
3. The guideline developers suggest that clinicians adjust the dose of UFH to prolong the activated partial thromboplastin time (aPTT) corresponding to an anti-factor Xa (anti-FXa) level of 0.35 to 0.7 U/mL (**Grade 2C**).
4. The guideline developers suggest that clinicians adjust the dose of LMWH to achieve an anti-FXa level of 0.5 to 1.0 U/mL (**Grade 2C**).
5. The guideline developers suggest that if the thrombus extends following the discontinuation of heparin therapy, clinicians administer vitamin K antagonists (VKAs) or extended LMWH therapy (**Grade 2C**).
6. The guideline developers suggest that clinicians **not** use thrombolytic therapy for the treatment of VTEs in neonates unless there is major vessel occlusion that is causing the critical compromise of organs or limbs (**Grade 2C**). If thrombolytic therapy is used, the guideline developers suggest supplementation with plasminogen (i.e., fresh frozen plasma [FFP]) immediately prior to thrombolysis (**Grade 2C**).
7. The guideline developers suggest that, in general, clinicians should remove either central venous lines (CVLs) or umbilical vein catheters (UVCs) that are

in situ. However, if either CVLs or UVCs are still in place at the completion of the above therapy, the guideline developers suggest prophylactic dosing with LMWH to prevent recurrent VTEs until such time as the CVL or UVC is removed (both **Grade 2C**).

Systemic Venous Thromboembolic Disease in Children

First Thromboembolic Event (TE) for Children (>2 months of age)

1. The guideline developers recommend treatment with intravenous (IV) heparin sufficient to prolong the aPTT to a range that corresponds to an anti-FXa level of 0.35 to 0.7 U/mL or with LMWH sufficient to achieve an anti-FXa level of 0.5 to 1.0 U/mL 4 hours after an injection (**Grade 1C+**).
2. The guideline developers recommend initial treatment with heparin or LMWH for 5 to 10 days (**Grade 1C+**). For patients in whom subsequent VKAs will be used, the guideline developers recommend beginning oral therapy as early as day 1 and discontinuing heparin/LMWH therapy on day 6 if the international normalized ratio (INR) is in the therapeutic range on two consecutive days (**Grade 1C+**). For massive pulmonary embolisms (PEs) or extensive deep vein thrombosis (DVT), the guideline developers recommend a longer period of heparin or LMWH therapy (**Grade 1C+**).
3. The guideline developers suggest continuing anticoagulant therapy for idiopathic TEs for at least 6 months using VKAs to achieve a target INR of 2.5 (INR range, 2.0 to 3.0) or, alternatively, LMWH to maintain an anti-FXa level of 0.5 to 1.0 U/mL (**Grade 2C**).

   Underlying values and preferences: The suggestion to administer anticoagulation therapy to children with idiopathic DVT for at least 6 months rather than on a lifelong basis places a relatively high value on the avoidance of the known risk of bleeding secondary to anticoagulant therapy in young active adults, and less importance on the unknown risk of recurrence in the absence of an ongoing clinical precipitating factor.

4. The guideline developers suggest that for secondary TEs anticoagulant therapy be continued for at least 3 months using VKAs to achieve a target INR of 2.5 (INR range, 2.0 to 3.0) or, alternatively, using LMWH to maintain an anti-FXa level of 0.5 to 1.0 U/mL (**Grade 2C**).
5. The guideline developers suggest that, in the presence of ongoing risk factors such as active nephrotic syndrome, ongoing asparaginase therapy, or administration of a lupus anticoagulant, anticoagulant therapy in either therapeutic or prophylactic doses continue until the risk factor has resolved (**Grade 2C**).
6. The guideline developers suggest that clinicians **not** use thrombolytic therapy routinely for the treatment of venous TE in children (**Grade 2C**). Treatment needs to be individualized, and based on the size and location of the thrombus, and the degree of organ compromise. If thrombolytic therapy is used, in the presence of physiologic or pathologic deficiencies of plasminogen, the guideline developers suggest supplementation with plasminogen (i.e., FFP) [**Grade 2C**].

Recurrent Idiopathic TEs in Children

1. The guideline developers recommend indefinite therapy with either therapeutic or prophylactic doses of VKAs (**Grade 1C+**). The guideline developers suggest LMWH therapy as an alternative if VKA therapy is too difficult (**Grade 2C**).

Recurrent Secondary TEs in Children

1. The guideline developers suggest that, following the initial 3 months of therapy, anticoagulation therapy be continued for at least a further 3 months or until removal of any precipitating factors (**Grade 2C**).

CVL-Related Thrombosis

There are two aspects to the management of CVL-related thrombosis. First, management of the CVL itself and, second, anticoagulation therapy.

1. The guideline developers suggest that if the CVL is no longer required, or is nonfunctioning, it be removed (**Grade 2C**). The guideline developers suggest at least 3 to 5 days of anticoagulation therapy prior to its removal. If CVL access is required and the CVL involved is still functioning, the guideline developers suggest that the CVL remain in situ (**Grade 2C**). Anticoagulation therapy should be administered as described in the recommendations above listed under "First TE for children (>2 months of age)."
2. For children with a first CVL-related DVT after the initial 3 months of therapy, the guideline developers suggest that prophylactic doses of VKAs (INR range, 1.5 to 1.8) or LMWH (anti-FXa level range, 0.1 to 0.3) be administered until the CVL is removed (**Grade 2C**).
3. For children with recurrent CVL-related TEs after the initial 3 months of therapy, the guideline developers suggest prophylactic doses of VKAs (INR range, 1.5 to 1.8) or LMWH (anti-FXa level range, 0.1 to 0.3) be continued until the removal of the CVL. If the recurrence occurs while children are receiving prophylactic therapy, the guideline developers suggest continuing therapeutic doses until the CVL is removed or for a minimum of 3 months (**Grade 2C**).

Renal Vein Thrombosis (RVT)

1. For unilateral RVT in the absence of uremia, and in the absence of extension into the inferior vena cava (IVC), the guideline developers suggest supportive care with careful monitoring of the RVT for extension (**Grade 2C**). Alternatively, the guideline developers suggest anticoagulation therapy with UFH or LMWH (**Grade 2C**).
2. For unilateral RVT that does extend into the IVC, the guideline developers suggest anticoagulation therapy with UFH or LMWH for 6 weeks to 3 months (**Grade 2C**).

   Remark: The therapeutic range is the same as that for treatment of venous thrombosis.

3. For bilateral RVT with various degrees of renal failure, the guideline developers suggest therapy with UFH (and not LMWH) and thrombolytic therapy (**Grade 2C**).

CVL Prophylaxis

1. For children with CVLs, the guideline developers recommend **against** routine primary prophylaxis (**Grade 1B**).
2. For children receiving long-term home total parenteral nutrition (TPN), the guideline developers suggest antithrombotic prophylaxis. The guideline developers suggest continuous therapy with VKAs (target INR, 2 to 2.5) or, alternatively, for the first 3 months after each CVL is inserted (all **Grade 2C**).

   Remark: The optimal drug and dose are unknown.

Primary Prophylaxis for Blalock-Taussig (BT) Shunts in Neonates

1. For neonates having BT shunts, the guideline developers suggest therapy with intraoperative heparin followed by either aspirin (5 mg/kg/day) or no further anticoagulant therapy (**Grade 2C**).

Primary Prophylaxis for Stage 1 Norwood Procedures in Neonates

1. For patients who have undergone the Norwood procedure, the guideline developers suggest heparin therapy immediately after the procedure (**Grade 2C**).

Primary Prophylaxis for Fontan Surgery in Children

1. For children after Fontan surgery, the guideline developers suggest therapy with aspirin (5 mg/kg/day) or therapeutic heparin followed by VKAs to achieve a target INR of 2.5 (INR range, 2 to 3) (**Grade 2C**).

   Remark: The optimal duration of therapy is unknown. Whether patients with fenestrations require more intensive therapy until fenestration closure is unknown.

Primary Prophylaxis for Endovascular Stents in Children

1. For children having endovascular stents inserted, the guideline developers suggest the administration of heparin perioperatively (**Grade 2C**).

Primary Prophylaxis for Dilated Cardiomyopathy in Neonates and Children

1. For children with cardiomyopathy, the guideline developers suggest that they receive VKAs to achieve a target INR of 2.5 (INR range, 2 to 3) commencing no later than at the time of their activation on a cardiac transplant waiting list (**Grade 2C**).

   Underlying values and preferences: The suggestion for the administration of VKAs places a high value on avoiding thrombotic complications, and a

relatively low value on avoiding the inconvenience, discomfort, and limitations of anticoagulant monitoring in children who have a potentially curative therapy (for their cardiomyopathy) available to them.

Primary Prophylaxis for Biological Prosthetic Heart Valves in Children

1. For children with biological prosthetic heart valves, the guideline developers recommend treatment according to the adult guidelines (see the National Guideline Clearinghouse (NGC) summary of the American College of Chest Physicians guideline Antithrombotic therapy in valvular heart disease – native and prosthetic) (**Grade 1C+**).

Primary Prophylaxis for Mechanical Prosthetic Heart Valves in Children

1. For children with mechanical prosthetic heart valves, the guideline developers recommend the administration of VKAs following adult guidelines (see the NGC summary Antithrombotic therapy in valvular heart disease – native and prosthetic) for the intensity of therapy (i.e., target INRs) (**Grade 1C+**).
2. In children in whom additional antithrombotic therapy is required due to lack of response to therapy with VKAs or a contraindication to therapy with full-dose VKAs, the guideline developers suggest adding therapy with aspirin (6 to 20 mg/kg/day) (**Grade 2C**).

Thromboprophylaxis for Cardiac Catheterization (CC) in Neonates and Children

1. For neonates and children requiring CC via an artery, the guideline developers recommend IV heparin prophylaxis (**Grade 1A**).
2. The guideline developers suggest the use of heparin doses of 100 to 150 U/kg as a bolus. Further doses may be required in prolonged procedures (both **Grade 2B**).
3. For prophylaxis for CC, the guideline developers recommend **against** aspirin therapy (**Grade 1B**).

Femoral Artery Thrombosis Following CC

1. For children or neonates with a femoral artery thrombosis, the guideline developers recommend therapeutic doses of IV heparin (**Grade 1C**). The guideline developers suggest treatment for at least 5 to 7 days (**Grade 2C**).

   Remark: The optimal duration of therapy is unknown.

2. For children or neonates with limb-threatening or organ-threatening (via proximal extension) femoral artery thrombosis who fail to respond to initial heparin therapy, and who have no known contraindications, the guideline developers recommend the administration of thrombolytic therapy (**Grade 1C**).
3. For children with femoral artery thrombosis in selected cases, the guideline developers suggest surgical intervention, in particular when there is a contraindication to thrombolytic therapy, or when organ or limb death is imminent (**Grade 2C**).

Peripheral Artery Thrombosis

1. For neonates and children with peripheral arterial catheters in situ, the guideline developers recommend the administration of low-dose heparin through the catheter, preferably by continuous infusion, to prolong the catheter patency (**Grade 1A**).
2. For children with a peripheral arterial catheter-related TE, the guideline developers suggest the immediate removal of the catheter (**Grade 2C**). The guideline developers suggest subsequent anticoagulation therapy with or without thrombolysis, depending on the clinical situation (**Grade 2C**).

Aortic Thrombosis Secondary to Umbilical Arterial Catheters (UACs) in Neonates

1. For neonates with UACs, the guideline developers suggest therapy with low-dose heparin infusion (1 to 5 U/hour) (**Grade 2A**).
2. The guideline developers suggest that aortic thrombosis secondary to UACs be managed by the same principles as those for femoral artery thrombosis secondary to cardiac catheters. If there is evidence of renal failure, then urgent restoration of renal blood flow is required, and the guideline developers suggest thrombolysis or thrombectomy (all **Grade 2C**).

Spontaneous Aortic Thrombosis in Neonates

1. For children experiencing spontaneous aortic thrombosis with evidence of renal ischemia, the guideline developers suggest urgent, aggressive use of thrombolytic or surgical therapy, supported by anticoagulation therapy with heparin or LMWH (**Grade 2C**).

Kawasaki Disease in Children

1. The guideline developers recommend aspirin therapy in high doses (i.e., 80 to 100 mg/kg/day during the acute phase, for up to 14 days) as an anti-inflammatory agent, then in lower doses (i.e., 3 to 5 mg/kg/day for $\geq$ 7 weeks) as an antiplatelet agent (**Grade 1C+**).
2. The guideline developers recommend therapy with IV gammaglobulin (2 g/kg as a single dose) within 10 days of the onset of symptoms (**Grade 1A**).

Anticoagulation Therapy for Kawasaki Disease in Children with Giant Aneurysms

1. In children with giant coronary aneurysms following Kawasaki disease, the guideline developers suggest therapy with warfarin (target INR, 2.5; INR range, 2.0 to 3.0) in addition to low-dose aspirin (**Grade 2C**).

Sinovenous Thrombosis in Neonates

1. For neonates with cerebral sinovenous thrombosis (CSVT), without large ischemic infarctions or intracranial hemorrhage (ICH), the guideline developers suggest initial treatment with either UFH or LMWH followed by treatment with LMWH for 3 months (**Grade 2C**).

2. For neonates with CSVT, with large ischemic infarctions or ICH, the guideline developers suggest radiographic monitoring and the commencement of anticoagulation therapy if extension occurs (**Grade 2C**).

Sinovenous Thrombosis in Children

1. For children with CSVT, the guideline developers suggest treatment for 5 to 7 days with either UFH or LMWH followed by treatment with LMWH or VKAs (target INR, 2.5; INR range, 2.0 to 3.0) for 3 to 6 months even in the presence of a localized hemorrhagic infarction (**Grade 2C**).

Arterial Ischemic Stroke (AIS) in Neonates

1. For neonates with noncardioembolic AIS, the guideline developers suggest that clinicians do **not** use anticoagulation or aspirin therapy (**Grade 2C**).
2. For neonates with cardioembolic AIS, the guideline developers suggest anticoagulation therapy with either UFH or LMWH for 3 months (**Grade 2C**).

AIS in Children

1. For children with AIS, the guideline developers suggest treatment with UFH or LMWH for 5 to 7 days and until cardioembolic stroke or vascular dissection has been excluded (**Grade 2C**).
2. For children with AIS and cardioembolic stroke or vascular dissection, the guideline developers suggest treatment for 5 to 7 days with UFH or LMWH followed by treatment with LMWH or VKAs for 3 to 6 months (**Grade 2C**).
3. For all children with AIS, the guideline developers suggest treatment with 2 to 5 mg/kg/day aspirin after anticoagulation therapy has been discontinued (**Grade 2C**).
4. For children with sickle cell disease who are >2 years of age, the guideline developers recommend screening for stroke using transcranial Doppler imaging. If transcranial Doppler imaging is unavailable, the guideline developers recommend intermittent screening with magnetic resonance imaging (MRI) (**Grade 1C**).
5. For children with sickle cell disease who have ischemic stroke, the guideline developers recommend therapy with IV hydration and exchange transfusion to reduce hemoglobin S levels to <30% of total hemoglobin (**Grade 1C**).
6. For children with sickle cell disease who have ischemic stroke, after an initial exchange transfusion the guideline developers suggest a long-term transfusion program (**Grade 2C**).

Purpura Fulminans

1. For neonates with homozygous protein C (PC) deficiency, the guideline developers recommend the administration of either 10 to 20 mL/kg FFP every 12 hours or PC concentrate, when available, at a concentration of 20 to 60 U/kg until the clinical lesions resolve (**Grade 1C+**).
2. The guideline developers suggest long-term treatment with VKAs (**Grade 2C**), LMWH (**Grade 2C**), PC replacement (**Grade 1C+**), or liver transplantation (**Grade 2C**).

Definitions

Grade of Recommendation	Clarity of Risk/Benefit	Methodological Strength of Supporting Evidence	Implications
1A	Clear	Randomized controlled trials (RCTs) without important limitations	Strong recommendation; can apply to most patients in most circumstances without reservation
1C+	Clear	No RCTs, but strong RCT results can be unequivocally extrapolated, or overwhelming evidence from observational studies	Strong recommendation; can apply to most patients in most circumstances
1B	Clear	RCTs with important limitations (inconsistent results, methodological flaws*)	Strong recommendation; likely to apply to most patients
1C	Clear	Observational studies	Intermediate-strength recommendation; may change when stronger evidence is available
2A	Unclear	RCTs without important limitations	Intermediate-strength recommendation; best action may differ depending on circumstances or patients' or societal values
2C+	Unclear	No RCTs, but	Weak

Grade of Recommendation	Clarity of Risk/Benefit	Methodological Strength of Supporting Evidence	Implications
		strong RCT results can be unequivocally extrapolated, or overwhelming evidence from observational studies	recommendation; best action may differ depending on circumstances or patients' or societal values
2B	Unclear	RCTs with important limitations (inconsistent results, methodological flaws*)	Weak recommendation; alternative approaches likely to be better for some patients under some circumstances
2C	Unclear	Observational studies	Very weak recommendation; other alternatives may be equally reasonable

**These situations include RCTs with both lack of blinding and subjective outcomes, where the risk of bias in measurement of outcomes is high, or RCTs with large loss to follow-up.*

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate use of antithrombotic therapy in selected pediatric populations may help clinicians prevent, manage, and treat thromboembolic complications, while minimizing the risk of adverse effects, such as bleeding, heparin induced thrombocytopenia, and osteoporosis.

POTENTIAL HARMS

- *Heparin*. Further studies are required to determine the true frequency of heparin-induced bleeding in children. There are only three case reports of pediatric heparin-induced osteoporosis, and in two of them patients received concurrent steroid therapy. The third received high-dose intravenous (IV) heparin therapy for a prolonged period. However, given the convincing relationship between heparin and osteoporosis in adults, the long-term use of heparin in children should be avoided when other alternative anticoagulant agents are available. There have been a number of case reports of pediatric heparin-induced thrombocytopenia (HIT) in the literature, and the patients described in those case reports range in age from 3 months to 15 years.
- *Low-molecular-weight heparin (LMWH)*. Although the risk of major bleeding is not precisely known in neonates, there are studies reporting the risk of bleeding in neonates as part of larger patient populations. There are no data on the frequency of osteoporosis, HIT, or other hypersensitivity reactions secondary to LMWH use in children.
- *Vitamin K Antagonists (VKAs)*. Bleeding is the main complication of VKAs. The risk of serious bleeding in children receiving VKAs for mechanical prosthetic valves is <3.2% per patient-year (13 case series). Nonhemorrhagic complications of VKAs, such as tracheal calcification or hair loss, have been described on rare occasions in young children. Two cohort studies have described reduced bone density in children who have received warfarin for >1 year. However, these were uncontrolled studies, and the role of the underlying disorders in reducing bone density remains unclear.
- *Aspirin*. The clearance of aspirin is slower in neonates potentially placing them at risk for bleeding for longer periods of time. In neonates, additive antiplatelet effect must be considered if concurrent indomethacin therapy is required. In older children, aspirin rarely causes clinically important hemorrhaging, except in the presence of an underlying hemostatic defect or in children who also have been treated with anticoagulant or thrombolytic therapy. The relatively low doses of aspirin used as antiplatelet therapy, compared to the much higher doses used for anti-inflammatory therapy, seldom cause other side effects. For example, although aspirin is associated with Reye syndrome, this appears to be a dose-dependent effect of aspirin and is usually associated with doses of >40 mg/kg.
- *Thrombolytic Therapy*. Thrombolytic therapy has been reported to have significant bleeding complications in children, occurring in 68% of patients, with bleeding requiring transfusion in 39%. The prolonged duration of thrombolytic infusion was associated with increased bleeding. Earlier literature reviews (including 255 patients) had concluded that the incidence of bleeding requiring treatment with packed red blood cells (RBCs) was approximately 20% in pediatric patients. The most frequent problem was bleeding at sites of invasive procedures that required treatment with blood products. Another review reported intracranial hemorrhage (ICH) in 14 of the 929 (1.5%) analyzed. When subdivided according to age, ICH was identified in 2 of 468 children (0.4%) after the neonatal period, 1 of 83 term infants

(1.2%), and 11 of 86 preterm infants (13.8%). However, in the largest study of premature infants included in this review, the incidence of ICH was the same in patients in the control arm of the study, who had not received thrombolytic therapy.

CONTRAINDICATIONS

CONTRAINDICATIONS

- Danaparoid sodium (Orgaran) is predominantly removed from the circulation through the kidneys. Consequently, its use is contraindicated in patients with severe impaired renal function.
- There are well-defined contraindications to thrombolytic therapy in adults. These include a history of stroke, transient ischemic attacks, other neurologic disease, and hypertension. Similar problems in children should be considered as relative, but not absolute, contraindications to thrombolytic therapy.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

Interpreting the Recommendations

Clinicians, third-party payers, institutional review committees, or the courts should not construe these guidelines in any way as absolute dictates. In general, anything other than a **Grade 1A** recommendation indicates that the article authors acknowledge that other interpretations of the evidence, and other clinical policies, may be reasonable and appropriate. Even **Grade 1A** recommendations will not apply to all circumstances and all patients. For instance, the guideline developers have been conservative in their considerations of cost and have seldom downgraded recommendations from **Grade 1** to **Grade 2** on the basis of expense. As a result, in jurisdictions in which resource constraints are severe, alternative allocations may serve the health of the public far better than some of the interventions that are designated as **Grade 1A**. This will likely be true for all less industrialized countries and, with the increasing promotion of expensive drugs with marginal benefits, may be increasingly true for wealthier nations.

Similarly, following **Grade 1A** recommendations will at times not serve the best interests of patients with atypical values or preferences or of those whose risks differ markedly from those of the usual patient. For instance, consider patients who find anticoagulant therapy extremely aversive, either because it interferes with their lifestyle (e.g., prevents participation in contact sports) or because of the need for monitoring. Clinicians may reasonably conclude that following some **Grade 1A** recommendations for anticoagulation therapy for either group of patients will be a mistake. The same may be true for patients with particular comorbidities (e.g., a recent gastrointestinal bleed or a balance disorder with repeated falls) or other special circumstances (e.g., very advanced age) that put them at unusual risk.

The guideline developers trust that these observations convey their acknowledgment that no recommendations or clinical practice guidelines can take

into account the often compelling and unique features of individual clinical circumstances. No clinician, and no body charged with evaluating a clinician´s actions, should attempt to apply these recommendations in a rote or blanket fashion.

Limitations of Guideline Development Methods

The limitations of these guidelines include the possibility that some authors followed this methodology more closely than others, although the development process was centralized and supervised by the editors. Second, it is possible that the guideline developers missed relevant studies despite the comprehensive searching process. Third, the guideline developers did not centralize the methodological evaluation of all studies to facilitate uniformity in the validity assessments of the research incorporated into these guidelines. Fourth, if high-quality meta-analyses were unavailable, the guideline developers did not statistically pool primary study results using meta-analysis. Finally, sparse data on patient preferences and values, resources, and other costs represent additional limitations that are inherent to most guideline development methods.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Guideline Implementation Strategies

A full review of implementation strategies for practice guidelines is provided in the companion document titled "Antithrombotic and Antithrombolytic Therapy: From Evidence to Application." The review suggests that there are few implementation strategies that are of unequivocal, consistent benefit, and that are clearly and consistently worth resource investment. The following is a summary of the recommendations (see "Major Recommendations" for a definition of the recommendation grades).

To encourage uptake of guidelines, the guideline developers recommend that appreciable resources be devoted to distribution of educational material (**Grade 2B**).

They also suggest that:

- Few resources be devoted to educational meetings (**Grade 2B**)
- Few resources be devoted to educational outreach visits (**Grade 2A**)
- Appreciable resources be devoted to computer reminders (**Grade 2A**)
- Appreciable resources be devoted to patient-mediated interventions to encourage uptake of the guidelines (**Grade 2B**)
- Few resources be devoted to audit and feedback (**Grade 2B**)

IMPLEMENTATION TOOLS

Patient Resources
Personal Digital Assistant (PDA) Downloads
Quick Reference Guides/Physician Guides

Resources
Slide Presentation
Tool Kits

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Monagle P, Chan A, Massicotte P, Chalmers E, Michelson AD. Antithrombotic therapy in children: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004 Sep;126(3 Suppl):645S-87S. [487 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

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GUIDELINE DEVELOPER(S)

American College of Chest Physicians - Medical Specialty Society

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Dr. Chan has received research funding from Leo Pharma and Pfizer, and has received honoraria for his participation on the advisory boards from Aventis Pharma, Bayer, and Wyeth.

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GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Monagle P, Michelson AD, Bovill E, Andrew M. Antithrombotic therapy in children. Chest 2001 Jan;119(1 Suppl):344S-370S.

GUIDELINE AVAILABILITY

Electronic copies: Available from the Chest - The Cardiopulmonary and Critical Care Journal.

Print copies: Available from the American College of Chest Physicians, Products and Registration Division, 3300 Dundee Road, Northbrook IL 60062-2348.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Evidence-based guidelines. Northbrook, IL: ACCP, 2004 Sep.
- Methodology for guideline development for the Seventh American College of Chest Physicians Conference on Antithrombotic and Thrombolytic Therapy. Northbrook, IL: ACCP, 2004 Sep.
- Applying the grades of recommendation for antithrombotic and thrombolytic therapy: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Northbrook, IL: ACCP, 2004 Sep.
- Hemorrhagic complications of anticoagulant treatment: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Northbrook, IL: ACCP, 2004 Sep.
- Antithrombotic and thrombolytic therapy: from evidence to application: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Northbrook, IL: ACCP, 2004 Sep.
- Platelet-active drugs: the relationships among dose, effectiveness, and side effects: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Northbrook, IL: ACCP, 2004 Sep.

Electronic copies: Available from the Chest - The Cardiopulmonary and Critical Care Journal Web site.

Print copies: Available from the American College of Chest Physicians (ACCP), Products and Registration Division, 3300 Dundee Road, Northbrook IL 60062-2348.

The following is also available:

- Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence-based guidelines; quick reference guide. Northbrook, IL: ACCP, 2004 Sep. Personal Digital Assistant (PDA) download available at ACCP Web site.

Additional implementation tools are also available:

- Clinical resource: antithrombotic and thrombolytic therapy. Northbrook, IL. ACCP, 2004. Ordering information: Available from the ACCP Web site.

PATIENT RESOURCES

The following is available:

- A patient's guide to antithrombotic and thrombolytic therapy. In: Clinical resource: antithrombotic and thrombolytic therapy. Northbrook (IL): American College of Chest Physicians (ACCP). 2004.

Ordering information is available from the ACCP Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

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