Complete Summary

GUIDELINE TITLE

Heparin-induced thrombocytopenia: recognition, treatment, and prevention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy.

BIBLIOGRAPHIC SOURCE(S)

Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia: recognition, treatment, and prevention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004 Sep;126(3 Suppl):311S-37S. [179 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

** 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)

Heparin-induced thrombocytopenia (HIT)

GUIDELINE CATEGORY

Evaluation
Management
Prevention
Treatment

CLINICAL SPECIALTY

Cardiology
Critical Care
Family Practice
Internal Medicine

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To provide evidence-based guidelines on the recognition, treatment, and prevention of heparin-induced thrombocytopenia (HIT)

TARGET POPULATION

- Patients receiving therapeutic-dose unfractionated heparin (UFH)
    - Patients receiving porcine UFH for the treatment of venous or arterial thrombosis
- Postoperative patients receiving UFH antithrombotic prophylaxis
    - Postoperative orthopedic, cardiac, and vascular surgery patients receiving UFH for 1 to 2 weeks
- Patients in whom heparin-induced thrombocytopenia (HIT) is infrequent (0.1 to 1%)
    - Medical/obstetric patients receiving prophylactic-dose UFH for the prevention of thrombosis
    - Postoperative patients receiving low molecular weight heparin (LMWH)
    - Postoperative/critical care patients receiving UFH flushes

    - Medical patients receiving LMWH after having received one or more preceding doses of UFH
- Patients in whom HIT is rare (<0.1%)
    - Medical/obstetric patients receiving LMWH
- Patients undergoing cardiopulmonary bypass (CPB) surgery
- Patients undergoing percutaneous coronary interventions (PCIs)

INTERVENTIONS AND PRACTICES CONSIDERED

Evaluation

1. Platelet count
2. Activated clotting time (ACT)
3. Activated partial thromboplastin time (APTT)
4. Ecarin clotting time (ECT)
5. International normalized ratio (INR)
6. Protein C level
7. Thrombin-antithrombin complex
8. Platelet activation (or "functional") assay using washed platelets (e.g., ^{14}C-SRA, heparin-induced platelet activation assay)
9. Platelet factor 4 (PF4)-dependent enzyme immunoassay
10. Ultrasonography of the lower-limb veins

Treatment

1. Heparins
    - Unfractionated heparin (UFH)
        - Bovine lung UFH
        - Porcine gut UFH
    - Low-molecular-weight heparin (LMWH)
2. Vitamin K antagonists
    - Warfarin
    - Phenprocoumon
3. Direct thrombin inhibitors (DTI)
    - Lepirudin
    - Argatroban
    - Bivalirudin
4. Factor Xa inhibitors
    - Danaparoid (Note: Withdrawn from US market; still available in Canada, continental Europe, and New Zealand)
    - Fondaparinux
5. Ancrod (defibrinogenating snake venom)
6. Dextran
7. Vitamin K
8. Platelet transfusions
9. Epoprostenol
10. Tirofiban
11. Vasopressors

MAJOR OUTCOMES CONSIDERED

- Frequency of heparin-induced thrombocytopenia (HIT)

- Frequency of HIT antibody formation
- Incidence of new thrombosis
- Mortality
- Limb amputation
- Drug anaphylaxis
- Platelet count recovery
- Repeat formation of HIT antibodies
- Procedural success
- Vitamin K antagonist (VKA) therapy-associated thrombosis, including venous limb gangrene and skin necrosis
- Sensitivity and specificity of diagnostic tests
- Predictive value of diagnostic tests

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 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

Grade of Recommendation	Clarity of Risk/Benefit	Methodological Strength of Supporting Evidence	Implications
			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 studies	Weak 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.*

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 their 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.

Recognition of Heparin-Induced Thrombocytopenia (HIT)

Platelet Count Monitoring for HIT

1. For patients receiving heparin in whom the risk of HIT is considered to be >0.1%, the guideline developers recommend platelet count monitoring over no platelet count monitoring (**Grade 1C**).

   Underlying values and preferences: This recommendation places a high value on diagnosis and early treatment of HIT to prevent sequelae and a lower value on the burden and cost of monitoring platelet counts.

Platelet Count Monitoring of Patients Recently Treated with Heparin

1. For patients who are starting unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) treatment and who have received UFH within the past 100 days, or those patients in whom exposure history is uncertain, the guideline developers suggest obtaining a baseline platelet count and then a repeat platelet count within 24 hours of starting heparin (**Grade 2C**).

Acute Systemic Reactions after Intravenous (IV) UFH Bolus

1. For patients who acquire acute inflammatory, cardiorespiratory, neurologic, or other unusual symptoms and signs within 30 min following an IV UFH bolus, the guideline developers recommend performing an immediate platelet count measurement, and comparing this value to recent prior platelet counts, in comparison with not performing a platelet count measure(**Grade 1C**).

Platelet Count Monitoring in Patients Receiving Therapeutic-Dose UFH

1. For patients who are receiving therapeutic-dose UFH, the guideline developers suggest at least every-other-day platelet count monitoring until day 14, or until UFH is stopped, whichever occurs first (**Grade 2C**).

   Underlying values and preferences: This recommendation places a high value on diagnosis and early treatment of HIT to prevent sequelae, and a lower value on the burden and cost of monitoring platelet counts.

Platelet Count Monitoring in Postoperative Patients Receiving UFH Antithrombotic Prophylaxis

1. For patients who are receiving postoperative antithrombotic prophylaxis with UFH (HIT risk >1%), the guideline developers suggest at least every-other-day platelet count monitoring between postoperative days 4 to 14, or until UFH is stopped, whichever occurs first (**Grade 2C**).

   Underlying values and preferences: This recommendation places a high value on diagnosis and early treatment of HIT to prevent sequelae, and a lower value on the burden and cost of monitoring platelet counts.

Platelet Count Monitoring in Patients in Whom HIT is Infrequent (0.1 to 1%)

1. For medical/obstetrical patients who are receiving prophylactic-dose UFH, postoperative patients receiving prophylactic-dose LMWH, postoperative patients receiving intravascular catheter UFH "flushes," or medical/obstetrical

patients receiving LMWH after first receiving UFH (HIT risk 0.1 to 1%), the guideline developers suggest platelet count monitoring every 2 to 3 days from day 4 to day 14 (or until heparin is stopped, whichever occurs first), when practical (**Grade 2C**).

Underlying values and preferences: This recommendation places a high value on diagnosis and early treatment of HIT to prevent sequelae, and a lower value on the burden and cost of monitoring platelet counts.

Platelet Count Monitoring When HIT is Rare (<0.1%)

1. For medical/obstetrical patients who are only receiving LMWH, or medical patients who are receiving only intravascular catheter UFH flushes (HIT risk <0.1%), the guideline developers suggest clinicians do **not** use routine platelet count monitoring (**Grade 2C**).

   Underlying values and preferences: This recommendation places a lower value on the rare diagnosis and early treatment of HIT to prevent sequelae, and a higher value on the burden and cost of monitoring platelet counts.

Screening for Subclinical HIT Antibody Seroconversion

1. In patients who receive heparin, the guideline developers recommend **against** routine HIT antibody testing in the absence of thrombocytopenia, thrombosis, heparin-induced skin lesions, or other sequelae of HIT (**Grade 1C**).

When Should HIT Be Suspected?

1. For patients receiving heparin, or who have received heparin within the previous 2 weeks, the guideline developers recommend excluding a diagnosis of HIT if the platelet count falls by ≥50%, and/or a thrombotic event occurs, between days 4 to 14 following initiation of heparin, even if the patient is no longer receiving heparin therapy when thrombosis or thrombocytopenia have occurred (**Grade 1C**).

Special Situation: Anticoagulant Prophylaxis and Platelet Count Monitoring after Cardiac Surgery

1. For postoperative cardiac surgery patients, the guideline developers recommend excluding a diagnosis of HIT if the platelet count falls by ≥50% (and/or a thrombotic event occurs) between postoperative days 4 to day 14 (day of cardiac surgery = day zero) [**Grade 1C**].

Treatment of HIT

Nonheparin Anticoagulants for HIT

1. For patients with strongly suspected (or confirmed) HIT, whether or not complicated by thrombosis, the guideline developers recommend use of an alternative, nonheparin anticoagulant, such as lepirudin (**Grade 1C+**),

argatroban (**Grade 1C**), bivalirudin (**Grade 2C**), or danaparoid (**Grade 1B**), over further UFH or LMWH therapy, and over no further anticoagulation (with or without vena caval filter).

2. For patients with strongly suspected (or confirmed) HIT, whether or not there is clinical evidence of lower-limb deep vein thrombosis (DVT), the guideline developers recommend routine ultrasonography of the lower-limb veins for investigation of DVT, over not performing routine ultrasonography (**Grade 1C**).

Vitamin K Antagonists (VKAs)

Management of Direct Thrombin Inhibitor (DTI)-VKA Overlap

1. For patients with strongly suspected or confirmed HIT, the guideline developers recommend **against** the use of vitamin K antagonist (coumarin) therapy until after the platelet count has substantially recovered (e.g., to at least 100 x 10^9/L, and preferably, 150 x 10^9/L); that the VKA be administered only during overlapping alternative anticoagulation (minimum 5-day overlap), and begun with low, maintenance doses (maximum, 5 mg of warfarin, and 6 mg of phenprocoumon); that the alternative anticoagulant not be stopped until the platelet count has reached a stable plateau, and with at least the last 2 days the international normalized ration (INR) within the target therapeutic range (**Grade 1C**).

Reversal of VKA Anticoagulation

1. For patients receiving VKAs at the time of diagnosis of HIT, the guideline developers recommend use of vitamin K (**Grade 2C**).

LMWH for HIT

1. For patients with strongly suspected HIT, whether or not complicated by thrombosis, the guideline developers recommend **against** use of LMWH (**Grade 1C+**).

Prophylactic Platelet Transfusions for HIT

1. For patients with strongly-suspected or confirmed HIT who do not have active bleeding, the guideline developers suggest that prophylactic platelet transfusions not be administered (**Grade 2C**).

<u>Special Patient Populations</u>

Patients with Previous HIT Undergoing Cardiac or Vascular Surgery

1. For patients with a history of HIT who are HIT antibody negative and require cardiac surgery, the guideline developers recommend the use of UFH over a nonheparin anticoagulant (**Grade 1C**).

   Remark: Preoperative and postoperative anticoagulation, if indicated, should be administered with a nonheparin anticoagulant.

Patients with Acute or Subacute HIT Undergoing Cardiac Surgery

1. For patients with acute HIT (thrombocytopenic, HIT antibody positive) who require cardiac surgery, the guideline developers recommend one of the following alternative anticoagulant approaches (in descending order of preference):
    - Delaying surgery (if possible) until HIT antibodies are negative (see recommendation above concerning patients with previous HIT undergoing cardiac or vascular surgery) (**Grade 1C**);
    - Using bivalirudin for intraoperative anticoagulation during cardiopulmonary bypass (CPB) (if ecarin clotting time [ECT] available) (**Grade 1C**) or during off-pump cardiac surgery (**Grade 1C+**);
    - Using lepirudin for intraoperative anticoagulation (if ECT available and patient has normal renal function) (**Grade 1C**);
    - Using UFH plus the antiplatelet agent, epoprostenol (if ECT monitoring not available or renal insufficiency precludes lepirudin use) (**Grade 2C**);
    - Using UFH plus the antiplatelet agent, tirofiban (**Grade 2C**);
    - Using danaparoid for intraoperative anticoagulation (if anti-factor Xa levels are available) (**Grade 2C**)
2. For patients with subacute HIT (platelet count recovery, but continuing HIT antibody-positive), the guideline developers recommend delaying surgery (if possible) until HIT antibodies are negative, then using heparin (see recommendation above concerning patients with previous HIT undergoing cardiac or vascular surgery) (**Grade 1C**). Alternatively, the guideline developers suggest the use of a nonheparin anticoagulant (see recommendation directly above concerning patients with acute HIT [thrombocytopenic, HIT antibody positive] who require cardiac surgery) (**Grade 2C**).

Percutaneous Coronary Interventions (PCIs)

1. For patients with acute or previous HIT who require cardiac catheterization or PCI, the guideline developers recommend use of an alternative anticoagulant, such as argatroban (**Grade 1C**), bivalirudin (**Grade 1C**), lepirudin (**Grade 1C**), or danaparoid (**Grade 2C**), over the use of heparin.

<u>Prevention of HIT</u>

Reducing HIT Antibody Formation and Clinical HIT

UFH vs. LMWH

1. For postoperative orthopedic surgery patients, the guideline developers recommend the use of LMWH over UFH (**Grade 1A**).

Bovine vs. Porcine UFH

1. For the treatment of patients with thrombosis, the guideline developers recommend **against** the use of bovine UFH, in comparison with porcine UFH or LMWH (**Grade 1A**).

2. For patients undergoing cardiac surgery, the guideline developers recommend the use of porcine UFH for intraoperative anticoagulation, in comparison with bovine UFH (**Grade 1B**).

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

Grade of Recommendation	Clarity of Risk/Benefit	Methodological Strength of Supporting Evidence	Implications
			values
2C+	Unclear	No RCTs, but strong RCT results can be unequivocally extrapolated, or overwhelming evidence from observational studies	Weak 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 recognition, treatment, and prevention of heparin-induced thrombocytopenia (HIT)

Subgroups Most Likely to Benefit:

Patient groups most likely to benefit from platelet count monitoring are those at the highest risk of HIT (1 to 5%) and include postoperative orthopedic, cardiac, and vascular surgery patients who are receiving unfractionated heparin for 1 to 2 weeks.

POTENTIAL HARMS

There are risks involved in the use of any antithrombotic agent for treatment of heparin-induced thrombocytopenia, including risks of fatal bleeding. None of these agents has an antidote, and thus careful drug selection for the appropriate patient is a relevant issue.

CONTRAINDICATIONS

CONTRAINDICATIONS

- Given the availability of nonheparin anticoagulants to treat heparin-induced thrombocytopenia (HIT), low molecular weight heparin (LMWH) should be considered contraindicated for treatment of acute HIT.
- Platelet transfusions are generally considered as being relatively contraindicated for the prevention of bleeding in patients with acute HIT. This is because petechiae and other mucocutaneous bleeding typical of thrombocytopenia are not clinical features of HIT, despite even severe thrombocytopenia, and platelet transfusions have been linked with thrombotic events, albeit only in anecdotal reports.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- In making recommendations for the management of HIT, the guideline developers have chosen to combine the approach to patients with "isolated HIT" and HIT-associated thrombosis.
- The American College of Chest Physicians (ACCP) conference members examined the question of whether they should make a general recommendation favoring LMWH over UFH for the prevention of HIT. The participants—in the view of lack of sufficient evidence for all patient groups—disagreed about making this recommendation. Some participants believed that prevention of HIT was an important primary goal, sufficiently dominant to determine the decision regarding choice of LMWH and UFH. Other participants believed that the question of whether LMWH is safer in terms of

HIT prevention in non-orthopedic surgery settings is unproven, and that HIT risk should only be one among a number of considerations in the choice. Moreover, this latter group of participants noted that such a general recommendation would have considerable economic consequences, particularly in North America where costs of LMWH exceed those in Europe. Thus, the guideline developers have not provided a recommendation on this question, except in post-orthopedic surgery patients in whom randomized controlled trial evidence is available indicating a difference in both risk of HIT and HIT-associated thrombosis between LMWH and UFH.

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
Staying Healthy

IOM DOMAIN

Effectiveness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia: recognition, treatment, and prevention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004 Sep;126(3 Suppl):311S-37S. [179 references] PubMed

ADAPTATION

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

DATE RELEASED

2004 Sep

GUIDELINE DEVELOPER(S)

American College of Chest Physicians - Medical Specialty Society

SOURCE(S) OF FUNDING

Funding was provided through an unrestricted educational grant by AstraZeneca LP, Aventis Pharmaceuticals, GlaxoSmithKline, Bristol-Myer Squibb/Sanofi-Synthelabo Partnership, and Organon Sanofi-Synthelabo LLC.

GUIDELINE COMMITTEE

American College of Chest Physicians Consensus Panel on Antithrombotic and Thrombolytic Therapy

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Primary Authors: Theodore E. Warkentin, MD (*Chair*); Andreas Greinacher, MD

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Dr. Warkentin has received research funding from Organon and Sanofi-Synthelabo, and has received honoraria for his participation on advisory boards and/or as a speaker at educational events from Aventis, Berlex Laboratories,

Genentech, Glaxo Smith Kline, Medicines Company, Novartis, NovoNordisk, Organon, Pharmion, RenalTech International, and Sanofi-Synthelabo.

Dr. Greinacher has received research funding from Celltech, Berlex, Pharmion, Novartis, and has received honoraria for his participation on advisory boards and/or as a speaker at educational events from Berlex, Pharmion, Celltech, Mitsubishi, Aventis Pharma, SheringAG.

GUIDELINE STATUS

This is the current release of the guideline.

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.

NGC STATUS

This NGC summary was completed by ECRI on November 19, 2004. The information was verified by the guideline developer on January 12, 2005. This summary was updated by ECRI on March 6, 2007 following the U.S. Food and Drug Administration (FDA) advisory on Coumadin (warfarin sodium). This summary was updated by ECRI Institute on June 22, 2007 following the U.S. Food and Drug Administration (FDA) advisory on heparin sodium injection. This summary was updated by ECRI Institute on September 7, 2007 following the revised U.S. Food and Drug Administration (FDA) advisory on Coumadin (warfarin). This summary was updated by ECRI Institute on March 14, 2008 following the updated FDA advisory on heparin sodium injection.

COPYRIGHT STATEMENT

This NGC summary is based on the original guideline, which is subject to the guideline developer's copyright restrictions.

DISCLAIMER

NGC DISCLAIMER

The National Guideline Clearinghouse™ (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the NGC Inclusion Criteria which may be found at http://www.guideline.gov/about/inclusion.aspx .

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.

© 1998-2008 National Guideline Clearinghouse

Date Modified: 9/15/2008