



## Complete Summary

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### GUIDELINE TITLE

Heparin and low molecular weight heparin. In: Sixth ACCP Consensus Conference on Antithrombotic Therapy.

### BIBLIOGRAPHIC SOURCE(S)

Hirsh J, Warkentin TE, Shaughnessy SG, Anand SS, Halperin JL, Raschke R, Granger C, Ohman EM, Dalen JE. Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. Chest 2001 Jan; 119(1 Suppl):64S-94S. [377 references]

## COMPLETE SUMMARY CONTENT

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INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT

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## SCOPE

### DISEASE/CONDITION(S)

1. Thromboembolic disorders and conditions that predispose to thromboembolism, including the following:
  - Venous thrombosis
  - Pulmonary embolism
  - Unstable angina
  - Acute myocardial infarction
  - Cardiac surgery (cardiac bypass, vascular surgery, or coronary angioplasty)
  - Coronary stents
  - Disseminated intravascular coagulation
2. Heparin induced thrombocytopenia with or without thrombosis

### GUIDELINE CATEGORY

Management  
Prevention  
Treatment

#### CLINICAL SPECIALTY

Cardiology  
Critical Care  
Emergency Medicine  
Family Practice  
Internal Medicine  
Obstetrics and Gynecology  
Pulmonary Medicine  
Surgery

#### INTENDED USERS

Physicians

#### GUIDELINE OBJECTIVE(S)

- To review the mechanisms of action of heparin and low-molecular-weight-heparins, their pharmacokinetics, anticoagulant effects, side effects, and laboratory monitoring
- To discuss the clinical uses of heparin and low-molecular-weight-heparins and the results of clinical trials
- To make evidence-based recommendations for the management and treatment of heparin-induced thrombocytopenia

#### TARGET POPULATION

1. Patients who might benefit from therapy with heparin or low-molecular-weight heparin, including:
  - Patients at risk of developing venous thromboembolism
  - Patients with venous thrombosis, pulmonary embolism, unstable angina, or acute myocardial infarction
  - Patients undergoing cardiac surgery using cardiac bypass, vascular surgery, or coronary angioplasty
  - Patients with coronary stents
  - Selected patients with disseminated intravascular coagulation
2. Patients with heparin-induced thrombocytopenia with or without thrombosis

#### INTERVENTIONS AND PRACTICES CONSIDERED

1. The use of heparin and low-molecular-weight heparin in a variety of clinical situations:
  - Laboratory monitoring with activated partial thromboplastin time of the anticoagulant response to heparin
  - Dosing nomograms
  - Management of heparin resistance
2. Pharmacomanagement of acute heparin-induced thrombocytopenia:

- Danaparoid sodium
- Recombinant hirudin (lepirudin)
- Argatroban
- Warfarin in patients who have been adequately anticoagulated with one of the above drugs

Note:

- Warfarin alone to treat acute heparin-induced thrombocytopenia complicated by deep vein thrombosis is considered but not recommended.
- Low-molecular-weight heparin and prophylactic platelet transfusions are considered but not recommended for acute heparin-induced thrombocytopenia.

## MAJOR OUTCOMES CONSIDERED

Therapeutic efficacy and safety as evidence by the following outcome measures:

- Laboratory measurements (anti-Xa levels, activated partial prothrombin time levels, platelet counts)
- Rates of thrombosis
- Rates of bleeding
- Rates of relative risk reduction
- Mortality rates

## 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

The participants reviewed information from an exhaustive review of the literature.

### 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) (see "Rating Scheme for the Strength of the Recommendations") and the methodologic quality of the underlying evidence (A, B, C+, or C).

Grades of evidence for antithrombotic agents:

1A

Methodological strength of supporting evidence: randomized controlled trials without important limitations

1B

Methodological strength of supporting evidence: randomized controlled trials with important limitations (inconsistent results, methodologic flaws\*)

1C+

Methodological strength of supporting evidence: no randomized controlled trials, but randomized controlled trial results can be unequivocally extrapolated; or, overwhelming evidence from observational studies

1C

Methodological strength of supporting evidence: observation studies

2A

Methodological strength of supporting evidence: randomized controlled trials without important limitations

2B

Methodological strength of supporting evidence: randomized controlled trials with important limitations (inconsistent results, methodologic flaws\*)

2C

Methodological strength of supporting evidence: observational studies

\* Such situations include randomized controlled trials with lack of blinding, and subjective outcomes, in which the risk of bias in measurement of outcomes is high; and randomized controlled trials with large loss to follow-up.

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

Not stated

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 two factors: the trade-off between benefits and risks, and the strength of the methodology that leads to estimates of the treatment effect. The rating scheme used for this guideline captures these factors. The guideline developers grade the trade-off between benefits and risks in two categories: (1) the trade-off is clear enough that most patients, despite differences in values, would make the same choice; and (2) the trade-off is less clear, and each patient's values will likely lead to different choices.

When randomized trials provide precise estimates suggesting large treatment effects, and 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 uncertain, 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/consistency and the balance of positive and negative impacts of treatment on the strength of recommendations. In situations when 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 are precise estimates of both benefit and harm, and the balance between the two clearly favors recommending or not recommending the intervention for the average patient with compatible values and preferences. Table 2 of the original guideline document summarizes how 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 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 venous thrombosis); if the magnitude of risk reduction in the overall group is small; if the risk is low in a particular subgroup of patients; if the estimate of the treatment effect, reflected in a wide confidence interval (CI) around the effect, is imprecise; if there is substantial potential harm associated with therapy; or if 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. If they understand the benefits and risks, virtually all patients will take aspirin after myocardial infarction or will comply with prophylaxis to reduce thromboembolism after hip replacement. Thus, one way of thinking about a grade 1 recommendation is that variability in patient values or individual physician 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 will 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.

## RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

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

### Grades of recommendation for antithrombotic agents:

#### 1A

Clarity of risk/benefit: risk/benefit clear

Implications: strong recommendation; can apply to most circumstances, without reservation

#### 1B

Clarity of risk/benefit: risk/benefit clear

Implications: strong recommendation; likely to apply to most patients

#### 1C+

Clarity of risk/benefit: risk/benefit clear

Implications: strong recommendation; can apply to most patients in most circumstances

#### 1C

Clarity of risk/benefit: risk/benefit clear

Implications: intermediate-strength recommendation; may change when stronger evidence available

#### 2A

Clarity of risk/benefit: risk/benefit unclear

Implications: intermediate strength recommendation; best action may differ, depending on circumstances or patients' societal values

#### 2B

Clarity of risk/benefit: risk/benefit unclear

Implications: weak recommendation; alternative approaches likely to be better for some patients under some circumstances

#### 2C

Clarity of risk/benefit: risk/benefit unclear

Implications: very weak recommendation; other alternatives may be equally reasonable

## COST ANALYSIS

While the American College of Chest Physicians conference participants considered cost in deciding on the strength of recommendations, the paucity of rigorous cost-effective analyses and the wide variability of costs across jurisdictions led the

guideline developers to take a conservative approach to cost issues. That is, cost considerations influenced the recommendations and the grades of those recommendations only when the gradient between alternatives was very large.

## METHOD OF GUIDELINE VALIDATION

Peer Review

## DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The initial guidelines were prepared by the chapter committee (the primary authors) and then reviewed separately by the Committee Co-Chairs and methodology experts and finally by the entire group of Consensus Guideline participants.

# RECOMMENDATIONS

## MAJOR RECOMMENDATIONS

Excerpted by the National Guideline Clearinghouse (NGC):

The grading scheme is defined at the end of the Major Recommendations.

### Treatment of heparin-induced thrombocytopenia

1. The guideline developers recommend the use of one of the following anticoagulant drugs to treat acute heparin-induced thrombocytopenia complicated by thrombosis (see Table 18 in the original guideline document for specific dosing information).
  - Danaparoid sodium (grade 1B)
  - Lepirudin (grade 1C)
  - Argatroban (grade 1C)
2. The guideline developers recommend that anticoagulation with one of these agents until the platelet count has recovered should also be considered for patients with acute heparin-induced thrombocytopenia without thrombosis (isolated heparin-induced thrombocytopenia), as there is a high risk for subsequent clinically evident thrombosis in these patients (all grade 2C in comparison to no treatment).
3. The guideline developers recommend that clinicians do not use warfarin alone to treat acute heparin-induced thrombocytopenia complicated by deep vein thrombosis because of the risk of causing venous limb gangrene (grade 1C).
4. Warfarin appears to be safe in acute heparin-induced thrombocytopenia when it is given to a patient who is adequately anticoagulated with a drug that reduces thrombin generation in heparin-induced thrombocytopenia, such as danaparoid, lepirudin, or argatroban, although it may be prudent to delay starting warfarin therapy until the platelet count has risen to greater than  $100 \times 10^9/L$ . The guideline developers recommend that if warfarin is given to patients with acute heparin-induced thrombocytopenia, it should be administered together with a drug that reduces thrombin generation in heparin-induced thrombocytopenia, until the platelet count has recovered. Then, warfarin can be continued alone (grade 1C).

5. Low-molecular-weight-heparin is contraindicated in heparin-induced thrombocytopenia. The guideline developers recommend that clinicians do not administer low-molecular-weight-heparin for the treatment of acute heparin-induced thrombocytopenia (grade 1C+).
6. The guideline developers recommend that clinicians do not administer prophylactic platelet transfusions for the treatment of acute heparin-induced thrombocytopenia (grade 2C).

The rating scheme framework captures the trade-off between benefits and risks (1 or 2) and the methodologic quality of the underlying evidence (A, B, C+, or C).

Definitions:

Grades of recommendations:

1A

Clarity of risk/benefit: risk/benefit clear

Methodological strength of supporting evidence: randomized controlled trials without important limitations

Implications: strong recommendation; can apply to most circumstances, without reservation

1B

Clarity of risk/benefit: risk/benefit clear

Methodological strength of supporting evidence: randomized controlled trials with important limitations (inconsistent results, methodologic flaws\*)

Implications: strong recommendation; likely to apply to most patients

1C+

Clarity of risk/benefit: risk/benefit clear

Methodological strength of supporting evidence: no randomized controlled trials, but randomized controlled trial results can be unequivocally extrapolated; or, overwhelming evidence from observational studies

Implications: strong recommendation; can apply to most patients in most circumstances

1C

Clarity of risk/benefit: risk/benefit clear

Methodological strength of supporting evidence: observation studies

Implications: intermediate-strength recommendation; may change when stronger evidence available

2A

Clarity of risk/benefit: risk/benefit unclear

Methodological strength of supporting evidence: randomized controlled trials without important limitations

Implications: intermediate strength recommendation; best action may differ, depending on circumstances or patients' societal values

2B

Clarity of risk/benefit: risk/benefit unclear

Methodological strength of supporting evidence: randomized controlled trials with important limitations (inconsistent results, methodologic flaws\*)

Implications: weak recommendation; alternative approaches likely to be better for some patients under some circumstances

2C

Clarity of risk/benefit: risk/benefit unclear

Methodological strength of supporting evidence: observational studies

Implications: very weak recommendation; other alternatives may be equally reasonable

\* Such situations include randomized controlled trials with lack of blinding, and subjective outcomes, in which the risk of bias in measurement of outcomes is high; and randomized controlled trials 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 for each recommendation (refer to "Major Recommendations").

### BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

#### POTENTIAL BENEFITS

Appropriate selection, dosing, and monitoring of anticoagulants in heparin-induced thrombocytopenia can help maximize therapeutic effectiveness while minimizing the risk of side effects or adverse reactions.

#### POTENTIAL HARMS

Lepirudin is renally excreted, and there are risks of bleeding. A high proportion of patients develop antihirudin antibodies, which occasionally result in an increase in anticoagulant effects.

Subgroups Most Likely to be Harmed:

- Patients with renal failure who are taking Lepirudin are at high risk of accumulation and bleeding. Ongoing monitoring is recommended throughout the course of lepirudin treatment, even when the initial anticoagulant effect appears stable.
- Although argatroban is excreted normally in patients with moderate renal failure, the dose must be reduced in patients with hepatic failure.
- Monitoring of danaparoid is recommended for very small and large patients, patients with renal failure, and patients with life-or-limb-threatening thrombosis.

## QUALIFYING STATEMENTS

### QUALIFYING STATEMENTS

#### Interpreting the Recommendations

The authors of these guidelines offer recommendations that should not be construed as dictates by the readers, including clinicians, third-party payers, institutional review committees, and courts. In general, anything other than a 1A recommendation indicates that the chapter 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 1 to 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 more than some of the interventions that we designate grade 1A. This will likely be true for all less-industrialized countries. However, a weak recommendation (2C) that reduces resource consumption may be more strongly indicated in less-industrialized countries.

Similarly, following grade 1A recommendations will at times not serve the best interests of patients with atypical values or preferences. For instance, consider patients who find anticoagulant therapy extremely aversive, either because it interferes with their lifestyle (prevents participation in contact sports, for instance) or because of the need for monitoring. For such patients, clinicians may reasonably conclude that following some grade 1A recommendations for anticoagulation will be a mistake. The same may be true for patients with particular comorbidities (such as a recent GI bleed or a balance disorder with repeated falls) or other special circumstances (such as very advanced age).

The guideline developers trust that these observations convey their acknowledgment that no guidelines or recommendations can take into account the often compelling idiosyncrasies of individual clinical circumstances. No clinician and no one charged with evaluating the actions of a clinician should attempt to apply their recommendations in a rote or blanket fashion.

## IMPLEMENTATION OF THE GUIDELINE

### DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

## INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

### IOM CARE NEED

Living with Illness  
Staying Healthy

### IOM DOMAIN

Effectiveness

## IDENTIFYING INFORMATION AND AVAILABILITY

### BIBLIOGRAPHIC SOURCE(S)

Hirsh J, Warkentin TE, Shaughnessy SG, Anand SS, Halperin JL, Raschke R, Granger C, Ohman EM, Dalen JE. Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. *Chest* 2001 Jan; 119(1 Suppl):64S-94S. [377 references]

### ADAPTATION

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

### DATE RELEASED

2001 Jan

### GUIDELINE DEVELOPER(S)

American College of Chest Physicians - Medical Specialty Society

### SOURCE(S) OF FUNDING

Funding was supplied by DuPont Pharmaceuticals.

### GUIDELINE COMMITTEE

American College of Chest Physicians Consensus Panel on Antithrombotic Therapy

### COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Primary Authors: Jack Hirsh, MD, FCCP, Chair; Theodore E. Warkentin, MD; Stephen G. Shaughnessy, PhD; Sonia S. Anand, MD; Jonathan L. Halperin, MD; Robert Raschke, MD, MS; Christopher Granger, MD; E. Magnus Ohman, MBBCh, FCCP; James E. Dalen, MD, MPH, Master FCCP.

Committee Co-Chairs: James E. Dalen, MD, MPH, FCCP; Jack Hirsh, MD, FCCP.

Participants: Giancarlo Agnelli, MD; Gregory W. Albers, MD; Joseph S. Alpert, MD, FCCP; Pierre Amarenco, MD; Sonia S. Anand, MD; David Anderson, MD; Frederick A. Anderson, PhD; Maureen Andrew, MD; Jack E. Ansell, MD; Peter B. Berger, MD; Edward Bovill, MD; Heiner Bucher, MD, MPH; Henry I. Bussey, PharmD; Christopher P. Cannon, MD; John Cairns, MD; G. Patrick Clagett, MD; Clifford W. Colwell, Jr., MD; Barry S. Collier, MD; Deborah J. Cook, MD, MSc, FCCP; Mark Crowther, MD; Denise Hartnett Daudelin, RN, MPH; Daniel Deykin, MD; J. Donald Easton, MD; Mark H. Eckman, MD; Michael Ezekowitz, MD; Garrett FitzGerald, MD; Valentin Fuster, MD; William Geerts, MD, FCCP; Michael Gent, DSc; Jeffrey S. Ginsberg, MD, FCCP; Steve Goldman, MD; Christopher Granger, MD; Ian A. Greer, MD; Gordon H. Guyatt, MD; Jonathan L. Halperin, MD; Robert A. Harrington, MD; John Heit, MD; Russell D. Hull, MBBS, FCCP; Thomas M. Hyers, MD, FCCP; Mark R. Jackson, MD; Alan K. Jacobson, MD; Roman Jaeschke, MD, MSc, Clive Kearon, MB, PhD, FCCP; J. Ward Kennedy, MD; Seth Landefeld, MD; Mark N. Levine, MD; Herbert J. Levine, MD; H Daniel Lewis, Jr., MD; A. Michael Lincoff, MD; David Matchar, MD; Kevin M. McIntyre, MD, JD; Thomas W. Meade, DM, Alan D. Michelson, MD; Paul Monagle, MBBS; Timothy A. Morris, MD; E. Magnus Ohman, MD, FCCP; Guy Paiement, MD; Carlo Patrono, MD; Stephen G. Pauker, MD; Palle Petersen, MD, DMSc; Graham Frederick Pineo, MD Leon Poller, DSc, MD; Jeffrey J. Popma, MD; Robert Raschke, MD, MS; Gary Raskob, PhD; Joshua Riff; Gerald Roth, MD; Ralph L. Sacco, MD; Eduardo Salazar, MD; Deeb N. Salem, MD, FCCP; Michel M. Samama, MD; Holger J. Schunemann, MD, MSc; Stephen G. Shaughnessy, PhD; Daniel Singer, MD; Paul D. Stein, MD, FCCP; Victor F. Tapson, MD, FCCP; Philip Teal, MD; Pierre Theroux, MD; Alexander G. G. Turpie, MD; Ted Warkentin, MD; John G. Weg, MD, FCCP; Jeffrey Weitz, MD; H. Brownell Wheeler, MD.

#### FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

#### GUIDELINE STATUS

This is the current release of the guideline.

This guideline is an updated version of the 1998 Fifth ACCP consensus conference on antithrombotic therapy (Chest 1998 Nov; 114[5 Suppl]:439S-769S).

#### GUIDELINE AVAILABILITY

Electronic copies of the updated guideline: Available from the [Chest - The Cardiopulmonary and Critical Care Journal Web site](#).

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 is available:

- Sixth ACCP Consensus Conference on Antithrombotic Therapy (2001): summary recommendations. Northbrook, IL: ACCP, 2001. (Quick reference guide for clinicians).

Electronic copies: Available from the [American College of Chest Physicians Web site](#). (HTML, Portable Document Format [PDF], and downloadable files intended for use with Palm OS compatible devices are available.)

Print copies: Available from the American College of Chest Physicians, Products and Registration Division, 3300 Dundee Road, Northbrook IL 60062-2348, or by calling 1 (800) 343-2227.

#### PATIENT RESOURCES

None available

#### NGC STATUS

This summary was completed by ECRI on July 12, 2001. The information was verified by the guideline developer on September 27, 2001.

#### COPYRIGHT STATEMENT

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