Complete Summary

GUIDELINE TITLE

Antithrombotic therapy for venous thromboembolic disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy.

BIBLIOGRAPHIC SOURCE(S)

Buller HR, Agnelli G, Hull RD, Hyers TM, Prins MH, Raskob GE. Antithrombotic therapy for venous thromboembolic disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004 Sep;126(3 Suppl):401S-28S. [196 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

This guideline is updates a previous version: Hyers TM, Agnelli G, Hull RD, Morris TA, Samama M, Tapson V, Weg JG. Antithrombotic therapy for venous thromboembolic disease. Chest 2001 Jan;119(1 Suppl):176S-193S.

** 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
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IMPLEMENTATION OF THE GUIDELINE
INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES
IDENTIFYING INFORMATION AND AVAILABILITY
DISCLAIMER

SCOPE

DISEASE/CONDITION(S)

- Venous thromboembolism (VTE), including:
  - Deep venous thrombosis (DVT)
  - Pulmonary embolism (PE)
  - Acute upper-extremity DVT
- Complications of VTE, including:
  - Postthrombotic syndrome (PTS)
  - Chronic thromboembolic pulmonary hypertension (CTPH)

GUIDELINE CATEGORY

Management
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 describe the effectiveness of and provide evidence-based recommendations about the use of antithrombotic agents, as well as devices or surgical techniques, in the treatment of acute venous thromboembolism (VTE)

- To provide evidence-based recommendations for the treatment of acute upper-extremity deep vein thrombosis (DVT) and two important complications of venous thromboembolism, postthrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension (CTPH)

TARGET POPULATION

Patients with venous thromboembolism (VTE), including deep venous thrombosis (DVT), pulmonary embolism (PE), and acute upper-extremity deep venous thrombosis, or complications of venous thromboembolism, including postthrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension (CTPH)

INTERVENTIONS AND PRACTICES CONSIDERED

Treatment/Management

Pharmacological Management

1. Heparins
    - Subcutaneous (SC) low-molecular-weight heparin (LMWH), including dalteparin, enoxaparin, nadroparin, and tinzaparin
    - Intravenous (IV) or SC unfractionated heparin (UFH)
    - Adjusted-dose heparin and heparinoids
2. Other anticoagulants, including fondaparinux and ximelagatran
3. Vitamin K antagonists (VKAs), including warfarin and acenocoumarol
4. IV thrombolytic therapy, including streptokinase, urokinase, and recombinant tissue plasminogen activator (tPA)
5. Nonsteroidal anti-inflammatory agents

Mechanical Management

1. Ambulation
2. Elastic compression stockings
3. Intermittent pneumatic compression
4. Catheter-directed thrombolysis
5. Catheter extraction or fragmentation

Surgical Management

1. Venous thrombectomy
2. Pulmonary embolectomy
3. Pulmonary thromboendarterectomy
4. Insertion of vena caval filter

Monitoring

1. Activated partial thromboplastin time (aPTT)
2. Plasma heparin level
3. Anti-Xa activity (amidolytic assay)
4. International normalized ratio (INR)

5. Compression ultrasonography

MAJOR OUTCOMES CONSIDERED

- Effectiveness of antithrombotic therapy in treating venous thromboembolism (VTE)
- Adverse effects of therapy, such as bleeding, heparin-induced thrombocytopenia (HIT)
- Thromboembolic recurrence rates, including recurrent deep vein thrombosis (DVT) and pulmonary embolism (PE)
- Mortality rates
- Incidence of DVT complications, including postthrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension (CTPH)
- Quality of life

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

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

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

Low-Molecular-Weight Heparin (LMWH) for the Initial Treatment of Deep Vein Thrombosis (DVT)

Taken together, the results of three studies showed that patients with proximal venous thrombosis can be treated at home with LMWH and vitamin K antagonist (VKA) initiated together. Treatment at home leads to cost savings and improved quality of life. In addition, selected patients can be discharged from the hospital early with a component of LMWH treatment at home. There have been several cohort studies supporting the efficacy and safety of out-of-hospital treatment; these studies strongly support the view that replacing unfractionated heparin (UFH) with LMWH in the treatment of acute deep vein thrombosis is safe and cost-effective.

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.

Treatment of Deep Venous Thrombosis (DVT)

Initial Treatment of Acute DVT of the Leg

1. For patients with objectively confirmed DVT, the guideline developers recommend short-term treatment with subcutaneous (SC) low-molecular-weight heparin (LMWH) or intravenous (IV) unfractionated heparin (UFH) or SC UFH (all **Grade 1A**).
2. For patients with a high clinical suspicion of DVT, the guideline developers recommend treatment with anticoagulants while awaiting the outcome of diagnostic tests (**Grade 1C+**).
3. In acute DVT, the guideline developers recommend initial treatment with LMWH or UFH for at least 5 days (**Grade 1C**).
4. The guideline developers recommend initiation of vitamin K antagonist (VKA) together with LMWH or UFH on the first treatment day and discontinuation of heparin when the international normalized ratio (INR) is stable and >2.0 (**Grade 1A**).

IV UFH for the Initial Treatment of DVT

1. If IV UFH is chosen, the guideline developers recommend that it be administered by continuous infusion with dose adjustment to achieve and maintain an activated partial thromboplastin time (aPTT) prolongation corresponding to plasma heparin levels from 0.3 to 0.7 IU/mL anti-Xa activity by the amidolytic assay (**Grade 1C+**).
2. In patients requiring large daily doses of UFH without achieving a therapeutic aPTT, the guideline developers recommend the measurement of the anti-Xa level for dose guidance (**Grade 1B**).

SC UFH for the Initial Treatment of DVT

1. In patients with acute DVT, the guideline developers recommend that SC administered UFH can be used as an adequate alternative to IV UFH (**Grade 1A**).
2. For patients who receive SC UFH, the guideline developers recommend an initial dose of 35,000 U/24 hours SC, with subsequent dosing to maintain the aPTT in the therapeutic range (**Grade 1C+**).

LMWH for the Initial Treatment of DVT

1. In patients with acute DVT, the guideline developers recommend initial treatment with LMWH SC once or twice daily over UFH as an outpatient if possible (**Grade 1C**), and as inpatient if necessary (**Grade 1A**).
2. In patients with acute DVT treated with LMWH, the guideline developers recommend against routine monitoring with anti-factor Xa level measurements (**Grade 1A**).
3. In patients with severe renal failure, the guideline developers suggest IV UFH over LMWH (**Grade 2C**).

Systematically Administered Thrombolysis in the Initial Treatment of DVT

1. In patients with DVT, the guideline developers recommend **against** the routine use of IV thrombolytic treatment (**Grade 1A**).
2. In selected patients, such as those with massive ileofemoral DVT at risk of limb gangrene secondary to venous occlusion, the guideline developers suggest IV thrombolysis (**Grade 2C**).

Catheter-Directed Thrombolysis in the Initial Treatment of DVT

1. In patients with DVT, the guideline developers recommend **against** the routine use of catheter-directed thrombolysis (**Grade 1C**).
2. The guideline developers suggest that this treatment should be confined to selected patients such as those requiring limb salvage (**Grade 2C**).

Catheter Extraction or Fragmentation and Surgical Thrombectomy for the Initial Treatment of DVT

1. In patients with DVT, the guideline developers recommend **against** the routine use of venous thrombectomy (**Grade 1C**).
2. In selected patients such as patients with massive ileofemoral DVT at risk of limb gangrene secondary to venous occlusion, the guideline developers suggest venous thrombectomy (**Grade 2C**).

Vena Caval Interruption for the Initial Treatment of DVT

1. For most patients with DVT, the guideline developers recommend **against** the routine use of a vena cava filter in addition to anticoagulants (**Grade 1A**).
2. The guideline developers suggest the placement of an inferior vena cava filter in patients with a contraindication for or a complication of anticoagulant treatment (**Grade 2C**), as well as in those with recurrent thromboembolism despite adequate anticoagulation (**Grade 2C**).

Nonsteroidal Anti-inflammatory Agents for the Initial Treatment of DVT

1. For the initial treatment of DVT, the guideline developers recommend **against** the use of nonsteroidal anti-inflammatory agents (**Grade 2B**).

Immobilization

1. For patients with DVT, the guideline developers recommend ambulation as tolerated (**Grade 1B**).

Long-term Treatment of Acute DVT of the Leg

VKAs for the Long-term Treatment of DVT

1. For patients with a first episode of DVT secondary to a transient (reversible) risk factor, the guideline developers recommend long-term treatment with a VKA for 3 months over a treatment for shorter periods (**Grade 1A**).

   Underlying values and preferences: This recommendation ascribes a relatively high value to preventing recurrent thromboembolic events and a relatively low value on bleeding and cost.

   Remark: The latter recommendation applies both to patients with proximal vein thrombosis and to patients with symptomatic DVT confined to the calf veins.

2. For patients with a first episode of idiopathic DVT, the guideline developers recommend treatment with a VKA at least 6 to 12 months (**Grade 1A**).
3. The guideline developers suggest that patients with first-episode idiopathic DVT be considered for indefinite anticoagulant therapy (**Grade 2A**).

   Underlying values and preferences: This recommendation ascribes a relatively high value to preventing recurrent thromboembolic events and a relatively low value on bleeding and cost.

4. For patients with DVT and cancer, the guideline developers recommend LMWH for the first 3 to 6 months of long-term anticoagulant therapy (**Grade 1A**). For the patients, the guideline developers recommend anticoagulant therapy indefinitely or until the cancer is resolved (**Grade 1C**).
5. For patients with a first episode of DVT who have documented antiphospholipid antibodies or who have two or more thrombophilic conditions (e.g., combined factor V Leiden and prothrombin 20210 gene mutations), the guideline developers recommend treatment for 12 months (**Grade 1C+**). The guideline developers suggest indefinite anticoagulant therapy in these patients (**Grade 2C**).

   Underlying values and preferences: This recommendation ascribes a relatively high value to preventing recurrent thromboembolic events and a relatively low value on bleeding and cost.

6. For patients with a first episode of DVT who have documented deficiency of antithrombin, deficiency of protein C or protein S, or the factor V Leiden or prothrombin 20210 gene mutation, homocysteinemia, or high factor VIII levels (>90th percentile of normal), the guideline developers recommend treatment for 6 to 12 months (**Grade 1A**). The guideline developers suggest indefinite therapy as for patients with idiopathic thrombosis (**Grade 2C**).

   Underlying values and preferences: This recommendation ascribes a relatively high value to preventing recurrent thromboembolic events and a relatively low value on bleeding and cost.

7. For patients with two or more episodes of objectively documented DVT, the guideline developers suggest indefinite treatment (**Grade 2A**).
8. The guideline developers recommend that the dose of VKA be adjusted to maintain a target international normalized ratio (INR) of 2.5 (range, 2.0 and 3.0) for all treatment durations (**Grade 1A**). The guideline developers recommend **against** high-intensity VKA therapy (INR range, 3.1 to 4.0) (**Grade 1A)**. The guideline developers recommend **against** low-intensity therapy (INR range, 1.5 to 1.9) compared to INR range of 2.0 to 3.0 (**Grade 1A**).
9. In patients who receive indefinite anticoagulant treatment, the risk-benefit of continuing such treatment should be reassessed in the individual patient at periodic intervals (**Grade 1C**).
10. The guideline developers suggest repeat testing with compression ultrasonography for the presence or absence of residual thrombosis or measurement of plasma D-dimer (**Grade 2C**).

LMWH for the Long-term Treatment of DVT

1. For most patients with DVT and cancer, the guideline developers recommend treatment with LMWH for at least the first 3 to 6 months of long-term treatment (**Grade 1A**).

   Remark: The regimens of LMWH that have been established to be effective for long-term treatment in randomized trials are dalteparin, 200 IU/kg body weight daily (qd) for 1 month, followed by 150 IU/kg qd thereafter, or tinzaparin at 175 IU/kg body weight SC qd.

<u>The Post-Thrombotic Syndrome</u>

Elastic Stockings for the Prevention of the Post-Thrombotic Syndrome (PTS)

1. The guideline developers recommend the use of an elastic compression stocking with a pressure of 30 to 40 mm Hg at the ankle during 2 years after an episode of DVT (**Grade 1A**).

Physical Treatment of the PTS

1. The guideline developers suggest a course of intermittent pneumatic compression for patients with severe edema of the leg due to PTS (**Grade 2B**).
2. The guideline developers suggest the use of elastic compression stockings for patients with mild edema of the leg due to the PTS (**Grade 2C**).

Drug Treatment of the PTS

1. In patients with mild edema due to PTS, the guideline developers suggest administration of rutosides (**Grade 2B**).

<u>Initial Treatment of Acute Pulmonary Embolism (PE)</u>

IV UFH or LMWH for the Initial Treatment of PE

1. For patients with objectively confirmed nonmassive PE, the guideline developers recommend short-term treatment with SC LMWH or IV UFH (both **Grade 1A**).
2. For patients with a high clinical suspicion of PE, the guideline developers recommend treatment with anticoagulants while awaiting the outcome of diagnostic tests (**Grade 1C+**).
3. In patients with acute nonmassive PE, the guideline developers recommend LMWH over UFH (**Grade 1A**).
4. In acute nonmassive PE, the guideline developers recommend initial treatment with LMWH or UFH for at least 5 days (**Grade 1C**).
5. In patients with acute nonmassive PE treated with LMWH, the guideline developers recommend **against** routine monitoring with anti-factor Xa levels (**Grade 1A**).
6. In patients with severe renal failure, the guideline developers suggest IV UFH over LMWH (**Grade 2C**).
7. If IV UFH is chosen, the guideline developers recommend administration by continuous infusion with dose adjustment to achieve and maintain an aPTT prolongation corresponding to plasma heparin levels from 0.3 to 0.7 IU/mL anti-Xa activity by the amidolytic assay (**Grade 1C+**).
8. In patients requiring large daily doses of UFH without achieving a therapeutic aPTT, the guideline developers recommend the measurement of the anti-Xa level for dose guidance (**Grade 1B**).
9. The guideline developers recommend initiation of VKA together with LMWH or UFH on the first treatment day and discontinuation of heparin when the INR is stable and >2.0 (**Grade 1A**).

Systemically and Locally Administered Thrombolytic Drugs for the Initial Treatment of PE

1. For most patients with PE, the guideline developers recommend clinicians **not** use systemic thrombolytic therapy (**Grade 1A**). In selected patients, the guideline developers suggest systemic administration of thrombolytic therapy (**Grade 2B**). For patients who are hemodynamically unstable, the guideline developers suggest use of thrombolytic therapy (**Grade 2B**).
2. The guideline developers suggest clinicians **not** use local administration of thrombolytic therapy via a catheter (**Grade 1C**).
3. For patients with PE who receive thrombolytic regimens, the guideline developers suggest the use of thrombolytic regimens with a short infusion time over those with prolonged infusion times (**Grade 2C**).

Catheter Extraction or Fragmentation for the Initial Treatment of PE

1. For most patients with PE, the guideline developers recommend **against** use of mechanical approaches (**Grade 1C**). In selected highly compromised patients who are unable to receive thrombolytic therapy or whose critical status does not allow sufficient time to infuse thrombolytic therapy, the guideline developers suggest use of mechanical approaches (**Grade 2C**).

Pulmonary Embolectomy for the Initial Treatment of PE

1. For most patients with PE, the guideline developers recommend **against** pulmonary embolectomy (**Grade 1C**). In selected highly compromised patients who are unable to receive thrombolytic therapy or whose critical status does not allow sufficient time to infuse thrombolytic therapy, the guideline developers suggest pulmonary embolectomy (**Grade 2C**).

Vena Caval Interruption for the Initial Treatment of PE

1. In PE patients with a contraindication for or a complication of anticoagulant treatment, as well as in those with recurrent thromboembolism despite adequate anticoagulation, the guideline developers suggest placement of an inferior vena caval filter (both **Grade 2C**).

<u>Long-term Treatment of Acute PE</u>

VKAs for the Long-term Treatment of PE

1. For patients with a first episode of PE secondary to a transient (reversible) risk factor, the guideline developers recommend long-term treatment with a VKA for at least 3 months (**Grade 1A**).
2. For patients with a first episode of idiopathic PE, the guideline developers recommend treatment with a VKA at least 6 to 12 months (**Grade 1A**).
3. The guideline developers suggest that patients with first-episode idiopathic PE be considered for indefinite anticoagulant therapy (**Grade 2A**).

   Underlying values and preferences: This recommendation ascribes a relatively high value to preventing recurrent thromboembolic events and a relatively low value on bleeding and cost.

4. For patients with PE and cancer, the guideline developers recommend LMWH for the first 3 to 6 months of long-term anticoagulant therapy (**Grade 1A**). These patients should then receive anticoagulant therapy indefinitely or until the cancer is resolved (**Grade 1C**).
5. For patients with a first episode of PE who have documented antiphospholipid antibodies or who have two or more thrombophilic conditions (e.g., combined factor V Leiden and prothrombin 20210 gene mutations), the guideline developers recommend treatment for 12 months (**Grade 1C+**). For these patients, the guideline developers suggest indefinite anticoagulant therapy (**Grade 2C**).

   Underlying values and preferences: This recommendation ascribes a relatively high value to preventing recurrent thromboembolic events and a relatively low value on bleeding and cost.

6. For patients with a first episode of PE who have documented deficiency of antithrombin, deficiency of protein C or protein S, or the factor V Leiden or prothrombin 20210 gene mutation, homocysteinemia, or high factor VIII levels (>90th percentile of normal), the guideline developers recommend treatment for 6 to 12 months (**Grade 1A**). The guideline developers suggest indefinite therapy for patients with idiopathic PE (**Grade 2C**).

Underlying values and preferences: This recommendation ascribes a relatively high value to preventing recurrent thromboembolic events and a relatively low value on bleeding and cost.

7. For patients with two or more episodes of objectively documented PE, the guideline developers suggest indefinite treatment (**Grade 2A**).
8. The guideline developers recommend that the dose of VKA be adjusted to maintain a target INR of 2.5 (INR range, 2.0 and 3.0) for all treatment durations (**Grade 1A**). The guideline developers recommend **against** high-intensity VKA therapy (INR range, 3.1 to 4.0) [**Grade 1A**]. The guideline developers recommend **against** low-intensity therapy (INR range, 1.5 to 1.9) compared to INR range of 2.0 to 3.0 (**Grade 1A**).
9. In patients who receive indefinite anticoagulant treatment, the risk-benefit of continuing such treatment should be reassessed in the individual patient at periodic intervals (**Grade 1C**).

LMWH for the Long-term Treatment of PE

1. For most patients with PE and concurrent cancer, the guideline developers recommend treatment with LMWH for at least the first 3 to 6 months of long-term treatment (**Grade 1A**).

   Remark: The LMWH regimens that have been established to be effective for long-term treatment are dalteparin, 200 IU/kg body weight qd for 1 month followed by 150 IU/kg qd thereafter, and tinzaparin at 175 IU/kg body weight SC qd.

Chronic Thromboembolic Pulmonary Hypertension (CTPH)

Pulmonary Thromboendarterectomy, VKAs, and Caval Filter for the Treatment of CTPH

1. In selected patients with CTPH (i.e., patients with central disease under the care of an experienced surgical/medical team), the guideline developers recommend pulmonary thromboendarterectomy (**Grade 1C**).
2. The guideline developers recommend that life-long treatment with VKA to an INR of 2.0 to 3.0 be administered following pulmonary thromboendarterectomy, and also be administered to patients with CTPH who are ineligible for pulmonary thromboendarterectomy (**Grade 1C**).
3. The guideline developers suggest the placement of a vena caval filter before or at the time of pulmonary thromboendarterectomy for CTPH (**Grade 2C**).

Superficial Thrombophlebitis

Treatment for Superficial Thrombophlebitis

1. For patients with superficial thrombophlebitis as a complication of an infusion, the guideline developers suggest topical diclofenac gel (**Grade 1B**) or oral diclofenac (**Grade 2B**).

2. For patients affected by spontaneous superficial thrombophlebitis, the guideline developers suggest intermediate dosages of UFH or LMWH for at least 4 weeks (**Grade 2B**).

Acute Upper Extremity DVT

IV UFH or LMWH for the Initial Treatment of Upper Extremity DVT

1. For patients with acute upper-extremity DVT, the guideline developers recommend initial treatment with UFH (**Grade 1C+**) or LMWH (**Grade 1C+**).

Thrombolytic Therapy for the Initial Treatment of Upper Extremity DVT

1. In selected patients with acute upper-extremity DVT (e.g., in those with a low risk of bleeding and symptoms of recent onset), the guideline developers suggest a short course of thrombolytic therapy for initial treatment (**Grade 2C**).

Catheter Extraction, Surgical Thrombectomy, or Superior Vena Caval Filter for the Initial Treatment of Upper Extremity DVT

1. In selected patients with acute upper-extremity DVT (e.g., those with failure of anticoagulant or thrombolytic treatment and persistent symptoms), the guideline developers suggest surgical embolectomy (**Grade 2C**) or catheter extraction (**Grade 2C**).
2. In selected patients with acute upper-extremity DVT (e.g., those in whom anticoagulant treatment is contraindicated), a superior vena caval filter (**Grade 2C**) could be considered for initial treatment.

Anticoagulants for the Long-term Treatment of Upper Extremity DVT

1. For patients with acute upper-extremity DVT, the guideline developers recommend long-term treatment with a VKA (**Grade 1C+**).

   Remark: As for acute DVT of the leg (see above), a similar process should be considered for determining the duration of VKA treatment.

Elastic Bandages for the Long-term Treatment of Upper Extremity DVT

1. In patients with upper-extremity DVT who have persistent edema and pain, the guideline developers suggest elastic bandages for symptomatic relief (**Grade 2C**).

Definitions

Grade of Recommendation	Clarity of Risk/Benefit	Methodological Strength of Supporting Evidence	Implications

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 strong RCT results can be unequivocally	Weak recommendation; best action may differ depending on

Grade of Recommendation	Clarity of Risk/Benefit	Methodological Strength of Supporting Evidence	Implications
		extrapolated, or overwhelming evidence from observational studies	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 management/treatment of antithrombotic therapy in patients with thromboembolism may improve patient outcomes, while reducing the risk for adverse events, recurrence, and unnecessary cost.

POTENTIAL HARMS

- Antithrombotic pharmacotherapy has the potential for adverse side effects, such as bleeding, heparin-induced thrombocytopenia, and hypersensitivity reactions.
- Catheter-directed thrombolysis has been reported to be associated with local and systemic bleeding, and should be reserved essentially for limb salvage in individual cases after a careful assessment of its benefit/risk ratio compared to routine anticoagulation.
- Surgical thrombectomy is commonly complicated by a recurrence of thrombus formation.

CONTRAINDICATIONS

CONTRAINDICATIONS

- Treatment with vitamin K antagonists (VKA) is the preferred approach for long-term treatment in most patients with deep vein thrombosis (DVT) of the legs. Treatment with adjusted doses of unfractionated heparin (UFH) or therapeutic doses of low-molecular-weight heparin (LMWH) is indicated for selected patients in whom VKAs are contraindicated (e.g., pregnancy) or impractical, or in patients with concurrent cancer, for whom LMWH regimens have been shown to be more effective and safer.
- Venous anatomic abnormalities, pregnancy, and thrombus proximal to the intended point of placement are considered to be contraindications to filter insertion.
- Treatment with VKA is the preferred approach for long-term treatment in most patients with pulmonary embolism (PE). Treatment with adjusted doses of UFH or therapeutic doses of LMWH is indicated for selected patients in whom VKAs are contraindicated (e.g., pregnancy) or impractical, or in patients with concurrent cancer, for whom LMWH regimens have been shown to be more effective and at least as safe for the first 3 to 6 months of 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

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Buller HR, Agnelli G, Hull RD, Hyers TM, Prins MH, Raskob GE. Antithrombotic therapy for venous thromboembolic disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004 Sep;126(3 Suppl):401S-28S. [196 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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GUIDELINE COMMITTEE

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

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Primary Authors: Harry R. Büller, MD (Chair); Giancarlo Agnelli, MD; Russel D. Hull, MBBS, MSc, FCCP; Thomas M. Hyers, MD, FCCP; Martin H. Prins, MD; Gary E. Raskob, PhD

Committee Co-Chairs: Jack Hirsh, MD, FCCP (Chair); Gregory W. Albers, MD; Gordon H. Guyatt, MD, MSc; Holger J. Schünemann, MD, MSc, PhD, FCCP

Participants: Giancarlo Agnelli, MD; Amin Al-Ahmad, MD; Pierre Amarenco, MD; Jack E. Ansell, MD; Shannon M. Bates, MD; Richard C. Becker, MD; Peter B. Berger, MD; David Bergqvist, MD, PhD, FRCS; Rebecca J. Beyth, MD, MSc; Stewart Brower, MLIS; Harry R. Buller, MD; Henry I. Bussey, PharmD, FCCP; Christopher P. Cannon, MD, FACC; Elizabeth A. Chalmers, MB, ChB, MD, MRCP(UK). FRCPath; Anthony K.C. Chan, MD; G. Patrick Clagett, MD; Barry Coller, MD; Clifford W. Colwell, MD; Deborah Cook, MD, MSc; James E. Dalen, MD, MPH, FCCP; J. Donald Easton, MD; Michael Ezekowitz, MD; Garret A. Fitzgerald, MD; William H. Geerts, MD, FCCP; Jeffrey S. Ginsberg, MD, FCCP; Alan S. Go, MD; Shaun D. Goodman, MD, FACC; Ian A. Greer, MD, FRCP, FRCOG; Andreas Greinacher, MD; Jeremy Grimshaw, MD, PhD; Cindy Grines, MD; Jonathan L. Halperin, MD; Robert A. Harrington, MD; John Heffner, MD, MPH; John A. Heit, MD; Judith S. Hochman, MD, FACC; Dieter Horstkotte, MD, FESC; Russell D. Hull, MBBS, MSc, FCCP; Elaine Hylek, MD; Thomas M. Hyers, MD, FCCP; Mark R. Jackson, MD; Alan Jacobson, MD; Roman Jaeschke, MD, MSc; Ajay Kakkar BSc, PhD; Clive Kearon, MD, PhD, FCCP; Matthew Kraay; Michael R. Lassen, MD; Mark N. Levine, MD, MSc; Alessandro Liberati, MD; Gregory YH Lip, MD, FESC, FACC; Warren J. Manning, MD; M. Patricia Massicotte, MD, MSc, FRCPC, MSc; Thomas W. Meade, MD; Venu Menon, MD, FACC; Alan D. Michelson, MD; Nancy Miller, RN; Paul Monagle, MBBS, MSc, MD, FRACP, FRCPA, FCCP; Heather Munger, MLS; Christopher M. O´Connor, MD; Martin O´Donnell, MD; E. Magnus Ohman, MD, FCCP; Carlo Patrono, MD; Stephen G. Pauker, MD; Graham F. Pineo, MD; Leon Poller, MD; Jeffrey J. Popma, MD; Martin H. Prins, MD; Robert Raschke, MD, MS; Gary Raskob, PhD; Joel G. Ray, MD, MSc; Gerald Roth, MD; Ralph L. Sacco, MD; Deeb N. Salem, MD, FCCP; Meyer M. Samama, MD; Andrew

Schafer; Sam Schulman, MD, PhD; Daniel Singer, MD; Michael Sobel, MD; Paul D. Stein, MD, FCCP; Marco Tangelder, MD; Victor F. Tapson, MD, FCCP; Philip Teal, MD; Raymond Verhaeghe, MD; David A. Vorchheimer, MD; Theodore E. Warkentin, MD; Jeffrey Weitz, MD; Robert G. Wilcox, MD

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Dr. Büller has received speaker's honoraria and consultancy fees. The total did not exceed $10,000US/year. In addition, clinical studies are supported by educational grants.

Dr. Agnelli has received honoraria for his participation on advisory boards and/or as speaker at educational events from AstraZeneca, Aventis Pharma and Sanofi-Synthelabo-Organon.

Dr. Hull has received research funding from Aventis, Pharmacia (now Pfizer), Leo Pharma, Emisphere Technologies, Dupont Pharmaceuticals (now Bristol-Myers Squibb) and Pharmion. He has received honoraria for his participation on advisory boards and/or as a speaker at educational events from Aventis, Bayer, Pharmacia (now Pfizer), Leo Pharma, Emisphere Technologies, Dupont Pharmaceuticals (now Bristol-Myers Squibb) and Pharmion.

Dr. Hyers has received honoraria as a speaker for AstraZeneca, Aventis, Boehringer Ingelheim, GlaxoSmithKline, Organon-Sanofi, and Pharmacia. He has served as a consultant for AstraZeneca and Aventis.

Dr. Raskob has received research funding from Sanofi-Synthelabo, Organon, Aventis, and Bristol-Myers Squibb, and has received honoraria for his participation on advisory boards and/or as a speaker at educational events for Sanofi-Synthelabo, Organon, AstraZeneca, Pharmacia, Aventis, Amgen, and Pharmion.

GUIDELINE STATUS

This is the current release of the guideline.

This guideline is updates a previous version: Hyers TM, Agnelli G, Hull RD, Morris TA, Samama M, Tapson V, Weg JG. Antithrombotic therapy for venous thromboembolic disease. Chest 2001 Jan;119(1 Suppl):176S-193S.

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

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