Complete Summary

GUIDELINE TITLE

Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy.

BIBLIOGRAPHIC SOURCE(S)

Geerts WH, Pineo GF, Heit JA, Bergqvist D, Lassen MR, Colwell CW, Ray JG. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004 Sep;126(3 Suppl):338S-400S. [794 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Geerts WH, Heit JA, Clagett GP, Pineo GF, Colwell CW, Anderson FA Jr, Wheeler HB. Prevention of venous thromboembolism. Chest 2001 Jan;119(1 Suppl):132S-175S.

** 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.

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)

Venous thromboembolism

GUIDELINE CATEGORY

Prevention

CLINICAL SPECIALTY

Cardiology
Critical Care
Emergency Medicine
Family Practice
Internal Medicine
Neurological Surgery
Obstetrics and Gynecology
Orthopedic Surgery
Preventive Medicine
Pulmonary Medicine
Surgery
Urology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To systematically review the literature related to the risks of venous thromboembolism (VTE) and its prevention
- To recommend evidence-based prophylaxis strategies for the prevention of venous thromboembolism

TARGET POPULATION

1. Patients undergoing surgery, such as:
    - Major general, vascular, gynecologic, urologic, and laparoscopic surgery

    - Lower extremity arthroplasty and arthroscopy, and hip arthroplasty and fracture repair
    - Neurosurgery
    - Elective spine surgery
2. Patients admitted to the hospital with major trauma, acute spinal cord injury (SCI), lower extremity injuries, or burns.
3. Medical patients with risk factors for thromboembolism, including:
    - Congestive heart failure
    - Severe respiratory disease
    - Other medical conditions, such as active cancer, bedrest, previous venous thromboembolism (VTE), sepsis, acute neurologic disease, or inflammatory bowel disease
4. Cancer patients
5. Critical care patients
6. Long distance travelers

INTERVENTIONS AND PRACTICES CONSIDERED

Prevention of Venous Thromboembolism (VTE)

1. Assessment of clinical risk factors for venous thromboembolism
2. Selective screening for venous thromboembolism with Doppler ultrasonography (DUS) or contrast venography (Note: Contrast venography is not recommended routinely. Other screening methods, such as fibrinogen uptake test [FUT] and impedance plethysmography are considered but are no longer clinically utilized.)
3. Nonpharmacologic prophylaxis measures:
    - Early and persistent ambulation or mobilization
    - Mechanical prophylaxis, such as graduated compression stockings (GCS), intermittent pneumatic compression (IPC), or venous foot pumps (VFP)
4. Pharmacologic prophylaxis:
    - Heparin therapy; low-dose unfractionated heparin (LDUH); low-molecular-weight heparin (LMWH); adjusted-dose heparin therapy; heparinoid, such as danaparoid; direct thrombin inhibitors; factor Xa inhibitors, such as fondaparinux
    - Adjusted-dose oral anticoagulation

    Note: Aspirin and dextran were considered for prophylaxis but not recommended for any patient group.

5. Selected inferior vena cava filter insertion for demonstrated proximal deep vein thrombosis in the presence of a contraindication to therapeutic anticoagulation

MAJOR OUTCOMES CONSIDERED

- Effectiveness of prophylactic strategies for venous thromboembolism (VTE)
- Rates and relative risk of venous thromboembolism outcomes, such as:
    - Fatal pulmonary embolism (PE)
    - Symptomatic, proven deep vein thrombosis (DVT) or pulmonary embolism

    - Asymptomatic proximal deep vein thrombosis
    - All-cause mortality
- Sensitivity and specificity of diagnostic tests
- Cost effectiveness of prophylaxis

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

Meta-Analysis of Randomized Controlled Trials
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).

This article adhered closely to the model for developing American College of Chest Physicians guidelines that is described by the companion document "Methodology for Guideline Development" by Schunemann et al. A priori criteria for inclusion of studies were applied whenever possible (see table 1 of the original guideline document), and always when the results of multiple trials were pooled. The number needed to treat (NNT) was used to estimate the number of patients who

would need to receive a specific thromboprophylaxis regimen to prevent one additional deep-vein thrombosis (DVT), compared with patients receiving no prophylaxis or another prophylaxis regimen. The number needed to harm (NNH) was defined as the number of patients who would need to receive the thromboprophylaxis regimen to result in one additional adverse event, such as major bleeding.

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.

In formulating the final text and recommendations, the guideline developers considered the comments of external reviewers (usually 5 to 10) who provided feedback on each section of this article. Although the recommendations are evidence-based, the guideline developers also provide suggestions that clinicians might find useful when the evidence is weak.

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	Strong recommendation; can apply to most patients in most circumstances

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

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

A vast number of randomized clinical trials over the past 30 years provide irrefutable evidence that primary thromboprophylaxis reduces deep vein thrombosis (DVT), pulmonary embolism (PE), and fatal PE. PE is the most common preventable cause of hospital death and the appropriate use of thromboprophylaxis is the number one strategy to improve patient safety in hospitals. The Agency for Healthcare Research and Quality has published a report entitled "Making Health Care Safer: a Critical Analysis of Patient Safety Practices." This systematic review ranked 79 patient safety interventions based on the strength of the evidence supporting more widespread implementation of these procedures. The highest ranked safety practice was the "appropriate use of prophylaxis to prevent venous thromboembolism (VTE) in patients at risk." This recommendation was based on overwhelming evidence that thromboprophylaxis

reduces adverse patient outcomes while, at the same time, decreasing overall costs.

Concerns are sometimes raised about the complications of thromboprophylaxis, especially bleeding. However, abundant data from meta-analyses and placebo-controlled, blinded, randomized clinical trials have demonstrated little or no increase in the rates of clinically important bleeding with prophylactic doses of low-dose unfractionated heparin (LDUH), low molecular weight heparin (LMWH), or a vitamin K antagonist (VKA). There is good evidence that appropriately used thromboprophylaxis has a desirable risk/benefit ratio and is cost-effective. Thromboprophylaxis, therefore, provides an opportunity both to improve patient outcomes and also to reduce hospital costs.

General Surgery

The clinical advantages of LMWH over LDUH include its once-daily administration and the lower risk of heparin-induced thrombocytopenia (HIT), while, at least in North America, LMWH is more costly.

Elective Hip Arthroplasty

Studies that withheld primary prophylaxis and instead screened for DVT using noninvasive methods have not demonstrated that screening is an alternative to primary prophylaxis. Many studies found noninvasive screening tests to have unacceptably low measures of sensitivity and specificity after total hip replacement (THR), even for the detection of proximal DVT. Moreover, a strategy of screening for proximal DVT with prehospital discharge Doppler ultrasonography (DUS) was ineffective in patients who received prophylaxis with LMWH or warfarin. While a similar strategy using prehospital discharge venography appeared to be cost-effective in one study, routine venography is no longer widely available or considered to be an acceptable option by most clinicians. Consequently, primary prophylaxis is recommended for all total hip replacement patients.

Elective Knee Arthroplasty

Similar to total hip replacement, the guideline developers suggest that the choice of LMWH or warfarin prophylaxis for total knee replacement (TKR) surgery be an institutional decision. The overall financial cost of warfarin or LMWH prophylaxis following lower extremity arthroplasty appears to be similar. In one US study, adjusted-dose warfarin prophylaxis was slightly more cost-effective than LMWH prophylaxis, although the other analyses came to the opposite conclusion.

Other Prophylaxis Issues in Major Orthopedic Surgery

Duration of Prophylaxis

The results of a number of economic studies have suggested that extended, post-hospital discharge prophylaxis may be cost-effective in comparison with in-hospital prophylaxis. Based on all of the data about duration of prophylaxis in orthopedic surgery, patients undergoing major orthopedic surgery should receive

prophylaxis with LMWH, fondaparinux, or a VKA for at least 10 days. Given that current hospital stays are generally <5 days, this recommendation implies that post-hospital discharge prophylaxis should be provided to most patients. For patients undergoing total hip replacement or hip fracture surgery (HFS), more prolonged prophylaxis for up to 28 to 35 days is recommended for those patients who are considered to be at high risk for VTE. Although further studies are needed to define who is at high risk, factors shown to predispose patients to VTE following major orthopedic surgery include a history of VTE or current obesity, delayed mobilization, advanced age, or cancer. Other risk factors that might be clinically important include a history of congestive heart failure or chronic obstructive pulmonary disease (COPD), as well as female gender. The extended use of a VKA (international normalized ratio (INR) target 2.5, range, 2.0 to 3.0) is an acceptable alternative to LMWH, although the incidence of major bleeding may be higher with oral anticoagulants. The pentasaccharide fondaparinux is recommended for extended prophylaxis following hip fracture surgery. The use of either LMWH or an oral VKA also may be effective in hip fracture surgery patients, although prolonged use of these agents has not been properly studied in this patient group.

Trauma

LMWH was shown to be superior to LDUH in a double-blinded, randomized clinical trial among 344 major trauma patients without frank intracranial bleeding or ongoing bleeding at other sites. LDUH, 5,000 U subcutaneously (SC) bid, was compared with enoxaparin, 30 mg SC bid, both initiated within 36 hours of the injury. Bilateral contrast venography was performed between days 10 and 14. The relative risk reductions (RRRs) for DVT (30%) and proximal DVT (58%) significantly favored LMWH ($p = 0.01$ for each of these comparisons). This benefit of LMWH was seen in both higher risk patients with lower extremity fractures and in lower risk patients without leg fractures. The overall rate of major bleeding was <2%, and there was no significant difference in the rate of bleeding, blood transfusion, or changes in hematocrit. The low rate of bleeding was at least partly due to the initial exclusion of 267 patients who had intracranial bleeding or uncontrolled bleeding at another site. In addition to the demonstrated efficacy and safety of LMWH, cost-effectiveness analyses also support the superiority of LMWH over LDUH prophylaxis in high-risk trauma patients.

Greenfield estimated that the annual cost of prophylactic inferior vena cava filter (IVCF) insertions in the United States would be $900,000,000 if they were placed in just 1% of all disabling trauma cases. Others have concluded that routine screening or prophylactic IVCF insertion would not prevent any deaths or otherwise benefit trauma patients. Finally, PE and the occasional fatal PE may occur despite the presence of an IVCF.

With modern insertion techniques performed by experienced clinicians, the short-term and long-term complications of IVCF are low. Newer technology, including bedside insertion, use of retrievable filters, and ultrasound guidance, may increase the temptation to use filters with greater frequency. However, the lack of evidence for their efficacy or cost-effectiveness poses the greatest challenge to their increased use. Until these issues are resolved, the guideline developers and others do not recommend the use of IVCFs as prophylaxis, even in patients who are at high risk for VTE. IVCF insertion is indicated in the presence of proven

proximal DVT and either an absolute contraindication to full-dose anticoagulation therapy or planned major surgery in the near future. In either case, even with an IVCF, therapeutic anticoagulation should be commenced as soon as it is safe to do so.

Medical Conditions

Several economic analyses have concluded that LDUH and LMWH are cost-effective thromboprophylaxis interventions in medical patients.

Cancer Patients

In the only clinical trial of thromboprophylaxis during chemotherapy, 311 women with metastatic breast cancer received either very-low-dose warfarin (INR range, 1.3 to 1.9) or placebo. Prophylaxis with warfarin significantly, and cost-effectively, reduced the incidence of VTE compared to placebo, with no increased risk of major bleeding.

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

General Recommendations

1. The guideline developers recommend that mechanical methods of prophylaxis be used primarily in patients who are at high risk of bleeding (**Grade 1C+**) or as an adjunct to anticoagulant-based prophylaxis (**Grade 2A**). The guideline developers recommend that careful attention be directed toward ensuring the

proper use of, and optimal compliance with, the mechanical device (**Grade 1C+**).

2. The guideline developers recommend **against** the use of aspirin alone as prophylaxis against venous thromboembolism (VTE) for any patient group (**Grade 1A**).
3. For each of the antithrombotics agents, the guideline developers recommend that clinicians consider the manufacturer´s suggested dosing guidelines (**Grade 1C**).
4. The guideline developers recommend consideration of renal impairment when deciding on doses of low-molecular-weight heparin (LMWH), fondaparinux, the direct thrombin inhibitors, and other antithrombotic drugs that are cleared by the kidneys, particularly in elderly patients and those who are at high risk for bleeding (**Grade 1C+**).
5. In all patients undergoing neuraxial anesthesia or analgesia, the guideline developers recommend special caution when using anticoagulant prophylaxis (**Grade 1C+**).

General, Vascular, Gynecologic, and Urologic Surgery

General Surgery

1. In low-risk general surgery patients (see Table 5 in the original guideline document) who are undergoing a minor procedure, are <40 years of age, and have no additional risk factors, the guideline developers recommend **against** the use of specific prophylaxis other than early and persistent ambulation (**Grade 1C+**).
2. Moderate-risk general surgery patients are those patients undergoing a nonmajor procedure and are between the ages of 40 and 60 years or have additional risk factors, or those patients who are undergoing major operations and are <40 years of age with no additional risk factors. The guideline developers recommend prophylaxis with low-dose unfractionated heparin (LDUH), 5,000 U twice a day (bid), or LMWH, ≤3,400 U once daily (both **Grade 1A**).
3. Higher-risk general surgery patients are those undergoing nonmajor surgery and are >60 years of age or have additional risk factors, or patients undergoing major surgery who are >40 years of age or have additional risk factors. The guideline developers recommend thromboprophylaxis with LDUH, 5,000 U three times a day (tid), or LMWH, >3,400 U daily (both **Grade 1A**).
4. In high-risk general surgery patients with multiple risk factors, the guideline developers recommend that pharmacologic methods (i.e., LDUH, tid, or LMWH, >3,400 U daily) be combined with the use of graduated compression stockings (GCS) and/or intermittent pneumatic compression (IPC) (**Grade 1C+**).
5. In general surgery patients with a high risk of bleeding, the guideline developers recommend the use of mechanical prophylaxis with properly fitted GCS or IPC, at least initially until the bleeding risk decreases (**Grade 1A**).
6. In selected high-risk general surgery patients, including those who have undergone major cancer surgery, the guideline developers suggest post-hospital discharge prophylaxis with LMWH (**Grade 2A**).

Vascular Surgery

1. In patients undergoing vascular surgery who do not have additional thromboembolic risk factors, the guideline developers suggest that clinicians **not** routinely use thromboprophylaxis (**Grade 2B**).
2. For patients undergoing major vascular surgical procedures who have additional thromboembolic risk factors, the guideline developers recommend prophylaxis with LDUH or LMWH (**Grade 1C+**).

Gynecologic Surgery

1. For gynecologic surgery patients undergoing brief procedures of ≤30 minutes for benign disease, the guideline developers recommend **against** the use of specific prophylaxis other than early and persistent mobilization (**Grade 1C+**).
2. For patients undergoing laparoscopic gynecologic procedures, in whom additional VTE risk factors are present, the guideline developers recommend the use of thromboprophylaxis with one or more of the following: LDUH, LMWH, IPC, or GCS (all **Grade 1C**).
3. The guideline developers recommend that thromboprophylaxis be used in all major gynecologic surgery patients (**Grade 1A**).
4. For patients undergoing major gynecologic surgery for benign disease, without additional risk factors, the guideline developers recommend LDUH, 5,000 U bid (**Grade 1A**). Alternatives include once-daily prophylaxis with LMWH, ≤3,400 U/d (**Grade 1C+**), or IPC started just before surgery and used continuously while the patient is not ambulating (**Grade 1B**).
5. For patients undergoing extensive surgery for malignancy, and for patients with additional VTE risk factors, the guideline developers recommend routine prophylaxis with LDUH, 5,000 U tid (**Grade 1A**), or higher doses of LMWH (i.e., >3,400 U/d) [**Grade 1A**]. Alternative considerations include IPC alone continued until hospital discharge (**Grade 1A**), or a combination of LDUH or LMWH plus mechanical prophylaxis with GCS or IPC (all **Grade 1C**).
6. For patients undergoing major gynecologic procedures, the guideline developers suggest that prophylaxis continue until discharge from the hospital (**Grade 1C**). For patients who are at particularly high risk, including those who have undergone cancer surgery and are >60 years of age or have previously experienced VTE, the guideline developers suggest continuing prophylaxis for 2 to 4 weeks after hospital discharge (**Grade 2C**).

Urologic Surgery

1. In patients undergoing transurethral or other low-risk urologic procedures, the guideline developers recommend **against** the use of specific prophylaxis other than early and persistent mobilization (**Grade 1C+**).
2. For patients undergoing major, open urologic procedures, the guideline developers recommend routine prophylaxis with LDUH twice daily or three times daily (**Grade 1A**). Acceptable alternatives include prophylaxis with IPC and/or GCS (**Grade 1B**) or LMWH (**Grade 1C+**).
3. For urologic surgery patients who are actively bleeding or are at very high risk for bleeding, the guideline developers recommend the use of mechanical prophylaxis with GCS and/or IPC at least until the bleeding risk decreases (**Grade 1C+**).
4. For patients with multiple risk factors, the guideline developers recommend combining GCS and/or IPC with LDUH or LMWH (**Grade 1C+**).

Laparoscopic Surgery

1. The guideline developers recommend against routine thromboprophylaxis in these patients, other than aggressive mobilization (**Grade 1A**).
2. For patients undergoing laparoscopic procedures and who have additional thromboembolic risk factors, the guideline developers recommend the use of thromboprophylaxis with one or more of the following: LDUH, LMWH, IPC, or GCS (**Grade 1C+**).

<u>Orthopedic Surgery</u>

Elective Hip Arthroplasty

1. For patients undergoing elective total hip replacement (THR), the guideline developers recommend the routine use of one of the following three anticoagulants: (1) LMWH (at a usual high-risk dose, started 12 hours before surgery or 12 to 24 hours after surgery, or 4 to 6 hours after surgery at half the usual high-risk dose and then increasing to the usual high-risk dose the following day); (2) fondaparinux (2.5 mg started 6 to 8 hours after surgery); or (3) adjusted-dose vitamin K antagonist (VKA) started preoperatively or the evening after surgery (international normalized ratio [INR] target, 2.5; INR range, 2.0 to 3.0) (all **Grade 1A**).

   Underlying values and preferences: The guideline developers have not recommended the use of fondaparinux over LMWH and VKA, or the use of LMWH over VKA, because they place a relatively low value on the prevention of venographic thrombosis and a relatively high value on minimizing bleeding complications.

2. The guideline developers recommend **against** the use of aspirin, dextran, LDUH, GCS, IPC, or venous foot pump (VFP) as the only method of thromboprophylaxis in these patients (**Grade 1A**).

Elective Knee Arthroplasty

1. For patients undergoing elective total knee replacement arthroplasty (TKA), the guideline developers recommend routine thromboprophylaxis using LMWH (at the usual high-risk dose), fondaparinux, or adjusted-dose VKA (target INR, 2.5; INR range, 2.0 to 3.0) (all **Grade 1A**).

   Underlying values and preferences: The guideline developers have not recommended fondaparinux over LMWH and VKA, or LMWH over VKA, because they place a relatively low value on the prevention of venographic thrombosis and a relatively high value on minimizing bleeding complications.

2. The optimal use of IPC is an alternative option to anticoagulant prophylaxis (**Grade 1B**).
3. The guideline developers recommend **against** the use of any of the following as sole methods of thromboprophylaxis: aspirin (**Grade 1A**); LDUH (**Grade 1A**); or VFP (**Grade 1B**).

Knee Arthroscopy

1. The guideline developers suggest clinicians do **not** use routine thromboprophylaxis in these patients, other than early mobilization (**Grade 2B**).
2. For patients undergoing arthroscopic knee surgery who are at a higher than usual risk, based on preexisting VTE risk factors or following a prolonged complicated procedure, the guideline developers suggest thromboprophylaxis with LMWH (**Grade 2B**).

Hip Fracture Surgery

1. For patients undergoing hip fracture surgery (HFS), the guideline developers recommend the routine use of fondaparinux (**Grade 1A**), LMWH at the usual high-risk dose (**Grade 1C+**), adjusted-dose VKA (target INR, 2.5; INR range, 2.0 to 3.0) (**Grade 2B**), or LDUH (**Grade 1B**).
2. The guideline developers recommend **against** the use of aspirin alone (**Grade 1A**).
3. If surgery will likely be delayed, the guideline developers recommend that prophylaxis with either LDUH or LMWH be initiated during the time between hospital admission and surgery (**Grade 1C+**).
4. The guideline developers recommend mechanical prophylaxis if anticoagulant prophylaxis is contraindicated because of a high risk of bleeding (**Grade 1C+**).

Other Prophylaxis Issues in Major Orthopedic Surgery

1. For major orthopedic surgical procedures, the guideline developers recommend that a decision about the timing of the initiation of pharmacologic prophylaxis be based on the efficacy-to-bleeding tradeoffs for that particular agent (**Grade 1A**). For LMWH, there are only small differences between starting preoperatively or postoperatively, and both options are acceptable (**Grade 1A**).
2. The guideline developers recommend **against** the routine use of Doppler ultrasonography (DUS) screening at the time of hospital discharge in asymptomatic patients following major orthopedic surgery (**Grade 1A**).
3. The guideline developers recommend that patients undergoing THR, TKA, or HFS receive thromboprophylaxis with LMWH (using a high-risk dose), fondaparinux (2.5 mg daily), or a VKA (target INR, 2.5; INR range, 2.0 to 3.0) for at least 10 days (**Grade 1A**).
4. The guideline developers recommend that patients undergoing THR or HFS be given extended prophylaxis for up to 28 to 35 days after surgery (**Grade 1A**). The recommended options for THR include LMWH (**Grade 1A**), a VKA (**Grade 1A**), or fondaparinux (**Grade 1C+**). The recommended options following HFS are fondaparinux (**Grade 1A**), LMWH (**Grade 1C+**), or a VKA (**Grade 1C+**).

Elective Spine Surgery

1. For spinal surgery patients with no additional risk factors, the guideline developers recommend against the routine use of any thromboprophylaxis modality, apart from early and persistent mobilization (**Grade 1C**).

2. The guideline developers recommend that some form of prophylaxis be used in patients undergoing spinal surgery who exhibit additional risk factors such as advanced age, known malignancy, presence of a neurologic deficit, previous VTE, or an anterior surgical approach (**Grade 1B**).
3. For patients with additional risk factors, the guideline developers recommend any of the following prophylaxis options: postoperative LDUH alone (**Grade 1C+**); postoperative LMWH alone (**Grade 1B**); or perioperative IPC alone (**Grade 1B**). Other considerations include perioperative GCS alone (**Grade 2B**), or perioperative IPC combined with GCS (**Grade 2C**). In patients with multiple risk factors for VTE, the guideline developers recommend combining LDUH or LMWH with GCS and/or IPC (**Grade 1C+**).

Isolated Lower Extremity Injuries

The guideline developers suggest that clinicians **not** use thromboprophylaxis routinely in patients with isolated lower extremity injuries (**Grade 2A**).

Neurosurgery

1. The guideline developers recommend that thromboprophylaxis be routinely used in patients undergoing major neurosurgery (**Grade 1A**).
2. The guideline developers recommend the use of IPC with or without GCS in patients undergoing intracranial neurosurgery (**Grade 1A**).
3. Acceptable alternatives to the above options are prophylaxis with LDUH (**Grade 2B**) or postoperative LMWH (**Grade 2A**).
4. The guideline developers suggest the combination of mechanical prophylaxis (i.e., GCS and/or IPC) and pharmacologic prophylaxis (i.e., LDUH or LMWH) in high-risk neurosurgery patients (**Grade 2B**).

Trauma, Spinal Cord Injury, Burns

Trauma

1. The guideline developers recommend that all trauma patients with at least one risk factor for VTE receive thromboprophylaxis, if possible (**Grade 1A**).
2. In the absence of a major contraindication, the guideline developers recommend that clinicians use LMWH prophylaxis starting as soon as it is considered safe to do so (**Grade 1A**).
3. The guideline developers recommend that mechanical prophylaxis with IPC, or possibly with GCS alone, be used if LMWH prophylaxis is delayed or if it is currently contraindicated due to active bleeding or a high risk for hemorrhage (**Grade 1B**).
4. The guideline developers recommend DUS screening in patients who are at high risk for VTE (e.g., the presence of a spinal cord injury [SCI], lower extremity or pelvic fracture, major head injury, or an indwelling femoral venous line), and who have received suboptimal prophylaxis or no prophylaxis (**Grade 1C**).
5. The guideline developers recommend against the use of inferior vena cava filters (IVCFs) as primary prophylaxis in trauma patients (**Grade 1C**).
6. The guideline developers recommend the continuation of thromboprophylaxis until hospital discharge, including the period of inpatient rehabilitation (**Grade 1C+**). The guideline developers suggest continuing prophylaxis after hospital

discharge with LMWH or a VKA (target INR, 2.5; INR range, 2.0 to 3.0) in patients with major impaired mobility (**Grade 2C**).

Acute SCI

1. The guideline developers recommend that thromboprophylaxis be provided for all patients with acute SCIs (**Grade 1A**).
2. The guideline developers recommend **against** the use of LDUH, GCS, or IPC as single prophylaxis modalities (**Grade 1A**).
3. In patients with acute SCI, the guideline developers recommend prophylaxis with LMWH, to be commenced once primary hemostasis is evident (**Grade 1B**). The guideline developers suggest the combined use of IPC and either LDUH (**Grade 2B**) or LWMH (**Grade 2C**) as alternatives to LMWH.
4. The guideline developers recommend the use of IPC and/or GCS when anticoagulant prophylaxis is contraindicated early after injury (**Grade 1C+**).
5. The guideline developers recommend **against** the use of an IVCF as primary prophylaxis against pulmonary embolism (PE) (**Grade 1C**).
6. During the rehabilitation phase following acute SCI, the guideline developers recommend the continuation of LMWH prophylaxis or conversion to an oral VKA (INR target, 2.5; INR range, 2.0 to 3.0) (**Grade 1C**).

Burns

1. The guideline developers recommend that burn patients with additional risk factors for VTE, including one or more of the following: advanced age, morbid obesity, extensive or lower extremity burns, concomitant lower extremity trauma, use of a femoral venous catheter, and/or prolonged immobility, receive thromboprophylaxis, if possible (**Grade 1C+**).
2. If there are no contraindications, the guideline developers recommend the use of either LDUH or LMWH, starting as soon as is considered safe to do so (**Grade 1C+**).

<u>Medical Conditions</u>

1. In acutely ill medical patients who have been admitted to the hospital with congestive heart failure or severe respiratory disease, or who are confined to bed and have one or more additional risk factors, including active cancer, previous VTE, sepsis, acute neurologic disease, or inflammatory bowel disease, the guideline developers recommend prophylaxis with LDUH (**Grade 1A**) or LMWH (**Grade 1A**).
2. In medical patients with risk factors for VTE, and in whom there is a contraindication to anticoagulant prophylaxis, the guideline developers recommend the use of mechanical prophylaxis with GCS or IPC (**Grade 1C+**).

<u>Cancer Patients</u>

1. The guideline developers recommend that cancer patients undergoing surgical procedures receive prophylaxis that is appropriate for their current risk state (**Grade 1A**). Refer to the recommendations in the relevant surgical subsections.
2. The guideline developers recommend that hospitalized cancer patients who are bedridden with an acute medical illness receive prophylaxis that is

appropriate for their current risk state (**Grade 1A**). Refer to the recommendations in the section dealing with medical patients.

3. The guideline developers suggest that clinicians not routinely use prophylaxis to try to prevent thrombosis related to long-term indwelling central venous catheters (CVCs) in cancer patients (**Grade 2B**). Specifically, the guideline developers suggest that clinicians **not** use LMWH (**Grade 2B**), and the guideline developers recommend **against** the use of fixed-dose warfarin (**Grade 1B**) for this indication.

Critical Care

1. The guideline developers recommend that, on admission to a critical care unit, all patients be assessed for their risk of VTE. Accordingly, most patients should receive thromboprophylaxis (**Grade 1A**).
2. For patients who are at high risk for bleeding, the guideline developers recommend mechanical prophylaxis with GCS and/or IPC until the bleeding risk decreases (**Grade 1C+**).
3. For intensive care unit (ICU) patients who are at moderate risk for VTE (e.g., medically ill or postoperative patients), the guideline developers recommend using LDUH or LMWH prophylaxis (**Grade 1A**).
4. For patients who are at higher risk, such as that following major trauma or orthopedic surgery, the guideline developers recommend LMWH prophylaxis (**Grade 1A**).

Long Distance Travel

1. The guideline developers recommend the following general measures for long-distance travelers (i.e., flights of >6 hours duration): avoidance of constrictive clothing around the lower extremities or waist, avoidance of dehydration, and frequent calf muscle stretching (**Grade 1C**).
2. For long-distance travelers with additional risk factors for VTE, the guideline developers recommend the general strategies listed above. If active prophylaxis is considered, because of the perceived increased risk of venous thrombosis, the guideline developers suggest the use of properly fitted, below-knee GCS providing 15 to 30 mm Hg of pressure at the ankle (**Grade 2B**), or a single prophylactic dose of LMWH injected prior to departure (**Grade 2B**).
3. The guideline developers recommend against the use of aspirin for VTE prevention associated with travel (**Grade 1B**).

Definitions

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

Grade of Recommendation	Clarity of Risk/Benefit	Methodological Strength of Supporting Evidence	Implications
		important limitations	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 extrapolated, or overwhelming evidence from	Weak recommendation; best action may differ depending on circumstances or patients' or societal values

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

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

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 prevention strategies for venous thromboembolism may lead to:

- Decreased rates and relative risk of deep vein thrombosis and other adverse venous thromboembolism outcomes including pulmonary embolism and fatal pulmonary embolism

- Decreased health care costs. Studies addressing cost have uniformly concluded that broad application of prophylaxis is highly cost-effective.

Subgroups Most Likely to Benefit:

The guideline developers have described four levels of thromboembolism risk and summarized the successful prophylaxis strategies (see Table 5 in the original guideline document). For each of the major patient groups, the guideline developers discuss recommendations for average-risk and higher-risk patients. In general, the patients most likely to benefit from the guidelines are those in the higher risk groups (these groups will have the lowest number-needed-to-treat).

POTENTIAL HARMS

Adverse effects of pharmacologic agents may occur, including:

- *Bleeding complications* from anticoagulants
- *Heparin-induced thrombocytopenia*. The rate of thrombocytopenia with prophylactic use of heparin is 1 to 5%, and the incidence of clinically overt vascular thrombosis in postoperative patients with heparin-induced thrombocytopenia is approximately 50%. Low-molecular-weight heparins are much less likely to produce heparin-induced thrombocytopenia than unfractionated heparin.
- *Wound hematomas*, which are seen more frequently with low-dose unfractionated heparin or low-molecular-weight heparin than with mechanical or no prophylaxis or, in some studies, than oral anticoagulation. These agents may potentially increase the risk of wound infection, dehiscence, and infection of a prosthetic device placed at the time of operation.
- *Perispinal hematoma* after neuraxial blockade (i.e., spinal or epidural anesthesia and continuous epidural analgesia). The risk of perispinal hematoma, a very rare but potentially devastating complication after neuraxial blockade, may be increased with the concomitant use of antithrombotic drugs.

Subgroups Most Likely to Experience Harm:

Much less is known about the predictors of adverse effects of thromboprophylaxis than about efficacy, in large part because most of the patients at increased risk for complications related to the prophylaxis interventions were excluded from the clinical trials.

- Patients with an increased risk of bleeding with anticoagulant prophylaxis may include those with inherited or acquired bleeding disorders, patients with renal failure, the very elderly, those also taking antiplatelet agents, patients with a recent bleeding event, and those in whom primary hemostasis has not been achieved.
- Patients with a previous history of heparin-induced thrombocytopenia or who have been exposed to heparin within the past few months may be at increased risk for this complication related to prophylactic heparin exposure. Patients who have had proven heparin-induced thrombocytopenia should not be given a course of low-molecular-weight heparin because of the very high rate of at least in vitro cross-reactivity.

- Wound hematomas may be more prevalent in patients who commence anticoagulant prophylaxis before or shortly following surgery and in those with bleeding disorders.
- Although rare, the seriousness of *perispinal hematoma* mandates cautious use of antithrombotic medication in patients having neuraxial blockade. Increased awareness of this problem arose from observations made with low-molecular-weight heparin but it has also been reported with low-dose unfractionated heparin, although with apparent lower frequency. The benefit versus risk of any anticoagulant prophylaxis or therapy for patients with spinal/epidural anesthesia or analgesia is difficult to assess. Possible predictors of anticoagulant-related perispinal hematomas may include: history of a bleeding disorder, traumatic or very difficult epidural catheter insertion, and the dose of anticoagulant.

CONTRAINDICATIONS

CONTRAINDICATIONS

- For hip fracture surgery (HFS), the guideline developers recommend mechanical prophylaxis if anticoagulant prophylaxis is contraindicated because of a high risk of bleeding.
- Although intermittent pneumatic compression (IPC) and graduated compression stockings (GCS) cannot be recommended as routine prophylaxis in trauma patients, such therapy may be beneficial in patients with an active contraindication to anticoagulant prophylaxis, such as those currently at high risk for bleeding (until anticoagulants can be given later).
- With respect to trauma, current contraindications to the early initiation of low-molecular-weight heparin (LMWH) prophylaxis include the presence of intracranial bleeding, ongoing and uncontrolled bleeding, an uncorrected major coagulopathy, or incomplete spinal cord injury (SCI) associated with suspected or proven perispinal hematoma. Head injury without frank hemorrhage, lacerations or contusions of internal organs (such as the lungs, liver, spleen, or kidneys), the presence of a retroperitoneal hematoma associated with pelvic fracture, or complete SCIs are not themselves contraindications to LMWH thromboprophylaxis, provided that there is no evidence of ongoing bleeding.

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.

Important Issues Related to Studies of Thromboprophylaxis

- The appropriate interpretation of published information about thromboprophylaxis requires the consideration of a number of important issues:
    - **Limitations of DVT Screening Methods**:
      Despite the limitations of each of these screening methods, and thus the possibility of error in the estimates of the absolute rates of deep-vein thrombosis (DVT), the relative risk reductions (RRRs), derived from studies comparing two prophylaxis regimens are likely to be valid as long as systematic bias has been reduced through the concealed randomization of patients, caregivers, and outcome adjudicators to the

study interventions received, and through the complete follow-up of patients.

- **Appropriate End Points in Clinical Trials of Thromboprophylaxis**:
  Physicians differ widely in their views on the appropriate end points for studies of thromboprophylaxis. While some believe that contrast venography should be used as the "best" test to detect all deep vein thrombosis (DVTs), others argue that evidence of effectiveness should be based on a proven reduction in all-cause mortality. Both of these antithetical positions clearly have limitations.
- **Mechanical Methods of Prophylaxis**:
  No mechanical prophylaxis option has been shown to reduce the risk of death or pulmonary embolism (PE). Special caution also should be exercised when interpreting the risk reductions ascribed to mechanical methods of prophylaxis for three reasons. Most trials were not blinded, increasing the chance of diagnostic suspicion bias. In the studies that used fibrinogen leg scanning to screen for DVT, mechanical prophylaxis may have factitiously lowered the 10 to 30% false-positive rate seen with the use of fibrinogen uptake test (FUT) (caused by venous pooling), while the rate remained unchanged in the nonmechanical treatment/control group. Finally, because of relatively poor compliance with all mechanical options, they may not perform as well in routine clinical practice as in research studies in which major efforts are made to optimize proper use. Graduated compression stockings (GCS) should be used with caution in patients with arterial insufficiency.
- **Aspirin and Thromboprophylaxis**:
  The guideline developers do not recommend the use of aspirin alone as VTE prophylaxis for several reasons. First, much of the evidence citing a benefit for the use of antiplatelet drugs against VTE is based on methodologically limited studies. For example, the Antiplatelet Trialists´ Collaboration meta-analysis pooled data from generally small studies that were conducted > 25 years ago and that were of variable quality. Only one third of the studies included a group that received aspirin alone, and, of these, generally acceptable methods of screening for DVT were performed in only 38%. Second, a number of trials found no significant benefit from aspirin therapy, or found that aspirin was inferior to other prophylactic modalities. Finally, aspirin use is associated with a small but significant increased risk of major bleeding, especially if combined with other antithrombotic agents.
- **Application of Evidence to Individual Patients**:
  The prophylaxis recommendations contained in this report apply to groups of patients for whom the benefits of prophylaxis appear to outweigh the risks. Decisions about prescribing prophylaxis for the individual patient are best made by combining knowledge of the literature (including the recommendations provided herein) with clinical judgment, the latter based on specific knowledge about each patient´s risk factors for VTE, the potential for adverse consequences with prophylaxis, and the availability of various options within one´s center. Since most thromboprophylaxis studies excluded patients who were at high risk for either VTE or adverse outcomes, their results may not apply to those patients with previous VTE or who have an increased risk of bleeding. In these circumstances, clinical judgment

may appropriately warrant the use of a prophylaxis option that differs from the recommended approach.

Renal clearance is the primary mode of elimination for several anticoagulants, including low molecular weight heparin (LMWH), fondaparinux, and the direct thrombin inhibitor melagatran. With reduced creatinine clearance, these drugs may accumulate and increase the risk of bleeding. However, each agent must be evaluated separately since there appears to be considerable variability in the relationship between renal impairment and drug accumulation even for various LMWHs.

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

Staying Healthy

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Geerts WH, Pineo GF, Heit JA, Bergqvist D, Lassen MR, Colwell CW, Ray JG. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004 Sep;126(3 Suppl):338S-400S. [794 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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American College of Chest Physicians Consensus Panel on Antithrombotic and Thrombolytic Therapy

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Dr. Geerts has received research funding from AstraZeneca, Aventis Pharma, and Pharmacia and has participated on advisory boards and/or research steering committees for AstraZeneca, Aventis Pharma, Eli Lilly, Pharmacia, and Sanofi-Synthelabo-Organon;

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Dr. Heit has received research funding from AstraZeneca, Aventis, and Corvas and has participated on advisory boards and/or research steering committees for AstraZeneca, Aventis, and Pharmacia;

Dr. Bergqvist has participated on advisory boards and/or research steering committees for AstraZeneca, Aventis, Boehringer Ingelheim, Pharmacia/Pfizer, and Sanofi-Synthelabo;

Dr. Lassen has received research funding from Sanofi-Synthelabo and has participated on advisory boards and/or research steering committees for AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Leo Pharma, Mitsubishi Pharma, Vivolution Inc, Wyeth, and Yamanautchi;

Dr. Colwell has received research funding from Amgen, AstraZeneca, Baxter, and Sanofi-Synthelabo and has participated on advisory boards and/or research steering committees for AstraZeneca, Aventis, Pharmacia, and Sanofi-Synthelabo; and Dr. Ray has no potential conflicts.

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Geerts WH, Heit JA, Clagett GP, Pineo GF, Colwell CW, Anderson FA Jr, Wheeler HB. Prevention of venous thromboembolism. Chest 2001 Jan;119(1 Suppl):132S-175S.

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 summary was completed by ECRI on July 12, 2001. The information was verified by the guideline developer on September 27, 2001. This summary was updated by ECRI on December 28, 2004. The updated information was verified by the guideline developer on January 12, 2005. 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 March 14, 2008 following the updated FDA advisory on heparin sodium injection.

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