

CHEST[®]

Official publication of the American College of Chest Physicians



Prevention of Venous Thromboembolism: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy

William H. Geerts, Graham F. Pineo, John A. Heit, David Bergqvist,
Michael R. Lassen, Clifford W. Colwell and Joel G. Ray

Chest 2004;126;338-400
DOI 10.1378/chest.126.3_suppl.338S

The online version of this article, along with updated information
and services can be found online on the World Wide Web at:
http://chestjournal.org/cgi/content/abstract/126/3_suppl/338S

CHEST is the official journal of the American College of Chest Physicians. It has been published monthly since 1935. Copyright 2007 by the American College of Chest Physicians, 3300 Dundee Road, Northbrook IL 60062. All rights reserved. No part of this article or PDF may be reproduced or distributed without the prior written permission of the copyright holder (<http://www.chestjournal.org/misc/reprints.shtml>). ISSN: 0012-3692.

A M E R I C A N C O L L E G E O F



P H Y S I C I A N S[®]

Prevention of Venous Thromboembolism

The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy

William H. Geerts, MD, FCCP; Graham F. Pineo, MD;
John A. Heit, MD; David Bergqvist, MD, PhD;
Michael R. Lassen, MD; Clifford W. Colwell, MD; and
Joel G. Ray, MD, MS

This article discusses the prevention of venous thromboembolism (VTE) and is part of the Seventh American College of Chest Physicians Conference on Antithrombotic and Thrombolytic Therapy: Evidence-Based Guidelines. Grade 1 recommendations are strong and indicate that the benefits do, or do not, outweigh risks, burden, and costs. Grade 2 suggests that individual patients' values may lead to different choices (for a full understanding of the grading see Guyatt et al, *CHEST* 2004; 126:179S–187S). Among the key recommendations in this chapter are the following. We recommend against the use of aspirin alone as thromboprophylaxis for any patient group (Grade 1A). For moderate-risk general surgery patients, we recommend prophylaxis with low-dose unfractionated heparin (LDUH) (5,000 U bid) or low-molecular-weight heparin (LMWH) [$\leq 3,400$ U once daily] (both Grade 1A). For higher risk general surgery patients, we recommend thromboprophylaxis with LDUH (5,000 U tid) or LMWH ($> 3,400$ U daily) [both Grade 1A]. For high-risk general surgery patients with multiple risk factors, we recommend combining pharmacologic methods (LDUH three times daily or LMWH, $> 3,400$ U daily) with the use of graduated compression stockings and/or intermittent pneumatic compression devices (Grade 1C+). We recommend that thromboprophylaxis be used in all patients undergoing major gynecologic surgery (Grade 1A) or major, open urologic procedures, and we recommend prophylaxis with LDUH two times or three times daily (Grade 1A). For patients undergoing elective total hip or knee arthroplasty, we recommend one of the following three anticoagulant agents: LMWH, fondaparinux, or adjusted-dose vitamin K antagonist (VKA) [international normalized ratio (INR) target, 2.5; range, 2.0 to 3.0] (all Grade 1A). For patients undergoing hip fracture surgery (HFS), we recommend the routine use of fondaparinux (Grade 1A), LMWH (Grade 1C+), VKA (target INR, 2.5; range, 2.0 to 3.0) [Grade

2B], or LDUH (Grade 1B). We recommend that patients undergoing hip or knee arthroplasty, or HFS receive thromboprophylaxis for at least 10 days (Grade 1A). We recommend that all trauma patients with at least one risk factor for VTE receive thromboprophylaxis (Grade 1A). 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, we recommend prophylaxis with LDUH (Grade 1A) or LMWH (Grade 1A). We recommend, on admission to the intensive care unit, all patients be assessed for their risk of VTE. Accordingly, most patients should receive thromboprophylaxis (Grade 1A).

(*CHEST* 2004; 126:338S–400S)

Key words: aspirin; deep-vein thrombosis; fondaparinux; heparin; low-molecular-weight heparin; prophylaxis; thromboembolism; warfarin

Abbreviations: CI = confidence interval; DUS = Doppler ultrasonography; CVC = central venous catheter; DVT = deep-vein thrombosis; FUT = fibrinogen uptake test; GCS = graduated compression stockings; HFS = hip fracture surgery; HIT = heparin-induced thrombocytopenia; INR = international normalized ratio; IPC = intermittent pneumatic compression; IVCF = inferior vena cava filter; LDUH = low-dose unfractionated heparin; LMWH = low-molecular-weight heparin; NNH = number needed to harm; NNT = number needed to treat; OR = odds ratio; PE = pulmonary embolism; RRR = relative risk reduction; SC = subcutaneous; SCI = spinal cord injury; THR = total hip replacement; TKA = total knee arthroplasty; VFP = venous foot pump; VKA = vitamin K antagonist; VTE = venous thromboembolism

1.0 Introduction

This article systematically reviews the literature related to the risks of venous thromboembolism (VTE) and its prevention. Other evidence-based reviews are also available.^{1–3}

1.1 Methods

This article adhered closely to the model for developing American College of Chest Physicians guidelines that is described by Schünemann et al in this Supplement.⁴ *A priori* criteria for inclusion of studies were applied whenever possible (Table 1), 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. In formulating the final text and recommendations, we 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, we also provide suggestions that clinicians might find useful when the evidence is weak.

Reproduction of this article is prohibited without written permission from the American College of Chest Physicians (e-mail: permissions@chestnet.org).

Correspondence to: William H. Geerts, MD, Thromboembolism Program, Sunnybrook & Women's College Health Sciences Centre, Room D674, 2075 Bayview Ave, Toronto, ON, Canada M4N 3M5

Table 1—Criteria for Inclusion of Studies

Variables	Description
Patients	Identifiable as belonging to the group of interest
Outcome assessment	
Orthopedic studies	Contrast venography (bilateral or ipsilateral) or DUS (although the results of trials using these 2 outcomes were not pooled)
Nonorthopedic studies	Contrast venography, fibrinogen leg scanning, or DUS
Sample size	At least 10 patients per group
Numerator	Objectively demonstrated DVT
Denominator	Patients with adequate outcome assessments for DVT
Baseline risks of thrombosis	
Design	Either prospective cohort studies or the control groups within randomized clinical trials
Interventions	No prophylaxis used
Prophylaxis Efficacy	
Design	Randomized clinical trials only
Interventions	Clinically relevant, commercially available options; for drugs, currently approved or utilized agents and doses were necessary

1.2 Rationale for thromboprophylaxis

The rationale for the use of thromboprophylaxis is based on solid principles and scientific evidence (Table 2).^{1,2,5} Most hospitalized patients have one or more risk factors for VTE (Table 3).^{3,6–10} These risk factors are generally cumulative.¹¹ For example, patients with fractures of the hip are at particularly high risk for VTE because of their usual advanced age, the presence of a proximal lower extremity injury as well as its operative repair, and the frequent marked reduction in mobility for weeks after surgery. If cancer is also present, the risk is

even greater. Without prophylaxis, the incidence of objectively confirmed, hospital-acquired DVT is approximately 10 to 40% among medical or general surgical patients and 40 to 60% following major orthopedic surgery (Table 4).^{2,12} One quarter to one third of these thrombi involve the proximal deep veins, and these thrombi are much more likely to produce symptoms and to result in PE.

In many of these patient groups, VTE is the most common serious complication.^{13–20} Approximately 10% of hospital deaths are attributed to pulmonary embolism (PE).^{14,21} For example, among 1,234 hospitalized patients who died and underwent autopsy within 30 days of a surgical procedure, the rate of PE was 32%, and PE was considered to be the cause of death in 29% of these cases.¹⁴ In a second study of 51,645 hospitalized patients,¹⁵ the prevalence of acute PE was 1%, and PE was believed to have caused or contributed to death in 37% of these cases. Although improved patient care may have attenuated some of the risk factors for VTE, patients currently in the hospital may well be at greater risk than those studied in the past because of their more advanced age, greater prevalence of cancer and intensive cancer therapy, more extensive surgical procedures, and prolonged stays in a critical care unit.

Most studies of VTE and its prevention have used sensitive diagnostic tests to detect DVT. The majority of the thrombi diagnosed by these screening tests were confined to the calf, were clinically silent, and remained so without any adverse consequences.^{22–25} However, approximately 10 to 20% of calf thrombi do extend to the proximal veins,^{22,26–30} and, particularly in patients undergoing major surgery involving the hip, isolated femoral vein DVT is common.^{31–34} There is also a strong association between asymptomatic DVT and the subsequent development of symptomatic VTE.^{22,35–42} For example, one study⁴² found that among critical care patients with asymptomatic DVT detected by screening DUS there was a significantly greater rate of PE development during their index hospitalization compared to those patients without

Table 2—Rationale for Thromboprophylaxis in Hospitalized Patients

Rationale	Description
High prevalence of VTE	Most hospitalized patients have risk factors for VTE DVT is common in many hospitalized patient groups Hospital-acquired DVT and PE are usually clinically silent Difficult to predict which at-risk patients will develop symptomatic thromboembolic complications Screening at-risk patients using physical examination or noninvasive testing is neither effective nor cost-effective
Adverse consequences of unprevented VTE	Symptomatic DVT and PE Fatal PE Costs of investigating symptomatic patients Risks and costs of treating unprevented VTE, especially bleeding Increased future risk of recurrent VTE Chronic post-thrombotic syndrome
Efficacy and effectiveness of thromboprophylaxis	Thromboprophylaxis is highly efficacious at preventing DVT and proximal DVT Thromboprophylaxis is highly effective at preventing symptomatic VTE and fatal PE The prevention of DVT also prevents PE Cost-effectiveness of prophylaxis has repeatedly been demonstrated

Table 3—Risk Factors for VTE

Surgery
Trauma (major or lower extremity)
Immobility, paresis
Malignancy
Cancer therapy (hormonal, chemotherapy, or radiotherapy)
Previous VTE
Increasing age
Pregnancy and the postpartum period
Estrogen-containing oral contraception or hormone replacement therapy
Selective estrogen receptor modulators
Acute medical illness
Heart or respiratory failure
Inflammatory bowel disease
Nephrotic syndrome
Myeloproliferative disorders
Paroxysmal nocturnal hemoglobinuria
Obesity
Smoking
Varicose veins
Central venous catheterization
Inherited or acquired thrombophilia

silent DVT (11.5% vs 0%, respectively; $p = 0.01$). Furthermore, the in-hospital case-fatality rate of VTE is 12%,¹² and the data suggest a case-fatality rate at 1 year of 29 to 34%.^{12,43}

While high-risk groups for VTE can be identified, it is not possible to predict which individual patients in a given risk group will develop a clinically important thromboembolic event. Furthermore, massive PE usually occurs without warning, and there is often no potential to resuscitate patients who experience this complication.¹⁵ In 70 to 80% of patients who die in the hospital of PE, this diagnosis was not even considered prior to death.^{15,44–48} Although the prevention of fatal PE remains the top priority for prophylaxis programs, this outcome is uncommon in most hospital groups. Furthermore, the prevention of fatal PE is not the only objective of thromboprophylaxis. The prevention of symptomatic DVT and PE are also important objectives since these outcomes are associated

Table 4—Absolute Risk of DVT in Hospitalized Patients*

Patient Group	DVT Prevalence, %
Medical patients	10–20
General surgery	15–40
Major gynecologic surgery	15–40
Major urologic surgery	15–40
Neurosurgery	15–40
Stroke	20–50
Hip or knee arthroplasty, hip fracture surgery	40–60
Major trauma	40–80
Spinal cord injury	60–80
Critical care patients	10–80

*Rates based on objective diagnostic testing for DVT in patients not receiving thromboprophylaxis.

with considerable acute morbidity, substantial consumption of resources, and long-term sequelae of clinical and economic significance.^{5,49}

The majority of symptomatic VTE associated with hospital admissions occur after hospital discharge.^{41,50–52} When symptomatic hospital-acquired VTE is suspected, costly diagnostic testing procedures are required and, if VTE is confirmed, therapeutic anticoagulation therapy, with its potential for serious bleeding complications, should be instituted. Therefore, the failure to prevent VTE also results in delayed hospital discharge or readmission, in complications from anticoagulation therapy, in an increased risk of long-term morbidity from the post-thrombotic syndrome, and in recurrent thrombosis in the future.^{30,53,54} A high proportion of venous thrombi leave residual venous abnormalities including persistent occlusion and/or venous valvular incompetence.^{54–56} Post-thrombotic syndrome may result in chronic leg swelling, discomfort, dermatitis, and leg ulcers, reduces patient quality of life, and has considerable adverse economic effects.^{57–60} These delayed consequences of inadequate prophylaxis are often overlooked.

Reliance on symptoms or signs of early DVT is an unreliable strategy to prevent clinically important thromboembolic events. The first manifestation of VTE may be fatal PE. The routine screening of patients for asymptomatic DVT is logistically difficult and is neither effective in preventing clinically important VTE nor cost-effective.^{61–67} Accordingly, prophylaxis against VTE remains the most appropriate strategy to reduce the sequelae discussed above.

A vast number of randomized clinical trials over the past 30 years provide irrefutable evidence that primary thromboprophylaxis reduces DVT, PE, and fatal PE.^{2,50,68–71} PE is the most common preventable cause of hospital death and is the number one strategy to improve patient safety in hospitals.^{12,72} The Agency for Healthcare Research and Quality has published a report entitled “Making Health Care Safer: a Critical Analysis of Patient Safety Practices.”⁷² 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 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.^{5,60,73–75}

Concerns are sometimes raised about the complications of thromboprophylaxis, especially bleeding.^{50,76} However, abundant data from metaanalyses 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).^{71,77–83} There is good evidence that appropriately used thromboprophylaxis has a desirable risk/benefit ratio and is cost-effective.^{5,60,61,73–75,84} Thromboprophylaxis, therefore, provides an opportunity both to improve patient outcomes and also to reduce hospital costs.

1.3 Risk factor stratification

There are two general approaches to making thromboprophylaxis decisions. One approach considers the risk of VTE in each patient, based on their individual predisposing factors and the risk associated with their current illness or procedure. Prophylaxis is then individually prescribed based on the composite risk estimate. Formal risk assessment models for DVT have been proposed to assist with this process.^{1,67,85–93} Because the approach of individual prophylaxis prescribing, based on formal risk-assessment models, has not been adequately validated and is cumbersome without the use of computer technology, it is unlikely to be used routinely by most clinicians. Furthermore, there is little formal understanding of how the various risk factors interact to determine the position of each patient along a continuous spectrum of thromboembolic risk. One simplification of this process for surgical patients involves assigning them to one of four VTE risk levels based on the type of operation (*eg*, minor or major), age (*eg*, < 40 years, 40 to 60 years, and > 60 years), and the presence of additional risk factors (*eg*, cancer or previous VTE) [Table 5]. Despite its limitations, this classification system, which was derived using prospective study data, provides both an estimate of VTE risk and related prophylaxis recommendations.

The second approach involves the implementation of group-specific prophylaxis routinely for all patients who belong to each of the major target groups. We support the latter for several reasons. First, we are unable to confidently identify individual patients who do not require prophylaxis.⁹⁴ Second, an individualized approach to prophylaxis has not been subjected to rigorous clinical evaluation. Third, individualizing prophylaxis is logistically complex and is likely associated with suboptimal compliance.

After discussing several important issues related to the

interpretation of thromboprophylaxis evidence, the remainder of this article categorizes patients according to the type of hospital service that is providing care for their primary surgical or medical disorder. Within each patient category, the risks of VTE and the effective methods of prophylaxis are discussed, if they are known. For most patient groups, sufficient numbers of randomized clinical trials are available to allow strong recommendations (*ie*, **Grade 1A** or **Grade 1B**) to be made with regard to the benefits and risks of specific thromboprophylaxis options.

VTE is an important health-care problem, resulting in significant mortality, morbidity, and resource expenditure. Despite the continuing need for additional data, we believe that there is sufficient evidence to recommend routine thromboprophylaxis for many hospitalized patient groups. The implementation of evidence-based and thoughtful prophylaxis strategies provides benefit to patients, and should also protect their caregivers and the hospitals providing care from legal liability. We recommend that every hospital develop a formal strategy that addresses the prevention of thromboembolic complications. This should generally be in the form of a written thromboprophylaxis policy, especially for high-risk groups.

1.4 Important issues related to studies of thromboprophylaxis

The appropriate interpretation of published information about thromboprophylaxis requires the consideration of a number of important issues.

1.4.1 Limitations of DVT screening methods

Each of the methods used to screen for DVT in clinical trials has its own limitations.⁹⁵ Fibrinogen leg scanning, also called the *fibrinogen uptake test* (FUT), was used

Table 5—Levels of Thromboembolism Risk in Surgical Patients Without Prophylaxis*

Level of Risk	DVT, %		PE, %		Successful Prevention Strategies
	Calf	Proximal	Clinical	Fatal	
Low risk Minor surgery in patients < 40 yr with no additional risk factors	2	0.4	0.2	< 0.01	No specific prophylaxis; early and “aggressive” mobilization
Moderate risk Minor surgery in patients with additional risk factors Surgery in patients aged 40–60 yr with no additional risk factors	10–20	2–4	1–2	0.1–0.4	LDUH (q12h), LMWH (\leq 3,400 U daily), GCS, or IPC
High risk Surgery in patients > 60 yr, or age 40–60 with additional risk factors (prior VTE, cancer, molecular hypercoagulability)	20–40	4–8	2–4	0.4–1.0	LDUH (q8h), LMWH (> 3,400 U daily), or IPC
Highest risk Surgery in patients with multiple risk factors (age > 40 yr, cancer, prior VTE) Hip or knee arthroplasty, HFS Major trauma; SCI	40–80	10–20	4–10	0.2–5	LMWH (> 3,400 U daily), fondaparinux, oral VKAs (INR, 2–3), or IPC/GCS + LDUH/LMWH

*Modified from Geerts et al.²

extensively to detect subclinical DVT in many early prophylaxis trials.⁹⁶ The test is no longer available because of concerns about the potential for viral transmission with this human blood product. Furthermore, the FUT has been shown to lack both specificity and sensitivity for the detection of DVT,^{97–102} and is poorly correlated with major thromboembolic events.¹⁰³ Impedance plethysmography also has been shown to have low accuracy in the screening of asymptomatic high-risk patients, and is no longer utilized.^{104–107}

Contrast venography has long been the diagnostic standard in thromboprophylaxis trials¹⁰⁸ because of its high sensitivity for detecting DVT and the availability of hard-copy images for blinded study adjudication. Many pivotal, practice-changing prophylaxis trials have used venography as the primary outcome measure of efficacy. Although venography remains an important screening test for DVT, especially in evaluating the efficacy of new antithrombotic interventions, it has a number of well-recognized limitations, including the following: (1) limited availability in many medical centers; (2) questionable clinical relevance of small or distal thrombi; (3) incomplete or nondiagnostic rates of at least 20 to 40%; (4) moderate interobserver variability in its interpretation; (5) patient discomfort and risks related to the use of a contrast agent; and (6) high financial costs.^{109–112} Furthermore, because venography is not readily repeatable, it can only provide information about thrombosis at a single point in time rather than over a longer a time course during which clinically important VTE may arise.

Venous Doppler ultrasonography (DUS) is now the most universally accepted test for the diagnosis of lower extremity DVT, because it is highly accurate for symptomatic DVT, widely available, and noninvasive, and can be repeated.^{106,112} At the same time, the accuracy of DUS varies among both operators and medical centers.¹¹³ While DUS has reduced sensitivity for detecting DVT in asymptomatic patients,^{106,114–118} the accuracy of DUS appears to be improving.¹¹⁹ The lower sensitivity of DUS for detecting small and/or nonocclusive DVTs may even be considered advantageous, since such thrombi appear to be of doubtful clinical significance.^{120,121} The standardization of the DUS technique is critical in reducing the potential for the false-positive test results reported in some trials.¹²² As a result of recent improvements in DUS accuracy, an increasing number of clinical trials in thromboprophylaxis are utilizing ultrasound outcomes. We believe that DUS-positive proximal DVT is a clinically relevant finding because of the known association between proximal DVT and PE, and because patients with this finding generally receive anticoagulation therapy in routine practice.

Despite the limitations of each of these screening methods, and thus the possibility of error in the estimates of the absolute rates of 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.¹²³

1.4.2 *Appropriate end points in clinical trials of thromboprophylaxis*

Physicians differ widely in their views on the appropriate end points for studies of thromboprophylaxis.^{95,112,124} While some believe that contrast venography should be used as the “best” test to detect all 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.

Over the years, the majority of prophylaxis trials have used DVT, detected by sensitive screening methods, as the primary efficacy outcome. While most asymptomatic DVTs are not clinically relevant, there is strong concordance between the “surrogate” outcome of asymptomatic DVT and clinically important VTE.^{34,36,38–40} In most studies, the ratio of asymptomatic DVT to symptomatic VTE ranges from 5:1 to 10:1. However, studies that employ routine screening for DVT may underestimate the true rate of symptomatic VTE or fatal PE because early screening for, and treatment of, asymptomatic DVT virtually eliminates the potential for these thrombi to progress and become symptomatic. With few exceptions, interventions that reduce asymptomatic DVT also convey similar RRRs in symptomatic VTE.^{34,38–40,52,71,125}

Proving a reduction in all-cause mortality or fatal PE as the objective of a thromboprophylaxis trial is problematic. Such studies require thousands of patients, and autopsy confirmation of VTE as the cause of death is increasingly difficult. Furthermore, an insistence on mortality or fatal PE as the only important outcome dismisses the significant burden of illness due to symptomatic thromboembolic events as well as the risks of anticoagulation therapy and the utilization of health-care resources when these events arise.

We (and others) have suggested^{95,112,124} a combination of these two approaches. Phase II and some phase III clinical trials should continue to utilize sensitive imaging modalities for the detection of largely asymptomatic DVT as a means of testing the biological efficacy of a new intervention. These studies should be followed by large clinical trials that use a clinically important VTE outcome, such as the combination of symptomatic and objectively proven DVT or PE, and asymptomatic proximal DVT detected by a noninvasive test such as DUS.

1.4.3 *Mechanical methods of prophylaxis*

Mechanical methods of prophylaxis, which include graduated compression stockings (GCS), and the use of intermittent pneumatic compression (IPC) devices and the venous foot pump (VFP), increase venous outflow and/or reduce stasis within the leg veins. The primary attraction of mechanical prophylaxis is the lack of bleeding potential. These modalities are, therefore, considerations for patients with high bleeding risks. While all three of the mechanical methods of prophylaxis have been shown to reduce the risk of DVT in a number of patient groups,^{2,126–133} they have been studied much less inten-

sively than anticoagulant-based options and are generally less efficacious than the latter for the prevention of DVT.^{2,131,134–136}

No mechanical prophylaxis option has been shown to reduce the risk of death or 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 FUT (caused by venous pooling), while the rate remained unchanged in the nonmechanical treatment/control group.^{126,137} 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.^{138–140} GCS should be used with caution in patients with arterial insufficiency.^{141–143}

In the recommendations that follow, the use of mechanical prophylaxis is an acceptable option in certain patient groups, especially in those patients who are at high risk for bleeding, or when used in combination with anticoagulant prophylaxis to improve efficacy.^{133,144–146} For all situations, the clinical staff must select the correct size of the device, must properly apply them,¹⁴⁷ and must ensure that they are removed for only a short time each day. Furthermore, nursing and physiotherapy initiatives should ensure that the devices do not impede ambulation.

Recommendation: Mechanical Methods of Prophylaxis

1.4.3. We 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**). We recommend that careful attention be directed toward ensuring the proper use of, and optimal compliance with, the mechanical device (**Grade 1C+**).

1.4.4 Aspirin as thromboprophylaxis

Aspirin and other antiplatelet drugs are highly effective at reducing major vascular events in patients who are at risk for or who have established atherosclerotic disease.¹⁴⁸ Evidence^{3,149–151} suggests that antiplatelet agents also provide some protection against VTE in hospitalized patients who are at risk. However, we 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 metaanalysis¹⁴⁹ 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%.^{149,152} Second, a number of trials found no significant benefit from aspirin therapy,^{151,153–156} or found that aspirin was

inferior to other prophylactic modalities.^{2,156–158} Finally, aspirin use is associated with a small but significant increased risk of major bleeding, especially if combined with other antithrombotic agents.^{149,151}

The inferior efficacy of aspirin compared to other methods of VTE prophylaxis has been demonstrated in clinical trials. Among 205 patients undergoing hip or knee arthroplasty, who were randomized to receive aspirin or the LMWH ardeparin, the relative reduction in the risk of VTE with the use of LMWH over aspirin was 63% ($p < 0.001$).¹⁵⁷ The RRRs for DVT and proximal DVT in patients who have received prophylaxis with a VFP plus aspirin over that with aspirin alone following total knee arthroplasty (TKA) were 32% and > 95%, respectively ($p < 0.001$ for both comparisons).¹⁵⁶ Among hip fracture surgery (HFS) patients who were randomized to receive either aspirin or danaparoid, a low-molecular-weight heparinoid, VTE was detected in 44% and 28% of the patients, respectively ($p = 0.028$).¹⁵⁸

Recommendation: Aspirin

1.4.4. We recommend **against** the use of aspirin alone as prophylaxis against VTE for any patient group (**Grade 1A**).

1.4.5 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 LMWH, fondaparinux, and the direct thrombin inhibitor melagatran. With reduced creatinine clearance, these drugs may accumulate and increase the risk of bleeding.^{159,160} 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.¹⁶¹

Recommendations: Dosing and Renal Impairment

1.4.5.1. For each of the antithrombotic agents, we recommend that clinicians consider the manufacturer's suggested dosing guidelines (**Grade 1C**).

1.4.5.2. We recommend consideration of renal impairment when deciding on doses of 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+).

1.5 Antithrombotic drugs and neuraxial anesthesia/analgesia

The benefits of neuraxial blockade (*ie*, spinal or epidural anesthesia and continuous epidural analgesia) are well-established.^{162–167} 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.^{168,169} Bleeding into the enclosed space of the spinal canal can produce spinal cord ischemia and subsequent paraplegia. The seriousness of this complication mandates the cautious use of all antithrombotic medications in patients undergoing neuraxial blockade. A 1997 Food and Drug Administration public health advisory^{170,171} reported 41 US patients who developed perispinal hematoma after receiving the LMWH enoxaparin around the time of spinal/epidural anesthesia. Some patients had preexisting spinal abnormalities, and a third had received additional hemostasis-inhibiting medications. Nearly 90% of the cases occurred among patients receiving enoxaparin as thromboprophylaxis after knee or hip replacement or after spinal surgery. Many of these patients experienced neurologic impairment, including permanent paralysis, despite undergoing a decompressive laminectomy. Additional cases of perispinal hematoma in patients who have received LMWH have been reported. This complication also has been reported with the use of LDUH, although apparently with lower frequency.

Most patients who develop perispinal hematomas have more than one risk factor for local or systemic bleeding, including the presence of an underlying hemostatic disorder, anatomic or vascular vertebral column abnormalities, traumatic needle or catheter insertion, repeated insertion attempts, insertion in the presence of high levels of an anticoagulant, the use of continuous epidural catheters, the concurrent administration of medications known to increase bleeding, high anticoagulant dosage, older age, and female gender.^{168,170,171} Removal of the epidural catheter, especially in the presence of an anticoagulant effect, has also been associated with hematoma.¹⁶⁸ Unfortunately, the prevalence of perispinal hematoma and the predictive value of the various risk factors remain unknown. As a result, reviews on the use of antithrombotic therapy among recipients of neuraxial anesthesia^{169,172,173} combine the limited available evidence with practical advice. A detailed discussion of this topic is available through the American Society of Regional Anesthesia and Pain Medicine (www.asra.com).¹⁶⁹

Consideration of neuraxial anesthesia plus or minus postoperative epidural analgesia requires a review of the intended benefits and the potential risks. A careful history will identify most patients with an important underlying bleeding disorder and those receiving agents that affect hemostasis or platelet function. In keeping with the

American Society of Regional Anesthesia recommendations, we believe that neuraxial blockade and anticoagulant thromboprophylaxis, including the use of LDUH and LMWH, can generally be used concurrently as long as there is appropriate caution.

The following suggestions may improve the safety of neuraxial blockade in patients who have or will receive anticoagulant prophylaxis. (1) Neuraxial anesthesia/analgesia should generally be avoided in patients with a known bleeding disorder. (2) Neuraxial anesthesia should generally be avoided in patients whose preoperative hemostasis is impaired by antithrombotic drugs. Nonsteroidal anti-inflammatory agents and aspirin do not appear to increase the risk of perispinal hematoma. Since less is known about the safety of the thienopyridine platelet inhibitors clopidogrel and ticlopidine in patients undergoing neuraxial block, the discontinuation of these drugs 5 to 14 days before the procedure should be considered. In patients receiving preoperative anticoagulants, the insertion of the spinal needle or epidural catheter should be delayed until the anticoagulant effect of the medication is minimal. This is usually at least 8 to 12 h after a subcutaneous dose of heparin or a twice daily prophylactic dose of LMWH, or at least 18 h after a once-daily LMWH injection. (3) Anticoagulant prophylaxis should be delayed if a hemorrhagic aspirate (*ie*, a “bloody tap”) is encountered during the initial spinal needle placement. (4) Removal of an epidural catheter should be done when the anticoagulant effect is at a minimum (usually just before the next scheduled subcutaneous injection). (5) Anticoagulant prophylaxis should be delayed for at least 2 h after spinal needle or epidural catheter removal. (6) If prophylaxis with a VKA, such as warfarin, is used, we recommend that continuous epidural analgesia not be used for longer than 1 or 2 days because of the unpredictable anticoagulant effect of the anticoagulant. Furthermore, if prophylaxis with a VKA is used at the same time as epidural analgesia, the international normalized ratio (INR) should be < 1.5 at the time of catheter removal. (7) Although postoperative prophylaxis with fondaparinux appears to be safe in patients who have received a spinal anesthetic, there are no safety data about its use along with postoperative continuous epidural analgesia. The long half-life of fondaparinux and its renal mode of excretion raise concerns about the potential for accumulation of the drug, especially in the elderly because of the associated impairment of renal function. Until further data are available, we recommend that fondaparinux not be administered along with continuous epidural analgesia.

With the concurrent use of epidural analgesia and anticoagulant prophylaxis, all patients should be monitored carefully and frequently for the symptoms and signs of cord compression. These symptoms include progression of lower extremity numbness or weakness, bowel or bladder dysfunction, and new onset of back pain. If spinal hematoma is suspected, diagnostic imaging and definitive surgical therapy must be performed rapidly to reduce the risk of permanent paresis. We encourage every hospital that uses neuraxial anesthesia/analgesia to develop written protocols that cover the most common scenarios in which these techniques will be used along with antithrombotic agents.

Recommendation: Neuraxial Anesthesia/analgesia

1.5.1. In all patients undergoing neuraxial anesthesia or analgesia, we recommend special caution when using anticoagulant prophylaxis (**Grade 1C+**).

2.0 General, Vascular, Gynecologic, and Urologic Surgery

2.1 General surgery

In studies published between 1969 and 1984,^{40,77,174} the observed rate of DVT among general surgical patients not receiving prophylaxis varied between 15% and 30%, with rates of fatal PE between 0.2% and 0.9%. The current risk of thromboembolic complications in general surgery is unknown because studies without prophylaxis are no longer performed in these patients. More rapid mobilization, greater use of thromboprophylaxis, and other advances in perioperative care may tend toward reducing the thromboembolic risk. However, the performance of more extensive operative procedures in older and sicker patients, the use of preoperative chemotherapy, and the shorter lengths of stay in the hospital (leading to shorter durations of prophylaxis) may heighten the risk of VTE in contemporary patients undergoing inpatient, general surgery.

The type and duration of surgery clearly influence the risk of DVT.^{90,175–178} Most individuals undergoing outpatient surgery appear to have a low frequency of DVT. For example, only one case of symptomatic VTE arose in the first month following 2,281 day-case hernia repairs (0.04%).¹⁷⁹ Additional factors that alter the risk of VTE in general surgery patients include the following:

- Traditional risk factors such as cancer, previous VTE, obesity, varicose veins, and estrogen use^{175–178};
- Increasing age, an independent risk factor for VTE^{176,177};
- Type of anesthesia. In the absence of prophylaxis, the risk of DVT is lower following spinal/epidural anesthesia than after general anesthesia.¹⁸⁰ This protective effect is less apparent, at least in orthopedic surgery, when pharmacologic prophylaxis is used^{181,182}; and
- General perioperative care, including degree of mobilization, fluid status, and transfusion practices.

Furthermore, the diagnostic screening test used (*ie*, FUT, venography, or DUS) and the quality of its interpretation greatly affect the rate of detection of thrombi, as discussed in section 1.4.1.^{95,99,100,103,110,123}

Based on the results of numerous randomized clinical trials and metaanalyses, we recommend the routine use of thromboprophylaxis following major general surgical procedures.^{1–3,89} Both LDUH and LMWH reduce the risk of both asymptomatic and symptomatic VTE in general surgery by at least 60%.^{2,71,77} Most prophylaxis trials of subcutaneous LDUH administered 5,000 U 1 to 2 h before surgery, followed by administration of 5,000 U bid or tid until patients were either ambulating or were discharged from hospital. A metaanalysis of 46 random-

ized clinical trials in general surgery⁷¹ compared therapy with LDUH with no prophylaxis or placebo. The rate of DVT was significantly reduced (from 22 to 9%; odds ratio [OR], 0.3; NNT, 7), as were the rates of symptomatic PE (from 2.0 to 1.3%; OR, 0.5; NNT, 143), fatal PE (from 0.8 to 0.3%; OR, 0.4; NNT, 182), and all-cause mortality (from 4.2 to 3.2%; OR, 0.8; NNT, 97). Prophylaxis with LDUH was associated with a small increase in the rate of bleeding events (from 3.8 to 5.9%; OR, 1.6; NNH, 47). These findings were verified in another metaanalysis⁷⁷ in which the rate of wound hematomas was increased with LDUH use (6.3% vs 4.1% in control subjects; OR, 1.6; NNH, 45), although the rate of major bleeding was not. While both meta-analyses concluded that the administration of heparin, 5,000 U tid, was more efficacious than that of 5,000 U bid, without increasing bleeding, this was based on indirect comparisons, and we are not aware of any studies that directly compared these two regimens.

LMWHs have been evaluated extensively in general surgery patients, usually in comparison with LDUH.^{79,102,183–199} Clinical trials also have compared different LMWHs²⁰⁰ or different regimens of the same LMWH.^{101,188,190,201–206} One metaanalysis⁴⁰ found that LMWH prophylaxis reduced the risk of asymptomatic DVT and symptomatic VTE in general surgery patients by > 70% compared with no prophylaxis.

When LDUH and LMWH were directly compared, no single study showed a difference in the rates of symptomatic VTE, although several trials^{183,185,187} found that LMWH was associated with significantly fewer asymptomatic DVTs. There are at least nine metaanalyses and systematic reviews comparing these two agents.^{40,78,80–82,207–210} Small differences in their results can be explained by the variability in the inclusion criteria for the original studies. The various LMWHs were grouped together as a single class agent, despite differences in their pharmacologic properties and the position statements made by regulatory authorities that each LMWH should be considered as a distinct drug. We are not aware of any direct comparisons of comparable doses of different LMWHs in this patient population.²⁰⁰

In summary, for general surgery patients, LDUH and LMWHs have similar efficacy and bleeding rates. In high-risk general surgery patients, higher doses of LMWH provide greater protection than lower doses.^{101,195,211,212} For example, in cancer patients, prophylaxis with dalteparin, 5,000 U daily, was significantly more efficacious than with 2,500 U daily, without an increased risk of bleeding.¹⁰¹

Some studies^{79,102,193,196} have reported significantly fewer wound hematomas and other bleeding complications with LMWH than with LDUH, while other trials^{184,185,199} have shown the opposite effect. Two metaanalyses^{40,81} that found similar efficacy for LDUH and LMWH described differences in bleeding rates that were dependent on the dose of LMWH used. Lower doses of LMWH (*ie*, ≤ 3,400 U daily) were associated with less bleeding than LDUH (3.8% vs 5.4%, respectively; OR, 0.7), while higher doses resulted in more bleeding events (7.9% vs 5.3%, respectively; OR, 1.5).⁸¹

The clinical advantages of LMWH over LDUH include its once-daily administration and the lower risk of heparin-

induced thrombocytopenia (HIT),²¹³ while, at least in North America, LMWH is more costly.

Several large studies in general surgery patients have evaluated the risk of death among patients given LDUH or LMWH. Two clinical trials^{50,69} were specifically designed to test the effectiveness of LDUH in preventing fatal PE, compared with no prophylaxis. Both studies demonstrated a significant beneficial effect (overall RRR for fatal PE with LDUH, 91%; NNT, 106).^{50,69} A placebo-controlled, multicenter study¹⁷⁴ found that the LMWH fraxiparine significantly reduced the all-cause mortality rate (from 0.8 to 0.4%) among 4,498 general surgery patients (NNT, 250). Two additional randomized clinical trials,^{191,197} with a combined sample of 35,000 surgical patients, found no difference in the rates of total mortality, fatal PE, or bleeding between LDUH (5,000 U tid) and the LMWH certoparin (3,000 U once daily). In both studies, the follow-up duration was brief (14 days and the in-hospital period only).

The selective inhibitor of factor Xa fondaparinux has been evaluated in a randomized, double-blinded clinical trial²¹⁴ among almost 3,000 patients undergoing high-risk abdominal surgery. Prophylaxis with fondaparinux, started postoperatively, was compared with prophylaxis with dalteparin started before surgery. There were no significant differences in the rates of VTE, major bleeding, or death between the two prophylaxis groups.

Although mechanical methods of prophylaxis (*ie*, GCS and IPC) are attractive options in general surgery patients who have a high risk of bleeding, they have not been studied as extensively as has pharmacologic prophylaxis.⁷⁷ A systematic review¹³³ observed a significant 52% reduction in the rate of DVT with the use of GCS (13%) compared with no prophylaxis (27%), which is equivalent to a pooled OR of 0.3 (NNT, 7). This finding was confirmed by two additional meta-analyses.^{130,215} The use of GCS has also been shown to enhance the protective effect of LDUH against DVT by a further 75% compared with LDUH alone (DVT rates of 4% and 15% in the combined and LDUH groups, respectively), for a pooled OR of 0.2 (NNT, 9).¹³³ The effect of GCS on the risk of proximal DVT or symptomatic PE, and their effectiveness in patients with malignancies remains unknown due to the presence of only a few small studies. Some practical limitations of GCS include a lack of standardization of the quality of the stockings, difficulty with fitting patients with unusual limb sizes or shapes, and poor compliance with their use by both health-care providers and patients.^{138,140}

Several small, older studies^{216–218} have suggested that prophylaxis with IPC might reduce the incidence of DVT in general surgical patients to an extent similar to LDUH, although another study²¹⁹ found that IPC provided no protection at all. There is insufficient evidence to assess whether IPC prophylaxis alone has any effect on symptomatic VTE or mortality. In a single randomized clinical trial of 2,551 cardiac surgery patients,¹⁴⁶ the rate of symptomatic PE was lower with combined IPC and LDUH (1.5%) than with LDUH alone (4.0%).

Although the risk of developing postoperative DVT is highest within the first week or two after undergoing general surgery, VTE complications, including fatal PE,

may occur later.^{9,14,177,220} In one study,²²¹ 51 patients who underwent major abdominal surgery received thromboprophylaxis in the hospital and had DVT excluded at the time of hospital discharge. Follow-up at home over the next 4 weeks, using serial FUT and DUS, detected DVT in 13 patients (25%). These studies and the current brief lengths of hospital stay have prompted assessments of the optimal duration of prophylaxis following general surgical procedures.

Three clinical trials^{204–206} have addressed the use of extended prophylaxis beyond the period of hospitalization following general surgery. In a small, nonblinded trial in 118 major abdominal or thoracic surgery patients, 4 weeks of tinzaparin, 3,500 U daily, was associated with a nonsignificant reduction in the risk of asymptomatic DVT detected by bilateral screening venography, compared with the same dose given for just 1 week (DVT rates, 5% and 10%, respectively).²⁰⁴ In another open-label study conducted in 233 major abdominal surgery patients,²⁰⁶ dalteparin, 5,000 U, was administered once daily for 1 or 4 weeks. Bilateral venography detected DVT in 16% and 6%, respectively, of the patients who received prophylaxis for 1 week or 1 month ($p = 0.09$) [proximal DVT rates, 9% and 0%, respectively; $p = 0.001$]. A subgroup analysis²²² of the patients in this study who had malignancies reported statistically significant RRRs in the rates of DVT and proximal DVT with extended prophylaxis. The ENOXACAN II study,²⁰⁵ a double-blinded, multicenter trial conducted in 332 abdominal or pelvic cancer surgery patients, compared the administration of enoxaparin, 40 mg daily, for an average of 9 or 28 days. Routine venography, performed between days 25 and 31, showed a significant reduction in DVT rates with the prolonged prophylaxis (from 12 to 5%; OR, 0.36; $p = 0.02$). However, proximal DVT was identified in only three patients in the short-duration group and in one patient in the extended prophylaxis group. Over the entire 3-month follow-up period, there were only two symptomatic thromboembolic events among the short-duration patients and one event in the extended prophylaxis group.

In conclusion, among patients undergoing major general surgical procedures, routine thromboprophylaxis is recommended.^{1–3,87,89} The options that have clearly been shown to reduce DVT and PE are LDUH and LMWH. Mechanical prophylactic methods (*ie*, GCS and/or IPC) appear to reduce DVT rates and should be considered for patients who are at a particularly high risk of bleeding. Prophylaxis with LMWH for 2 to 3 weeks after hospital discharge appears to reduce the incidence of asymptomatic DVT in cancer surgery patients.

Recommendations: General Surgery

2.1.1. In low-risk general surgery patients (Table 5) who are undergoing a minor procedure, are < 40 years of age, and have no additional risk factors, we recommend **against** the use of specific prophylaxis other than early and persistent mobilization (**Grade 1C+**).

2.1.2. 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. We recommend prophylaxis with LDUH, 5,000 U bid or LMWH \leq 3,400 U once daily (both **Grade 1A**).

2.1.3. 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. We recommend thromboprophylaxis with LDUH, 5,000 U tid or LMWH, > 3,400 U daily (both **Grade 1A**).

2.1.4. In high-risk general surgery patients with multiple risk factors, we recommend that pharmacologic methods (*ie*, LDUH, tid or LMWH, > 3,400 U daily) be combined with the use of GCS and/or IPC (**Grade 1C+**).

2.1.5. In general surgery patients with a high risk of bleeding, we recommend the use of mechanical prophylaxis with properly fitted GCS or IPC, at least initially until the bleeding risk decreases (**Grade 1A**).

2.1.6. In selected high-risk general surgery patients, including those who have undergone major cancer surgery, we suggest post-hospital discharge prophylaxis with LMWH (**Grade 2A**).

2.2 Vascular surgery

Most patients undergoing vascular surgery routinely receive one or more antithrombotic agents to prevent vascular occlusion. This is achieved using perioperative platelet inhibitors, such as aspirin or clopidogrel, and intraoperative heparins or dextran before vascular clamping. Postoperative anticoagulation therapy with unfractionated heparin, warfarin, and/or LMWH is also common in these patients.^{223–225} Because of the widespread use of these agents, little is known about the frequency of VTE in vascular surgery patients, especially among those not receiving antithrombotic drugs. In a population-based study²⁰ of 1.6 million patients, the incidence of symptomatic VTE within 3 months of major vascular surgery was 1.7 to 2.8%. Potential thromboembolic risk factors in vascular surgery include advanced age, limb ischemia, long duration of surgery, and intraoperative local trauma, including possible venous injury.⁶ Preliminary evidence²²⁶ suggests that atherosclerosis also may be an independent risk factor for VTE.

The 20 to 30% rate of asymptomatic DVT after aortoiliac or aortofemoral surgery is similar to that reported in other abdominal and pelvic procedures.^{227–230} However, these rates may have been inflated by the high false-positive rates (25 to 81%) seen with FUT, which were clearly identified when patients with abnormal FUT results also underwent venography.^{228,231,232} In five prospective studies of vascular surgery patients not receiving any thromboprophylaxis, the pooled rate of postoperative DVT was 21% (18 of 86 patients) using contrast venography^{233–235} and 15% (15 of 98 patients) using DUS.^{230,236} In another study of 50 patients undergoing aortic aneurysm repair,²³⁵ asymptomatic DVT was diagnosed in 18% of patients using contrast venography, while the rate of

proximal DVT was 4%. Among 142 patients who underwent a variety of vascular surgical procedures, all of whom received thromboprophylaxis with intraoperative IPC and perioperative LDUH, the respective rates of DVT and proximal DVT, which were detected by routine screening with DUS on days 7 to 10, were 10% and 6%, respectively.²³⁷

Aortic aneurysm resection or aortofemoral bypass appears to confer a higher risk of DVT than femorodistal bypass. We are aware of only three studies that routinely screened for DVT and also included both groups of patients.^{230,237,238} In one randomized trial,²³⁸ patients received either subcutaneous LDUH or LMWH. Using DUS screening at days 7 to 10 after surgery, with venography confirmation of a positive DUS result, DVT was detected in 8% of patients (11 of 146 patients) who underwent aortic surgery and in 3% of those who underwent femorodistal bypass (3 of 87 patients). In a second study,²³⁷ routine DUS was performed in vascular surgery patients, who also received prophylaxis with IPC and LDUH. The respective rates of DVT were 12% (6 of 52 patients) and 9% (5 of 54 patients), respectively, among the patients who had aortic and femorodistal surgery. In the most recent study,²³⁰ a pre-hospital discharge DUS was obtained in 50 vascular surgery patients, none of whom had received thromboprophylaxis. Again, the rate of DVT was higher in the aortic surgery patients (41%) than in the peripheral arterial surgery patients (18%). A prospective registry²³⁹ of 7,533 vascular surgery procedures performed in Finland reported clinical DVT in 0.9% of patients after aortic surgery and 0.7% after femorodistal reconstruction.

In patients with lower limb ischemia, preoperative DVT may be present. One study detected DVT by DUS in 20% of 136 peripheral vascular disease patients prior to arteriography or surgery, although no DVT appeared to be acute by ultrasonographic assessment.²⁴⁰ Logistic regression analysis showed that increased severity of ischemia, expressed as a reduced ankle pressure/brachial pressure index, was the only independent risk factor for DVT. In another prospective study,²³⁰ only 1 of 53 vascular surgery patients was found to have DVT on preoperative DUS. A third DUS-based study²⁴¹ reported low rates of preoperative asymptomatic DVT (4%) and postoperative asymptomatic DVT (3%) in patients undergoing infrainguinal arterial reconstruction, although 25% of the patients received anticoagulation therapy postoperatively. Even patients who have had endovascular treatment of abdominal aortic aneurysms are at risk for DVT. For example, 6% of 50 consecutive patients who had DUS on the first and 30th days postprocedure were found to have DVTs.²⁴²

Only four randomized clinical trials of thromboprophylaxis after arterial reconstructive surgery have been performed.^{228,236,238,243} In each of the studies, patients received IV heparin during the procedure. The first trial²²⁸ compared LDUH, 5,000 U bid, to placebo in 49 patients undergoing elective aortic bifurcation surgery. Using FUT, confirmed by venography if positive, DVT was detected in 24% of placebo recipients and in 4% of LDUH recipients. However, clinical bleeding was significantly greater in those who received LDUH, leading to the premature termination of the study. A second study²⁴³

found no benefit of LDUH over no prophylaxis, although only 43 patients were included. In the third trial,²³⁶ 100 patients having aortic surgery were randomized to receive LDUH plus GCS or no prophylaxis. Proximal DVT was detected in 2% of patients in both groups using serial DUS. The final study²³⁸ compared LDUH, 7,500 U bid, with enoxaparin, 40 mg daily, with each administered for ≤ 2 days, among 233 patients undergoing aortic or infringuinal reconstructions. Using DUS at days 7 to 10, DVT was detected in 4% and 8% of patients, respectively (not statistically significant), while major bleeding occurred in 2% of patients in both groups.

Recommendations: Vascular Surgery

2.2.1. In patients undergoing vascular surgery who do not have additional thromboembolic risk factors, we suggest that clinicians **not** routinely use thromboprophylaxis (**Grade 2B**).

2.2.2. For patients undergoing major vascular surgical procedures who have additional thromboembolic risk factors, we recommend prophylaxis with LDUH or LMWH (**Grade 1C+**).

2.3 Gynecologic surgery

VTE is an important and potentially preventable complication of major gynecologic surgery, with rates of DVT, PE, and fatal PE comparable to those seen after general surgical procedures.^{2,244,245} Several factors appear to increase the risk of VTE following gynecologic surgery, including malignancy, older age, previous VTE, prior pelvic radiation therapy, and use of an abdominal surgical approach.^{20,246,247} Gynecologic oncology patients are often elderly, and they all have cancer, with or without compression of the major pelvic veins by a mass.^{246,248} Venous intimal injury may occur following preoperative radiotherapy or during surgery (especially with pelvic lymph node dissection), the procedures are frequently lengthy, and residual tumor may be left *in situ*. Postoperative mobility is often impaired after such extensive surgery, and chemotherapy itself is thrombogenic. As in other surgical patients, thrombi generally form during or shortly after the procedure,²⁴⁹ although most symptomatic thromboemboli occur after hospital discharge.^{247,250}

Despite substantial changes in surgical and postoperative care, few randomized clinical trials of thromboprophylaxis in gynecologic surgery have been reported in the past decade,^{245,251–255} and some of these have major methodological limitations.

Several practice guidelines have addressed the issue of thromboprophylaxis in patients undergoing gynecologic surgery.^{2,256,257} Patients who are otherwise well and undergo brief procedures, typically defined as < 30 min, do not require any specific prophylaxis but should be encouraged to mobilize early after surgery. The previous American College of Chest Physicians Consensus Conference on Antithrombotic Therapy concluded that twice daily dosing of LDUH was effective in patients undergoing gynecologic surgery for benign disease in the absence of additional risk factors.² Mechanical prophylaxis with IPC

also appears to be efficacious in this group^{251,258,259} and should be considered for patients who are at a high risk of bleeding. IPC prophylaxis should be started just before surgery, used continuously while the patient is not ambulating, and stopped just before hospital discharge. Formal strategies to optimize compliance with IPC by patients and nursing staff are essential.

Patients having surgery for gynecologic cancers appear to derive less protection from twice daily dosing of LDUH than those with benign disease.^{260,261} LDUH, given three times daily, or LMWH, at daily doses of at least 4,000 U, appear to be more effective in these cancer patients.^{195,251,255,261,262} Four randomized clinical trials^{195,248,254,263} compared LDUH, given three times daily, with LMWH in gynecologic surgery patients, and suggested similar effectiveness and safety with either approach. In an uncontrolled case series of 2,030 patients who were undergoing major gynecologic surgery and were given enoxaparin, 20 mg once daily, there were no fatal PEs, and only seven patients (0.3%) developed symptomatic VTE.²⁶⁴ Combining mechanical prophylaxis with LDUH or LMWH therapy may enhance efficacy, although, to our knowledge, this has not been studied in gynecology patients.

Although the risk of VTE after laparoscopic gynecologic surgery is unknown (and appears to be lower than that for open procedures), laparoscopic procedures result in impaired venous return from the legs and activation of coagulation. Therefore, we recommend that a decision to provide prophylaxis be individualized, considering a patient's comorbid and procedure-related risk factors.

Another unresolved issue is the duration of antithrombotic prophylaxis following gynecologic surgery. One randomized, double-blind study²⁰⁵ compared 1 week with 1 month of LMWH prophylaxis in patients undergoing curative surgery for abdominal or pelvic malignancy (8% of the patients had a gynecologic oncology procedure). Extended prophylaxis conferred a RRR of 60% for both venographically screened DVT and proximal DVT. While this trial suggested a potential advantage of post-hospital discharge prophylaxis in certain high-risk surgical oncology patients, the specific risk factors that warrant extended prophylaxis remain to be defined. In a recent study of 1,862 patients who underwent gynecologic surgery and received IPC prophylaxis,²⁴⁷ the risk factors for symptomatic VTE included cancer surgery, previous DVT, and age > 60 years.

Recommendations: Gynecologic Surgery

2.3.1. For gynecologic surgery patients undergoing brief procedures of ≤ 30 min for benign disease, we recommend **against** the use of specific prophylaxis other than early and persistent mobilization (**Grade 1C+**).

2.3.2. For patients undergoing laparoscopic gynecologic procedures, in whom additional VTE risk factors are present, we recommend the use of thromboprophylaxis with one or more of the following: LDUH, LMWH, IPC, or GCS (all **Grade 1C**).

2.3.3. We recommend that thromboprophylaxis be used in all major gynecologic surgery patients (**Grade 1A**).

2.3.4. For patients undergoing major gynecologic surgery for benign disease, without additional risk factors, we recommend LDUH, 5,000 U bid (**Grade 1A**). Alternatives include once-daily prophylaxis with LMWH, $\leq 3,400$ U/d (**Grade 1C+**), or IPC started just before surgery and used continuously while the patient is not ambulating (**Grade 1B**).

2.3.5. For patients undergoing extensive surgery for malignancy, and for patients with additional VTE risk factors, we recommend routine prophylaxis with LDUH, 5,000 U tid (**Grade 1A**), or higher doses of LMWH (*ie*, $> 3,400$ 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**).

2.3.6. For patients undergoing major gynecologic procedures, we 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, we suggest continuing prophylaxis for 2 to 4 weeks after hospital discharge (**Grade 2C**).

2.4 Urologic surgery

VTE is considered to be the most important nonsurgical complication following major urologic procedures.^{2,265–269} Unfortunately, most of the epidemiologic data related to VTE in this population were derived 10 to 30 years ago. Subsequent changes in surgical care, earlier mobilization, and possibly greater use of prophylaxis have been associated with declining rates of VTE over time.^{270–272} However, 1 to 5% of contemporary patients undergoing major urologic surgery experience symptomatic VTE, with PE believed to be the most common cause of postoperative death, at a risk of < 1 in 500.^{20,266,270–280}

Patients undergoing major urologic surgery often have multiple risk factors for VTE, including advanced age, malignancy, use of the lithotomy position intraoperatively, and pelvic surgery with or without lymph node dissection. Additional factors for DVT include the use of open (vs transurethral) procedures and a longer duration of the procedure.

Most of the information about VTE and its prevention were derived from patients undergoing open prostatectomy. Other urologic procedures, including major renal surgery and transplantation, radical cystectomy, and urethral reconstruction, are also associated with an increased risk for thrombosis and warrant consideration for prophylaxis.^{281–283}

We identified only one randomized clinical trial of thromboprophylaxis in urologic surgery published over the past 2 decades that met the minimal methodological criteria (Table 1).²⁸⁴ Thus, the optimal approach to thromboprophylaxis in these patients is not known.^{2,285} Many older studies were small, and lacked blinding and objective outcome assessments. Modern anesthesia techniques have

improved, and there is generally a more aggressive approach to postoperative mobilization. At the same time, radical cancer operations are being performed more frequently than in the past. Despite a sparse literature on thromboprophylaxis in patients undergoing urologic surgery, the risks of VTE and the protection offered by various prophylaxis methods appear to be similar to those seen in patients undergoing major general or gynecologic surgery.^{2,3,71} Furthermore, consideration of bleeding risk is particularly important in urologic surgery, especially following prostatectomy.

While the use of GCS or IPC prophylaxis is likely to be efficacious in urologic surgery,^{126,274,280,284,286} IPC is more expensive and may provide no additional protection over the use of GCS alone.^{274,286} Both LDUH and LMWH are efficacious in patients undergoing urologic surgery.^{71,264,268,279,287–289} Concerns about the potential for pelvic hematomas and lymphoceles in patients receiving anticoagulant prophylaxis have been raised by some investigators,^{268,272,290} but not by others.^{268,279,289} The combination of mechanical and pharmacologic prophylaxis may be more effective than either alone but may not be necessary and is more expensive.^{268,279,291}

For patients undergoing transurethral prostatectomy, the risks of VTE are low,^{20,71,264,280,289,292} and perioperative use of LDUH or LMWH may increase the risk of bleeding.^{290,293,294} Early postoperative mobilization is probably the only intervention warranted in these and other low-risk urologic surgery patients. Routine prophylaxis is recommended for more extensive, open procedures including radical prostatectomy, cystectomy, or nephrectomy. Until further data are available, VTE prophylaxis options to consider for these patients include the following: LDUH; LMWH; GCS; and IPC. For urology patients who are at particularly high risk, commencing prophylaxis with GCS with or without IPC just prior to surgery and then adding LDUH or LMWH postoperatively should be considered, even though this approach has not been formally evaluated in this patient population. With the current brief lengths of hospitalization, even for major urologic procedures, the risk of post-hospital discharge, symptomatic VTE is likely to increase.^{20,295} Therefore, the optimal duration of prophylaxis is uncertain. Patients who are believed to be at high risk for thromboembolism, including elderly patients undergoing radical prostatectomy, patients with a history of VTE, or patients who have limited mobility at hospital discharge, should be considered for post-hospital discharge thromboprophylaxis.²⁰⁵

Recommendations: Urologic Surgery

2.4.1. In patients undergoing transurethral or other low-risk urologic procedures, we recommend **against** the use of specific prophylaxis other than early and persistent mobilization (**Grade 1C+**).

2.4.2. For patients undergoing major, open urologic procedures, we 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+**).

2.4.3. For urologic surgery patients who are actively bleeding, or are at very high risk for bleeding, we recommend the use of mechanical prophylaxis with GCS and/or IPC at least until the bleeding risk decreases (**Grade 1C+**).

2.4.4. For patients with multiple risk factors, we recommend combining GCS and/or IPC with LDUH or LMWH (**Grade 1C+**).

2.5 Laparoscopic surgery

The expanding use of laparoscopic techniques over the past 2 decades has profoundly changed surgical diagnosis and therapy. There is, however, considerable controversy related to thromboembolic complications after these procedures.²⁹⁶ Laparoscopic cholecystectomy is associated with a modest thrombogenic activation of the coagulation system,^{297–304} as well as stimulation of fibrinolysis.^{305,306} In some studies,^{298,305} the magnitude of these changes was similar to that of changes seen after open cholecystectomy, while other studies^{299,302,306} found smaller changes among the patients undergoing laparoscopic cholecystectomy. Laparoscopic operations are often associated with longer surgical times than are open procedures. Both pneumoperitoneum and the reverse Trendelenburg position reduce venous return from the legs, creating lower extremity venous stasis.^{307–309} While laparoscopic procedures are generally associated with a shorter hospital stay, patients undergoing them may not mobilize more rapidly at home than those undergoing open procedures.

Although the risks of VTE and its prevention have been less intensively studied in laparoscopic procedures compared with other abdominal procedures, the risks appear to be low.²⁰ For example, among 417 UK surgeons, 91% reported having never encountered a thromboembolic complication following laparoscopic cholecystectomy, although the majority reported using LDUH routinely in these patients.³¹⁰ A Danish survey³¹¹ found that 80% of surgical departments were not aware of any thromboembolic complications following laparoscopic surgery, although, again, prophylaxis was commonly used. In another

study, no DVT or PE was encountered in the first month after laparoscopic cholecystectomy among 587 cases, of whom only 3% received thromboprophylaxis.³¹²

Among 25 patients undergoing laparoscopic cholecystectomy without any thromboprophylaxis, screening contrast venography on postoperative days 6 to 10, failed to detect any DVT.³¹³ Eight cases of DVT (0.3%) and no cases of PE were seen in another series of 2,384 consecutive patients who underwent GI laparoscopic procedures followed by a short course of LMWH prophylaxis.³¹⁴ A review of 50,427 gynecologic laparoscopies³¹⁵ observed a symptomatic VTE rate of only 2 per 10,000 patients. In a literature review of laparoscopic cholecystectomy³¹⁶ including 11,863 patients, only 3 of the 10 postoperative deaths were attributed to PE. In another literature review of 153,832 laparoscopic cholecystectomies,³¹⁷ using various types of prophylaxis, the average rates of clinical DVT, PE, and fatal PE were 0.03%, 0.06%, and 0.02%, respectively. In a prospective national Swedish registry,³¹⁸ VTE was encountered in only 0.2% of the 11,164 patients who underwent laparoscopic cholecystectomies. However, the proportion of patients who received thromboprophylaxis was not reported. Finally, in a population-based study of 105,850 laparoscopic cholecystectomies performed in California,²⁰ the risk of symptomatic VTE within 3 months of the procedure was 0.2%, compared with 0.5% after open cholecystectomy.

Table 6 shows the rates of objectively proven DVT after laparoscopy, which were derived from prospective studies that used various forms of prophylaxis.^{297,313,319–325} Although the studies were generally small, with a single exception the rates of asymptomatic DVT were very low. Among the eight prospective studies that used routine postoperative DUS, the pooled rate of DVT was 1.4% (17 of 1,248 patients). Excluding one outlier study, the DVT rate was 0.5% among the 1,228 patients. When no prophylaxis was given, the rate of asymptomatic DVT in the 219 patients rose to 0.9%.

We are aware of only two randomized clinical trials of thromboprophylaxis in laparoscopic surgery patients.^{313,320}

Table 6—DVT After Laparoscopic Procedures*

Study/Year	Prophylaxis	Diagnostic Test for DVT	Day Screened	Patients, No.	Patients With DVT, No.
Caprini et al ^{297/1995}	GCS + IPC (+ LDUH in 26%)	DUS	7	100	1 (1)
Patel et al ^{319/1996}	GCS + LDUH + ECS in 80%	DUS	1, 7, 30	20	11 (55)
Baca et al ^{320/1997}	GCS	DUS	5–7	359	0
	GCS + LMWH			359	1 (0.3)
Bounameaux et al ^{313/1997}	Placebo	Venography	6–10	25	0
	LMWH			15	0
Healey et al ^{321/1998}	ECS	DUS	1–3, 7	20	0
Lord et al ^{322/1998}	GCS + IPC + LMWH	DUS	1, 14–28	59	1 (2)
Wazz et al ^{323/2000}	None	DUS	1	61	0
Mall et al ^{324/2001}	IPC + LMWH	DUS	5	32	0
Schaepkens van Riepmst et al ^{325/2002}	None	DUS	10	133	2 (2)
	LMWH			105	1 (1)

*Values in parentheses are %. Prospective studies of patients who had routine screening for DVT following laparoscopic procedures. ECS = electrical calf stimulation. The laparoscopic procedures performed in the studies were as follows: laparoscopic cholecystectomy^{297,313,319,322,325}; gynecologic laparoscopy³²¹; colon resection³²⁴; and various procedures.^{320,323}

Contrast venography was the primary outcome in one trial³¹³ that randomized 82 laparoscopic cholecystectomy patients to receive prophylaxis with either dalteparin, 2,500 U once daily, or placebo for 6 to 10 days. Among the 40 patients who had adequate venograms from the combined groups, none had DVT. In the second trial,³²⁰ 718 patients undergoing laparoscopic surgery were randomized to receive prophylaxis with GCS alone or GCS plus the LMWH reviparin at a dose of 1,750 U subcutaneously (SC) daily. Patients with three or more risk factors for VTE were excluded, and 88% had undergone laparoscopic cholecystectomy. Using a combination of clinical follow-up and DUS at 5 to 7 days after surgery, only one calf DVT and one nonfatal PE were observed, with equal bleeding rates in both groups. While IPC prophylaxis may prevent reduced femoral vein flow associated with pneumoperitoneum,^{326,327} no randomized trial has shown that IPC is efficacious in preventing DVT in these patients.

Despite a paucity of epidemiologic or prospective data, the European Association for Endoscopic Surgery has recommended that intraoperative IPC be used for all prolonged laparoscopic procedures.³²⁸ The Society of American Gastrointestinal Endoscopic Surgeons has recommended the use of the same thromboprophylaxis options with laparoscopic procedures as for the equivalent open surgical procedures.³²⁹ However, we think that the evidence is inadequate to recommend the routine use of thromboprophylaxis in these patients.^{312,330} Patients who are at particularly high risk can be considered for brief prophylaxis with any of the currently available modalities. Clearly, more prospective trials are required to better define patient risk and the need for prophylaxis following laparoscopic procedures.

Recommendations: Laparoscopic Surgery

2.5.1. We recommend against routine thromboprophylaxis in these patients, other than aggressive mobilization (**Grade IA**).

2.5.2. For patients undergoing laparoscopic procedures, and who have additional thromboembolic risk factors, we recommend the use of thromboprophylaxis with one or more of the following: LDUH, LMWH, IPC, or GCS (**Grade IC+**).

3.0 Orthopedic Surgery

Patients undergoing major orthopedic surgery, which includes hip and knee arthroplasty and hip fracture repair,

represent a group that is at particularly high risk for VTE, and routine thromboprophylaxis has been the standard of care for > 15 years.^{2,331} Randomized clinical trials have demonstrated that the rates of venographic DVT and proximal DVT 7 to 14 days following major orthopedic surgery in patients who received no prophylaxis are approximately 40 to 60% and 10 to 30%, respectively (Table 7).^{3,16,18,65,131,134,137,150,155,156,273,332–353} The incidence of PE is much less certain. Among patients undergoing total hip replacement (THR) and TKA in whom ventilation-perfusion lung scanning was routinely performed, 3 to 28% had scan findings with a high probability of PE within 2 weeks following surgery.^{23,337,344,354} With the routine use of thromboprophylaxis, fatal PE is now uncommon,^{355,356} although symptomatic VTE continues to be reported in 1.5 to 10% of patients within 3 months after surgery.^{20,65,338,343,357–360} Even with prophylaxis, symptomatic VTE was seen in 2.4% and 1.7%, respectively, of patients within 3 months of hip or knee arthroplasty from 1992 to 1996.⁵¹ Most symptomatic VTE occurs after hospital discharge, and the risk continues to be higher than expected for at least 2 months after surgery.^{41,51,65,361} Furthermore, VTE is the most common cause for readmission to the hospital following THR.³⁵⁵

The natural history of VTE after major orthopedic surgery has become better defined over the past 30 years. Asymptomatic DVT is common and, in the absence of prophylaxis, affects at least half of all patients. Most of these thrombi are clinically silent, and resolve spontaneously without any long-term sequelae.^{362,363} However, for some patients, the presence of silent postoperative DVT, persistent venous injury, stasis due to prolonged decreased mobility,³⁶⁴ impairment of the endogenous anticoagulant or fibrinolytic systems,^{365,366} prolonged impairment of venous function,³⁶⁷ or a combination of these factors allows an existing small thrombus to propagate (or a new thrombus to develop). This thrombus then may produce symptoms as a result of venous occlusion or embolization to the lungs. Symptomatic VTE often presents after orthopedic patients are discharged from hospital.⁵¹ Among some patients with post-hospital discharge DVT, the thrombus is present early after surgery, and, as thromboprophylaxis is discontinued, the silent DVT extends.²⁸ For others who do not have DVT at hospital discharge, a new thrombosis may develop during recovery in a rehabilitation center or at home. In one study,³⁶⁸ approximately 20% of THR patients who had a negative venogram at hospital discharge developed a new DVT over the subsequent 3 weeks. Unfortunately, there is currently no way to identify

Table 7—VTE Prevalence After Major Orthopedic Surgery*

Procedure	DVT, %		PE, %	
	Total	Proximal	Total	Fatal
Hip arthroplasty	42–57 ^{131,134,137,332–336}	18–36 ^{131,134,137,332–336}	0.9–28 ^{131,333–335,337–340}	0.1–2.0 ^{18,334,338,341–343}
Knee arthroplasty	41–85 ^{150,156,344–349}	5–22 ^{150,156,344–348}	1.5–10 ^{156,344,346,347,350}	0.1–1.7 ^{65,341,349–351}
Hip fracture surgery	46–60 ^{155,352,353}	23–30 ^{155,353}	3–11 ^{155,334,352}	2.5–7.5 ^{16,334,353}

*DVT rates are based on the use of mandatory venography in prospective clinical trials published since 1980 in which patients received either no prophylaxis or placebo. PE rates were derived from prospective studies that may have included prophylaxis. Modified from Geerts et al.²

which orthopedic patients will develop symptomatic VTE. Therefore, thromboprophylaxis is recommended for all patients undergoing major orthopedic surgery of the lower extremities.

The next sections summarize the data derived from numerous randomized clinical trials of thromboprophylaxis following THR, TKA, and HFS. Areas of orthopedic surgery for which there are much less data, including knee arthroscopy, elective spine surgery, and isolated lower extremity injuries, are also reviewed. We discuss important aspects of prophylaxis such as the timing of the initiation of prophylaxis and its optimal duration, as well as the role of noninvasive screening for DVT.

3.1 Elective hip arthroplasty

THR is a common surgical procedure that is predicted to increase substantially among the aging population. Patients undergoing elective THR are at high risk for both asymptomatic DVT (incidence, 40 to 60%) and symptomatic VTE (incidence, 2 to 5%).^{2,3,369} Fatal PE occurs in approximately one patient per 500 elective hip arthroplasties.^{18,370–372} In the first consensus conference on the prevention of VTE,³³¹ published in 1986, the routine use of thromboprophylaxis was recommended for these patients. Since that time, numerous randomized clinical trials have been conducted in this patient group, and evidence-based guidelines have been refined.^{2,3}

Studies that withheld primary prophylaxis and instead screened for DVT using noninvasive methods have not demonstrated that screening is an alternative to primary prophylaxis.⁹⁵ Many studies found noninvasive screening tests to have unacceptably low measures of sensitivity and specificity after THR, even for the detection of proximal DVT.^{104,105,114,116,117,373–379} Moreover, a strategy of screening for proximal DVT with pre-hospital discharge DUS was ineffective in patients who received prophylaxis with LMWH or warfarin.^{64,65} While a similar strategy using pre-hospital discharge venography appeared to be cost-effective in one study,³⁶¹ routine venography is no longer widely available or considered to be an acceptable option by most clinicians. Consequently, primary prophylaxis is recommended for all THR patients.

Several nonpharmacologic prophylaxis methods have been studied in THR patients, including GCS,^{335,338,380–383} IPC,^{134,137,384–388} and venous foot compression.^{129,382} While each of these mechanical prophylaxis methods may confer average RRRs against DVT of 20 to 70%, their protection is lower than current anticoagulant-based prophylaxis strategies, especially for preventing proximal DVT.^{2,137,383,387} Two studies^{129,382} have suggested that pneumatic foot pumps appear to be effective at reducing the risk of total DVT. However, because the published experience with foot pumps in THR patients is small, we cannot recommend this modality for primary prophylaxis. Mechanical modalities are also logistically problematic for continued prophylaxis after hospital discharge.

Although multimodal prophylaxis is commonly used in major orthopedic surgery, we are not aware of any randomized clinical trials comparing this approach with single modalities. For example, studies that have combined

epidural anesthesia, IPC, plus aspirin³⁸⁹ or aspirin plus GCS or IPC,³⁹⁰ cannot be compared with other approaches, because each uses a different combination of interventions, they had no comparison groups, and did not use contrast venography to assess efficacy outcomes.

The use of spinal or epidural regional anesthesia is associated with a significant reduction in the incidence of postoperative DVT among THR recipients, especially in the absence of other thromboprophylaxis measures.^{181,391} However, regional anesthesia alone cannot be considered adequate thromboprophylaxis because the risk of VTE remains unacceptably high in this patient population.

Many different anticoagulant-based prophylaxis regimens have been studied for THR patients. Although metaanalyses have shown that prophylaxis with LDUH⁷¹ or aspirin¹⁴⁹ is superior to no prophylaxis, both agents are less effective than other prophylactic regimens in this high-risk group.^{131,151,392–398} Aspirin should not be used as the only prophylactic agent after THR. Among 4,088 hip and knee arthroplasty patients who were randomized to receive aspirin or placebo, with other thromboprophylaxis measures administered according to individual physician practice, aspirin did not lower the risk of symptomatic VTE.¹⁵¹ Although the use of preoperative LDUH, followed postoperatively with dose-adjusted heparin to maintain the activated partial thromboplastin time around the upper range of normal appears safe and highly effective, it is impractical for use in routine clinical practice.^{393,399–401}

Adjusted-dose oral VKAs like warfarin continue to be the most common form of prophylaxis used in North America following THR.^{402–407} The primary advantages of VKAs are their delayed onset of action, allowing surgical hemostasis to develop, and the ability to be continued after hospital discharge (as long as the infrastructure is in place to do this effectively and safely). In Europe, VKAs have largely been abandoned as DVT prophylaxis out of concerns about their delayed onset of action, variable response between patients, lower efficacy compared to LMWH, need for frequent monitoring, interactions with other drugs, and the complexity of both in-hospital and post-hospital discharge supervision of dose adjustments according to the INR.

If VKAs are used, they should be administered in doses that are sufficient to prolong the INR to a target of 2.5 (range, 2.0 to 3.0). Although lower target ranges are sometimes used for orthopedic prophylaxis, we recommend an INR of 2.0 to 3.0, a range that is used in the published efficacy trials. A lower INR may not provide optimal protection against VTE, and is unlikely to reduce the risk of bleeding. The initial dose of VKA should be administered either the evening before surgery or the evening after surgery. With this approach, the target range for the INR usually is not reached until at least the third postoperative day.^{360,408–410} In a large cohort study,³⁶⁰ the use of a VKA dosing nomogram simplified the management of warfarin in hip and knee arthroplasty patients.

LMWHs have been studied extensively in THR patients, and provide both highly effective and safe VTE prophylaxis. LMWH is more efficacious than LDUH.^{78,82,131,394,411,412} While three clinical trials^{408,413,414} comparing LMWH prophylaxis to adjusted-dose warfarin

found no difference in either total or proximal DVT, a fourth trial⁴⁰⁹ found LMWH, started preoperatively, to be significantly more efficacious than warfarin. However, in the latter study, LMWH was associated with a significantly greater rate of both bleeding at the operative site and blood product transfusion. A fifth study⁴¹⁵ compared LMWH prophylaxis, started at half the usual daily dose, either < 2 h before surgery or at least 4 h after surgery, with warfarin started postoperatively. The use of LMWH was associated with a significant reduction in the risk of both total and proximal DVT, and with a lower incidence of symptomatic, objectively confirmed DVT (2.2% vs 4.4%, respectively).

When the results from the five large clinical trials directly comparing adjusted-dose warfarin prophylaxis with LMWH among THR patients^{408,409,413-415} are pooled, the respective rates of all DVT were 20.7% (256 of 1,238 patients) and 13.7% (238 of 1,741 patients; $p = 0.0002$). The proximal DVT rates were 4.8% and 3.4%, respectively ($p = 0.08$). The pooled rates of major bleeding, using somewhat different definitions in the five studies, were 3.3% in the VKA recipients and 5.3% in the LMWH recipients. In other randomized clinical trials of THR patients,^{332,416} a comparable 4% rate of major bleeding was documented in the placebo control patients. In a large, nonblinded clinical trial,³⁴³ > 3,000 THR patients randomly received in-hospital prophylaxis with either enoxaparin, 30 mg SC bid, started postoperatively or warfarin dose-adjusted for an INR of 2.0 to 3.0. The in-hospital incidences of symptomatic, objectively documented VTE were 0.3% and 1.1%, respectively ($p = 0.008$). Because of a slightly higher rate of DVT after hospital discharge in the LMWH group, the overall rates of VTE by 3 months after surgery were not significantly different. Major bleeding occurred in 1.2% of LMWH recipients and in 0.5% of warfarin recipients ($p = 0.06$).

The synthetic pentasaccharide fondaparinux selectively inhibits coagulation factor Xa and has been shown to be highly efficacious in the prevention of DVT among THR patients in two large clinical trials.^{417,418} In the European study,⁴¹⁷ 2,309 patients were randomized to fondaparinux, 2.5 mg SC once daily starting 4 to 8 h after surgery, or enoxaparin, 40 mg SC once daily starting 12 h before surgery. The overall rates of VTE were 4% and 9%, respectively ($p < 0.0001$). The rate of proximal DVT was lower among recipients of fondaparinux (1%) compared to recipients of enoxaparin (2%; $p = 0.002$). In the North American study,⁴¹⁸ the same fondaparinux regimen was compared to enoxaparin, 30 mg bid starting 12 to 24 h after elective THR, among 2,275 patients. Neither the overall rate of VTE (6% vs 8%, respectively; $p = 0.1$) nor the rate of proximal DVT (2% vs 1%, respectively; $p = 0.5$) differed significantly between the respective groups. The first postoperative dose of fondaparinux was given approximately 6 h after surgery, while enoxaparin therapy was started approximately 18 h after surgery. Both trials showed nonsignificant trends toward increased bleeding with fondaparinux, which were consistent with other comparisons of LMWH and fondaparinux.^{419,420}

Because of its long half-life (approximately 18 h), patients whose creatinine clearance is < 30 mL/min may

experience an accumulation of fondaparinux and thus may be at greater risk of bleeding. The safety of fondaparinux among patients receiving postoperative analgesia with an indwelling epidural catheter also has not been established.¹⁶⁹

From these data, we conclude that the LMWHs, and likely fondaparinux by indirect comparison, are more effective than VKAs in preventing asymptomatic and symptomatic in-hospital VTE. There is a slight increase in surgical site bleeding and wound hematomas with these more effective forms of prophylaxis. The higher efficacy and bleeding risks are likely attributable to the more rapid onset of anticoagulant activity with LMWH and fondaparinux compared to VKAs.

Three randomized clinical trials have found that prophylaxis with the direct thrombin inhibitor recombinant hirudin, 15 mg SC bid beginning just before THR, is more efficacious than LDUH^{396,397} or LMWH,⁴²¹ with no differences in bleeding. At this time, hirudin is not approved for thromboprophylaxis in North America. A number of prospective trials⁴²²⁻⁴²⁵ have studied prophylaxis with another direct thrombin inhibitor, melagatran, given SC for 1 to 3 days, followed by the oral prodrug of this compound, ximelagatran, in THR and TKA patients. No anticoagulant laboratory testing was performed among the melagatran/ximelagatran recipients. In one phase III study,⁴²⁴ 2,764 patients were randomly assigned to receive melagatran, 2 mg SC immediately before surgery and 3 mg SC on the same evening after surgery, followed by ximelagatran, 24 mg po bid, or enoxaparin, 40 mg SC on the evening before surgery and then once daily starting on the following day. The rates of overall and proximal DVT were significantly lower in the melagatran/ximelagatran group, although the bleeding and transfusion rates were also higher. In a second large European clinical trial,⁴²⁵ the same enoxaparin regimen was compared to a postoperatively initiated melagatran/ximelagatran regimen. DVT occurred significantly less often among enoxaparin recipients, with no differences in the rates of proximal DVT or bleeding. In a North American study of 1,838 patients undergoing THR,⁴²⁶ enoxaparin, 30 mg bid starting after surgery, was compared with ximelagatran, 24 mg bid also started the morning after surgery and continued for 7 to 12 days. DVT or symptomatic VTE was detected in 4.6% of enoxaparin recipients and in 7.9% of ximelagatran recipients ($p = 0.03$). Major bleeding was documented in < 1% of patients in both groups. At the time of this writing, melagatran/ximelagatran therapy had not been approved in North America.

In summary, decisions about thromboprophylaxis around the time of THR, using LMWH, fondaparinux, or a VKA, should be made at a specific hospital level and, on occasion, at the level of the individual patient. These decisions are formed according to comparative drug pricing, the ability to safely monitor oral VKA use, and the planned duration of prophylaxis.

Recommendations: Elective Hip Arthroplasty

3.1.1. For patients undergoing elective THR, we recommend the routine use of one of the following three

anticoagulants: (1) LMWH (at a usual high-risk dose, started 12 h before surgery or 12 to 24 h after surgery, or 4 to 6 h 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 h after surgery); or (3) adjusted-dose VKA started preoperatively or the evening after surgery (INR target, 2.5; INR range, 2.0 to 3.0) [all **Grade IA**].

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

3.1.2. We recommend **against** the use of aspirin, dextran, LDUH, GCS, IPC, or VFP as the only method of thromboprophylaxis in these patients (**Grade IA**).

3.2 Elective knee arthroplasty

In terms of VTE prevention, TKA differs from THR in several important respects.² Without prophylaxis, the rate of venographically detected DVT is higher after TKA than after THR, although TKA patients appear to experience lower rates of proximal DVT and symptomatic VTE. Some prophylaxis measures that have been used successfully in THR patients are less efficacious when used among TKA patients. Although major bleeding may not be more common in TKA patients, greater concern has been expressed about bleeding consequences in these patients. Finally, the RRR conferred by the use of LMWH vs warfarin is even greater after TKA than after THR.

The results of four small studies^{154,386,427,428} have suggested that IPC devices provide efficacious prophylaxis in TKA patients. These devices are most effective when applied either intraoperatively or immediately postoperatively, and are worn continuously at least until the patient is fully ambulatory. Poor compliance, improper use of the devices, patient intolerance, and the inability to continue prophylaxis after hospital discharge limit the utility of IPC. Because the combined patient enrollments in the LMWH and warfarin prophylaxis trials are > 25 times greater than in the combined IPC trials, more confident estimates of the protection against VTE are available for LMWH and warfarin prophylaxis than for IPC. IPC may be useful as an in-hospital adjunct to anticoagulant-based prophylaxis in the presence of multiple risk factors for postoperative VTE, although combined prophylaxis using IPC and either LMWH or adjusted-dose VKA has not been studied in a randomized clinical trial.

The use of a venous foot pump (VFP) was shown to be efficacious in two small clinical trials among TKA patients^{156,429} but was considerably less efficacious than LMWH in two other trials.^{135,430} In a more recent study, VFP and LMWH were equally ineffective, with a 54% overall rate of DVT in the LMWH group, which was higher than expected.³⁴⁹ While the rate of proximal DVT in this study was low, there were two PE-related deaths in the VFP group. The limited data suggest that GCS provide no protection in TKA patients.^{348,431} Continuous passive-

motion devices also have been shown to not reduce the rate of DVT among TKA patients, compared with routine physiotherapy alone.³⁴⁵

Because of their limited efficacy in TKA patients, LDUH^{416,432} and aspirin^{150,151,154,156,345,428} are not recommended as sole prophylaxis modalities. Adjusted-dose oral VKAs, including warfarin, were assessed in 12 randomized clinical trials with routine venography outcomes.^{150,386,408,413,414,433–439} As with most of the thromboprophylaxis interventions in patients undergoing TKA, the residual rate of asymptomatic DVT, detected by routine contrast venography, was quite high (25 to 50%) with use of a VKA. However, the rate of symptomatic VTE with VKA thromboprophylaxis is low. In one clinical trial, of 257 TKA patients who received about 10 days of warfarin prophylaxis (target INR range, 1.8 to 2.5), only 0.8% experienced symptomatic VTE by 3 months.⁶⁴ In a similar study of 815 patients who received VKA for an average of 12 days after TKA, only 1.3% developed asymptomatic VTE by 3 months, and none had fatal PE.⁴⁴⁰ While adjusted-dose VKAs are effective as prophylaxis after TKA, achieving and maintaining a target INR is difficult in routine practice. Moreover, VKAs are less efficacious than LMWH or fondaparinux, and proper post-hospital discharge management of VKA prophylaxis is more complex.

Extensive data have shown that LMWH prophylaxis is safe and effective after TKA.^{65,135,347,348,408,413,414,416,419,430,432,434–436,441,442} Considering the six randomized clinical trials^{408,413,414,434–436} that directly compared the use of VKA with LMWH after TKA, the pooled DVT rates were 48% and 33%, respectively. The respective rates of proximal DVT were 10.4% and 7.1%. In two of these studies,^{413,436} there was a higher risk of bleeding, but not major bleeding, among LMWH recipients. Two recent meta-analyses^{443,444} confirmed the superior efficacy of LMWH over both LDUH and warfarin, without an increased risk in bleeding. While LMWH prevents more venographic total DVTs and proximal DVTs than warfarin, starting LMWH prophylaxis within 12 h after surgery may be associated with a small increase in wound hematomas. We are not aware of any clinical trials comparing LMWH and warfarin prophylaxis among TKA patients using symptomatic, objectively confirmed VTE as the measure of effectiveness.

The overall financial cost of warfarin or LMWH prophylaxis following lower extremity arthroplasty appears to be similar.^{445–449} In one US study,⁴⁴⁷ adjusted-dose warfarin prophylaxis was slightly more cost-effective than LMWH prophylaxis, although the other analyses came to the opposite conclusion.

In a recent blinded clinical trial of > 1,000 patients undergoing elective major knee surgery, fondaparinux, administered at a dose of 2.5 mg SC once daily starting about 6 h after surgery, was compared to enoxaparin, 30 mg SC bid starting 12 to 24 h after surgery.⁴¹⁹ The rates of VTE (12.5% vs 27.8%, respectively; $p < 0.001$) and proximal DVT (2.4% vs 5.4%, respectively; $p = 0.06$) were more than halved using fondaparinux. Major bleeding was significantly more common in the fondaparinux group (2.1% vs 0.2%, respectively; $p = 0.006$) due to a higher bleeding index, which was calculated as the number of

units of blood transfused added to the change in hemoglobin concentration before and after the bleeding episode. In a metaanalysis of the four phase III clinical trials comparing fondaparinux and enoxaparin prophylaxis in patients undergoing orthopedic surgery,³⁵⁶ major bleeding was significantly more common with fondaparinux when the first dose of fondaparinux was given within 6 h following surgery.

A number of studies^{423–425,437–439,441} have assessed a direct thrombin inhibitor that has been developed in a parenteral formulation (melagatran) and an oral formulation (ximelagatran). Phase II studies^{423,441} have shown that either perioperative prophylaxis with SC melagatran followed by oral ximelagatran or postoperative oral ximelagatran alone provided similar efficacy and safety as LMWH. Three blinded clinical trials have compared ximelagatran prophylaxis with adjusted-dose warfarin.^{437–439} In the first trial,⁴³⁷ 680 patients undergoing elective TKA were randomly assigned to receive oral ximelagatran, 24 mg bid starting the morning after surgery, or adjusted-dose warfarin (target INR, 2.5; INR range, 1.8 to 3.0, starting on the evening after surgery). The rates of total VTE (19.2% vs 25.7%, respectively; $p = 0.07$) and proximal DVT (3.3% vs 5.0%, respectively; $p > 0.2$) did not differ significantly between the ximelagatran and warfarin groups. The rates of major and minor bleeding were low and also not significantly different. In the second trial,⁴³⁹ 2,301 patients undergoing TKA were randomly assigned to prophylaxis with oral ximelagatran (24 mg bid or 36 mg bid, starting the morning after surgery) or adjusted-dose warfarin (target INR, 2.5; INR range, 1.8 to 3.0, starting the evening after surgery). The rates of overall VTE or death were significantly lower with the 36-mg dose of ximelagatran than with warfarin (20.3% vs 27.6%, respectively; $p = 0.003$), while the DVT rate with ximelagatran, 24 mg bid, was similar to that seen in the warfarin patients. The rates of proximal DVT in the patients who received ximelagatran, 24 mg bid, ximelagatran, 36 mg bid, or warfarin were not significantly different (2.0%, 2.1% and 3.8%, respectively), while the rates of major and minor bleeding were low and did not differ significantly among the three groups. The third clinical trial⁴³⁸ compared the postoperative initiation of ximelagatran, 36 mg bid, with that of adjusted-dose warfarin in 2,299 TKA patients. The rate of total VTE plus death was significantly lower with ximelagatran prophylaxis than with warfarin therapy (22.5% vs 31.9%, respectively). There were no significant differences in the rates of major VTE and bleeding.

Recommendations: Elective Knee Arthroplasty

3.2.1. For patients undergoing elective TKA, we 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 IA**].

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

3.2.2. The optimal use of IPC is an alternative option to anticoagulant prophylaxis (**Grade IB**).

3.2.3. We recommend **against** the use of any of the following as sole methods of thromboprophylaxis: aspirin (**Grade IA**); LDUH (**Grade IA**); or VFP (**Grade IB**).

3.3 Knee arthroscopy

As discussed in section 3.2, VTE is a frequent and important complication of knee arthroplasty, and most medical centers now routinely use thromboprophylaxis in these patients. Fewer data exist about the risks of VTE associated with arthroscopy of the knee,^{330,450} which is the most common orthopedic procedure performed in the United States. Arthroscopy and arthroscopy-assisted knee surgery (*eg*, meniscectomy, synovectomy, and reconstruction of the cruciate ligaments) are now performed more commonly than arthroplasty, and in a younger age group. One early prospective study of 8,791 knee arthroscopies, performed by 21 members of the Arthroscopy Association of North America,⁴⁵¹ reported symptomatic VTE in $< 0.15\%$ of cases, with no fatal PE. In another series of 8,500 arthroscopic procedures,⁴⁵² clinical DVT was reported in only four patients, with no fatal PE. More recently, symptomatic, objectively confirmed DVT was found in only 0.6% of 1,355 patients after diagnostic knee arthroscopy without the use of thromboprophylaxis, and only one patient developed proximal DVT.³⁵⁸

The prospective studies of knee arthroscopy, without thromboprophylaxis, but with routine screening for DVT, are shown in Table 8.^{346,453–460} The rates of DVT range from 2 to 18% in these studies. Stringer and coworkers³⁴⁶ found a 4% incidence of DVT, using venography, in 48 patients after arthroscopy, compared to a rate of 56% among those who underwent TKA. Another study⁴⁵³ had a rate of venographically detected DVT of only 3% among 170 patients after arthroscopic knee surgery. In a prospective study of 184 patients who had adequate venography 1 week after therapeutic knee arthroscopy,⁴⁵⁴ the rates of DVT and proximal DVT were 18% (95% confidence interval [CI], 13 to 24%) and 5% (95% CI, 2 to 9%), respectively. No patient presented with clinically suspected PE. In a fourth study,⁴⁵⁷ routine DUS was performed 5 to 10 days after knee arthroscopy. Asymptomatic DVT was detected in 2% of 239 patients, a rate 10 times that for symptomatic DVT (0.2%) among a cohort of 2,050 similar knee arthroscopy patients from the same institution who did not undergo DUS. When data from the six prospective studies of knee arthroscopy that used routine postoperative DUS screening (but no thromboprophylaxis) are pooled, DVT was found in 5% of the 600 cases, and proximal DVT was found in 0.6% of cases.

The available studies permit a limited assessment of VTE risk factors among arthroscopy patients. It appears that therapeutic arthroscopy is associated with a higher VTE risk than diagnostic arthroscopy, and tourniquet time, perhaps reflecting the complexity of the surgery, also appears to be a risk factor.^{454,457}

We are aware of only two small randomized clinical trials of thromboprophylaxis in knee arthroscopy patients (Table 9).^{459,460} In the first, patients were randomized to

Table 8—Prospective Studies of DVT Rates After Knee Arthroscopy*

Study/Year	Method of Diagnosis	When Screened After Surgery	No.	DVT, No.	Proximal DVT, No.
Stringer et al ³⁴⁶ /1989	Venography	7–10 d	48	2 (4)	0
Durica et al ⁴⁵³ /1997	Venography	10–14 d	161	5 (3)	2 (1)
Demers et al ⁴⁵⁴ /1998	Venography	1 wk	184	33 (18)	9 (5)
Williams et al ⁴⁵⁵ /1995	DUS	7–14 d	85	3 (4)	0
Cullison et al ⁴⁵⁶ /1996	DUS	2–3 d	67	NR	1 (1)
Jaureguito et al ⁴⁵⁷ /1999	DUS	5–10 d	239	5 (2)	0–1
Delis et al ⁴⁵⁸ /2001	DUS	≤ 1 wk	102	8 (8)	0
Wirth et al ⁴⁵⁹ /2001	DUS	7–10 d	111	5 (5)	2 (2)
Michot et al ⁴⁶⁰ /2002	DUS	12 and 30 d	63	10 (16)	0

*Routine screening for DVT in patients undergoing knee arthroscopy with no thromboprophylaxis. Values in parentheses are %. NR = not reported.

receive either no prophylaxis or the LMWH reviparin, 1,750 AXa U once daily for 7 to 10 days.⁴⁵⁹ Among the 239 patients with adequate compression ultrasonography findings at the end of the study period, DVT was found in 4% of control subjects and in 1% of those patients who received LMWH ($p = 0.2$). This study had a number of methodological limitations that render the findings uncertain. In a second trial,⁴⁶⁰ 130 patients undergoing diagnostic or therapeutic arthroscopy were randomized to receive either no prophylaxis or once-daily dalteparin for up to 30 days. DUS was obtained at 12 and 30 days after surgery. The DVT rates in the control and LMWH groups were 16% and 2%, respectively ($p = 0.004$). There were no cases of proximal DVT. No major bleeding complications were reported in any of the 182 patients who received LMWH in these two prophylaxis trials.^{459,460}

In summary, although uncertainty remains about the risk of VTE in patients undergoing knee arthroscopy, compared to most other major orthopedic surgery procedures, the risk appears to be low. The results of two small trials have suggested that LMWHs reduce the rate of asymptomatic DVT, but further studies are required before prophylaxis recommendations can be made. In the meantime, prophylaxis decisions should be made at the institutional or individual patient level. At a minimum, when appropriate, patients should be encouraged to ambulate early after the procedure and should be made aware of the symptoms of VTE so that they will present for investigation if there is a reasonable suspicion of this complication.

Recommendations: Knee Arthroscopy

3.3.1. We suggest clinicians do **not** use routine thromboprophylaxis in these patients, other than early mobilization (**Grade 2B**).

3.3.2. For patients undergoing arthroscopic knee surgery who are at higher than usual risk, based on preexisting VTE risk factors or following a prolonged or complicated procedure, we suggest thromboprophylaxis with LMWH (**Grade 2B**).

3.4 Hip fracture surgery

It is established that HFS patients are at very high risk of VTE. After HFS, the rates of total and proximal DVT, which were derived from eight prospective studies using routine contrast venography,^{155,352,353,461–465} were approximately 50% and 27%, respectively, without prophylaxis. The rate of fatal PE was reported to be in the range of 1.4 to 7.5% within 3 months after HFS, a range higher than that seen after hip or knee arthroplasty.^{16,334} In a population-based autopsy study of 581 patients who died after hip fracture from 1953 to 1992,⁴⁶⁶ PE was consistently the fourth leading cause of death, accounting for 14% of all deaths. In addition to the initial injury and its surgical repair, factors that may further increase the risk of VTE after HFS include advanced age and delayed surgery,^{466–469} while the influence of general anesthesia, vs regional anesthesia, remains uncertain.⁴⁷⁰

As demonstrated by Sevitt and Gallagher⁶⁸ > 40 years

Table 9—Thromboprophylaxis Trials in Patients Undergoing Knee Arthroscopy*

Study/Year	Method of Diagnosis	Intervention		DVT†	
		Control	Experimental	Control	Experimental
Wirth et al ⁴⁵⁹ /2001	DUS day 7–10	No prophylaxis	Reviparin, 1,750 AXa U daily × 7–10 d	5/117 (4)	1/116 (1)
Michot et al ⁴⁶⁰ /2002	DUS days 12 and 31	No prophylaxis	Dalteparin, 2,500 or 5,000 U daily ≤ 30 d	10/63 (16)	1/61 (2)

*Randomized clinical trials in which routine screening with objective diagnostic tests for DVT were performed in arthroscopy patients.

†Values given as No. of patients with DVT/total No. of patients (%).

ago, symptomatic VTE and fatal PE after HFS can be prevented with thromboprophylaxis. A prospective, regional audit¹⁶ observed no fatal PE among 261 HFS patients who received thromboprophylaxis, vs 4% of the 305 patients who received no prophylaxis. Accordingly, it is recommended that routine thromboprophylaxis be provided to all patients undergoing HFS, including those with major comorbidity or cognitive impairment, given the morbidity associated with symptomatic VTE and the resource utilization associated with investigation and treatment when VTE arises.

Compared with elective hip and knee arthroplasty, fewer thromboprophylaxis trials have been conducted in patients undergoing HFS. Mechanical prophylaxis with IPC or VFP appears to prevent DVT in some other patient groups, but we are not aware of any trials in HFS patients that meet our study inclusion criteria, and poor compliance with these devices remains a problem.⁴⁷¹ In one randomized clinical trial of 231 HFS patients,⁴⁷² the rate of VTE was reduced among those who received postoperative IPC prophylaxis. The combined outcome of PE or proximal DVT, using serial DUS, occurred in 4% of the IPC patients vs 12% of control subjects who did not receive prophylaxis ($p = 0.03$). We are unaware of published trials comparing IPC or VFP with other methods of prophylaxis in HFS patients, using routine contrast venography to detect DVT. There is also insufficient evidence to determine whether GCS provide protection in these patients.^{97,151}

A metaanalysis¹⁴⁹ has suggested that aspirin and other antiplatelet agents are effective in preventing postoperative VTE. However, none of the studies included in this metaanalysis used routine contrast venography as an outcome measure, and, compared with other prophylaxis regimens, antiplatelet drugs provide much less protection. In the Pulmonary Embolism Prevention Trial,¹⁵¹ 13,356 HFS patients in five countries were randomized to receive either 160 mg enteric-coated aspirin or placebo, starting before surgery in 82% of patients and continuing for 35 days thereafter. Additional prophylaxis with GCS, LMWH, or LDUH was used in 18%, 26%, and 30% of patients, respectively. The rates of fatal PE and DVT were both significantly reduced by the addition of aspirin, each by an absolute risk reduction of 0.4%, while the rates of fatal and nonfatal myocardial infarction or stroke, as well as all-cause mortality, were not reduced. There was a small but significant increase in wound-related and GI bleeding, and in the need for blood transfusion among the aspirin-treated patients. In the subgroup of 3,424 patients who also received prophylaxis with an LMWH, no statistically significant difference in the rate of symptomatic VTE was detected between aspirin and placebo recipients, but the Pulmonary Embolism Prevention trial was not designed to directly address this point.

A recent Cochrane review of VTE prophylaxis after HFS⁴⁷¹ included 31 trials and 2,958 patients. LDUH and LMWH were found to be protective against DVT, without increasing wound hematoma rates, although the superiority of one agent over the other could not be determined due to a lack of sufficient evidence. Also included in this systematic review, were five clinical trials of mechanical

prophylaxis in 487 patients.⁴⁷¹ It was concluded that, although the rate of DVT was reduced with these devices, the studies were small and methodologically flawed.

LDUH has been assessed in only one small randomized clinical trial that used routine venography following HFS.⁴⁷³ In this study, heparin, 5,000 U tid, was more efficacious than dalteparin, 5,000 U once daily, with DVT detected in 6 of 30 LDUH recipients and in 14 of 32 LMWH recipients ($p = 0.04$). LDUH may be more effective in HFS patients than in other high-risk patient groups because the usual prophylactic dose of heparin may provide a greater anticoagulant effect in many of these elderly patients with low body weight.

With one exception, the five trials of LMWH in HFS patients^{420,465,473–475} had small sample sizes. The single placebo-controlled clinical trial⁴⁶⁵ did not demonstrate a significant benefit of LMWH. To our knowledge, no clinical trials have directly compared the use of LMWH and VKA in HFS patients. Two studies found no significant difference in bleeding rates when LMWH therapy was compared with placebo⁴⁶⁵ or with LDUH,⁴⁷³ although the sample sizes were small.

Limited evidence suggests that prophylaxis with oral VKAs is effective and safe in HFS patients. One randomized clinical trial¹⁵⁵ compared postoperative prophylaxis with warfarin (target INR, 2.0 to 2.7) with that using aspirin, 650 mg twice daily, and with no prophylaxis. The rates of DVT were 20%, 41%, and 46% respectively, ($p = 0.005$) and the rates of proximal DVT were 9%, 11%, and 30%, respectively ($p = 0.001$). Bleeding rates were similar across the three groups. The pooled results from three studies of adjusted-dose VKA prophylaxis showed a 61% RRR for DVT, and a 66% reduction for proximal DVT, compared with no prophylaxis.^{155,461,462} The reported bleeding rates for VKA prophylaxis ranged from 0 to 47%,^{155,461,462} with the most recent and largest trial¹⁵⁵ finding no difference in bleeding compared with placebo.

The synthetic pentasaccharide fondaparinux, which is a selective factor Xa inhibitor, has been investigated in patients undergoing HFS.^{52,420} Eriksson and coworkers⁴²⁰ randomized 1,711 HFS patients to receive either enoxaparin, 40 mg SC once daily starting 12 to 24 h postoperatively, or fondaparinux, 2.5 mg SC once daily starting 4 to 8 h after surgery. Enoxaparin and fondaparinux were administered preoperatively in 26% and 11% of patients, respectively. The rates of VTE by postoperative day 11 were 19.1% and 8.3%, respectively ($p < 0.001$). The rate of proximal DVT was also significantly reduced with fondaparinux (rates of 4.3% vs 0.9%, respectively; $p < 0.001$). While major bleeding was documented in 2.2% of patients in both groups, minor bleeding was encountered in 2.1% and 4.1%, respectively, of the enoxaparin and fondaparinux patients ($p = 0.02$).

There is sometimes a delay between the hip fracture and hospital admission. More frequently, there is a further delay between hospital admission and surgery, while the patient is being assessed and medically “optimized,” and while waiting for operating room availability. Surgical delay appears to heighten the risk of VTE in hip fracture, and proximal DVT may develop between the time of injury and the delayed fixation.^{466,468,469,476–478} For exam-

ple, among 21 patients who had HFS delayed by at least 48 h, and who underwent preoperative venography, DVT occurred in 62% of patients and proximal DVT occurred in 14%.⁴⁶⁹ Therefore, if surgery is likely to be delayed, strong consideration should be given to commencing prophylaxis during the preoperative period, although we are not aware of any prophylaxis trials that specifically address this issue. When there is uncertainty about the timing of “on-call” surgery, use of a short-acting anticoagulant, like LDUH or LMWH, appears to be the most feasible option. As discussed in section 1.5, the type of anesthesia used also may influence the selection of the prophylactic agent and its timing.

The recommended prophylaxis options for HFS patients are fondaparinux, LMWH, or a VKA. Because the risk of VTE begins soon after the fracture occurs, prophylaxis should commence preoperatively if surgery will likely be delayed, and should be restarted once postoperative hemostasis has been demonstrated.

Recommendations: Hip Fracture Surgery

3.4.1. For patients undergoing HFS, we 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**).

3.4.2. We recommend **against** the use of aspirin alone (**Grade 1A**).

3.4.3. If surgery will likely be delayed, we recommend that prophylaxis with either LDUH or LMWH be initiated during the time between hospital admission and surgery (**Grade 1C+**).

3.4.4. We recommend mechanical prophylaxis if anticoagulant prophylaxis is contraindicated because of a high risk of bleeding (**Grade 1C+**).

3.5 Other prophylaxis issues in major orthopedic surgery

3.5.1 Timing of prophylaxis initiation

Two important issues should be highlighted about the timing of prophylaxis in patients undergoing major orthopedic surgery. The first relates to preoperative initiation of prophylaxis vs postoperative initiation, and the second concerns how early after surgery anticoagulant prophylaxis should be started.⁴⁷⁹

Because venous thrombosis may begin during the operation itself, it has been common practice to start prophylaxis before surgery. In Europe, LMWH prophylaxis has generally been started 10 to 12 h before surgery, usually the night before. In North America, prophylaxis with LMWH usually commences 12 to 24 h after surgery, to both minimize the risk of bleeding and to simplify same-day hospital admission for elective surgery. One review⁴⁸⁰ has suggested that any difference in efficacy between the preoperative and postoperative commencement of LMWH is likely to be small, although a subsequent metaanalysis concluded that preoperative initiation

of LMWH was significantly more efficacious and safer than postoperative commencement.⁴⁸¹

This controversy was recently addressed by the North American Fragmin Trial,^{415,482} in which THR patients were randomly allocated to receive the following: (1) preoperative dalteparin, 2,500 U SC started about 1 h before surgery, followed by a second dose of 2,500 U given about 7 h after surgery, and then 5,000 U once daily; (2) postoperative dalteparin, 2,500 U SC started about 7 h after surgery, and then 5,000 U once daily; or (3) postoperative adjusted-dose warfarin. Based on the findings of pre-hospital discharge venography, the respective rates of total and proximal DVT in the preoperative LMWH group (10.7% and 0.8%, respectively) and postoperative LMWH group (13.1% and 0.8%, respectively) were not significantly different, while the rates among the warfarin recipients (24.0% and 3.0%, respectively) were significantly higher than those for either LMWH regimen. The rate of major bleeding was significantly higher with preoperative LMWH prophylaxis than with warfarin and there was also a higher, but nonsignificant, trend toward more bleeding with preoperative LMWH prophylaxis when compared with postoperative LMWH. There was no increased risk of bleeding when the postoperative administration of LMWH was compared to the administration of warfarin. A systematic review⁴⁸³ also concluded that starting LMWH prophylaxis postoperatively provided comparable protection to the preoperative initiation of LMWH. For most patients undergoing major, elective orthopedic surgery, we recommend that the first dose of LMWH thromboprophylaxis be administered either before or after surgery, although there is little or no advantage to the former. For those patients who are at high risk for bleeding, the initial dose of LMWH should be delayed for 12 to 24 h after surgery, and until primary hemostasis has been demonstrated based on an examination of the surgical site.

The administration of prophylaxis in close proximity to surgery has been shown to enhance its efficacy.⁴⁷⁹ In a systematic review that compared prophylaxis with LMWH to that with VKA,⁴⁸⁴ a large risk reduction was observed when LMWH was initiated at half of the usual high-risk dose in close proximity to THR (*ie*, either < 2 h before surgery or 6 to 8 h after surgery). In the studies in which LMWH therapy was started either 12 to 24 h before surgery or 18 to 24 h after surgery, this efficacy advantage was not observed. Only starting LMWH therapy just before THR was associated with an increased risk of major bleeding. Another systematic review⁴⁸³ also concluded that LMWH administered close to the time of surgery reduced the risk of VTE, but this benefit was offset by an increased risk of major bleeding.

Studies using hirudin, fondaparinux, or melagatran/ximelagatran support the idea that dosing in close proximity to orthopedic surgery enhances the prophylactic efficacy of the drug.^{160,356,421,485} For fondaparinux, the incidence of major bleeding was significantly higher ($p = 0.045$) in patients who received a first dose within 6 h of skin closure (3.2%), compared to waiting ≥ 6 h (2.1%).¹⁶⁰ Therefore, although the efficacy/bleeding ratio may differ among anticoagulant drugs, and each should be properly evaluated in clinical studies, it is likely true that

there is greater efficacy, but also greater bleeding, associated with an earlier postoperative initiation of anticoagulant thromboprophylaxis.⁴⁷⁹

Recommendation: Commencement of Prophylaxis

3.5.1. For major orthopedic surgical procedures, we 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 IA**). For LMWH, there are only small differences between starting preoperatively or postoperatively, and both options are acceptable (**Grade IA**).

3.5.2 Pre-hospital discharge screening for DVT

Historically, some clinicians and researchers have advocated, in certain high-risk groups, the routine screening and treatment of asymptomatic, localized DVT before it could extend to produce symptomatic DVT or PE.⁴⁸⁶ We do not support this approach because it is neither clinically effective nor cost-effective. Routine screening for asymptomatic DVT, using DUS, was not validated in three large studies of THR and TKA patients.^{64,65,487} Only 3 of 1,936 arthroplasty patients (0.15%) who received both in-hospital LMWH prophylaxis and pre-hospital discharge ultrasonography were found to have asymptomatic DVT.⁶⁵ In the second trial,⁶⁴ hip and knee arthroplasty patients were randomized to receive pre-hospital discharge DUS or sham ultrasound. Active DUS screening detected DVT in 2.5% of patients, who then received anticoagulation therapy. However, this strategy was not associated with a reduced risk of symptomatic VTE. These findings were confirmed in a third trial,⁴⁸⁷ in which 346 hip and knee arthroplasty patients received LMWH prophylaxis for 10 days and then were randomized to continue receiving LMWH for another 3 weeks or to have pre-hospital discharge DUS screening, with anticoagulation therapy if the findings were positive. DUS screening identified almost twice as many proximal thrombi but did not reduce the rate of symptomatic VTE on the subsequent 3-month follow-up. The idea that pre-hospital discharge DUS screening is able to predict who can avoid post-hospital discharge prophylaxis has never been validated.⁴⁸⁸ Furthermore, this strategy is very costly, logistically impractical for many hospitals, uses a technique that has considerable interobserver variability and the potential to falsely diagnose DVT, and often identifies patients with asymptomatic thrombi in whom treatment may not be necessary.

Recommendation: Screening for DVT

3.5.2. We recommend **against** the routine use of DUS screening at the time of hospital discharge in asymptomatic patients following major orthopedic surgery (**Grade IA**).

3.5.3 Duration of prophylaxis

An excellent review of the duration of thromboprophylaxis after surgery has recently been published.⁴⁸⁹ Al-

though thromboprophylaxis is routinely administered to patients who have undergone major orthopedic surgery, it is typically stopped at the time of hospital discharge.⁴⁹⁰ A substantial proportion of these patients leave the hospital with clinically silent DVT. For example, when in-hospital prophylaxis with LMWH was given for 1 to 2 weeks, 15 to 20% of THR patients had venographic evidence of DVT at hospital discharge.^{354,491} There is evidence that the ongoing activation of coagulation persists for at least 4 weeks after THR,^{492,493} and an increasing number of studies^{51,358,361,492,494–497} have shown that the risk of VTE continues for up to 3 months after THR. In one epidemiologic study of almost 24,000 patients,⁵¹ in which the mean length of stay after primary hip arthroplasty was 6.9 days, 76% of VTEs were diagnosed after hospital discharge. Among the 26,000 TKA patients also studied, the rate of post-hospital discharge VTE (2.1%) was lower than that after THR (2.8%), and this diagnosis was made earlier following discharge from the hospital (mean length of time: TKA, 7 days; THR, 17 days). These observations suggest that the duration of extended prophylaxis may be shorter for patients undergoing TKA than for those undergoing THR. In a subsequent analysis of patients undergoing THR, most of whom received thromboprophylaxis, the risk factors for rehospitalization for symptomatic VTE included a body mass index of ≥ 25 kg/m², a history of VTE, and age > 85 years.⁴⁹⁸ Early ambulation before the second postoperative day and the use of warfarin after hospital discharge were protective factors against VTE.

Four large cohort studies and one randomized clinical trial^{64,65,343,365,405} examined the in-hospital use of LMWH or warfarin prophylaxis, for an average of 7 to 15 days, after THR or TKA. Symptomatic VTE, including fatal PE, occurred in only 1 to 3% of patients between hospital discharge, when thromboprophylaxis was discontinued, and 3 months later (Table 10). Despite the low absolute risk of symptomatic VTE seen in these studies, 45 to 80% of all symptomatic events related to THR or TKA occur after hospital discharge.^{20,51,65,343,370,499}

Three systematic reviews,^{38,41,500} which included both THR and TKA patients, found that post-hospital discharge prophylaxis was both effective at reducing VTE and safe. Major bleeding did not occur in any of the out-of-hospital LMWH recipients, suggesting that the risk/benefit ratio favored the use of extended prophylaxis. Those who underwent THR derived greater protection from symptomatic VTE using extended prophylaxis (pooled OR, 0.33; 95% CI, 0.19 to 0.56; NNT, 62) than patients who underwent TKA (pooled OR, 0.74; 95% CI, 0.26 to 2.15; NNT, 250).³⁸ In many nonblinded studies included in these metaanalyses, awareness about the results of routine screening tests for DVT may have produced overdiagnosis of symptomatic events. In a recent metaanalysis,⁵⁰¹ which was restricted to THR trials that avoided this potential bias, the rates of symptomatic VTE among patients who received in-hospital LMWH therapy and those who were given post-hospital discharge LMWH therapy, were 2.7% and 1.1%, respectively (absolute risk reduction, 1.6%; 95% CI, -0.2 to 3.3; NNT, 64). The absolute risk reduction for symptomatic PE was 0.4% (95% CI, -0.3 to 1.4; NNT, 278), and for fatal PE it was 0.1% (95% CI, -0.1 to 0.3;

Table 10—Symptomatic VTE After In-hospital Prophylaxis for THR and TKA*

Study/Year	Operation	No.	Prophylaxis	Duration of Prophylaxis, d	Symptomatic VTE, No.	Fatal PE, No.
Lieberman et al ⁴⁰⁵ /1997	THR	940	Warfarin	15	8 (0.9)	1 (0.1)
Robinson et al ⁶⁴ /1997	THR	506	Warfarin	9.8	6 (1.2)	0
	TKA	518	Warfarin	9.8	3 (0.6)	0
Leclerc et al ⁶⁵ /1998	THR	1,142	LMWH	9.0	25 (2.2)	0
	TKA	842	LMWH	9.0	15 (1.8)	1 (0.1)
Colwell et al ³⁴³ /1999	THR	1,516	LMWH	7.5	51 (3.4)	≤ 2 (0.1)
	THR	1,495	Warfarin	7.0	39 (2.6)	≤ 2 (0.1)
Lindahl et al ³⁶⁵ /1999	THR	424	LMWH	~7	14 (3.3)	0
	TKA	221	LMWH	~7	2 (0.9)	0
Heit et al ³⁵⁹ /2000	THR/TKA	588	LMWH	7.3	12 (2.0)	3 (0.5)†
		607	LMWH	42	9 (1.5)	0

*Proven, symptomatic VTE or fatal PE occurring between discharge from hospital, when thromboprophylaxis was stopped, and 3 months later.

Values in parentheses are %.

†Sudden death occurred in three patients with known heart disease. No autopsies were performed, so PE was not excluded.

NNT, 1,093). Thus, while extended prophylaxis appears to reduce the relative risk of symptomatic VTE by about 60%, the absolute risk reduction is low, especially for PE.

Six randomized, placebo-controlled clinical trials^{354,368,482,497,502,503} have evaluated extended LMWH prophylaxis for up to 35 days among THR patients who completed in-hospital prophylaxis with either LMWH (*ie*, enoxaparin or dalteparin) or warfarin. Each study observed lower rates of venographically screened DVT with extended prophylaxis. A systematic review of these six trials³⁹ demonstrated a significant decrease in both total and proximal DVT with extended LMWH use, as well as reduced risk of symptomatic VTE arising during the treatment period. The rates of out-of-hospital symptomatic VTE were 4.2% with in-hospital prophylaxis and 1.4% with extended prophylaxis (relative risk, 0.36; $p < 0.001$; NNT, 36). In another randomized clinical trial³⁵⁹ that compared in-hospital use of LMWH and LMWH therapy that was continued after hospital discharge, extended prophylaxis did not further prevent symptomatic VTE.

One clinical trial⁵⁰⁴ also confirmed the benefit of post-hospital discharge prophylaxis with VKAs. More than 350 consecutive patients undergoing THR were randomized to receive warfarin prophylaxis (target INR, 2 to 3) until hospital discharge (mean duration, 9 days) or for another 4 weeks after hospital discharge. DUS was performed 1, 2, and 4 weeks post-hospital discharge. The study was prematurely terminated because of the demonstrated superiority of extended prophylaxis. VTE occurred in 5.1% of in-hospital prophylaxis patients, and in 0.5% of those who continued warfarin, a relative risk of 9.4 (95% CI, 1.2 to 73.5). The NNT to prevent one VTE using extended warfarin prophylaxis was 22. Only one patient experienced major bleeding. In another trial⁵⁰⁵ of 1,279 patients undergoing THR, the LMWH reviparin (4,200 U SC once daily) was compared with a VKA (target INR, 2 to 3), both administered for 6 weeks. Objectively confirmed, symptomatic VTE occurred in 2.3% of patients receiving LMWH, and in 3.3% of those receiving the VKA ($p = 0.3$). However, the rates of major bleeding were

1.3% and 5.5%, respectively ($p = 0.001$). Thus, these studies indicate that VKAs also may provide effective extended prophylaxis after THR, although major bleeding is more frequent with the use of these anticoagulants.

Extending LMWH prophylaxis to postoperative day 28 in one clinical trial of patients undergoing TKA⁵⁰³ did not significantly reduce the rate of objectively screened DVT (17.5%) compared to 7 to 10 days of prophylaxis (20.8%). Hospital readmission rates for VTE also did not differ significantly (3.2% and 5.4%, respectively).

The optimal duration of thromboprophylaxis has also been assessed in patients undergoing HFS. In a cohort study of 897 HFS patients who received perioperative prophylaxis with enoxaparin, 40 to 60 mg per day for about 5 weeks,⁵⁰⁶ objectively confirmed, symptomatic VTE occurred in only 7 patients (0.8%), with no cases of PE. However, major bleeding was encountered in 5% of patients, including 5 cases of intracranial bleeding (2 patients had intracranial hemorrhage that may have directly related to the drug and 3 patients had ICH subsequent to the fall and 20 cases (2.2%) of wound hematomas requiring surgical evacuation. A recent double-blinded clinical trial⁵² provided 656 HFS patients with fondaparinux, 2.5 mg SC once daily for about 7 days, followed by randomization to continuation of prophylaxis with fondaparinux or placebo for an additional 3 weeks. Venography, performed after 4 weeks of prophylaxis, documented DVT in 1.4% of the extended prophylaxis patients and in 35.0% of placebo recipients (RRR, 96%; $p < 0.001$). The rates of symptomatic VTE were 0.3% and 2.7%, respectively (RRR, 89%; $p = 0.02$). Bleeding rates were not significantly different.

The results of a number of economic studies^{449,507–509} 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.^{39,498,510} For patients undergoing THR or 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.^{364,498,504} Other risk factors that might be clinically important include a history of congestive heart failure or COPD, as well as female gender.^{498,499,511,512} The extended use of a VKA (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.⁵⁰⁵ The pentasaccharide fondaparinux is recommended for extended prophylaxis following HFS. The use of either LMWH or an oral VKA also may be effective in HFS patients, although prolonged use of these agents has not been properly studied in this patient group.

Recommendations: Duration of Prophylaxis

3.5.3.1. We 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**).

3.5.3.2. We 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+**).

3.6 Elective spine surgery

Unfortunately, most data about thromboprophylaxis in patients undergoing elective spine surgery come from small, retrospective studies of poor methodological quality.⁵¹³ Although the incidence of VTE in these patients appears to be considerably lower than that following major lower extremity surgery, some patients seem to be at high enough risk to consider prophylaxis.^{66,514–517} A systematic review of 20 studies reporting complications after lumbar spinal fusions⁵¹⁸ noted a 3.7% incidence of symptomatic DVT and a 2.2% rate of PE. In the only two studies that performed routine venography in patients undergoing spine surgery who did not receive VTE prophylaxis,^{515,517} DVT was detected in 18% of the 205 patients. In one of these studies,⁵¹⁷ increased age and surgery of the lumbar spine (21%) vs surgery of the cervical spine (6%; $p = 0.003$) were independent predictors for DVT. Other possible risk factors include an anterior or combined anterior/posterior surgical approach (possibly related to intraoperative manipulation of the iliac veins or inferior vena cava), surgery for malignancy, a prolonged procedure, and reduced preoperative or postoperative mobility.

Symptomatic VTE and fatal PE are occasionally observed in spinal surgery patients despite prophylaxis using IPC and/or GCS.^{19,66,519,520}

In a prospective but observational study of 306 patients undergoing elective spinal surgery,⁵¹⁵ venographic DVT was found less frequently in patients who received IPC (6%) than in those who had received no prophylaxis (21%). DUS identified DVT in 2% of 1,527 spinal surgery patients from 11 prospective studies,^{66,514,520–528} all of whom routinely used mechanical prophylaxis. Unfortunately, the absence of control subjects in these studies prevents one from validly estimating the degree of protection afforded by mechanical prophylaxis in this patient group. In one small clinical trial,⁵²⁷ no cases of symptomatic VTE or abnormal DUS findings were noted among any of the 110 patients randomized to receive prophylaxis with GCS alone, GCS plus IPC, or GCS plus warfarin. Another randomized clinical trial⁵²⁹ compared LDUH with no prophylaxis among 38 laminectomy patients, using the FUT to screen for thrombosis. DVTs were detected in none of the 18 LDUH patients and in 5 of 20 control subjects. Another small clinical trial⁵³⁰ randomized spinal surgery patients to receive enoxaparin, 40 mg SC daily, or IPC. No venographically detected DVTs were detected in any of the 30 patients who received enoxaparin, and in 3 of the 30 who had received prophylaxis with IPC. In a follow-up study⁵³¹ from the same center, no DVTs were found in the 60 patients who were given either enoxaparin, 20 or 40 mg daily. Another randomized trial⁵²⁸ failed to detect a difference in VTE rates in 136 major thoracolumbar reconstruction patients who had received prophylaxis with both GCS and either IPC or the VFP.

Given the paucity of data, we cannot make firm recommendations about thromboprophylaxis in spinal surgery patients. However, their risk of VTE appears to be low when any of the following methods of prophylaxis is routinely used: postoperative LDUH or LMWH; or intraoperative GCS or IPC, followed by postoperative GCS or IPC. Certainly, for spine surgery patients with additional VTE risk factors, such as a neurologic deficits or prolonged immobility, advanced age, known malignancy, previous VTE, or an anterior surgical approach, prophylaxis with one of these options is recommended.

Recommendations: Elective Spine Surgery

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

3.6.2. We 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**).

3.6.3. For patients with additional risk factors, we 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, we recommend combining LDUH or LMWH with GCS and/or IPC (**Grade 1C+**).

3.7 Isolated lower extremity injuries

Lower extremity fractures below the femur are very common in persons of all ages. In addition to fractures, this topic includes ligament and cartilage injuries of the knee and ankle, and rupture of the Achilles tendon. The popularity of recreational sports has contributed to an increase in these injuries in younger patients.⁵³² Although more below-knee fractures are being surgically repaired, sometimes without hospital admission, many are managed using plaster casts or braces. The epidemiology and prevention of VTE after lower extremity injuries have, unfortunately, been poorly studied. Patients with polytrauma, and those with femoral or pelvic fractures, are considered in section 5.1.

Four published prospective studies⁵³³⁻⁵³⁶ routinely screened for asymptomatic DVT, using contrast venography, in patients with isolated lower extremity fractures who had not received thromboprophylaxis. Hjelmstedt and Bergvall⁵³³ found DVT in 45% of 76 patients with tibial fractures, and proximal DVT in 8% of patients. The DVT rates in the patients who were managed surgically or nonoperatively were 71% and 39%, respectively. More recently, 82 patients with isolated below-knee fractures underwent contrast venography 3 to 22 days after early surgical repair.⁵³⁴ The corresponding DVT rates seen with fractures of the tibial plateau, tibial shaft, and tibial plafond were 43%, 22%, and 13%, respectively. In a randomized trial of patients with fractures distal to the femur or with a ruptured Achilles tendon,⁵³⁵ routine venography was obtained at least 5 weeks after injury. DVT, proximal DVT, and symptomatic VTE were diagnosed in 19%, 5%, and 2.7% of patients who had received placebo. A similarly designed study⁵³⁶ found venographic

DVT in 10% of 106 patients who had received no thromboprophylaxis, although only 1 patient was symptomatic.

Two randomized clinical trials in outpatients who sustained lower extremity injuries and were managed nonoperatively^{122,537} performed routine DUS after the plaster casts were removed. The reported rates of DVT in the control groups of these trials were 17% (21 of 127 patients)¹²² and 4% (7 of 163 patients),⁵³⁷ with corresponding rates of DVT in those with fractures of 29% (11 of 38 patients) and 6% (2 of 34 patients), respectively.

The risk factors for VTE following isolated lower extremity injury include advanced age,^{533,534,537,538} presence of fractures rather than soft tissue injuries alone,¹²² and obesity.⁵³⁸ It is not clear whether operative repair itself is a risk factor.^{533,535} The risk of DVT appears to increase with the proximity of the fracture to the knee, such that tibial plateau fractures pose the highest risk, followed by those of the tibial shaft and then the ankle.⁵³⁴ The risk of DVT after lower extremity tendon ruptures appears to be at least as high as that following lower extremity fracture.^{535,536}

Randomized clinical trials of thromboprophylaxis in patients with isolated lower extremity injuries are summarized in Table 11. In two studies,^{122,537} outpatients with plaster casts were randomized to receive either no prophylaxis or self-administered LMWH, followed by a DUS at the time of cast removal 2 to 10 weeks later. In the first study,¹²² 70% of the 253 study participants had soft-tissue injuries, and the remainder had fractures. The RRRs associated with LMWH use (*ie*, nadroparin, approximately 3,000 U once daily) were 71% (from 17 to 5%; $p < 0.01$) in all patients, and 64% (from 29 to 10%) among the 78 patients with fractures. In the second clinical trial,⁵³⁷ 391 outpatients were randomized to receive either no prophylaxis or the LMWH certoparin, 3,000 U once daily. Only 21% of the patients in this study had fractures. DVT was detected by DUS in 4% of control subjects and in none of the 176 LMWH recipients ($p = 0.006$). Among the 72 patients who had fractures, the respective DVT rates were

Table 11—Prevention of VTE in Patients With Isolated Lower Extremity Injuries*

Study/Year	Patients	Diagnostic Test for DVT	Interventions		DVT†	
			Control	Experimental	Control	Experimental
Kujath et al ¹²² /1993	Outpatients with leg injuries managed with plaster casts	DUS when cast removed	No prophylaxis	Nadroparin, approximately 3,000 U daily	21/127 (17)	6/126 (5)
Kock et al ⁵³⁷ /1995	Outpatients with leg injuries managed with plaster casts	DUS when cast removed	No prophylaxis	Certoparin, 3,000 U daily	7/163 (4)	0/176
Lassen et al ⁵³⁵ /2002	Below-knee fractures Achilles tendon repair	Venography ≥ 5 weeks	Placebo	Reviparin, 1,750 U daily	29/159 (18)	14/134 (10)
Jorgensen et al ⁵³⁶ /2002	Below-knee fractures Tendon ruptures	Venography ≥ 5 weeks	No prophylaxis	Tinzaparin, 3,500 U daily	10/77 (13)	8/73 (11)
					6/21 (29)	2/20 (10)

*Randomized clinical trials with routine screening using an objective outcome.

†Values given as No. of patients with DVT/total No. of patients (%).

6% and 0%. No bleeding events occurred in the 302 patients who received LMWH in these two studies. There were methodological problems with both studies, including lack of disclosure about patient selection and the method used for randomization, the presence of non-blinded interventions, high postrandomization dropout and cross-over rates, and a marked variation in study duration of between 1 to 72 days.

Two recent multicenter trials^{535,536} used screening venography to detect DVT in patients with lower extremity injuries after being randomized to either no prophylaxis or LMWH. In one trial,⁵³⁵ 440 patients with lower extremity fracture or Achilles tendon rupture were randomized to receive placebo or rivaroxaban, 1,750 U self-administered by daily subcutaneous injection for at least 5 weeks. The DVT rates in the placebo and rivaroxaban groups were 19% and 9%, respectively ($p = 0.01$). The corresponding rates of proximal DVT were 5% and 2%. Major bleeding was encountered in < 1% of patients in both groups. A second trial⁵³⁶ compared no prophylaxis to tinzaparin, 3,500 U, among 300 patients with lower extremity injuries whose conditions had been managed with plaster casts for at least 3 weeks. DVT was diagnosed in 17% of control patients and in 10% of those who received LMWH (difference not significant). The pooled DVT rate from these two trials was 18% among control subjects, and 9.6% with LMWH prophylaxis (OR, 2.1; $p = 0.005$). In neither trial did LMWH prophylaxis significantly reduce the risk of DVT in patients with fractures.

Patients with below-knee injuries have a 10 to 40% risk of asymptomatic DVT. Prophylaxis with LMWH reduces the frequency of asymptomatic DVT, particularly in those with tendon ruptures. The use of thromboprophylaxis, usually with LMWH, is considered to be a standard of care in some European countries. However, we do not believe that routine thromboprophylaxis in patients with isolated lower extremity injuries can be recommended, since it is uncertain whether prophylaxis similarly reduces the risk of clinically important VTE, or is cost-effective. Pending further data, clinicians may choose to provide no prophylaxis, in-hospital prophylaxis, or prophylaxis that is continued after hospital discharge. We are also unable to generate evidence-based recommendations to help clinicians decide which patients, if any, might benefit from prophylaxis, or the type, dose, or duration of prophylaxis.

Recommendation: Isolated Lower Extremity Injuries

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

4.0 Neurosurgery

Patients undergoing major neurosurgery are known to be at moderately increased risk of postoperative VTE and warrant the routine use of thromboprophylaxis.^{2,539–542} In several randomized clinical trials, which included a spectrum of neurosurgery patients, the rate of DVT, detected by FUT, among the control subjects was 22%, with a rate

of proximal DVT of 5%.² The risk factors for DVT in neurosurgery patients include intracranial surgery (rather than spinal surgery), active malignancy, more lengthy procedures, the presence of leg weakness, and advanced age.^{525,540,543–545} Patients with malignant brain tumors are at particularly high risk for VTE, both perioperatively and during subsequent follow-up.^{541,544–546} In one study of 264 patients with gliomas,⁵⁴⁷ 31% developed symptomatic, venographically confirmed DVT within 5 weeks of surgery. Brandes and colleagues⁵⁴⁸ effectively prevented postoperative VTE with aggressive use of perioperative LDUH. However, 1 year after surgery 21% of patients had experienced symptomatic, objectively proven DVT or PE. The Glioma Outcomes Project⁵⁴⁵ followed 688 patients undergoing resection of a primary glioma and reported a cumulative rate of symptomatic VTE of 23% over the 12 to 15 months of follow-up.

The evidence-based, recommended prophylaxis options in these patients are as follows: (1) perioperative use of IPC, with or without GCS; (2) perioperative use of LDUH; or (3) postoperative use of LMWH.^{2,136} Mechanical thromboprophylaxis is commonly used in neurosurgery out of concern for potential intracranial or spinal bleeding.⁵⁴⁹ IPC appears to be highly effective at preventing DVT in neurosurgical patients, producing an average RRR of 68% compared with no prophylaxis (lowering the absolute DVT rate from 22% in control subjects to 7% in those receiving IPC).² Although Turpie et al¹²⁷ found comparable DVT rates in patients receiving GCS alone and in those receiving prophylaxis with GCS plus IPC, both options were more effective than no prophylaxis. However, more recent studies^{550–553} have raised concerns about the efficacy of prophylaxis with GCS alone.

Only one randomized clinical trial⁵⁵⁴ compared LDUH and no prophylaxis in craniotomy patients, and found an 82% RRR in FUT-diagnosed DVT using perioperative LDUH. The two largest prophylaxis trials performed in neurosurgical patients^{551,553} compared prophylaxis with GCS alone with a combination of GCS plus LMWH, started postoperatively. With routine venography as the efficacy end point, both studies found a significant reduction in the risk of DVT using combined prophylaxis. In the trial by Nurmohamed et al,⁵⁵¹ the respective rates of all DVT and proximal DVT in patients who received GCS alone were 26% and 12%, respectively, compared to 19% and 7%, respectively, with the addition of LMWH. In another blinded trial,⁵⁵³ total and proximal DVT were diagnosed in 33% and 13% of GCS recipients, respectively, compared with 17% and 5%, respectively, of those who received combined prophylaxis.

Perioperative use of GCS combined with IPC was used routinely in 150 patients undergoing craniotomy for a brain tumor who were randomized to receive either LDUH, 5,000 U SC bid, or enoxaparin, 40 mg SC once daily.⁵⁵⁵ Pre-hospital discharge DUS detected DVT in 7% and 12%, respectively, of the LDUH and LMWH patients. Proximal DVT was found in 3% of patients in both groups. A recent pilot study⁵⁵⁶ randomized 100 patients undergoing craniotomy to receive prophylaxis with IPC plus LDUH, 5,000 U SC bid, or IPC plus dalteparin, 2,500 U SC once daily. Prophylaxis with LDUH and LMWH

was started just prior to surgery, and patients underwent a routine DUS 1 week after surgery. Among the 49 IPC/LDUH recipients, there were no DVTs and one surgically managed intracranial hemorrhage compared to two asymptomatic DVTs and two conservatively managed intracranial bleeds among the 51 patients who received prophylaxis with IPC/LMWH.

The risk of intracranial bleeding has not been shown to be increased in prospective studies of neurosurgical patients who received perioperative LDUH prophylaxis.^{49,554,557–560} However, pending further information, caution should be exercised with the use of preoperative or early postoperative LMWH in craniotomy patients.^{49,136,551–553,557–559,561,562} In one small, nonblinded clinical trial,⁵⁶¹ intracranial bleeding was found in 5 of 38 patients who had been randomized to commence LMWH therapy preoperatively, and in none of the 19 patients who received IPC. The pooled rates of intracranial hemorrhage in randomized trials^{550,551,553} of neurosurgery patients were 2.1% for postoperative LMWH, and 1.1% for mechanical prophylaxis or no prophylaxis. Most of these bleeds occurred within the first 2 days after surgery. In a metaanalysis,¹³⁶ all forms of bleeding were twice as common in patients who received postoperative LMWH prophylaxis as in those who received mechanical prophylaxis (6.1% vs 3.0%, respectively; $p = 0.02$).

A recent prospective management study⁵⁴² routinely provided thromboprophylaxis to consecutive craniotomy patients and performed DUS prior to mobilization. Patients with a positive DUS finding for DVT were fully anticoagulated. Among the 453 patients who were studied from 1998 to 2002, asymptomatic DVT was diagnosed in 12% of cases, despite the commencement of both GCS and LMWH the evening before surgery. However, in the entire cohort, there was only one patient with symptomatic PE over the study period.

In summary, IPC, with or without the use of GCS, is recommended as DVT prophylaxis in patients undergoing elective major neurosurgery. Other acceptable options include the use of perioperative LDUH and postoperative LMWH. The combination of prophylaxis with LMWH and GCS is more efficacious than that with GCS alone. The combination of LDUH and mechanical prophylaxis also appears to be highly effective.⁵⁵⁵ In some centers, mechanical prophylaxis is started at the time of surgery, and then, if a CT scan obtained the following day does not show bleeding, anticoagulant prophylaxis is either added or substituted. This sequential method of prophylaxis has also not been formally studied, however.

Recommendations: Neurosurgery

4.0.1. We recommend that thromboprophylaxis be routinely used in patients undergoing major neurosurgery (**Grade 1A**).

4.0.2. We recommend the use of IPC with or without GCS in patients undergoing intracranial neurosurgery (**Grade 1A**).

4.0.3. Acceptable alternatives to the above options are prophylaxis with LDUH (**Grade 2B**) or postoperative LMWH (**Grade 2A**).

4.0.4. We suggest the combination of mechanical prophylaxis (*ie*, GCS and/or IPC) and pharmacologic prophylaxis (*ie*, LDUH or LMWH) in high-risk neurosurgery patients (**Grade 2B**).

5.0 Trauma, Spinal Cord Injury, Burns

5.1 Trauma

Among hospitalized patients, those recovering from major trauma have the highest risk of developing VTE.^{2,62,563–565} Without prophylaxis, patients with multi-system or major trauma have a DVT risk exceeding 50%,^{2,62,566} with PE being the third leading cause of death in those who survive beyond the first day.^{62,567–570} In a prospective study of 443 major trauma patients not receiving any thromboprophylaxis, who had undergone routine bilateral contrast venography, the rates of DVT and proximal DVT were 58% and 18%, respectively.⁶² Even with the routine use of thromboprophylaxis, the respective rates of DVT and proximal DVT were 27% and 7%, respectively, with weekly DUS screening.⁵⁷¹

Based on a variety of trauma studies,^{2,62,565,571,572} factors that were independently associated with an increased risk of VTE include the following: spinal cord injury (SCI); lower extremity or pelvic fracture; need for a surgical procedure; increasing age; femoral venous line insertion or major venous repair; prolonged immobility; and longer duration of hospital stay. VTE risk was associated with the injury severity score in some studies^{67,572} but not in others.^{62,565,571} Although DVT risk increases with age, thromboprophylaxis should not be withheld simply because of young age. Trauma patients with single-system, nonorthopedic injuries have a lower risk of VTE than those with multiple injuries or with lower limb fractures.^{2,62,534} Limited data also suggest that patients with penetrating injuries have a lower risk of VTE than those who sustain blunt trauma.^{573,574}

Although the routine use of thromboprophylaxis in trauma patients was first recommended 60 years ago,⁵⁷⁵ there have been very few randomized clinical trials of prophylaxis in this patient group (Table 12).^{472,576–580} Therefore, because of the known high risks of VTE in trauma patients, recommendations for prophylaxis are based on data from these trials, as well as from data of studies conducted in other high-risk, nontrauma patient groups.^{2,565,581,582}

Mechanical prophylaxis is widely used in trauma because it does not increase the risk of bleeding. The use of GCS has never been evaluated in trauma patients. The best evidence of benefit with IPC devices has come from a trial conducted in 149 trauma patients without lower extremity fractures,⁵⁸⁰ who were randomized to receive prophylaxis with either thigh-length sequential compression devices or VFPs. Using DUS screening on day 8, DVT was detected in 6.5% of IPC recipients vs 21.0% of those who had foot pumps applied ($p = 0.009$). In two additional studies,^{573,578} IPC was shown to be effective in

Table 12—Thromboprophylaxis Trials in Trauma Patients*

Study/Year	Patient Group (mean age, yr/mean ISS/LEF)	Diagnostic Test for DVT	Intervention		DVT†	
			Control	Experimental	Control	Experimental
Fisher et al ^{472/} 1995	Pelvic fracture (NR/NR/100%)	DUS every 5 d	No prophylaxis	IPC	4/38 (11)	2/35 (6)
Geerts et al ^{576/} 1996	ISS > 9, no intracranial bleeding (38/23/54%)	Venography day 10–14	LDUH bid	Enoxaparin, 30 mg bid	60/136 (44)	40/129 (31)
Haentjens ^{577/} 1996	Orthopedic trauma (61/NR/96%)	DUS or IPG day 10	Nadroparin, 3,075 U daily	Nadroparin weight-adjusted	0/106	3/109 (3)
Knudson et al ^{578/} 1996	Moderate trauma (39/15/17%)	DUS every 5–7 d	IPC or VFP	Enoxaparin, 30 mg bid	2/82 (2)	1/120 (1)
Cohn et al ^{579/} 1999	Moderate trauma (41/11/NR)	DUS weekly	LDUH bid	Enoxaparin, 30 mg bid	2/32 (6)	0/34
Elliott et al ^{580/} 1999	Major trauma excluding LEF (32/31/0%)	DUS day 8	IPC	VFP	4/62 (6)	13/62 (21)

*Includes randomized clinical trials in which routine screening with an objective diagnostic test for DVT was used. ISS = injury severity score; LEF = lower extremity fractures; NR = not reported.

†Values given as No. of patients with DVT/total No. of patients (%).

patients with head injuries. However, a number of other studies^{472,573,583,584} and a metaanalysis⁵⁸⁵ were unable to demonstrate any significant benefit in DVT reduction with IPC vs no prophylaxis (OR, 0.77; 95% CI, 0.27 to 2.24). In addition to suboptimal protection, other important problems with IPC include its inability to be used in approximately one third of trauma patients due to lower extremity fractures, casts, or dressings,^{583,586} and poor compliance with proper use by both patients and nursing staff.^{138,140,587} Although IPC and 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).

The efficacy of the VFP was challenged by a randomized clinical trial⁵⁸⁰ in which the rate of DVT was three times greater with these devices than with IPC, as well as by a cohort study⁵⁸⁸ of 100 trauma patients in whom the rate of venographically screened DVT was 57%, despite prophylaxis with bilateral VFPs. Therefore, VFPs cannot currently be recommended for use in trauma patients.

LDUH is not a particularly effective prophylaxis modality in trauma patients.^{2,565,582,589} While those patients at lower risk might be protected against VTE with LDUH, its routine use in higher risk patients has been challenged by the results of a large clinical trial comparing LDUH to LMWH,⁵⁷⁶ and by a metaanalysis⁵⁸⁵ demonstrating that LDUH was not more effective than no prophylaxis (OR, 0.97; 95% CI, 0.35 to 2.64).

LMWH was shown to be superior to LDUH in a double-blinded, randomized clinical trial⁵⁷⁶ among 344 major trauma patients without frank intracranial bleeding or ongoing bleeding at other sites. LDUH, 5,000 U SC bid, was compared with enoxaparin, 30 mg SC bid, both initiated within 36 h of the injury. Bilateral contrast venography was performed between days 10 and 14. The 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^{590–593} also support the superiority of LMWH over LDUH prophylaxis in high-risk trauma patients.

Although combining mechanical with pharmacologic prophylaxis, either simultaneously or sequentially, may provide additive protection against VTE, this has not been formally studied in trauma patients. Such an approach might not only be more expensive, but could result in suboptimal compliance with both methods.

Because of the ongoing risk of VTE in trauma patients, even with the proper use of prophylaxis modalities, some have recommended that high-risk patients undergo screening for asymptomatic DVT using DUS.^{88,578,584,586,594–597} One limitation to this approach is the rather low sensitivity of DUS for detecting asymptomatic DVT.^{106,598} Even though the accuracy of DUS has improved, false-positive and false-negative results are still encountered, even for proximal DVT, and DUS screening may not prevent PE.^{67,578,594,599} In addition, at least 25% of trauma patients have suboptimal scans of the proximal deep venous system because of local injuries, dressings and casts, pain, or poor patient cooperation.^{88,586,600} Contrast-enhanced CT scanning and magnetic resonance venography are associated with unacceptably high false-positive rates for DVT and cannot be recommended for use in screening, at least in patients with pelvic fractures.⁶⁰¹ The costs of routine screening, even among high-risk trauma patients, is also prohibitive.^{63,586,595,598–600,602} Furthermore, reliance on screening has the potential to delay the initiation of thromboprophylaxis, and DUS screening provides little or no incremental gain in patient protection over the early and appropriate use of prophylaxis.^{67,602,603} Although routine screening for DVT cannot be justified in

most trauma patients, selective screening might benefit high-risk patients in whom early prophylaxis is not possible,⁶⁰³ or prior to a major surgical procedure when the use of aggressive prophylaxis has not been possible preoperatively.

Prophylactic inferior vena cava filter (IVCF) insertion has been recommended by some^{568,604–610} for use in trauma patients who were thought to be at very high risk for VTE. To our knowledge, no randomized clinical trials have studied the prophylactic use of IVCFs in any patient population, and we are not aware of any evidence that their use is beneficial in addition to proven and effective prophylaxis modalities.⁶¹¹ Several reports and a recent metaanalysis of prospective studies^{572,612} found no difference in the rates of PE among patients with, and without, prophylactic IVCFs. Furthermore, their use may be associated with both short-term and long-term complications, inappropriate delays in the use of effective prophylaxis, and increased risk of thrombosis at the insertion site.^{607,612–618} Greenfield⁶¹⁹ estimated that the annual cost of prophylactic IVCF insertions in the United States would be \$900,000,000 if they were placed in just 1% of all disabling trauma cases. Others⁶⁰² 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.^{605,606,612,620}

With modern insertion techniques performed by experienced clinicians, the short-term and long-term complications of IVCF are low.^{565,617,618,621,622} Newer technology, including bedside insertion,^{608,609} use of retrievable filters,⁶²³ and ultrasound guidance,^{624,625} may increase the temptation to use filters with greater frequency. However, the lack of evidence for their efficacy or cost-effectiveness pose the greatest challenge to their increased use. Until these issues are resolved, we and others do not recommend the use of IVCFs as prophylaxis, even in patients who are at high risk for VTE.^{581,595,602,611,612,626} 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.

The routine use of thromboprophylaxis in trauma patients has become a standard of care.^{2,565,582} Accordingly, every trauma unit should develop a management guideline for the prevention of VTE, with guideline compliance periodically assessed as a measure of quality of care. Every trauma patient should be assessed for his or her VTE risk soon after hospital admission, as well as for the method of prophylaxis that is to be administered, since symptomatic VTE and fatal PE often occur with suboptimal prophylaxis.^{67,88,569,586,596,599,602,627,628}

The use of LMWH, started once primary hemostasis has been achieved, is the most efficacious and simplest option for the majority of moderate-risk and high-risk trauma patients.^{2,564,565,582} Current contraindications to the early initiation of LMWH prophylaxis include the presence of intracranial bleeding, ongoing and uncontrolled bleeding, an uncorrected major coagulopathy, or incom-

plete 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 spinal cord injuries are not themselves contraindications to LMWH thromboprophylaxis, provided that there is no evidence of ongoing bleeding.^{629,630} Most trauma patients can be started on prophylaxis with LMWH within 36 h of injury, although briefly delaying its commencement seems appropriate while ensuring that hemostasis has been achieved.

For patients with contraindications to LMWH prophylaxis, mechanical modalities, like GCS and/or IPC devices, should be considered despite evidence that they provide only limited protection. These devices should be applied to both legs as soon as possible, and their use should be continued around the clock until LMWH can be started.^{138,140}

Although the optimal duration of prophylaxis is not known for these patients, it should generally continue until discharge from the hospital. If the hospital stay, including the period of rehabilitation, extends beyond 2 weeks, and if there is an ongoing risk of VTE, inpatient prophylaxis should continue either with LMWH, or by switching to a VKA. Therapeutic VKA doses (target INR, 2.5; INR range, 2.0 to 3.0) should be considered once the risk of major bleeding is low, and no surgical procedures are planned for the next while. While we are not aware of any clinical trials that have specifically addressed the extended use of a VKA in trauma patients, there is evidence for its use in other high-risk patients (see section 3.5.3). Although many trauma patients are not fully mobile at hospital discharge, and the potential for delayed symptomatic VTE exists, there are no data to quantify this risk. Until evidence becomes available, we cannot recommend the routine use of post-hospital discharge VTE prophylaxis. We are aware that some trauma centers continue prophylaxis with LMWH or a VKA after hospital discharge in selected patients with impaired mobility.

Recommendations: Trauma

5.1.1. We recommend that all trauma patients with at least one risk factor for VTE receive thromboprophylaxis, if possible (**Grade IA**).

5.1.2. In the absence of a major contraindication, we recommend that clinicians use LMWH prophylaxis starting as soon as it is considered safe to do so (**Grade IA**).

5.1.3. We 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 IB**).

5.1.4. We recommend DUS screening in patients who are at high risk for VTE (*eg*, in the presence of a 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 IC**).

5.1.5. We recommend against the use of IVCFs as primary prophylaxis in trauma patients (**Grade 1C**).

5.1.6. We recommend the continuation of thromboprophylaxis until hospital discharge, including the period of inpatient rehabilitation (**Grade 1C+**). We 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**).

5.2 Acute SCI

Without prophylaxis, patients with acute SCI have the highest incidence of DVT among all hospitalized groups.^{2,565,631} Asymptomatic DVT occurs in 60 to 100% of SCI patients who are subjected to routine screening.^{2,632,633} Despite an increased awareness of VTE as a complication of SCI, PE remains the third leading cause of death.^{634,635} In a registry of > 28,000 SCI patients, the incidence of fatal PE did not fall between the periods 1973 to 1977 and 1992 to 1998.⁶³⁵ Among trauma patients, the presence of SCI is the factor that poses the greatest risk for DVT, with an OR of 8.6.⁶² Among SCI patients, risk factors for DVT include the following: age^{633,634}; concomitant lower extremity fracture⁶²⁶; and delayed use of thromboprophylaxis.^{636–638} The level of injury and its degree (complete vs incomplete) do not appear to affect VTE risk.^{626,633,637} VTE after SCI is also associated with considerable long-term disability, as these patients have low rates of venous recanalization following DVT, and are subject to more bleeding complications associated with prolonged anticoagulation therapy.^{639,640}

Several, small randomized clinical trials (Table 13)^{576,633,641–644} have suggested that the use of LDUH alone^{576,642–644} or IPC alone⁶⁴¹ is ineffective for prophylaxis in SCI patients, while adjusted-dose unfractionated heparin⁶⁴² and LMWH^{576,644,645} are substantially more efficacious. The efficacy of LMWH is also supported by an uncontrolled study⁶⁴⁵ of 60 patients who were given enoxaparin, 30 mg SC q12h, in whom no DVTs were detected by DUS screening. In the most recent and largest

multicenter clinical trial,⁶³³ 476 patients with acute SCI were randomized to receive combined prophylaxis with LDUH, 5,000 U SC tid, and IPC, or enoxaparin, 30 mg SC bid. To compare their efficacy, contrast venography studies were successfully obtained in only 107 patients. DVT was demonstrated in 63% of the LDUH-IPC group and in 66% of the enoxaparin patients. The rates of major VTE (either proximal DVT or PE) were 16% and 12%, respectively, although no patient died of PE. Among all randomized patients, major bleeding was seen in 5% of LDUH-IPC patients and in 3% of those who received enoxaparin.

Four uncontrolled studies^{646–649} have suggested that the routine use of an oral VKA, started shortly after hospital admission, reduces the occurrence of symptomatic VTE compared with patients who did not receive anticoagulation therapy. The insertion of IVCFs has been advocated by some^{650,651} but not all investigators.^{2,626} In the context of suboptimal VTE prophylaxis, IVCFs may reduce the rate of PE, although this has never been proven for any patient group.⁶⁵⁰ These devices are unlikely to be necessary when appropriate prophylaxis is used.⁶²⁶ Furthermore, IVCF use is associated with complications^{652,653} and a substantial financial cost.⁶²⁶ For example, it is estimated that 100 IVCFs would need to be placed to prevent two nonfatal PEs in SCI patients who are already receiving thromboprophylaxis, at a cost of \$500,000.⁶²⁶

Although the period of greatest risk for VTE following SCI is the acute care phase, symptomatic DVT or PE, and fatal PE also may occur during the rehabilitation phase.^{637,640,643,654–658} For example, venographic evidence of DVT was found in 53% of 30 patients who were admitted to an SCI rehabilitation unit, none of whom had received prior thromboprophylaxis.⁶⁵⁶ Chen and colleagues⁶⁵⁹ observed that 10% of all 1,649 SCI patients undergoing rehabilitation developed symptomatic DVT, and that 3% had PE. In another study,⁶⁵⁴ 14% of SCI patients who had normal venogram findings on admission to a rehabilitation center had evidence of a new DVT by repeat venography 1 month later, despite the continuation of prophylaxis. A recent prospective study⁶⁵⁸ followed 119

Table 13—Randomized Clinical Trials of DVT Prevention After Acute SCI*

Study/Year	End Points	Prophylaxis Regimen	DVT†	Proximal DVT or PE†
Green et al ⁶⁴¹ /1982	FUT, IPG	IPC	6/15 (40)	3/15 (20)
		IPC + ASA + dipyridamole	3/12 (25)	1/12 (8)
Green et al ⁶⁴² /1988	IPG, Doppler	LDUH	6/29 (21)	5/29 (17)
		Adjusted-dose heparin	2/29 (7)	1/29 (3)
Merli et al ⁶⁴³ /1988	Venography	Placebo	8/17 (47)	NR
		LDUH	8/16 (50)	NR
		LDUH + ECS	1/15 (7)	NR
Green et al ⁶⁴⁴ /1990	IPG, DUS	LDUH	3/19 (16)	5/19 (26)
		LMWH	0/16 (0)	0/16 (0)
Geerts et al ⁵⁷⁶ /1996	Venography	LDUH	10/15 (67)	2/15 (13)
		LMWH	4/8 (50)	0/8 (0)
SCITI ⁶³³ /2003	Venography	LDUH + IPC	31/49 (63)	15/92 (16)
		LMWH	38/58 (66)	11/89 (12)

*Values in parentheses are %. IPG = impedance plethysmography; SCITI = Spinal Cord Injury Thromboprophylaxis Investigators. ECS = electrical calf stimulation; NR = not reported.

†Values given as No. of patients with condition/total No. of patients (%).

patients with normal DUS findings 2 weeks after experiencing an acute SCI for another 6 weeks, at which time the DUS was repeated. Sixty patients received LDUH tid and 59 patients received enoxaparin, 40 mg SC once daily, in a nonrandomized manner. The respective rates of new VTE were 22% and 8%, respectively, with one fatal PE in the LDUH group.

The very high risk of DVT and PE following SCI, combined with the results of currently available prevention studies, support the early use of thromboprophylaxis in all SCI patients.^{2,631,633,651,660} Prophylaxis with LDUH, IPC, or GCS does not appear to provide adequate protection when used alone. LMWH, or the combination of LMWH or LDUH plus IPC, are the recommended early options. Before commencing anticoagulant prophylaxis, there should be clinical evidence that primary hemostasis has been achieved. If concern persists about bleeding at the injury site or elsewhere, mechanical prophylaxis should be initiated as soon as possible after hospital admission, and anticoagulant prophylaxis should be started once the bleeding risk has decreased.^{2,631,661}

Studies have not addressed the value of routine DUS screening among SCI patients, but this is a reasonable consideration in those for whom prophylaxis is delayed for several days.^{631,638} After the acute injury phase, continuing prophylaxis with LMWH or conversion to a full-dose oral VKA (target INR, 2.5; INR range, 2.0 to 3.0) for the duration of the rehabilitation phase is likely to be beneficial and is recommended.^{2,631,651,658} For patients with incomplete SCIs, the initiation of LMWH should probably be delayed for 1 to 3 days in the presence of a perispinal hematoma on CT scan or MRI. The use of long-term, full-dose anticoagulation with a VKA should probably also be delayed for at least 1 week following injury in such patients, because of the unpredictable response to dosing with these agents. It is recommended that DVT prophylaxis be continued for a minimum of 3 months, or until completion of the inpatient phase of rehabilitation.^{2,631}

Recommendations: Acute SCI

5.2.1. We recommend that thromboprophylaxis be provided for all patients with acute SCIs (**Grade 1A**).

5.2.2. We recommend **against** the use of LDUH, GCS, or IPC as single prophylaxis modalities (**Grade 1A**).

5.2.3. In patients with acute SCI, we recommend prophylaxis with LMWH, to be commenced once primary hemostasis is evident (**Grade 1B**). We suggest the combined use of IPC and either LDUH (**Grade 2B**) or LMWH (**Grade 2C**) as alternatives to LMWH.

5.2.4. We recommend the use of IPC and/or GCS when anticoagulant prophylaxis is contraindicated early after injury (**Grade 1C+**).

5.2.5. We recommend **against** the use of an IVCF as primary prophylaxis against PE (**Grade 1C**).

5.2.6. During the rehabilitation phase following acute SCI, we 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**].

5.3 Burns

Burn patients are at increased risk for VTE because of the presence of a profound systemic hypercoagulable state,⁶⁶² as well as prolonged bed rest, performance of repeated surgical procedures, femoral venous catheter insertion, and recurrent bouts of sepsis. Retrospective case series suggest that symptomatic VTE occurs in 2.4 to 7.0% of burn patients.^{663–665} In studies^{663,666–669} that prospectively screened burn patients using DUS, the rate of DVT varied between 6% and 27%.

Potential risk factors for VTE in burn patients include the presence of advanced age,^{665,670–672} morbid obesity,^{665,673} extensive or lower extremity burns,^{665,668,670–672,674} concomitant lower extremity trauma,⁶² the use of CVCs,^{663,669,672,675} the presence of wound infections,⁶⁷² and prolonged immobility.^{663,672} Since there have been no published thromboprophylaxis trials in this area, a formal prophylaxis guideline cannot be generated.⁶⁷⁶ However, the frequency of VTE appears to be high enough to warrant prophylaxis in burn patients who have one or more additional VTE risk factors. Extrapolating from other patient groups, the use of LDUH or LMWH is recommended, once the bleeding risk is no longer high.

Recommendations: Burns

5.3.1. We 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+**).

5.3.2. If there are no contraindications, we recommend the use of either LDUH or LMWH, starting as soon as it is considered safe to do so (**Grade 1C+**).

6.0 Medical Conditions

Although VTE is most often considered to be associated with recent surgery or trauma, 50 to 70% of symptomatic thromboembolic events^{677,678} and 70 to 80% of fatal PEs^{12,17,21,679–681} occur in nonsurgical patients. Hospitalization for an acute medical illness is independently associated with about an eightfold increased relative risk for VTE⁴⁹⁹ and accounts for almost one quarter of all VTE events within the general population.⁹ Thus, the appropriate prophylaxis of medical inpatients offers an important opportunity to significantly reduce the burden of disease due to VTE.^{2,682} The prevention of VTE after myocardial infarction and stroke are discussed in the respective articles in this supplement dealing with these conditions.

General medical inpatients who are not receiving prophylaxis are at a low-to-moderate risk for the development of VTE, with a typical rate of asymptomatic DVT of approximately 15% using the FUT,^{683–686} 15% using venography,⁶⁸⁷ and 5 to 7% using DUS as the screening tests.^{688,689} One study⁶⁸⁸ observed a 6% rate of asymptomatic DVT among 234 patients who were screened with DUS on admission to a general internal medicine unit.

Because 90% of the thrombi were limited to the calf, the clinical importance of this finding is unknown. In this study, DVT was diagnosed in 18% of patients who were > 80 years of age, but in no one under the age of 55 years. Over the course of their hospital stay, an additional 2% of patients, all of whom were > 70 years of age, developed new DVTs. Similar findings were noted in patients with acute exacerbations of COPD.^{690,691} As in other low-to-moderate-risk patient groups, symptomatic VTE is uncommon in hospitalized medical patients. For example, in one retrospective review of 6,332 medical patients, there were just 239 cases (0.6%) of hospital-acquired VTE.⁶⁹²

Several attempts have been made to identify risk factors for VTE in hospitalized medical patients.^{512,687,693-696} Major risk factors include New York Heart Association class III and IV heart failure, COPD exacerbations, and sepsis. Additional risk factors include advanced age, history of VTE, cancer, stroke with lower extremity weakness, and bed rest. Many medical patients have multiple risk factors. A case-control study⁶⁹⁷ identified heart failure as an independent risk factor for VTE in outpatients, with the risk rising with declining ejection fraction. An administrative database⁶⁹⁸ of > 75,000 patients with end-stage renal disease also found that the risk of PE was increased in those patients undergoing long-term dialysis.

To our knowledge, no randomized clinical trials have evaluated mechanical methods of prophylaxis in general medical patients, although one small study⁶⁹⁹ found that the use of GCS reduced the frequency of DVT after acute stroke. Six thromboprophylaxis trials^{683-687,689} in medical patients have compared LDUH or LMWH with placebo (Table 14). To summarize these studies,⁶⁸³⁻⁶⁸⁶ compared with no prophylaxis, prophylaxis with both LDUH and LMWH at high prophylactic doses reduced the relative risk of FUT-detected DVT by approximately 70%, without an increased risk of bleeding. In the Prophylaxis in Medical Patients with Enoxaparin (MEDENOX) trial,⁶⁸⁷ enoxaparin, either 20 or 40 mg SC once daily, was

compared with placebo in 1,102 hospitalized medical patients, most of whom had congestive heart failure, acute respiratory failure, or an acute infection. The rates of DVT detected by venography or DUS between days 6 and 14 were 14.9% in the 288 patients receiving placebo, 15.0% in the 287 patients receiving enoxaparin, 20 mg, and 5.5% in the 291 patients receiving enoxaparin, 40 mg ($p < 0.001$ for enoxaparin, 40 mg, vs placebo). Major bleeding occurred in 1.1%, 0.3%, and 1.7% of the patients, respectively. There was no significant difference in mortality among the three groups. The protection observed with enoxaparin, 40 mg daily, extended to each of the major medical subgroups, including those with acute infection, heart failure, and respiratory failure.⁷⁰⁰ Follow-up of most study patients out to day 110 did not reveal any evidence of a rebound increase in symptomatic VTE after prophylaxis discontinuation.⁶⁸⁷

The PREVENT Thromboprophylaxis Study⁶⁸⁹ compared the efficacy and safety of prophylaxis with the LMWH dalteparin, 5,000 U SC once daily, with matching placebo in 3,706 hospitalized medical patients who were at moderately high risk for VTE. Prophylaxis was continued for 14 days, and a DUS was routinely obtained before day 21. The primary end point was the development of symptomatic VTE, sudden death, and/or DUS-screened proximal DVT. This end point was reached in 2.8% of dalteparin recipients, compared to 5.0% of those in the placebo group (RRR, 45%; 95% CI, 20 to 62%; $p = 0.0015$; NNT, 46). Two patients in the placebo group developed fatal PE by day 21, compared with none in the dalteparin group. Major bleeding occurred in 0.5% and 0.2%, respectively, of the dalteparin and placebo patients.

LDUH and LMWH have been directly compared in five randomized clinical trials (Table 15).⁷⁰¹⁻⁷⁰⁵ Four of the studies^{701-703,705} showed no significant differences in DVT rates or bleeding. In a study of 877 medical patients⁷⁰⁴ using routine venography to screen for DVT, the compos-

Table 14—Thromboprophylaxis Trials of LDUH or LMWH vs No Prophylaxis in General Medical Patients*

Study/Year	Patients (mean age/yr/ cancer rate)	Method of DVT Screening	Intervention		DVT†	
			Control	Experimental	Control	Experimental
Gallus et al ⁶⁸³ /1973	CHF (NR, NR)	FUT × 11 d	No prophylaxis	LDUH tid	7/15 (46.7)	1/11 (9.1)
Belch et al ⁶⁸⁴ /1981	CHF, pneumonia (66, NR)	FUT up to 14 d	No prophylaxis	LDUH tid	13/50 (26.0)	2/50 (4.0)
Cade ⁶⁸⁵ /1982	Medical patients + 2nd risk factor (NR, NR)	FUT × 4-10 d	Placebo	LDUH bid	7/67 (10.4)	1/64 (1.6)
Dahan et al ⁶⁸⁶ /1986	Age > 65 yr (80, 13%)	FUT × 10 d	Placebo	Enoxaparin, 60 mg daily	12/131 (9.2)	4/132 (3.0)
Samama et al ⁶⁸⁷ / 1999	Age > 40 + 2nd risk factor (73, 14%)	Venography or DUS day 6-14	Placebo	Enoxaparin, 20 mg daily Enoxaparin, 40 mg daily	43/288 (14.9)	43/287 (15.0) 16/291 (5.5)
Leizorovicz et al ⁶⁸⁹ / 2003	Acutely ill medical patients (NR, NR)	DUS day 21	Placebo	Dalteparin, 5,000 U daily	73/1473 (5.0)‡	42/1518 (2.8)‡

*Includes randomized clinical trials in which routine screening with an objective diagnostic test for DVT was used. CHF = congestive heart failure; NR = not reported.

†Values given as No. of patients with DVT/total No. of patients (%).

‡Clinically important VTE (composite of objectively verified symptomatic DVT or PE, sudden death, and asymptomatic proximal DVT).

Table 15—Thromboprophylaxis Trials of LDUH vs LMWH in General Medical Patients*

Study/Year	Patients (mean age/yr/ cancer rate)	Method of DVT Screening	Intervention		DVT†	
			LDUH	LMWH	LDUH	LMWH
Bergmann and Neuhart ⁷⁰¹ / 1996	Bedridden, age \geq 65 yr (83, 7%)	FUT \times 10 d	5,000 U bid	Enoxaparin, 20 mg daily	10/216 (4.6)	10/207 (4.8)
Harenberg et al ⁷⁰² /1996	Bedridden, age 50–80 yr + 2nd risk factor (70, 8%)	Proximal DUS day 8–11	5,000 U tid	Nadroparin, 3,400 AXa U daily	4/780 (0.5)	6/810 (0.7)
Lechler et al ⁷⁰³ /1996	Immobile \geq 7 d + 2nd risk factor (74, 14%)	DUS day 7	5,000 U tid	Enoxaparin, 40 mg daily	6/377 (1.6)	1/393 (0.3)
Harenberg et al ⁷⁰⁴ /1999	Severe respiratory disease, CHF, or stroke (NR, NR)	Venography	5,000 U tid	Enoxaparin, 40 mg daily	67/303 (22.1)‡	51/327 (15.6)‡
Kleber et al ⁷⁰⁵ / 2003	Severe respiratory disease or CHF (70, 6%)	Venography if D-dimer or fibrin monomer positive days 8–12	5,000 U tid	Enoxaparin, 40 mg daily	22/212 (10.4)	20/239 (8.4)

*Includes randomized clinical trials in which LDUH and LMWH were compared and routine screening with an objective diagnostic test for DVT was used. AXa = anti-factor Xa; CHF = congestive heart failure. NR=not reported.

†Values given as No. of patients with DVT/total No. of patients (%).

‡Composite outcome of VTE and death.

ite end point of VTE or death occurred in 22% of the patients who had been randomized to LDUH, 5,000 U SC tid, and in 15% of the patients who had received enoxaparin, 40 mg SC once daily ($p = 0.04$). Major bleeding was seen in only 3 of the 877 study patients.

Two randomized clinical trials have assessed the effect of LDUH on mortality. Halkin and colleagues⁷⁰ gave 927 general medical patients either LDUH, 5,000 U SC bid, or no prophylaxis until they were discharged from the hospital or were fully mobile. Randomization was based on the hospital record number and therefore was subject to recruitment bias. Using an intention-to-treat analysis, the all-cause mortality rate was 7.8% among those who were randomized to LDUH, and 10.9% in the control group ($p < 0.05$). VTE was not reported. In a Swedish clinical trial of 11,693 patients who were admitted to the hospital with acute infection,⁷⁰⁶ participants were randomized to receive either LDUH, 5,000 U SC bid until hospital discharge, or to not receive prophylaxis. Mortality rates were similar in the heparin and control groups (5.3% vs 5.6%, respectively; $p = 0.4$). Autopsy-proven PE rates were also similar, but there were fewer nonfatal VTE events in the LDUH group (116 vs 70, respectively; $p = 0.001$).

Three randomized clinical trials have assessed the effect of LMWH on mortality.^{686,687,707} In one study of 270 medical patients, there was a 4.4% mortality rate by 10 days in both the placebo and LMWH groups.⁶⁸⁶ Another group⁷⁰⁷ studied 2,474 patients who had been admitted to the hospital with an acute medical condition and randomized them to receive LMWH or placebo for up to 21 days. The overall in-hospital mortality rate was 10% in both groups. In the MEDENOX trial,⁶⁸⁷ mortality by 14 days was seen in 4.4%, 4.3% and 3.3%, respectively, of the placebo, enoxaparin, 20 mg, and enoxaparin, 40 mg, recipients.

Several economic analyses^{708–711} have concluded that LDUH and LMWH are cost-effective thromboprophylaxis interventions in medical patients. In one meta-analysis,¹²⁵ there was no significant difference in the risk of VTE or death between patients receiving LDUH and LMWH, but LMWH therapy was associated with a lower incidence of major bleeding (1.2% vs 0.4%, respectively). This metaanalysis has been criticized for its pooling of data from studies that were based on quite different patient populations and methods for assessing outcomes, and for including small and unpublished studies. A more recent systematic review⁷¹² found that major bleeding was not greater with LDUH than with LMWH. Thus, it can be concluded that therapy with both LDUH and LMWH lower the risk of asymptomatic and symptomatic VTE by at least 50% in a broad spectrum of medical patients, compared with no prophylaxis. The effect of prophylaxis on mortality in this patient group remains unclear, however. A recent prospective study⁷¹³ observed a 1.4% rate of HIT among 360 medical patients who had been prescribed LDUH for > 1 week. The prevalence of VTE in the patients with HIT (60%) was much higher than in those without HIT (3.5%).

The thromboprophylaxis efficacy of the synthetic factor Xa inhibitor fondaparinux, 2.5 mg SC once daily, has recently been assessed⁷¹⁴ in a blinded, placebo-controlled study in acutely ill medical patients. The primary outcome, a combination of DVT detected by routine venogram between days 6 and 15 and symptomatic VTE, occurred in 10.5% and 5.6%, respectively, of the patients who received placebo and fondaparinux ($p < 0.029$). Fatal PE, a secondary outcome, was also significantly reduced in the fondaparinux recipients (5 vs 0 events). Major bleeding was seen in 0.2% of patients in both groups.

The optimal duration of thromboprophylaxis in medical patients is unknown.

Recommendations: Medical Conditions

6.0.1. 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, we recommend prophylaxis with LDUH (**Grade 1A**) or LMWH (**Grade 1A**).

6.0.2. In medical patients with risk factors for VTE, and in whom there is a contraindication to anticoagulant prophylaxis, we recommend the use of mechanical prophylaxis with GCS or IPC (**Grade 1C+**).

7.0 Cancer Patients

Patients with cancer have a sixfold increased risk of VTE compared to those without cancer.⁴⁹⁹ Active cancer accounts for almost 20% of all new VTE events occurring in the community.⁹ Furthermore, VTE is one of the most common complications seen in cancer patients.^{715,716} Unfortunately, there are few data that allow one to predict which cancer patients will develop VTE. The risk varies by cancer type, and is especially high among patients with malignant brain tumors and adenocarcinoma of the ovary, pancreas, colon, stomach, lung, prostate, and kidney.⁷¹⁷⁻⁷¹⁹ However, more specific risk estimates of VTE by cancer type, stage, and treatment approaches are still largely unknown.⁷²⁰

As discussed in other sections of this article, cancer patients undergoing surgery have at least twice the risk of postoperative DVT and more than three times the risk of fatal PE than noncancer patients who are undergoing similar procedures.^{20,177,721-724} Cancer is also an independent predictor of lack of response to prophylaxis (*ie*, the development of postoperative DVT despite the use of prophylaxis).^{177,178,183,721}

There is strong evidence that LDUH effectively reduces the risk of DVT and fatal PE following cancer surgery.^{50,77} LMWH is at least as efficacious as LDUH in surgical oncology patients.^{40,195,199,724} In cancer surgery, the dose of prophylactic anticoagulants is important. For example, among gynecologic oncology patients, dosing of LDUH three times daily was more efficacious than twice-daily dosing.^{251,261,262} Among general surgical patients with underlying malignancy, prophylaxis with dalteparin, 5,000 U SC once daily, was more efficacious than with a dose of 2,500 U.¹⁰¹ Two clinical trials^{205,206} in cancer surgery patients have shown that the continuation of LMWH prophylaxis for 3 weeks after hospital discharge reduced the risk of late venographic DVT by 60%.

Nonsurgical cancer therapies also increase the risk of VTE.⁷²⁰ For example, in two large clinical trials^{725,726} of women with node-negative breast cancer, the 5-year incidence of VTE was 0.2% in those who received placebo, 0.9% in those who received tamoxifen, and 4.2% in those who received tamoxifen plus chemotherapy. Furthermore, the risk of VTE in women with stage II breast cancer declined dramatically once chemotherapy was completed.^{727,728} Compared to patients without cancer, those receiving cytotoxic or immunosuppressive therapy have a

6.5-fold increased risk of VTE.⁴⁹⁹ Cancer patients receiving chemotherapy account for 13% of the overall burden of VTE in the population.⁹ 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.⁷²⁹ Prophylaxis with warfarin significantly, and cost-effectively, reduced the incidence of VTE compared to placebo, with no increased risk of major bleeding.⁷³⁰ Despite these interesting findings, additional studies are required before recommendations can be made regarding thromboprophylaxis use in cancer patients receiving chemotherapy.

Hormonal manipulation also affects the thrombosis risk.^{725,728,731} The rate of VTE increases by twofold to fivefold among women whose breast cancer has been treated with the selective estrogen receptor modulator tamoxifen.^{720,725} This risk was greater in postmenopausal women and when tamoxifen was combined with chemotherapy.⁷³² In a double-blinded clinical trial of the primary prevention of breast cancer,⁷³¹ 13,000 women were randomized to receive tamoxifen or placebo for 5 years. The risk of DVT was increased in the tamoxifen group compared with those receiving placebo (0.13% vs 0.08% per year, respectively), as was the risk of PE (0.07% vs 0.02% per year, respectively). The use of the aromatase inhibitor anastrozole is associated with approximately half the risk of VTE compared with that for tamoxifen use.^{733,734} In a clinical trial⁷³³ of 1,017 women with advanced breast cancer who were randomized to receive tamoxifen or anastrozole, the respective rates of VTE were 6.5% and 3.6%, respectively, after a median follow-up period of 18 months. Among > 6,000 postmenopausal women with early breast cancer who were followed up over a median duration of 33 months, VTE occurred in 5.3% of those treated with tamoxifen, and in 3.1% of those treated with anastrozole.⁷³⁴ We are not aware of any clinical trials that have studied the use of VTE prophylaxis among cancer patients receiving hormonal manipulation therapy.

Several studies have assessed the role of anticoagulants in the primary prevention of VTE in cancer patients without another indication for anticoagulant therapy. In stage IV breast cancer patients, low-dose warfarin therapy (INR range, 1.3 to 1.9) reduced the risk of VTE when used in the long term.⁷²⁹ However, in the Fragmin Advanced Malignancy Outcome Study (FAMOUS),⁷³⁵ in which 382 patients with advanced cancer received dalteparin, 5,000 U SC once daily, or placebo for approximately 9 months, the rates of symptomatic VTE did not differ significantly (3.4% vs 2.4%, respectively). Since VTE was a secondary end point in this study, it may have been underpowered to detect this outcome. For the primary outcome, survival at 1 year, there was also no significant improvement with the long-term use of LMWH.

The presence of a CVC is an independent risk factor for upper extremity DVT in the general population.⁴⁹⁹ It is also well-known that cancer patients with indwelling CVCs sometimes develop symptomatic thrombosis of the axillary/subclavian veins,⁷³⁶ producing arm swelling and discomfort, predisposing them to catheter-related sepsis and the need to replace the catheter.⁷³⁷ For the prevention of

CVC-associated VTE, prophylaxis with fixed-dose warfarin, 1 mg daily, was compared to no prophylaxis in one clinical trial.⁷³⁸ Using screening venography of the upper limb at 90 days, DVT was reduced from a rate of 37.5% among control subjects to 9.5% among warfarin recipients. However, two subsequent clinical trials^{739,740} failed to show any benefit from a 1-mg daily dose of warfarin compared to no prophylaxis. The safety of unmonitored mini-dose warfarin in cancer patients is also questionable. For example, among 95 patients with central lines for chemotherapy who were given warfarin, 1 mg daily, 33% had an INR of > 2.0, 27% had an INR of > 3.0, and 7% had an INR of > 5.0.⁷⁴¹ Bleeding was observed in eight patients, seven of whom had an elevated INR.

LMWH also has been assessed for the prevention of catheter-associated thrombosis. In one study,⁷⁴² cancer patients with CVCs were randomly allocated to receive dalteparin, 2,500 U SC once daily, or no prophylaxis for 90 days, followed by upper extremity venography. The study was prematurely stopped after 8 of 13 control patients developed thrombosis compared to only 1 patient assigned to receive LMWH ($p = 0.002$). These findings were challenged by those of another clinical trial⁷⁴³ in which 425 cancer patients receiving chemotherapy through a CVC were randomized to receive dalteparin, 5,000 U SC once daily, or placebo. Clinically relevant VTE occurred in 3.7% and 3.4%, respectively, of the dalteparin and placebo recipients. To date, this study has been presented only in abstract form. Although this area remains controversial, neither mini-dose warfarin nor prophylactic LMWH can be recommended as prophylaxis for cancer patients with indwelling CVCs. Furthermore, the incidence of venous thrombosis requiring catheter removal was only 3.4% (1.14 per 1,000 catheter-days) among 351 patients with a peripherally inserted central catheter who were not receiving thromboprophylaxis.⁷⁴⁴ These studies^{739,743,744} suggest that the risk of clinically important VTE related to CVCs may be too low to warrant routine prophylaxis.

In summary, the appropriate thromboprophylaxis of hospitalized cancer patients with additional VTE risk factors provides an important opportunity to reduce the burden of this disease. The prevention of VTE in these patients is important, not only because cancer patients have a particularly high risk for VTE, but also because VTE is often more difficult to diagnose in oncology patients, and the treatment of VTE may be less effective, and associated with more bleeding complications.⁷⁴⁵⁻⁷⁴⁷ Cancer patients undergoing surgery should receive aggressive thromboprophylaxis, as recommended in the sections on general, gynecologic, urologic, and neurologic surgery in this article.⁷²² Cancer patients who are immobile or are bedridden with an acute medical illness also should receive prophylaxis using the guidelines for medical patients. However, we do not believe that ambulatory cancer patients require VTE prophylaxis.

The results of additional ongoing trials are required before any recommendations can be made about the use of anticoagulants in cancer patients who do not have a traditional indication for prophylaxis, or as a method to improve survival.

Recommendations: Cancer Patients

7.0.1. We 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.

7.0.2. We 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.

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

8.0 Critical Care

Two systematic reviews of VTE and its prevention in critical care settings^{632,748} have been published in the past few years. Most critically ill patients have multiple risk factors for VTE.⁷⁴⁸⁻⁷⁵⁰ Some of these risk factors predate admission to the ICU, and include recent surgery, trauma, sepsis, malignancy, immobilization, stroke, advanced age, heart or respiratory failure, previous VTE, and pregnancy. Other thrombotic risk factors may be acquired during an ICU stay, and include immobilization, use of pharmacologic paralysis or sedation, central venous lines, surgical procedures, sepsis, mechanical ventilation, vasopressor use, heart failure, renal dialysis, and depletion of endogenous anticoagulants.^{748,750,751}

The reported incidence of DVT in ICU patients ranges from < 10% to almost 100%, reflecting the wide spectrum of critically ill patients.^{632,748} Unsuspected DVT may be present prior to admission to the ICU. When DUS was performed at ICU entry in 990 patients, reported in five case series,^{691,751-754} the rate of DVT was 5.5%.

Only five studies^{685,752,754-756} have prospectively screened ICU patients who were not receiving thromboprophylaxis for asymptomatic, objectively confirmed DVT, with resulting rates ranging from 13 to 31% (Table 16). The largest study⁷⁵⁶ has only been published in abstract form. Despite the paucity of ICU-specific data about VTE, the risks in surgical, trauma/SCI, and medical patients are well-established and are relevant to the critical care population, which is principally based on those subgroups.^{2,62,632,748}

We identified only four published, randomized clinical trials^{685,754,756,757} of thromboprophylaxis in critical care patients that routinely used objective screening for DVT (Table 17). Two of the studies have been published in abstract form only.^{756,757} In the first trial, 119 general ICU patients received either LDUH or placebo.⁶⁸⁵ The DVT rates were 13% and 29%, respectively, which was equivalent to a RRR of 55% favoring LDUH ($p < 0.05$). In the second study,⁷⁵⁴ 223 patients who were receiving at least 48 h of mechanical ventilation for exacerbations of COPD were randomized to receive either placebo or nadroparin at a daily dose of approximately 65 U/kg. After a mean duration

Table 16—Prospective Studies of DVT Rates in Critical Care Patients Not Receiving Prophylaxis

Study/Year	Type of ICU patient	Method of Diagnosis	No.	DVT Prevalence, %
Moser et al ⁷⁵⁵ /1981	Respiratory ICU	FUT	33	13
Cade ⁶⁸⁵ /1982	General ICU	FUT	Approximately 60	29
Goldberg et al ⁷⁵² /1996	Respiratory failure	Proximal DUS	16	19
Kapoor et al ⁷⁵⁶ /1999	Medical ICU	Serial DUS	390	31
Fraisse et al ⁷⁵⁴ /2000	Ventilated COPD	Venography	85	28

of 12 days, DVT was detected by routine venography in 28% of control subjects and 15% of LMWH recipients (RRR, 45%; $p = 0.045$). Major bleeding rates were 3% and 6%, respectively, which was not statistically significant.

Serial DUS was used to screen medical ICU patients for DVT in the remaining two prophylaxis trials. In one study that compared LDUH with placebo,⁷⁵⁶ DVT was detected in 31% of the 390 placebo-treated patients and in 11% of the 401 patients who received LDUH (RRR, 65%; NNT, 5; $p = 0.001$). PE was diagnosed in 5% and 2% of patients, respectively. Finally, after 11,000 medical ICU patients were considered for participation in a 28-center randomized clinical trial comparing LDUH, 5,000 U SC bid, with enoxaparin, 30 mg SC bid, 325 patients were included.⁷⁵⁷ Serial DUS detected DVT in 16% and 13%, respectively, of the LDUH and LMWH patients, with no differences observed in the rates of proximal DVT or bleeding. Four additional, observational studies^{42,751,758,759} noted high rates of DVT ranging from 10 to 33% in ICU patients who did receive thromboprophylaxis.

The use of vasoactive drugs may reduce the effectiveness of VTE prophylaxis. In one study,⁷⁶⁰ critical care patients who received vasopressor drugs had significantly lower anti-Xa levels with LMWH prophylaxis than did patients not receiving vasopressors, an observation that may be related to reduced subcutaneous perfusion and drug absorption. Future studies should assess the pharmacokinetic response to LMWH in the presence of generalized edema, systemic shock, and moderate renal insufficiency, all of which are common states in ICU patients.^{761,762}

In view of the high risk of VTE in critically ill patients, it is essential for all ICUs to develop a standardized approach to thromboprophylaxis.⁷⁶³ On admission to the

ICU, all patients should be assessed for their risk of VTE. Since almost all critical care patients are at moderate to high risk, thromboprophylaxis will be warranted in most. The selection of prophylaxis for these heterogeneous patients involves the consideration of the VTE and bleeding risks, both of which may vary over time in the average ICU patient. When the bleeding risk is high, mechanical prophylaxis should be started using GCS alone, or GCS combined with IPC until the risk of bleeding decreases. However, this approach has never been formally tested in a general ICU setting. For ICU patients who are not at high risk for bleeding, anticoagulant prophylaxis with either LDUH or LMWH, depending on the subgroup under consideration, is recommended. For ICU patients who are at moderate risk for VTE, such as those with an active medical or general surgical condition, prophylaxis with LDUH or LMWH is recommended. For patients who are at higher risk, such as that following major trauma or orthopedic surgery, LMWH provides greater protection than LDUH and is recommended for prophylaxis. Specific prophylaxis recommendations should be included in the patient's orders when they are transferred from the ICU. A written policy for thromboprophylaxis, combined with preprinted or computerized ICU admission orders, has been shown to enhance compliance with prophylaxis use.⁷⁶⁴

Recommendations: Critical Care

8.1. We 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**).

Table 17—Thromboprophylaxis Trials in Critical Care Patients*

Study/Year	Method of Diagnosis	Intervention		DVT†	
		Control	Experimental	Control	Experimental
Cade ⁶⁸⁵ /1982	FUT for 4–10 d	Placebo	Heparin, 5,000 U SC bid	NR/NR (29)	NR/NR (13)
Kapoor et al ⁷⁵⁶ /1999	DUS on admission and every 3 d	Placebo	Heparin, 5,000 U SC bid	122/390 (31)	44/401 (11)
Fraisse et al ⁷⁵⁴ /2000	Venography before day 21	Placebo	Nadroparin, approximately 65 U/kg SC once daily	24/85 (28)	13/84 (15)
Goldhaber et al ⁷⁵⁷ /2000	DUS on days 3, 7, 10, and 14	Heparin, 5,000 U SC bid	Enoxaparin, 30 mg SC bid	NR/NR (13)	NR/NR (16)

*Randomized clinical trials in which routine screening with an objective diagnostic test for DVT was used in critical care unit patients.

†Values given as No. of patients with DVT/total No. of patients (%).

8.2. For patients who are at high risk for bleeding, we recommend mechanical prophylaxis with GCS and/or IPC until the bleeding risk decreases (**Grade 1C+**).

8.3. For ICU patients who are at moderate risk for VTE (eg, medically ill or postoperative patients), we recommend using LDUH or LMWH prophylaxis (**Grade 1A**).

8.4. For patients who are at higher risk, such as that following major trauma or orthopedic surgery, we recommend LMWH prophylaxis (**Grade 1A**).

9.0 Long Distance Travel

Despite extensive lay press coverage, the evidence for an association between prolonged travel, whether by air or by land, and VTE remains controversial.^{512,765-774} Retrospective studies^{512,765,771,775} have suggested that approximately 4 to 20% of patients presenting with VTE had traveled within a few weeks prior to the event. One study⁷⁷⁶ found an increased risk of VTE that was present only for the first 2 weeks after arrival from a long-haul flight. The incidence of travel-related PE and DVT appears to be related to the distance traveled during the air flights.⁷⁷⁷⁻⁷⁸¹ Some studies,^{766,769,774} however, found no association between VTE and air travel. A recent review of the literature⁷⁷⁴ also found no association between travel and symptomatic VTE, except when travel was for > 10 h. In one study,⁷⁷⁷ confirmed PE was diagnosed in only 56 of 135 million travelers arriving at Charles de Gaulle Airport in Paris. The corresponding rates were 1 per 100 million passengers who traveled for < 6 h, and 1 per 700,000 passengers who traveled for > 6 h. Most individuals with travel-associated VTE also exhibited one or more known risk factors for thrombosis, creating uncertainty about the causal or additive role of travel in VTE.^{771,782,783} Furthermore, whether the ascribed causation to travel relates to immobility and venous compression, dehydration, or high-altitude cabin pressure also requires clarification.^{767,772,784,785} Additional risk factors that have been

implicated, in the absence of direct evidence, include previous VTE, recent surgery or trauma, active malignancy or other chronic disease, estrogen use, advanced age, obesity, and thrombophilia.^{776,786-790}

Eight prospective studies^{768,778,779,788,790-793} included subjects embarking on airline flights of > 4 h duration to determine the incidence of DVT using screening DUS. The rate of asymptomatic DVT among all 3,051 unprotected participants was 2.2%, with a rate of 1.4% among the 2,056 usual or "low-risk" travelers,^{768,778,788,790,791} and 4.0% among the 995 "high-risk" travelers.^{768,779,791} Another prospective study⁷⁸⁰ obtained plasma d-dimer levels in 878 volunteers before and after away-and-return air flights that averaged 39 h. The travelers with positive d-dimer values on the return flight to New Zealand underwent objective investigations for both DVT and PE. VTE was detected in 1% of the participants, all of whom had a total duration of travel that exceeded 24 h.

We identified seven randomized clinical trials^{768,778,779,788,791-793} of active thromboprophylaxis use in travelers (Table 18). Although the flight durations and presence of additional risk factors were not consistent across these studies, the pooled rate of DUS-screened DVT was 3.7% (50 of 1,341 passengers) among passengers who received no prophylaxis. The use of below-knee GCS (providing 12 to 30 mm Hg compression) lowered the rate of asymptomatic DVT to 0.2% (2 of 1,255 passengers) in six randomized clinical trials. In the GCS studies, the intervention was not blinded, and in some trials it was not clear whether the DVT screening test was obtained by blinded assessors. A single dose of enoxaparin, either 100 U/kg or 4,000 U, administered 2 to 4 h before travel, also eliminated DVT in two studies that included a total of only 184 patients. In one small study,⁷⁹³ aspirin therapy, started 12 h before the flight and continued for 3 days, was not protective.

Although there are conflicting views about thromboprophylaxis use in travelers,^{772,774,794} we believe that there is

Table 18—Thromboprophylaxis Trials in Air Travelers*

Study/Year	Risk Group†	Mean Flight Duration, h‡	Intervention		DVT§	
			Control	Experimental	Control	Experimental
Belcaro et al ⁷⁶⁸ /2001	High	12.4 (10–15)	None	Stockings	19/422 (4.5)	1/411 (0.2)
Scurr et al ⁷⁸⁸ /2001	Low	23 (18–36) within 6 wk	None	Stockings	12/116 (10.3)	0/115
Belcaro et al ⁷⁷⁸ /2002	Low-medium	7–12	None	Stockings	7/314 (2.2)	0/315
Belcaro et al ⁷⁹¹ /2002	High	10–13	None	Stockings	6/101 (5.9)	1/104 (1.0)
Cesarone et al ⁷⁷⁹ /2002	High	> 10	None	Enoxaparin, 4,000 U Aspirin, 400 mg daily × 3	4/83 (4.8)	3/84 (3.6)
Cesarone et al ⁷⁹² /2003	Low-medium	7–12	None	Enoxaparin, 100 U/kg Stockings	0/169	0/172
Cesarone et al ⁷⁹³ /2003	Low-medium	7–12	None	Stockings	2/138 (1.4)	0/138

*Randomized clinical trials in which routine DUS was performed following air travel.

†Using the authors' definition of risk; generally, low risk = no thrombosis risk factors; high risk = one or more risk factors including previous DVT, coagulation disorder, limited mobility, current or recent cancer, large varicose veins, or severe obesity.

‡Values in parentheses are ranges.

§Values given as No. of patients with DVT/total No. of patients (%).

insufficient evidence supporting the routine use of active prophylaxis measures in any group of travelers. Until further studies are available, a decision about prophylaxis for passengers specifically deemed to be at increased risk of VTE should be made on an individual basis. The World Health Organization recently initiated an extensive research program to assess the risks, pathophysiology, and prevention of VTE associated with air travel (available at http://www.who.int/cardiovascular_diseases/wright_project/en/), and their final report is expected in 2006.

Recommendations: Long Distance Travel

9.1. We recommend the following general measures for long-distance travelers (*ie*, flights of > 6 h duration): avoidance of constrictive clothing around the lower extremities or waist; avoidance of dehydration and frequent calf muscle stretching (**Grade 1C**).

9.2. For long-distance travelers with additional risk factors for VTE, we recommend the general strategies listed above. If active prophylaxis is considered, because of the perceived increased risk of venous thrombosis, we 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**).

9.3. We recommend **against** the use of aspirin for VTE prevention associated with travel (**Grade 1B**).

SUMMARY OF RECOMMENDATIONS

1.0 General Recommendations

1.4.3. We 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**). We recommend that careful attention be directed toward ensuring the proper use of, and optimal compliance with, the mechanical device (**Grade 1C+**).

1.4.4. We recommend **against** the use of aspirin alone as prophylaxis against VTE for any patient group (**Grade 1A**).

1.4.5.1. For each of the antithrombotic agents, we recommend that clinicians consider the manufacturer's suggested dosing guidelines (**Grade 1C**).

1.4.5.2. We recommend consideration of renal impairment when deciding on doses of 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+**).

1.5.1. In all patients undergoing neuraxial anesthesia or analgesia, we recommend special caution when using anticoagulant prophylaxis (**Grade 1C+**).

2.0 General, Vascular, Gynecologic, and Urologic Surgery

2.1 General surgery

2.1.1. In low-risk general surgery patients (Table 5) who are undergoing a minor procedure, are < 40 years of age, and have no additional risk factors, we recommend **against** the use of specific prophylaxis other than early and persistent mobilization (**Grade 1C+**).

2.1.2. 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. We recommend prophylaxis with LDUH, 5,000 U bid, or LMWH, \leq 3,400 U once daily (both **Grade 1A**).

2.1.3. 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. We recommend thromboprophylaxis with LDUH, 5,000 U tid, or LMWH, > 3,400 U daily (both **Grade 1A**).

2.1.4. In high-risk general surgery patients with multiple risk factors, we recommend that pharmacologic methods (*ie*, LDUH, tid, or LMWH, > 3,400 U daily) be combined with the use of GCS and/or IPC (**Grade 1C+**).

2.1.5. In general surgery patients with a high risk of bleeding, we recommend the use of mechanical prophylaxis with properly fitted GCS or IPC, at least initially until the bleeding risk decreases (**Grade 1A**).

2.1.6. In selected high-risk general surgery patients, including those who have undergone major cancer surgery, we suggest post-hospital discharge prophylaxis with LMWH (**Grade 2A**).

2.2 Vascular surgery

2.2.1. In patients undergoing vascular surgery who do not have additional thromboembolic risk factors, we suggest that clinicians **not** routinely use thromboprophylaxis (**Grade 2B**).

2.2.2. For patients undergoing major vascular surgical procedures who have additional thromboembolic risk factors, we recommend prophylaxis with LDUH or LMWH (**Grade 1C+**).

2.3 Gynecologic surgery

2.3.1. For gynecologic surgery patients undergoing brief procedures of \leq 30 min for benign disease, we recommend **against** the use of specific prophylaxis other than early and persistent mobilization (**Grade 1C+**).

2.3.2. For patients undergoing laparoscopic gynecologic procedures, in whom additional VTE risk factors are present, we recommend the use of thromboprophylaxis with one or more of the following: LDUH, LMWH, IPC, or GCS (all **Grade 1C**).

2.3.3. We recommend that thromboprophylaxis be used in all major gynecologic surgery patients (**Grade 1A**).

2.3.4. For patients undergoing major gynecologic surgery for benign disease, without additional risk factors, we recommend LDUH, 5,000 U bid (**Grade 1A**). Alternatives include once-daily prophylaxis with LMWH, $\leq 3,400$ U/d (**Grade 1C+**), or IPC started just before surgery and used continuously while the patient is not ambulating (**Grade 1B**).

2.3.5. For patients undergoing extensive surgery for malignancy, and for patients with additional VTE risk factors, we recommend routine prophylaxis with LDUH, 5,000 U tid (**Grade 1A**), or higher doses of LMWH (*ie*, $> 3,400$ 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**).

2.3.6. For patients undergoing major gynecologic procedures, we 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 who are > 60 years of age or have previously experienced a VTE, we suggest continuing prophylaxis for 2 to 4 weeks after hospital discharge (**Grade 2C**).

2.4 Urologic surgery

2.4.1. In patients undergoing transurethral or other low-risk urologic procedures, we recommend **against** the use of specific prophylaxis other than early and persistent mobilization (**Grade 1C+**).

2.4.2. For patients undergoing major, open urologic procedures, we 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+**).

2.4.3. For urologic surgery patients who are actively bleeding or are at very high risk for bleeding, we recommend the use of mechanical prophylaxis with GCS and/or IPC at least until the bleeding risk decreases (**Grade 1C+**).

2.4.4. For patients with multiple risk factors, we recommend combining GCS and/or IPC with LDUH or LMWH (**Grade 1C+**).

2.5 Laparoscopic surgery

2.5.1. We recommend **against** routine thromboprophylaxis in these patients, other than aggressive mobilization (**Grade 1A**).

2.5.2. For patients undergoing laparoscopic procedures and who have additional thromboembolic risk factors, we recommend the use of thromboprophylaxis with one or more of the following: LDUH, LMWH, IPC, or GCS (**Grade 1C+**).

3.0 Orthopedic Surgery

3.1 Elective hip arthroplasty

3.1.1. For patients undergoing elective THR, we recommend the routine use of one of the following three anticoagulants: (1) LMWH (at a usual high-risk dose, started 12 h before surgery or 12 to 24 h after surgery, or 4 to 6 h 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 h after surgery) or (3) adjusted-dose VKA started preoperatively or the evening after surgery (INR target, 2.5; INR range, 2.0 to 3.0) [all **Grade 1A**].

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

3.1.2. We recommend **against** the use of aspirin, dextran, LDUH, GCS, IPC, or VFP as the only method of thromboprophylaxis in these patients (**Grade 1A**).

3.2 Elective knee arthroplasty

3.2.1. For patients undergoing elective TKA, we 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. We have not recommended fondaparinux over LMWH and VKA, or LMWH over VKA, because we place a relatively low value on the prevention of venographic thrombosis and a relatively high value on minimizing bleeding complications.

3.2.2. The optimal use of IPC is an alternative option to anticoagulant prophylaxis (**Grade 1B**).

3.2.3. We recommend **against** the use of any of the following as sole methods of thromboprophylaxis: aspirin (**Grade 1A**); LDUH (**Grade 1A**); or VFP (**Grade 1B**).

3.3 Knee arthroscopy

3.3.1. We suggest clinicians do **not** use routine thromboprophylaxis in these patients, other than early mobilization (**Grade 2B**).

3.3.2. For patients undergoing arthroscopic knee surgery who are at a higher than usual risk, based on preexisting VTE risk factors or following a prolonged or complicated procedure, we suggest thromboprophylaxis with LMWH (**Grade 2B**).

3.4 Hip fracture surgery

3.4.1. For patients undergoing HFS, we 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**).

3.4.2. We recommend **against** the use of aspirin alone (**Grade 1A**).

3.4.3. If surgery will likely be delayed, we recommend that prophylaxis with either LDUH or LMWH be initiated during the time between hospital admission and surgery (**Grade 1C+**).

3.4.4. We recommend mechanical prophylaxis if anticoagulant prophylaxis is contraindicated because of a high risk of bleeding (**Grade 1C+**).

3.5 Other prophylaxis issues in major orthopedic surgery

3.5.1. For major orthopedic surgical procedures, we 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**).

3.5.2. We recommend **against** the routine use of DUS screening at the time of hospital discharge in asymptomatic patients following major orthopedic surgery (**Grade 1A**).

3.5.3.1. We 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**).

3.5.3.2. We 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+**).

3.6 Elective spine surgery

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

3.6.2. We 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**).

3.6.3. For patients with additional risk factors, we 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, we recommend combining LDUH or LMWH with GCS and/or IPC (**Grade 1C+**).

3.7 Isolated lower extremity injuries

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

4.0 Neurosurgery

4.0.1. We recommend that thromboprophylaxis be routinely used in patients undergoing major neurosurgery (**Grade 1A**).

4.0.2. We recommend the use of IPC with or without GCS in patients undergoing intracranial neurosurgery (**Grade 1A**).

4.0.3. Acceptable alternatives to the above options are prophylaxis with LDUH (**Grade 2B**) or postoperative LMWH (**Grade 2A**).

4.0.4. We suggest the combination of mechanical prophylaxis (*ie*, GCS and/or IPC) and pharmacologic prophylaxis (*ie*, LDUH or LMWH) in high-risk neurosurgery patients (**Grade 2B**).

5.0 Trauma, Spinal Cord Injury, Burns

5.1 Trauma

5.1.1. We recommend that all trauma patients with at least one risk factor for VTE receive thromboprophylaxis, if possible (**Grade 1A**).

5.1.2. In the absence of a major contraindication, we recommend that clinicians use LMWH prophylaxis starting as soon as it is considered safe to do so (**Grade 1A**).

5.1.3. We 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**).

5.1.4. We recommend DUS screening in patients who are at high risk for VTE (*eg*, the presence of a 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**).

5.1.5. We recommend **against** the use of IVCFs as primary prophylaxis in trauma patients (**Grade 1C**).

5.1.6. We recommend the continuation of thromboprophylaxis until hospital discharge, including the period of inpatient rehabilitation (**Grade 1C+**). We 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**).

5.2 Acute SCI

5.2.1. We recommend that thromboprophylaxis be provided for all patients with acute SCIs (**Grade 1A**).

5.2.2. We recommend **against** the use of LDUH, GCS, or IPC as single prophylaxis modalities (**Grade 1A**).

5.2.3. In patients with acute SCI, we recommend prophylaxis with LMWH, to be commenced once primary hemostasis is evident (**Grade 1B**). We suggest the combined use of IPC and either LDUH (**Grade 2B**) or LMWH (**Grade 2C**) as alternatives to LMWH.

5.2.4. We recommend the use of IPC and/or GCS when anticoagulant prophylaxis is contraindicated early after injury (**Grade 1C+**).

5.2.5. We recommend **against** the use of an IVCF as primary prophylaxis against PE (**Grade 1C**).

5.2.6. During the rehabilitation phase following acute SCI, we 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**].

5.3 Burns

5.3.1. We 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+**).

5.3.2. If there are no contraindications, we recommend the use of either LDUH or LMWH, starting as soon as it is considered safe to do so (**Grade 1C+**).

6.0 Medical conditions

6.0.1. 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, we recommend prophylaxis with LDUH (**Grade 1A**) or LMWH (**Grade 1A**).

6.0.2. In medical patients with risk factors for VTE, and in whom there is a contraindication to anticoagulant prophylaxis, we recommend the use of mechanical prophylaxis with GCS or IPC (**Grade 1C+**).

7.0 Cancer patients

7.0.1. We 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.

7.0.2. We 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.

7.0.3. We suggest that clinicians not routinely use prophylaxis to try to prevent thrombosis related to long-term indwelling CVCs in cancer patients (**Grade 2B**). Specifically, we suggest that clinicians **not** use LMWH

(**Grade 2B**), and we recommend **against** the use of fixed-dose warfarin (**Grade 1B**) for this indication.

8.0 Critical care

8.1. We 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**).

8.2. For patients who are at high risk for bleeding, we recommend mechanical prophylaxis with GCS and/or IPC until the bleeding risk decreases (**Grade 1C+**).

8.3. For ICU patients who are at moderate risk for VTE (eg, medically ill or postoperative patients), we recommend using LDUH or LMWH prophylaxis (**Grade 1A**).

8.4. For patients who are at higher risk, such as that following major trauma or orthopedic surgery, we recommend LMWH prophylaxis (**Grade 1A**).

9.0 Long distance travel

9.1. We recommend the following general measures for long-distance travelers (ie, flights of > 6 h duration): avoidance of constrictive clothing around the lower extremities or waist; avoidance of dehydration; and frequent calf muscle stretching (**Grade 1C**).

9.2. For long-distance travelers with additional risk factors for VTE, we recommend the general strategies listed above. If active prophylaxis is considered, because of the perceived increased risk of venous thrombosis, we 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**).

9.3. We recommend **against** the use of aspirin for VTE prevention associated with travel (**Grade 1B**).

ACKNOWLEDGMENTS: We are grateful to the following external experts who reviewed specific subsections of this article (or the entire article = *) and provided written comments: W. Ageno (Varese, Italy); D. Anderson (Halifax, NS, Canada); R. Arya (London, UK); G. Belcaro (San Valentino, Italy); J.-F. Bergmann (Paris, France); F. Brenneman (Toronto, ON, Canada); R. Buckley (Calgary, AB, Canada); D. Cannavo (New York, NY); J. Caprini (Chicago, IL); M. Cipolle (Allentown, PA); D. Clarke-Pearson (Durham, NC); P. Comp (Oklahoma City, OK); S. Constantini (Tel Aviv, Israel); D. Cook (Hamilton, ON, Canada); B. Davidson (Seattle, WA); J. Douketis (Hamilton, ON, Canada); R. Eisele (Ulm, Germany); G. Elliott (Salt Lake City, UT); B. Eriksson (Goteborg, Sweden); E. Ferrari (Nice, France); J. Finkelstein (Toronto, ON, Canada); J. Fish (Toronto, ON, Canada); C. Francis (Rochester, NY); C. Gaebler (Vienna, Austria); A. Gallus (Bedford Park, SA, Australia); D. Green (Chicago, IL); I. Greer (Glasgow, Scotland, UK); C. Guest (Toronto, ON, Canada); G. Guyatt* (Hamilton, ON, Canada); H. Handoll (Edinburgh, Scotland, UK); J. Harenberg (Mannheim, Germany); S. Hu (San Francisco, CA); J. Hirsh* (Hamilton, ON, Canada); A. Kakkar* (London, UK); K. Koval (New York, NY); H. Kreder (Toronto, ON, Canada); F. Lapostolle (Bobigny, France); A. Lee (Hamilton, ON, Canada); P. Lotke (Philadelphia, PA); F. Luchette (Maywood, IL); L. Macdonald (Chicago, IL); J.

Marshall (Toronto, ON, Canada); C. McCartney (Toronto, ON, Canada); R. McLeod (Toronto, ON, Canada); M. Meissner (Seattle, WA); G. Merli (Philadelphia, PA); P. Mismetti (St. Etienne, France); R. Oates-Whitehead (London, UK); A. Panju (Hamilton, ON, Canada); V. Pellegrini (Baltimore, MD); R. Pittini (Toronto, ON, Canada); A. Planes (LaRochelle, France); M. Rasmussen (Copenhagen, Denmark); K. Saleh (Minneapolis, MN); C. Samama (Bobigny, France); M. Samama (Paris, France); J. Schneider (Chicago, IL); M. Schwartz (Toronto, ON, Canada); T. Schwartz (Lexington, KY); R. Selby* (Toronto, ON, Canada); N. Sharrock (New York, NY); J. Smith (Nashville, TN); M. Swiontkowski (Minneapolis, MN); H. Thaler (Vienna, Austria); A. Turpie (Hamilton, ON, Canada); G. Velmahos (Los Angeles, CA); D. Warwick (Southampton, UK); P. Wille-Jorgensen (Copenhagen, Denmark); C. Wu (Baltimore, MD); and L. Zacharski (White River Junction, VT). Special thanks to Penny deNobrega for invaluable assistance with the references.

REFERENCES

- 1 Second Thromboembolic Risk Factors (THRIFT II) Consensus Group. Risk of and prophylaxis for venous thromboembolism in hospital patients. *Phlebology* 1998; 13:87-97
- 2 Geerts WH, Heit JA, Clagett GP, et al. Prevention of venous thromboembolism. *Chest* 2001; 119:132S-175S
- 3 Scottish Intercollegiate Guidelines Network (SIGN). Prophylaxis of venous thromboembolism: a national clinical guideline. 2002; SIGN Publication No. 62. Available at: <http://www.sign.ac.uk>. Accessed April 16, 2003
- 4 Schünemann H, Munger H, Brower S, et al. Methodology for guideline development for the Seventh American College of Chest Physicians conference on antithrombotic and thrombolytic therapy. *Chest* 2004; 126:174S-178S
- 5 Sullivan SD, Kahn SR, Davidson BL, et al. Measuring the outcomes and pharmacoeconomic consequences of venous thromboembolism prophylaxis in major orthopaedic surgery. *Pharmacoeconomics* 2003; 21:477-496
- 6 Anderson FA, Wheeler HB, Goldberg RJ, et al. The prevalence of risk factors for venous thromboembolism among hospital patients. *Arch Intern Med* 1992; 152:1660-1664
- 7 Rosendaal FR. Risk factors for venous thrombotic disease. *Thromb Haemost* 1999; 82:610-619
- 8 Kearon C, Salzman EW, Hirsh J. Epidemiology, pathogenesis, and natural history of venous thrombosis. In: Colman RW, Hirsh J, Marder VJ, et al, eds. *Hemostasis and thrombosis: basic principles and clinical practice*. 4th ed. Philadelphia, PA: JB Lippincott, 2001; 1153-1177
- 9 Heit JA, O'Fallon WM, Petterson TM, et al. Relative impact of risk factors for deep vein thrombosis and pulmonary embolism: a population-based study. *Arch Intern Med* 2002; 162:1245-1248
- 10 Anderson FA, Spencer FA. Risk factors for venous thromboembolism. *Circulation* 2003; 107:19-116
- 11 Rosendaal FR. Venous thrombosis: a multicausal disease. *Lancet* 1999; 353:1167-1173
- 12 Anderson FA, Wheeler HB, Goldberg RJ, et al. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism: the Worcester DVT Study. *Arch Intern Med* 1991; 151:933-938
- 13 Prothero SR, Parkes JC, Stinchfield FE. Complications after low-back fusion in 1000 patients: a comparison of two series one decade apart. *J Bone Joint Surg Am* 1966; 48:57-69
- 14 Lindblad B, Eriksson A, Bergqvist D. Autopsy-verified pulmonary embolism in a surgical department: analysis of the period from 1951 to 1968. *Br J Surg* 1991; 78:849-852
- 15 Stein PD, Henry JW. Prevalence of acute pulmonary embolism among patients in a general hospital and at autopsy. *Chest* 1995; 108:978-981
- 16 Todd CJ, Freeman CJ, Camilleri-Ferrante C, et al. Differences in mortality after fracture of hip: the East Anglian audit. *BMJ* 1995; 310:904-908
- 17 Baglin TP, White K, Charles A. Fatal pulmonary embolism in hospitalised medical patients. *J Clin Pathol* 1997; 50:609-610
- 18 Fender D, Harper WM, Thompson JR, et al. Mortality and fatal pulmonary embolism after primary total hip replacement: results from a regional hip register. *J Bone Joint Surg Br* 1997; 79:896-899
- 19 Chang JY, Kostuik J, Sieber A. Complications of spinal fusion in treatment of adult spinal deformity [abstract]. *Spine J* 2002; 2:55S
- 20 White RH, Zhou H, Romano PS. Incidence of symptomatic venous thromboembolism after different elective or urgent surgical procedures. *Thromb Haemost* 2003; 90:446-455
- 21 Sandler DA, Martin JF. Autopsy proven pulmonary embolism in hospital patients: are we detecting enough deep vein thrombosis? *J R Soc Med* 1989; 82:203-205
- 22 Kakkar VV, Howe CT, Flanc C, et al. Natural history of postoperative deep-vein thrombosis. *Lancet* 1969; 2:230-233
- 23 Lotke PA, Ecker ML, Alavi A, et al. Indications for the treatment of deep venous thrombosis following total knee replacement. *J Bone Joint Surg Am* 1984; 66:202-208
- 24 Philbrick JT, Becker DM. Calf deep venous thrombosis: a wolf in sheep's clothing? *Arch Intern Med* 1988; 148:2131-2138
- 25 Agnelli G, Cosmi B, Radicchia S, et al. Features of thrombi and diagnostic accuracy of impedance plethysmography in symptomatic and asymptomatic deep vein thrombosis. *Thromb Haemost* 1993; 70:266-269
- 26 Hedlund PO. Postoperative venous thrombosis in benign prostatic disease: a study of 316 patients, using the ¹²⁵I-fibrinogen uptake test. *Scand J Urol Nephrol Suppl* 1975; 27:1-100
- 27 Lohr JM, Kerr TM, Lutter KS, et al. Lower extremity calf thrombosis: to treat or not to treat? *J Vasc Surg* 1991; 14:618-623
- 28 Maynard MJ, Sculco TP, Ghelman B. Progression and regression of deep vein thrombosis after total knee arthroplasty. *Clin Orthop* 1991; 273:125-130
- 29 Solis MM, Ranval TJ, Nix ML, et al. Is anticoagulation indicated for asymptomatic postoperative calf vein thrombosis? *J Vasc Surg* 1992; 16:414-418
- 30 Kearon C. Natural history of venous thromboembolism. *Circulation* 2003; 107:122-130
- 31 Stamatakis JD, Kakkar VV, Sagar S, et al. Femoral vein thrombosis and total hip replacement. *BMJ* 1977; 2:223-225
- 32 Cruickshank MK, Levine MN, Hirsh J, et al. An evaluation of impedance plethysmography and ¹²⁵I-fibrinogen leg scanning in patients following hip surgery. *Thromb Haemost* 1989; 62:830-834
- 33 Ascani A, Radicchia S, Parise P, et al. Distribution and occlusiveness of thrombi in patients with surveillance detected deep vein thrombosis after hip surgery. *Thromb Haemost* 1996; 75:239-241
- 34 Turpie AGG, Bauer KA, Eriksson BI, et al. Relevance of venographic distal thrombus assessment in venous thromboembolism (VTE) prophylaxis studies: lessons from the fondaparinux (Arixtra) database in major orthopedic surgery [abstract]. *J Thromb Haemost* 2003; 1(suppl):P2066
- 35 Moser KM, LeMoine JR. Is embolic risk conditioned by location of deep venous thrombosis? *Ann Intern Med* 1981; 94:439-444
- 36 Haas SB, Tribus CB, Insall JN, et al. The significance of calf

- thrombi after total knee arthroplasty. *J Bone Joint Surg Br* 1992; 74:799–802
- 37 Kalodiki E, Domjan J, Nicolaides AN, et al. V/Q defects and deep venous thrombosis following total hip replacement. *Clin Radiol* 1995; 50:400–403
 - 38 Eikelboom JW, Quinlan DJ, Douketis JD. Extended-duration prophylaxis against venous thromboembolism after total hip or knee replacement: a meta-analysis of the randomised trials. *Lancet* 2001; 358:9–15
 - 39 Hull RD, Pineo GF, Stein PD, et al. Extended out-of-hospital low-molecular-weight heparin prophylaxis against deep venous thrombosis in patients after elective hip arthroplasty: a systematic review. *Ann Intern Med* 2001; 135:858–869
 - 40 Mismetti P, Laporte S, Darmon JY, et al. Meta-analysis of low molecular weight heparin in the prevention of venous thromboembolism in general surgery. *Br J Surg* 2001; 88:913–930
 - 41 Douketis JD, Eikelboom JW, Quinlan DJ, et al. Short-duration prophylaxis against venous thromboembolism after total hip or knee replacement: a meta-analysis of prospective studies investigating symptomatic outcomes. *Arch Intern Med* 2002; 162:1465–1471
 - 42 Ibrahim EH, Iregui M, Prentice D, et al. Deep vein thrombosis during prolonged mechanical ventilation despite prophylaxis. *Crit Care Med* 2002; 30:771–774
 - 43 Heit JA, Silverstein MD, Mohr DN, et al. Predictors of survival after deep vein thrombosis and pulmonary embolism: a population-based, cohort study. *Arch Intern Med* 1999; 159:445–453
 - 44 Goldhaber SZ, Hennekens CH, Evans DA, et al. Factors associated with correct antemortem diagnosis of major pulmonary embolism. *Am J Med* 1982; 73:822–826
 - 45 Rubinstein I, Murray D, Hoffstein V. Fatal pulmonary emboli in hospitalized patients: an autopsy study. *Arch Intern Med* 1988; 148:1425–1426
 - 46 Karwinski B, Svendsen E. Comparison of clinical and post-mortem diagnosis of pulmonary embolism. *J Clin Pathol* 1989; 42:135–139
 - 47 Morgenthaler TI, Ryu JH. Clinical characteristics of fatal pulmonary embolism in a referral hospital. *Mayo Clin Proc* 1995; 70:417–424
 - 48 Ryu JH, Olson EJ, Pellikka PA. Clinical recognition of pulmonary embolism: problems of unrecognized and asymptomatic cases. *Mayo Clin Proc* 1998; 73:873–879
 - 49 Wen DY, Hall WA. Complications of subcutaneous low-dose heparin therapy in neurosurgical patients. *Surg Neurol* 1998; 50:521–525
 - 50 International Multicentre Trial. Prevention of fatal pulmonary embolism by low doses of heparin. *Lancet* 1975; 2:45–51
 - 51 White RH, Romano PS, Zhou H, et al. Incidence and time course of thromboembolic outcomes following total hip or knee arthroplasty. *Arch Intern Med* 1998; 158:1525–1531
 - 52 Eriksson BI, Lassen MR, the PENTAsaccharide in HIp-FRActure Surgery Plus (PENTHIFRA Plus) Investigators. Duration of prophylaxis against venous thromboembolism with fondaparinux after hip fracture surgery: a multicenter, randomized, placebo-controlled, double-blind study. *Arch Intern Med* 2003; 163:1337–1342
 - 53 Franzeck UK, Schalch I, Jager KA, et al. Prospective 12-year follow-up study of clinical and hemodynamic sequelae of deep vein thrombosis in low-risk patients (Zurich Study). *Circulation* 1996; 93:74–79
 - 54 Prandoni P, Lensing AW, Cogo A, et al. The long-term clinical course of acute deep venous thrombosis. *Ann Intern Med* 1996; 125:1–7
 - 55 Becker J, Borgstrom S, Saltzman GF. Occurrence and course of thrombosis following prostatectomy: a phlebographic investigation. *Acta Radiol Diagn (Stockh)* 1970; 10:513–533
 - 56 Lindner DJ, Edwards JM, Phinney ES, et al. Long-term hemodynamic and clinical sequelae of lower extremity deep vein thrombosis. *J Vasc Surg* 1986; 4:436–442
 - 57 Bergqvist D, Jendteg S, Johansen L, et al. Cost of long-term complications of deep venous thrombosis of the lower extremities: an analysis of a defined patient population in Sweden. *Ann Intern Med* 1997; 126:454–457
 - 58 Heit JA, Rooke TW, Silverstein MD, et al. Trends in the incidence of venous stasis syndrome and venous ulcer: a 25-year population-based study. *J Vasc Surg* 2001; 33:1022–1027
 - 59 Kahn SR, Hirsch A, Shrier I. Effect of postthrombotic syndrome on health-related quality of life after deep venous thrombosis. *Arch Intern Med* 2002; 162:1144–1148
 - 60 Caprini JA, Botteman MF, Stephens JM, et al. Economic burden of long-term complications of deep vein thrombosis after total hip replacement surgery in the United States. *Value Health* 2003; 6:59–74
 - 61 Paiement GD, Wessinger SJ, Harris WH. Cost-effectiveness of prophylaxis in total hip replacement. *Am J Surg* 1991; 161:519–524
 - 62 Geerts WH, Code KI, Jay RM, et al. A prospective study of venous thromboembolism after major trauma. *N Engl J Med* 1994; 331:1601–1606
 - 63 Meyer CS, Blebea J, Davis K, et al. Surveillance venous scans for deep venous thrombosis in multiple trauma patients. *Ann Vasc Surg* 1995; 9:109–114
 - 64 Robinson KS, Anderson DR, Gross M, et al. Ultrasonographic screening before hospital discharge for deep venous thrombosis after arthroplasty: the Post-Arthroplasty Screening Study; a randomized, controlled trial. *Ann Intern Med* 1997; 127:439–445
 - 65 Leclerc JR, Gent M, Hirsh J, et al. The incidence of symptomatic venous thromboembolism during and after prophylaxis with enoxaparin: a multi-institutional cohort study of patients who underwent hip or knee arthroplasty. *Arch Intern Med* 1998; 158:873–878
 - 66 Dearborn JT, Hu SS, Tribus CB, et al. Thromboembolic complications after major thoracolumbar spine surgery. *Spine* 1999; 24:1471–1476
 - 67 Cipolle MD, Wojcik R, Seislove E, et al. The role of surveillance duplex scanning in preventing venous thromboembolism in trauma patients. *J Trauma* 2002; 52:453–462
 - 68 Sevitt S, Gallagher NG. Prevention of venous thrombosis and pulmonary embolism in injured patients: a trial of anticoagulant prophylaxis with phenindione in middle-aged and elderly patients with fractured necks of femur. *Lancet* 1959; ii:981–989
 - 69 Sagar S, Massey J, Sanderson JM. Low-dose heparin prophylaxis against fatal pulmonary embolism. *BMJ* 1975; 2:257–259
 - 70 Halkin H, Goldberg J, Modan M, et al. Reduction of mortality in general medical in-patients by low-dose heparin prophylaxis. *Ann Intern Med* 1982; 96:561–565
 - 71 Collins R, Scrimgeour A, Yusuf S, et al. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin: overview of results of randomized trials in general, orthopedic, and urologic surgery. *N Engl J Med* 1988; 318:1162–1173
 - 72 Shojania KG, Duncan BW, McDonald KM, et al. Making health care safer: a critical analysis of patient safety practices. Evidence Report/Technology Assessment No. 43 (Prepared by the University of California at San Francisco-

- Stanford Evidence-based Practice Center under Contract No. 290-97-0013). Rockville, MD: Agency for Healthcare Research and Quality, July 2001; 332-346; AHRQ Publication No. 01-E058. Available at www.ahrq.gov/clinic/pt-safety/. Accessed January 3, 2002
- 73 Bergqvist D, Lindgren B, Matzsch T. Cost-effectiveness of preventing postoperative deep vein thrombosis. In: Hull RD, Pineo GF, eds. *Disorders of thrombosis*. Philadelphia, PA: WB Saunders, 1996; 228-233
 - 74 Mamdani MM, Weingarten CM, Stevenson JG. Thromboembolic prophylaxis in moderate-risk patients undergoing elective abdominal surgery: decision and cost-effectiveness analyses. *Pharmacotherapy* 1996; 16:1111-1127
 - 75 Bick RL. Proficient and cost-effective approaches for the prevention and treatment of venous thrombosis and thromboembolism. *Drugs* 2000; 60:575-595
 - 76 van Ooijen B. Subcutaneous heparin and postoperative wound hematomas: a prospective, double-blind, randomized study. *Arch Surg* 1986; 121:937-940
 - 77 Clagett GP, Reisch JS. Prevention of venous thromboembolism in general surgical patients: results of meta-analysis. *Ann Surg* 1988; 208:227-240
 - 78 Nurmohamed MT, Rosendaal FR, Buller HR, et al. Low-molecular-weight heparin versus standard heparin in general and orthopaedic surgery: a meta-analysis. *Lancet* 1992; 340:152-156
 - 79 Kakkar VV, Cohen AT, Edmonson RA, et al. Low molecular weight versus standard heparin for prevention of venous thromboembolism after major abdominal surgery. *Lancet* 1993; 341:259-265
 - 80 Jorgensen LN, Wille-Jorgensen P, Hauch O. Prophylaxis of postoperative thromboembolism with low molecular weight heparins. *Br J Surg* 1993; 80:689-704
 - 81 Koch A, Bouges S, Ziegler S, et al. Low molecular weight heparin and unfractionated heparin in thrombosis prophylaxis after major surgical intervention: update of previous meta-analyses. *Br J Surg* 1997; 84:750-759
 - 82 Koch A, Ziegler S, Breitschwerdt H, et al. Low molecular weight heparin and unfractionated heparin in thrombosis prophylaxis: meta-analysis based on original patient data. *Thromb Res* 2001; 102:295-309
 - 83 Thomas DP. Does low molecular weight heparin cause less bleeding? *Thromb Haemost* 1997; 78:1422-1425
 - 84 Oster G, Tuden RL, Colditz GA. A cost-effectiveness analysis of prophylaxis against deep-vein thrombosis in major orthopedic surgery. *JAMA* 1987; 257:203-208
 - 85 Brandjes DP, ten Cate JW, Buller HR. Pre-surgical identification of the patient at risk for developing venous thromboembolism post-operatively. *Acta Chir Scand Suppl* 1990; 556:18-21
 - 86 Caprini JA, Arcelus JI, Hasty JH, et al. Clinical assessment of venous thromboembolic risk in surgical patients. *Semin Thromb Hemost* 1991; 17(suppl):304-312
 - 87 Thromboembolic Risk Factors (THRIFT) Consensus Group. Risk of and prophylaxis for venous thromboembolism in hospital patients. *BMJ* 1992; 305:567-574
 - 88 Greenfield LJ, Proctor MC, Rodriguez JL, et al. Posttrauma thromboembolism prophylaxis. *J Trauma* 1997; 42:100-103
 - 89 Nicolaidis AN, Bergqvist D, Hull RD, et al. Prevention of venous thromboembolism: International consensus statement. *Int Angiol* 1997; 16:3-38
 - 90 Ageno W. Applying risk assessment models in general surgery: overview of our clinical experience. *Blood Coagul Fibrinolysis* 1999; 10(suppl):S71-S78
 - 91 Samama MM. Applying risk assessment models in general surgery: effective risk stratification. *Blood Coagul Fibrinolysis* 1999; 10(suppl):S79-S84
 - 92 Cohen A, Alikhan R, Arcelus J, et al. A risk assessment model for identifying medical patients who should receive thromboprophylaxis [abstract]. *J Thromb Haemost* 2003; 1(suppl):OC437
 - 93 Samama MM, Dahl OE, Mismetti P, et al. Individualizing the risk of venous thromboembolism in medical and surgical patients: development of the decision matrix for VTE prophylaxis [abstract]. *J Thromb Haemost* 2003; 1(suppl):OC436
 - 94 Lassen MR, Borris LC, Backs S, et al. Clinical limitations of risk assessment models. *Blood Coagul Fibrinolysis* 1999; 10(suppl):S45-S51
 - 95 Kearon C. Noninvasive diagnosis of deep vein thrombosis in postoperative patients. *Semin Thromb Haemost* 2001; 27:3-8
 - 96 Kakkar VV. The diagnosis of deep vein thrombosis using the ¹²⁵I fibrinogen test. *Arch Surg* 1972; 104:152-159
 - 97 Moskovitz PA, Ellenberg SS, Feffer HL, et al. Low-dose heparin for prevention of venous thromboembolism in total hip arthroplasty and surgical repair of hip fractures. *J Bone Joint Surg Am* 1978; 60:1065-1070
 - 98 Fauno P, Suomalainen O, Bergqvist D, et al. The use of fibrinogen uptake test in screening for deep vein thrombosis in patients with hip fracture. *Thromb Res* 1990; 60:185-190
 - 99 Lensing AW, Hirsh J. ¹²⁵I-fibrinogen leg scanning: reassessment of its role for the diagnosis of venous thrombosis in post-operative patients. *Thromb Haemost* 1993; 69:2-7
 - 100 Agnelli G, Radicchia S, Nenci GG. Diagnosis of deep vein thrombosis in asymptomatic high-risk patients. *Haemostasis* 1995; 25:40-48
 - 101 Bergqvist D, Burmark US, Flordal PA, et al. Low molecular weight heparin started before surgery as prophylaxis against deep vein thrombosis: 2500 versus 5000 XaI units in 2070 patients. *Br J Surg* 1995; 82:496-501
 - 102 Nurmohamed MT, Verhaeghe R, Haas S, et al. A comparative trial of a low molecular weight heparin (enoxaparin) versus standard heparin for the prophylaxis of postoperative deep vein thrombosis in general surgery. *Am J Surg* 1995; 169:567-571
 - 103 Flordal PA, Bergqvist D, Ljungstrom KG, et al. Clinical relevance of the fibrinogen uptake test in patients undergoing elective general abdominal surgery: relation to major thromboembolism and mortality. *Thromb Res* 1995; 80:491-497
 - 104 Paiement G, Wessinger SJ, Waltman AC, et al. Surveillance of deep vein thrombosis in asymptomatic total hip replacement patients: impedance plethysmography and fibrinogen scanning versus roentgenographic phlebography. *Am J Surg* 1988; 155:400-404
 - 105 Agnelli G, Cosmi B, Ranucci V, et al. Impedance plethysmography in the diagnosis of asymptomatic deep vein thrombosis in hip surgery: a venography-controlled study. *Arch Intern Med* 1991; 151:2167-2171
 - 106 Kearon C, Julian JA, Newman TE, et al. Noninvasive diagnosis of deep venous thrombosis. *Ann Intern Med* 1998; 128:663-677
 - 107 Kahn SR, Joseph L, Grover SA, et al. A randomized management study of impedance plethysmography vs. contrast venography in patients with a first episode of clinically suspected deep vein thrombosis. *Thromb Res* 2001; 102:15-24
 - 108 Rabinov K, Paulin S. Roentgen diagnosis of venous thrombosis in the leg. *Arch Surg* 1972; 104:134-144
 - 109 Picolet H, Leizorovicz A, Revel D, et al. Reliability of phlebography in the assessment of venous thrombosis in a clinical trial. *Haemostasis* 1990; 20:362-367
 - 110 Couson F, Bounameaux C, Didier D, et al. Influence of

- variability of interpretation of contrast venography for screening of postoperative deep venous thrombosis on the results of a thromboprophylactic study. *Thromb Haemost* 1993; 70:573–575
- 111 Kalebo P, Ekman S, Lindbratt S, et al. Percentage of inadequate phlebograms and observer agreement in thromboprophylactic multicenter trials using standardized methodology and central assessment. *Thromb Haemost* 1996; 76:893–896
 - 112 Leizorovicz A, Kassai B, Becker F, et al. The assessment of deep vein thromboses for therapeutic trials. *Angiology* 2003; 54:19–24
 - 113 Garino JP, Lotke PA, Kitziger KJ, et al. Deep venous thrombosis after total joint arthroplasty: the role of compression ultrasonography and the importance of the experience of the technician. *J Bone Joint Surg Am* 1996; 78:1359–1365
 - 114 Davidson BL, Elliott CG, Lensing AW, et al. Low accuracy of color Doppler ultrasound in the detection of proximal leg vein thrombosis in asymptomatic high-risk patients. *Ann Intern Med* 1992; 117:735–738
 - 115 Grady-Benson JC, Oishi CS, Hanson PB, et al. Postoperative surveillance for deep venous thrombosis with duplex ultrasonography after total knee arthroplasty. *J Bone Joint Surg Am* 1994; 76:1649–1657
 - 116 Wells PS, Lensing AW, Davidson BL, et al. Accuracy of ultrasound for the diagnosis of deep venous thrombosis in asymptomatic patients after orthopedic surgery: a meta-analysis. *Ann Intern Med* 1995; 122:47–53
 - 117 Ciccone WJ, Fox PS, Neumyer M, et al. Ultrasound surveillance for asymptomatic deep venous thrombosis after total joint replacement. *J Bone Joint Surg Am* 1998; 80:1167–1174
 - 118 Eskandari MK, Sugimoto H, Richardson T, et al. Is color-flow duplex a good diagnostic test for detection of isolated calf vein thrombosis in high-risk patients? *Angiology* 2000; 51:705–710
 - 119 Bressollette L, Nonent M, Oger E, et al. Diagnostic accuracy of compression ultrasonography for the detection of asymptomatic deep venous thrombosis in medical patients: the TADEUS project. *Thromb Haemost* 2001; 86:529–533
 - 120 Cronan JJ, Dorfman GS, Scola FH, et al. Deep venous thrombosis: US assessment using vein compression. *Radiology* 1987; 162:191–194
 - 121 Wright DJ, Shepard AD, McPharlin M, et al. Pitfalls in lower extremity venous duplex scanning. *J Vasc Surg* 1990; 11:675–679
 - 122 Kujath P, Spannagel U, Habscheid W. Incidence and prophylaxis of deep venous thrombosis in outpatients with injury of the lower limb. *Haemostasis* 1993; 23(suppl):20–26
 - 123 Rodgers A, MacMahon S. Systematic underestimation of treatment effects as a result of diagnostic test inaccuracy: Implications for the interpretation and design of thromboprophylaxis trials. *Thromb Haemost* 1995; 73:167–171
 - 124 Sonaglia F, Rossi R, Agnelli G. End points in studies on the prevention of deep vein thrombosis. *Semin Thromb Hemost* 2001; 27:41–46
 - 125 Mismetti P, Laporte-Simitsidis S, Tardy B, et al. Prevention of venous thromboembolism in internal medicine with unfractionated or low-molecular-weight heparins: a meta-analysis of randomised clinical trials. *Thromb Haemost* 2000; 83:14–19
 - 126 Coe NP, Collins RE, Klein LA, et al. Prevention of deep vein thrombosis in urological patients: a controlled, randomized trial of low-dose heparin and external pneumatic compression boots. *Surgery* 1978; 83:230–234
 - 127 Turpie AG, Hirsh J, Gent M, et al. Prevention of deep vein thrombosis in potential neurosurgical patients: a randomized trial comparing graduated compression stockings alone or graduated compression stockings plus intermittent pneumatic compression with control. *Arch Intern Med* 1989; 149:679–681
 - 128 Vanek VW. Meta-analysis of effectiveness of intermittent pneumatic compression devices with a comparison of thigh-high to knee-high sleeves. *Am Surg* 1998; 64:1050–1058
 - 129 Warwick D, Harrison J, Glew D, et al. Comparison of the use of a foot pump with the use of low-molecular-weight heparin for the prevention of deep-vein thrombosis after total hip replacement. *J Bone Joint Surg Am* 1998; 80:1158–1166
 - 130 Agu O, Hamilton G, Baker D. Graduated compression stockings in the prevention of venous thromboembolism. *Br J Surg* 1999; 86:992–1004
 - 131 Freedman KB, Brookenthal KR, Fitzgerald RH, et al. A meta-analysis of thromboembolic prophylaxis following elective total hip arthroplasty. *J Bone Joint Surg Am* 2000; 82:929–938
 - 132 Westrich GH, Haas SB, Mosca P, et al. Meta-analysis of thromboembolic prophylaxis after total knee arthroplasty. *J Bone Joint Surg Br* 2000; 82:795–800
 - 133 Amarigiri SV, Lees TA. Elastic compression stockings for prevention of deep vein thrombosis. *Cochrane Database Syst Rev* (database online). Issue 1, 2001
 - 134 Hull RD, Raskob GE, Gent M, et al. Effectiveness of intermittent pneumatic leg compression for preventing deep vein thrombosis after total hip replacement. *JAMA* 1990; 263:2313–2317
 - 135 Blanchard J, Meuwly JY, Leyvraz PF, et al. Prevention of deep-vein thrombosis after total knee replacement. randomised comparison between a low-molecular-weight heparin (nadroparin) and mechanical prophylaxis with a foot-pump system. *J Bone Joint Surg Br* 1999; 81:654–659
 - 136 Iorio A, Agnelli G. Low-molecular-weight and unfractionated heparin for prevention of venous thromboembolism in neurosurgery: a meta-analysis. *Arch Intern Med* 2000; 160:2327–2332
 - 137 Gallus A, Raman K, Darby T. Venous thrombosis after elective hip replacement—the influence of preventive intermittent calf compression and of surgical technique. *Br J Surg* 1983; 70:17–19
 - 138 Comerota AJ, Katz ML, White JV. Why does prophylaxis with external pneumatic compression for deep vein thrombosis fail? *Am J Surg* 1992; 164:265–268
 - 139 Haddad FS, Kerry RM, McEwen JA, et al. Unanticipated variations between expected and delivered pneumatic compression therapy after elective hip surgery: a possible source of variation in reported patient outcomes. *J Arthroplasty* 2001; 16:37–46
 - 140 Cornwell EE, Chang D, Velmahos G, et al. Compliance with sequential compression device prophylaxis in at-risk trauma patients: a prospective analysis. *Am Surg* 2002; 68:470–473
 - 141 Kay TW, Martin FI. Heel ulcers in patients with long-standing diabetes who wear antiembolism stockings. *Med J Aust* 1986; 145:290–291
 - 142 Heath DI, Kent SJ, Johns DL, et al. Arterial thrombosis associated with graduated pressure antiembolic stockings. *BMJ* 1987; 295:580
 - 143 Merrett ND, Hanel KC. Ischaemic complications of graduated compression stockings in the treatment of deep venous thrombosis. *Postgrad Med J* 1993; 69:232–234
 - 144 Wille-Jørgensen P. Prophylaxis of postoperative thromboembolism with a combination of heparin and graduated compression stockings. *Int Angiol* 1996; 15(suppl):15–20
 - 145 Kalodiiki EP, Hoppensteadt DA, Nicolaidis AN, et al. Deep venous thrombosis prophylaxis with low molecular weight

- heparin and elastic compression in patients having total hip replacement: a randomised controlled trial. *Int Angiol* 1996; 15:162–168
- 146 Ramos R, Salem BI, De Pawlikowski MP, et al. The efficacy of pneumatic compression stockings in the prevention of pulmonary embolism after cardiac surgery. *Chest* 1996; 109:82–85
 - 147 Best AJ, Williams S, Crozier A, et al. Graded compression stockings in elective orthopaedic surgery: an assessment of the *in vivo* performance of commercially available stockings in patients having hip and knee arthroplasty. *J Bone Joint Surg Br* 2000; 82:116–118
 - 148 Patrono C, Collier B, Dalen JE, et al. Platelet-active drugs: the relationships among dose, effectiveness, and side effects. *Chest* 2001; 119(suppl):39S–63S
 - 149 Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy: III. Reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. *BMJ* 1994; 308:235–246
 - 150 Lotke PA, Palevsky H, Keenan AM, et al. Aspirin and warfarin for thromboembolic disease after total joint arthroplasty. *Clin Orthop* 1996; 324:251–258
 - 151 Pulmonary Embolism Prevention (PEP) Trial Collaborative Group. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) Trial. *Lancet* 2000; 355:1295–1302
 - 152 Cohen AT, Skinner JA, Kakkar VV. Antiplatelet treatment for thromboprophylaxis: a step forward or backwards? *BMJ* 1994; 309:1213–1215
 - 153 Butterfield WJ, Hicks BH, Ambler AR, et al. Effect of aspirin on postoperative venous thrombosis. *Lancet* 1972; 2:441–445
 - 154 McKenna R, Galante J, Bachmann F, et al. Prevention of venous thromboembolism after total knee replacement by high-dose aspirin or intermittent calf and thigh compression. *BMJ* 1980; 280:514–517
 - 155 Powers PJ, Gent M, Jay RM, et al. A randomized trial of less intense postoperative warfarin or aspirin therapy in the prevention of venous thromboembolism after surgery for fractured hip. *Arch Intern Med* 1989; 149:771–774
 - 156 Westrich GH, Sculco TP. Prophylaxis against deep venous thrombosis after total knee arthroplasty: pneumatic planter compression and aspirin compared with aspirin alone. *J Bone Joint Surg Am* 1996; 78:826–834
 - 157 Graor RA, Stewart JH, Lotke PA, et al. RD heparin (ardeparin sodium) vs aspirin to prevent deep venous thrombosis after hip or knee replacement surgery [abstract]. *Chest* 1992; 102:118S
 - 158 Gent M, Hirsh J, Ginsberg JS, et al. Low-molecular-weight heparinoid organ is more effective than aspirin in the prevention of venous thromboembolism after surgery for hip fracture. *Circulation* 1996; 93:80–84
 - 159 Cestac P, Bagheri H, Lapeyre-Mestre M, et al. Utilisation and safety of low molecular weight heparins: prospective observational study in medical inpatients. *Drug Saf* 2003; 26:197–207
 - 160 Turpie A, Bauer K, Eriksson B, et al. Efficacy and safety of fondaparinux in major orthopedic surgery according to the timing of its first administration. *Thromb Haemost* 2003; 90:364–366
 - 161 Nagge J, Crowther M, Hirsh J. Is impaired renal function a contraindication to the use of low-molecular-weight heparin? *Arch Intern Med* 2002; 162:2605–2609
 - 162 Rodgers A, Walker N, Schug S, et al. Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. *BMJ* 2000; 321:1493–1497
 - 163 Beattie WS, Badner NH, Choi P. Epidural analgesia reduces postoperative myocardial infarction: a meta-analysis. *Anesth Analg* 2001; 93:853–858
 - 164 Wu CL, Naqibuddin M, Fleisher LA. Measurement of patient satisfaction as an outcome of regional anesthesia and analgesia: a systematic review. *Reg Anesth Pain Med* 2001; 26:196–208
 - 165 Carli F, Mayo N, Klubien K, et al. Epidural analgesia enhances functional exercise capacity and health-related quality of life after colonic surgery: results of a randomized trial. *Anesthesiology* 2002; 97:540–549
 - 166 Dolin SJ, Cashman JN, Bland JM. Effectiveness of acute postoperative pain management: I. Evidence from published data. *Br J Anaesth* 2002; 89:409–423
 - 167 Rigg JR, Jamrozik K, Myles PS, et al. Epidural anaesthesia and analgesia and outcome of major surgery: a randomised trial. *Lancet* 2002; 359:1276–1282
 - 168 Vandermeulen EP, Van Aken H, Vermeylen J. Anticoagulants and spinal-epidural anesthesia. *Anesth Analg* 1994; 79:1165–1177
 - 169 Horlocker TT, Wedel DJ, Benzon H, et al. Regional anesthesia in the anticoagulated patient: defining the risks (The Second ASRA Consensus Conference on Neuraxial Anesthesia and Anticoagulation). *Reg Anesth Pain Med* 2003; 28:172–197
 - 170 Lumpkin MM. FDA public health advisory. *Anesthesiology* 1998; 88:27A–28A
 - 171 Wysowski DK, Talarico L, Bacsanyi J, et al. Spinal and epidural hematoma and low-molecular-weight heparin [letter]. *N Engl J Med* 1998; 338:1774–1775
 - 172 Horlocker TT, Heit JA. Low molecular weight heparin: biochemistry, pharmacology, perioperative prophylaxis regimens, and guidelines for regional anesthetic management. *Anesth Analg* 1997; 85:874–885
 - 173 Horlocker TT, Wedel DJ. Neuraxial block and low-molecular-weight heparin: balancing perioperative analgesia and thromboprophylaxis. *Reg Anesth Pain Med* 1998; 23:164–177
 - 174 Pezzuoli G, Neri Serneri GG, Settembrini P, et al. Prophylaxis of fatal pulmonary embolism in general surgery using low-molecular-weight heparin Cy 216: a multicentre, double-blind, randomized, controlled, clinical trial versus placebo (STEP). *Int Surg* 1989; 74:205–210
 - 175 Nicolaidis A, Irving D, Pretzell M, et al. The risk of deep-vein thrombosis in surgical patients. *Br J Surg* 1973; 60:312
 - 176 Wille-Jorgensen P, Ott P. Predicting failure of low-dose heparin in general surgical procedures. *Surg Gynecol Obstet* 1990; 171:126–130
 - 177 Huber O, Bounameaux H, Borst F, et al. Postoperative pulmonary embolism after hospital discharge: an underestimated risk. *Arch Surg* 1992; 127:310–313
 - 178 Flordal PA, Bergqvist D, Burmark US, et al. Risk factors for major thromboembolism and bleeding tendency after elective general surgical operations. *Eur J Surg* 1996; 162:783–789
 - 179 Riber C, Alstrup N, Nymann T, et al. Postoperative thromboembolism after day-case herniorrhaphy. *Br J Surg* 1996; 83:420–421
 - 180 Hendolin H, Mattila MAK, Poikolainen E. The effect of lumbar epidural analgesia on the development of deep vein thrombosis of the legs after open prostatectomy. *Acta Chir Scand* 1981; 147:425–429
 - 181 Prins MH, Hirsh J. A comparison of general anesthesia and regional anesthesia as a risk factor for deep vein thrombosis

- following hip surgery: a critical review. *Thromb Haemost* 1990; 64:497–500
- 182 Lassen MR, Eriksson BI, Bauer KA, et al. Pentasaccharide (fondaparinux, Arixtra) versus enoxaparin for the prevention of venous thromboembolism (VTE) in major orthopedic surgery: subgroup analyses on efficacy [abstract]. *Blood* 2001; 98:266a
 - 183 Kakkar VV, Murray WJ. Efficacy and safety of low-molecular-weight heparin (CY216) in preventing postoperative venous thrombo-embolism: a co-operative study. *Br J Surg* 1985; 72:786–791
 - 184 Bergqvist D, Burmark US, Frisell J, et al. Low molecular weight heparin once daily compared with conventional low-dose heparin twice daily: a prospective double-blind multicentre trial on prevention of postoperative thrombosis. *Br J Surg* 1986; 73:204–208
 - 185 Bergqvist D, Matzsch T, Burmark US, et al. Low molecular weight heparin given the evening before surgery compared with conventional low-dose heparin in prevention of thrombosis. *Br J Surg* 1988; 75:888–891
 - 186 Caen JP. A randomized double-blind study between a low molecular weight heparin Kabi 2165 and standard heparin in the prevention of deep vein thrombosis in general surgery: a French multicenter trial. *Thromb Haemost* 1988; 59:216–220
 - 187 European Fraxiparin Study (EFS) Group. Comparison of a low molecular weight heparin and unfractionated heparin for the prevention of deep vein thrombosis in patients undergoing abdominal surgery. *Br J Surg* 1988; 75:1058–1063
 - 188 Samama MM, Bernard P, Bonnardot JP, et al. Low molecular weight heparin compared with unfractionated heparin in prevention of postoperative thrombosis. *Br J Surg* 1988; 75:128–131
 - 189 Hartl P, Brucke P, Dienstl E, et al. Prophylaxis of thromboembolism in general surgery: comparison between standard heparin and Fragmin. *Thromb Res* 1990; 57:577–584
 - 190 Liezorovicz A, Picolet H, Peyrieux JC, et al. Prevention of perioperative deep vein thrombosis in general surgery: a multicentre double blind study comparing two doses of Logiparin and standard heparin. *Br J Surg* 1991; 78:412–416
 - 191 Wolf H, Encke A, Haas S, et al. Comparison of the efficacy and safety of Sandoz low molecular weight heparin and unfractionated heparin: interim analysis of a multicenter trial. *Semin Thromb Haemost* 1991; 17:343–346
 - 192 Koppenhagen K, Adolf J, Matthes M, et al. Low molecular weight heparin and prevention of postoperative thrombosis in abdominal surgery. *Thromb Haemost* 1992; 67:627–630
 - 193 Boneu B. An international multicentre study: clivarin in the prevention of venous thromboembolism in patients undergoing general surgery; report of the International Clivarin Assessment Group. *Blood Coagul Fibrinolysis* 1993; 4(suppl):S21–S22
 - 194 Gazzaniga GM, Angelini G, Pastorino G, et al. Enoxaparin in the prevention of deep venous thrombosis after major surgery: multicentric study. *Int Surg* 1993; 78:271–275
 - 195 ENOXACAN Study Group. Efficacy and safety of enoxaparin versus unfractionated heparin for prevention of deep vein thrombosis in elective cancer surgery: a double-blind randomized multicentre trial with venographic assessment. *Br J Surg* 1997; 84:1099–1103
 - 196 Kakkar VV, Boeckl O, Boneu B, et al. Efficacy and safety of a low-molecular-weight heparin and standard unfractionated heparin for prophylaxis of postoperative venous thromboembolism: European multicenter trial. *World J Surg* 1997; 21:2–8
 - 197 Haas SK, Wolf H, Encke A, et al. Prevention of fatal postoperative pulmonary embolism by low molecular weight heparin: a double blind comparison of certoparin and unfractionated heparin [abstract]. *Thromb Haemost* 1999; 82(suppl):491
 - 198 Egger B, Schmid SW, Naef M, et al. Efficacy and safety of weight-adapted nadroparin calcium vs. heparin sodium in prevention of clinically evident thromboembolic complications in 1,190 general surgical patients. *Dig Surg* 2000; 17:602–609
 - 199 McLeod RS, Geerts WH, Sniderman KW, et al. Subcutaneous heparin versus low-molecular-weight heparin as thromboprophylaxis in patients undergoing colorectal surgery: results of the Canadian Colorectal DVT Prophylaxis Trial: a randomized, double-blind trial. *Ann Surg* 2001; 233:438–444
 - 200 Bounameaux H, Huber O, Khabiri E, et al. Unexpectedly high rate of phlebographic deep venous thrombosis following elective general abdominal surgery among patients given prophylaxis with low-molecular-weight heparin. *Arch Surg* 1993; 128:326–328
 - 201 Kakkar VV, Kakkar S, Sanderson RM, et al. Efficacy and safety of two regimens of low molecular weight heparin fragment (Fragmin) in preventing postoperative venous thrombolism. *Haemostasis* 1986; 16(suppl):19–24
 - 202 Haas S, Flosbach CW. Prevention of postoperative thromboembolism with enoxaparin in general surgery: a German multicenter trial. *Semin Thromb Haemost* 1993; 19(suppl): 164–173
 - 203 Bjerkeset O, Larsen S, Reiertsen O. Evaluation of enoxaparin given before and after operation to prevent venous thromboembolism during digestive surgery: play-the-winner designed study. *World J Surg* 1997; 21:584–588
 - 204 Lausen I, Jensen R, Jorgensen LN, et al. Incidence and prevention of deep venous thrombosis occurring late after general surgery: randomised controlled study of prolonged thromboprophylaxis. *Eur J Surg* 1998; 164:657–663
 - 205 Bergqvist D, Agnelli G, Cohen AT, et al. Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. *N Engl J Med* 2002; 346:975–980
 - 206 Rasmussen MS. Preventing thromboembolic complications in cancer patients after surgery: a role for prolonged thromboprophylaxis. *Cancer Treat Rev* 2002; 28:141–144
 - 207 Leizorovicz A, Haugh MC, Chapuis FR, et al. Low molecular weight heparin in prevention of perioperative thrombosis. *BMJ* 1992; 305:913–920
 - 208 Palmer AJ, Schramm W, Kirchhof B, et al. Low molecular weight heparin and unfractionated heparin for prevention of thrombo-embolism in general surgery: a meta-analysis of randomised clinical trials. *Haemostasis* 1997; 27:65–74
 - 209 Breddin HK. Low molecular weight heparins in the prevention of deep-vein thrombosis in general surgery. *Semin Thromb Haemost* 1999; 25(suppl):83–89
 - 210 Wille-Jorgensen P, Rasmussen MS, Andersen BR, et al. Heparins and mechanical methods for thromboprophylaxis in colorectal surgery. *Cochrane Database Syst Rev* (database online). Issue 1, 2003
 - 211 Wicky J, Couson F, Ambrosetti P, et al. Postoperative deep venous thrombosis (DVT) and low-molecular weight heparin (LMWH) type and dosage. *Thromb Haemost* 1993; 69:402–403
 - 212 Wiig JN, Solhaug JH, Bilberg T, et al. Prophylaxis of venographically diagnosed deep vein thrombosis in gastrointestinal surgery: multicentre trials 20 mg and 40 mg enoxaparin versus dextran. *Eur J Surg* 1995; 161:663–668
 - 213 Warkentin TE, Levine MN, Hirsh J, et al. Heparin-induced thrombocytopenia in patients treated with low-molecular-

- weight heparin or unfractionated heparin. *N Engl J Med* 1995; 332:1330–1335
- 214 Agnelli G, Bergqvist D, Cohen A, et al. Randomized double-blind study to compare the efficacy and safety of postoperative fondaparinux (Arixtra) and preoperative dalteparin in the prevention of venous thromboembolism after high-risk abdominal surgery: the PEGASUS Study [abstract]. *Blood* 2003; 102:15a
 - 215 Wells PS, Lensing AWA, Hirsh J. Graduated compression stockings in the prevention of postoperative venous thromboembolism: a meta-analysis. *Arch Intern Med* 1994; 154: 67–72
 - 216 Moser G, Krahenbuhl B, Barroussel R, et al. Mechanical versus pharmacologic prevention of deep venous thrombosis. *Surg Gynecol Obstet* 1981; 152:448–450
 - 217 Nicolaides AN, Miles C, Hoare M, et al. Intermittent sequential pneumatic compression of the legs and thromboembolism-deterrent stockings in the prevention of postoperative deep venous thrombosis. *Surgery* 1983; 94:21–25
 - 218 Scurr JH, Coleridge-Smith PD, Hasty JH. Regimen for improved effectiveness of intermittent pneumatic compression in deep venous thrombosis prophylaxis. *Surgery* 1987; 102:816–820
 - 219 Butson AR. Intermittent pneumatic calf compression for prevention of deep venous thrombosis in general abdominal surgery. *Am J Surg* 1981; 142:525–527
 - 220 Heit JA, Silverstein MD, Mohr DN, et al. The epidemiology of venous thromboembolism in the community. *Thromb Haemost* 2001; 86:452–463
 - 221 Scurr JH, Coleridge-Smith PD, Hasty JH. Deep venous thrombosis: a continuing problem. *BMJ* 1988; 297:28
 - 222 Rasmussen MS, Willie-Jorgensen P, Jorgensen LN, et al. Prolonged thromboprophylaxis with low molecular weight heparin (dalteparin) following major abdominal surgery for malignancy [abstract]. *Blood* 2003; 102:56a
 - 223 Dutch Bypass Oral Anticoagulants or Aspirin (BOA) Study Group. Efficacy of oral anticoagulants compared with aspirin after infrainguinal bypass surgery (The Dutch Bypass Oral Anticoagulants or Aspirin Study): a randomised trial. *Lancet* 2000; 355:346–351
 - 224 Jackson MR, Clagett GP. Antithrombotic therapy in peripheral arterial occlusive disease. *Chest* 2001; 119(suppl):283S–299S
 - 225 Jackson MR, Johnson WC, Williford WO, et al. The effect of anticoagulation therapy and graft selection on the ischemic consequences of femoropopliteal bypass graft occlusion: results from a multicenter randomized clinical trial. *J Vasc Surg* 2002; 35:292–298
 - 226 Prandoni P, Bilora F, Marchiori A, et al. An association between atherosclerosis and venous thrombosis. *N Engl J Med* 2003; 348:1435–1441
 - 227 Angelides NS, Nicolaides AN, Fernandes J, et al. Deep venous thrombosis in patients having aorto-iliac reconstruction. *Br J Surg* 1977; 64:517–518
 - 228 Belch JFF, Lowe GDO, Pollock JG, et al. Low dose heparin in the prevention of deep-vein thrombosis after aortic bifurcation graft surgery. *Thromb Haemost* 1979; 42:1429–1433
 - 229 Cass AJ, Jennings SA, Greenhalgh RM. Leg swelling after aortic surgery. *Int Angiol* 1986; 5:207–208
 - 230 Hollyoak M, Woodruff P, Muller M, et al. Deep venous thrombosis in postoperative vascular surgical patients: a frequent finding without prophylaxis. *J Vasc Surg* 2001; 34:656–660
 - 231 Santiani B, Kuhns M, Evans WE. Deep venous thrombosis following operations upon the abdominal aorta. *Surg Gynecol Obstet* 1980; 151:241–245
 - 232 Reilly MK, McCabe CJ, Abbott WM, et al. Deep venous thrombophlebitis following aortoiliac reconstructive surgery. *Arch Surg* 1982; 117:1210–1211
 - 233 Hamer JD. Investigation of oedema of the lower limb following successful femoropopliteal by-pass surgery: the role of phlebography in demonstrating venous thrombosis. *Br J Surg* 1972; 59:979–982
 - 234 Porter JM, Lindell TD, Lakin PC. Leg edema following femoropopliteal autogenous vein bypass. *Arch Surg* 1972; 105:883–888
 - 235 Olin JW, Graor RA, O'Hara P et al. The incidence of deep venous thrombosis in patients undergoing abdominal aortic aneurysm resection. *J Vasc Surg* 1993; 18:1037–1041
 - 236 Killewich LA, Aswad MA, Sandager GP, et al. A randomized, prospective trial of deep venous thrombosis prophylaxis in aortic surgery. *Arch Surg* 1997; 132:499–504
 - 237 Fletcher JP, Batiste P. Incidence of deep vein thrombosis following vascular surgery. *Int Angiol* 1997; 16:65–68
 - 238 Farkas JC, Chapuis C, Combe S, et al. A randomised controlled trial of a low-molecular-weight heparin (enoxaparin) to prevent deep-vein thrombosis in patients undergoing vascular surgery. *Eur J Vasc Surg* 1993; 7:554–560
 - 239 Saarinen J, Sisto T, Laurikka J, et al. The incidence of postoperative deep vein thrombosis in vascular procedures: FINNVASC Study Group. *Vasa* 1995; 24:126–129
 - 240 Libertiny G, Hands L. Deep venous thrombosis in peripheral vascular disease. *Br J Surg* 1999; 86:907–910
 - 241 Passman MA, Farber MA, Marston WA, et al. Prospective screening for postoperative deep venous thrombosis in patients undergoing infrainguinal revascularization. *J Vasc Surg* 2000; 32:669–675
 - 242 Eagleton MJ, Grigoryants V, Peterson DA, et al. Endovascular treatment of abdominal aortic aneurysm is associated with a low incidence of deep venous thrombosis. *J Vasc Surg* 2002; 36:912–916
 - 243 Spebar MJ, Collins GJ, Rich NM, et al. Perioperative heparin prophylaxis of deep venous thrombosis in patients with peripheral vascular disease. *Am J Surg* 1981; 142:649–650
 - 244 Greer IA. Epidemiology, risk factors and prophylaxis of venous thrombo-embolism in obstetrics and gynaecology. *Baillieres Clin Obstet Gynaecol* 1997; 11:403–430
 - 245 Heilmann L, von Tempelhoff GF, Schneider D. Prevention of thrombosis prophylaxis in gynecologic malignancy. *Clin Appl Thromb Hemost* 1998; 4:153–159
 - 246 Clarke-Pearson DL, DeLong ER, Synan IS, et al. Variables associated with postoperative deep venous thrombosis: a prospective study of 411 gynecology patients and creation of a prognostic model. *Obstet Gynecol* 1987; 69:146–150
 - 247 Clarke-Pearson DL, Dodge RK, Synan I, et al. Venous thromboembolism prophylaxis: patients at high risk to fail intermittent pneumatic compression. *Obstet Gynecol* 2003; 101:157–163
 - 248 Heilmann L, von Tempelhoff GF, Kirkpatrick C, et al. Comparison of unfractionated versus low molecular weight heparin for deep vein thrombosis prophylaxis during breast and pelvic cancer surgery: efficacy, safety, and follow-up. *Clin Appl Thromb Hemost* 1998; 4:268–273
 - 249 Clarke-Pearson DL, Synan IS, Coleman RE, et al. The natural history of postoperative venous thromboemboli in gynecologic oncology: a prospective study of 382 patients. *Am J Obstet Gynecol* 1984; 148:1051–1054
 - 250 Macklon NS, Greer IA. Venous thromboembolic disease in obstetrics and gynaecology: the Scottish experience. *Scott Med J* 1996; 41:83–86
 - 251 Clarke-Pearson DL, Synan IS, Dodge R, et al. A randomized trial of low-dose heparin and intermittent pneumatic calf

- compression for the prevention of deep venous thrombosis after gynecologic oncology surgery. *Am J Obstet Gynecol* 1993; 168:1146–1154
- 252 Urlep-Salinovic V, Jelatancev B, Gorisek B. Low doses of heparin and heparin dihydroderivative in post-operative thromboprophylaxis in gynaecological patients. *Thromb Haemost* 1994; 72:16–20
- 253 Ward B, Pradhan S. Comparison of low molecular weight heparin (Fragmin) with sodium heparin for prophylaxis against postoperative thrombosis in women undergoing major gynaecological surgery. *Aust N Z J Obstet Gynaecol* 1998; 38:91–92
- 254 Baykal C, Al A, Demirtas E, et al. Comparison of enoxaparin and standard heparin in gynaecologic oncologic surgery: a randomised prospective double-blind study. *Eur J Gynaecol Oncol* 2001; 22:127–130
- 255 Maxwell GL, Synan I, Dodge R, et al. Pneumatic compression versus low molecular weight heparin in gynecologic oncology surgery: a randomized trial. *Obstet Gynecol* 2001; 98:989–995
- 256 Dubuc-Lissoir J, Ehlen T, Heywood M, et al. Prevention and treatment of thromboembolic disease in gynaecological surgery. *J Soc Obstet Gynaecol Can* 1999; 21:1087–1094
- 257 ACOG Practice Bulletin. Prevention of deep vein thrombosis and pulmonary embolism. *Obstet Gynecol* 2000; 96(suppl):1–10
- 258 Clarke-Pearson DL, Creasman WT, Coleman RE, et al. Perioperative external pneumatic calf compression as thromboembolism prophylaxis in gynecologic oncology: report of a randomized controlled trial. *Obstet Gynecol* 1984; 18:226–232
- 259 Clarke-Pearson DL, Synan IS, Hinshaw WM, et al. Prevention of postoperative venous thromboembolism by external pneumatic calf compression in patients with gynecologic malignancy. *Obstet Gynecol* 1984; 63:92–98
- 260 Hohl MK, Luscher KP, Tichy J, et al. Prevention of postoperative thromboembolism by dextran 70 or low-dose heparin. *Obstet Gynecol* 1980; 55:497–500
- 261 Clarke-Pearson DL, Coleman RE, Synan IS, et al. Venous thromboembolism prophylaxis in gynecologic oncology: a prospective, controlled trial of low-dose heparin. *Am J Obstet Gynecol* 1983; 145:606–613
- 262 Clarke-Pearson DL, DeLong E, Synan IS, et al. A controlled trial of two low-dose heparin regimens for the prevention of postoperative deep vein thrombosis. *Obstet Gynecol* 1990; 75:684–689
- 263 Fricker JP, Vergnes Y, Schach R, et al. Low dose heparin versus low molecular weight heparin (Kabi 2165, Fragmin) in the prophylaxis of thromboembolic complications of abdominal oncological surgery. *Eur J Clin Invest* 1988; 18:561–567
- 264 Haas S, Flosbach CW. Antithrombotic efficacy and safety of enoxaparin in general surgery. *Eur J Surg* 1994; 571(suppl):37–43
- 265 Brenner DW, Fogle MA, Schellhammer PF. Venous thromboembolism. *J Urol* 1989; 142:1403–1411
- 266 Rossignol G, Leandri P, Gautier JR, et al. Radical retropubic prostatectomy: complications and quality of life (429 cases, 1983–1989). *Eur Urol* 1991; 19:186–191
- 267 Kibel AS, Loughlin KR. Pathogenesis and prophylaxis of postoperative thromboembolic disease in urological pelvic surgery. *J Urol* 1995; 153:1763–1774
- 268 Koch MO, Smith JA. Low molecular weight heparin and radical prostatectomy: a prospective analysis of safety and side effects. *Prostate Cancer Prostatic Dis* 1997; 1:101–104
- 269 Shekarriz B, Upadhyay J, Wood DP. Intraoperative, perioperative, and long-term complications of radical prostatectomy. *Urol Clin North Am* 2001; 28:639–653
- 270 Zincke H, Oesterling JE, Blute ML, et al. Long-term (15 years) results after radical prostatectomy for clinically localized (stage T2c or lower) prostate cancer. *J Urol* 1994; 152:1850–1857
- 271 Dillioglulugil O, Leibman BD, Leibman NS, et al. Risk factors for complications and morbidity after radical retropubic prostatectomy. *J Urol* 1997; 157:1760–1767
- 272 Heinzer H, Hammerer P, Graefen M, et al. Thromboembolic complication rate after radical retropubic prostatectomy: impact of routine ultrasonography for the detection of pelvic lymphoceles and hematomas. *Eur Urol* 1998; 33: 86–90
- 273 Leandri P, Rossignol G, Gautier J-R, et al. Radical retropubic prostatectomy: morbidity and quality of life: experience with 620 consecutive cases. *J Urol* 1992; 147:883–887
- 274 Cisek LJ, Walsh PC. Thromboembolic complications following radical retropubic prostatectomy: influence of external sequential pneumatic compression devices. *Urology* 1993; 42:406–408
- 275 Andriole GL, Smith DS, Rao G, et al. Early complications of contemporary anatomical radical retropubic prostatectomy. *J Urol* 1994; 152:1858–1860
- 276 Hautmann RE, Sauter TW, Wenderoth UK. Radical retropubic prostatectomy: morbidity and urinary continence in 418 consecutive cases. *Urology* 1994; 43(suppl):47–51
- 277 Leibovitch I, Foster RS, Wass JL, et al. Color Doppler flow imaging for deep venous thrombosis screening in patients undergoing pelvic lymphadenectomy and radical retropubic prostatectomy for prostatic carcinoma. *J Urol* 1995; 153: 1866–1869
- 278 Goldenberg SL, Klotz LH, Srigley J, et al. Randomized, prospective, controlled study comparing radical prostatectomy alone and neoadjuvant androgen withdrawal in the treatment of localized prostate cancer. *J Urol* 1996; 156:873–877
- 279 Sieber PR, Rommel FM, Agusta VE, et al. Is heparin contraindicated in pelvic lymphadenectomy and radical prostatectomy? *J Urol* 1997; 158:869–871
- 280 Donat R, Mancey-Jones B. Incidence of thromboembolism after transurethral resection of the prostate (TURP): a study on TED stocking prophylaxis and literature review. *Scand J Urol Nephrol* 2002; 36:119–123
- 281 Bergqvist D, Bergentz SE, Bornmyr S, et al. Deep vein thrombosis after renal transplantation: a prospective analysis of frequency and risk factors. *Eur Surg Res* 1985; 17:69–74
- 282 Allen RD, Michie CA, Murie JA, et al. Deep venous thrombosis after renal transplantation. *Surg Gynecol Obstet* 1987; 164:137–142
- 283 Angermeier KW, Jordan GH. Complications of the exaggerated lithotomy position: a review of 177 cases. *J Urol* 1994; 151:866–868
- 284 Soderdahl DW, Henderson SR, Hansberry KL. A comparison of intermittent pneumatic compression of the calf and whole leg in preventing deep venous thrombosis in urological surgery. *J Urol* 1997; 157:1774–1776
- 285 Geerts WH, Code KI, Singer S, et al. Thromboprophylaxis after radical prostatectomy: a survey of Canadian urologists [abstract]. *Thromb Haemost* 1997; 77(suppl):124
- 286 Van Arsdalen KN, Barnes RW, Clarke G, et al. Deep vein thrombosis and prostatectomy. *Urology* 1983; 21:461–463
- 287 Bergqvist D, Hallbook T. Prophylaxis of postoperative venous thrombosis in a controlled trial comparing dextran 70 and low-dose heparin. *World J Surg* 1980; 4:239–243
- 288 Vandendris M, Kutnowski M, Futeral B, et al. Prevention of postoperative deep-vein thrombosis by low-dose heparin in

- open prostatectomy. *Urol Res* 1980; 8:219–221
- 289 Hedlund PO, Blomback M. The effects of low-dose heparin treatment on patients undergoing transvesical prostatectomy. *Urol Res* 1981; 9:147–152
- 290 Bigg SW, Catalona WJ. Prophylactic mini-dose heparin in patients undergoing radical retropubic prostatectomy: a prospective trial. *Urology* 1992; 39:309–313
- 291 Sebeseri O, Kummer H, Zingg E. Controlled prevention of post-operative thrombosis in urological diseases with depot heparin. *Eur Urol* 1975; 1:229–230
- 292 Neal DE. The National Prostatectomy Audit. *Br J Urol* 1997; 79(suppl):69–75
- 293 Allen NH, Jenkins JD, Smart CJ. Surgical haemorrhage in patients given subcutaneous heparin as prophylaxis against thromboembolism. *BMJ* 1978; 1:1326
- 294 Sleight MW. The effect of prophylactic subcutaneous heparin on blood loss during and after transurethral prostatectomy. *Br J Urol* 1982; 54:164–165
- 295 Kibel AS, Creager MA, Goldhaber SZ, et al. Late venous thromboembolic disease after radical prostatectomy: effect of risk factors, warfarin and early discharge. *J Urol* 1997; 158:2211–2215
- 296 Zacharoulis D, Kakkar AK. Venous thromboembolism in laparoscopic surgery. *Curr Opin Pulm Med* 2003; 9:356–361
- 297 Caprini JA, Arcelus JI, Laubach M, et al. Postoperative hypercoagulability and deep-vein thrombosis after laparoscopic cholecystectomy. *Surg Endosc* 1995; 9:304–309
- 298 Dexter SP, Griffith JP, Grant PJ, et al. Activation of coagulation and fibrinolysis in open and laparoscopic cholecystectomy. *Surg Endosc* 1996; 10:1069–1074
- 299 Dabrowiecki S, Rosc D, Jurkowski P. The influence of laparoscopic cholecystectomy on perioperative blood clotting and fibrinolysis. *Blood Coagul Fibrinolysis* 1997; 8:1–5
- 300 Rahr HB, Fabrin K, Larsen JF, et al. Coagulation and fibrinolysis during laparoscopic cholecystectomy. *Thromb Res* 1999; 93:121–127
- 301 Lindberg F, Rasmussen I, Siegbahn A, et al. Coagulation activation after laparoscopic cholecystectomy in spite of thromboembolism prophylaxis. *Surg Endosc* 2000; 14:858–861
- 302 Prisco D, De Gaudio AR, Carla R, et al. Videolaparoscopic cholecystectomy induces a hemostasis activation of lower grade than does open surgery. *Surg Endosc* 2000; 14:170–174
- 303 Yol S, Kartal A, Caliskan U, et al. Effect of laparoscopic cholecystectomy on platelet aggregation. *World J Surg* 2000; 24:734–737
- 304 Larsen JF, Ejstrup P, Svendsen F, et al. Randomized study of coagulation and fibrinolysis during and after gasless and conventional laparoscopic cholecystectomy. *Br J Surg* 2001; 88:1001–1005
- 305 Vander Velpen G, Penninckx F, Kerremans R, et al. Interleukin-6 and coagulation-fibrinolysis fluctuations after laparoscopic and conventional cholecystectomy. *Surg Endosc* 1994; 8:1216–1220
- 306 Martinez-Ramos C, Lopez-Pastor A, Nunez-Pena JR, et al. Changes in hemostasis after laparoscopic cholecystectomy. *Surg Endosc* 1999; 13:476–479
- 307 Jorgensen JO, Lalak NJ, North L, et al. Venous stasis during laparoscopic cholecystectomy. *Surg Laparosc Endosc* 1994; 4:128–133
- 308 Wilson YG, Allen PE, Skidmore R, et al. Influence of compression stockings on lower-limb venous haemodynamics during laparoscopic cholecystectomy. *Br J Surg* 1994; 81:841–844
- 309 Sobolewski AP, Deshmukh RM, Brunson BL, et al. Venous hemodynamic changes during laparoscopic cholecystectomy. *J Laparosc Surg* 1995; 5:363–369
- 310 Bradbury AW, Chan YC, Darzi A, et al. Thromboembolism prophylaxis during laparoscopic cholecystectomy. *Br J Surg* 1997; 84:962–964
- 311 Tvedskov TF, Rasmussen MS, Willie-Jorgensen P. Survey of the use of thromboprophylaxis in laparoscopic surgery in Denmark. *Br J Surg* 2001; 88:1413–1416
- 312 Blake AM, Toker SI, Dunn E. Deep venous thrombosis prophylaxis is not indicated for laparoscopic cholecystectomy. *J Soc Laparosc Surg* 2001; 5:215–219
- 313 Bounameaux H, Didier D, Polat O, et al. Antithrombotic prophylaxis in patients undergoing laparoscopic cholecystectomy. *Thromb Res* 1997; 86:271–273
- 314 Catheline JM, Turner R, Gaillard JL, et al. Thromboembolism in laparoscopic surgery: risk factors and preventive measures. *Surg Laparosc Endosc Percutan Tech* 1999; 9:135–139
- 315 Chamberlain G, Brown JC. Gynecologic laparoscopy: the report of a working party in a confidential enquiry of gynaecological laparoscopy. London, Royal College of Obstetricians and Gynecologists, 1978
- 316 Scott TR, Zucker KA, Bailey RW. Laparoscopic cholecystectomy: a review of 12,397 patients. *Surg Laparosc Endosc* 1992; 2:191–198
- 317 Lindberg F, Bergqvist D, Rasmussen I. Incidence of thromboembolic complications after laparoscopic cholecystectomy: review of the literature. *Surg Laparosc Endosc* 1997; 7:324–331
- 318 Hjelmqvist B. Complications of laparoscopic cholecystectomy as recorded in the Swedish Laparoscopy Registry. *Eur J Surg* 2000; 585(suppl):18–21
- 319 Patel MI, Hardman DT, Nicholls D, et al. The incidence of deep venous thrombosis after laparoscopic cholecystectomy. *Med J Aust* 1996; 164:652–656
- 320 Baca I, Schneider B, Kohler T, et al. Prevention of venous thromboembolism in patients undergoing minimally invasive surgery with a short-term hospital stay: results of a multicentric, prospective, randomised, controlled clinical trial with a low-molecular-weight heparin. *Chirurg* 1997; 68:1275–1280
- 321 Healey MG, Maher PJ, Hill DJ, et al. The risk of venous thrombosis following gynaecological laparoscopic surgery. *Med J Aust* 1998; 168:524
- 322 Lord RV, Ling JJ, Hugh TB, et al. Incidence of deep vein thrombosis after laparoscopic vs minilaparotomy cholecystectomy. *Arch Surg* 1998; 133:967–973
- 323 Wazz G, Branicki F, Taji H, et al. Influence of pneumoperitoneum on the deep venous system during laparoscopy. *JLS* 2000; 4:291–295
- 324 Mall JW, Schwenk W, Rodiger O, et al. Blinded prospective study of the incidence of deep venous thrombosis following conventional or laparoscopic colorectal resection. *Br J Surg* 2001; 88:99–100
- 325 Schaepekens van Riepmst JT, Van Hee RH, Weyler JJ. Deep venous thrombosis after laparoscopic cholecystectomy and prevention with nadroparin. *Surg Endosc* 2002; 16:184–187
- 326 Schwenk W, Bohm B, Fugener A, et al. Intermittent pneumatic sequential compression (ISC) of the lower extremities prevents venous stasis during laparoscopic cholecystectomy: a prospective randomized study. *Surg Endosc* 1998; 12:7–11
- 327 Isoda N, Suzuki T, Ido K, et al. Femoral vein stasis during laparoscopic cholecystectomy: effect of an intermittent sequential pneumatic compression device. *Digest Endosc* 2000; 12:225–228
- 328 Neudecker J, Sauerland S, Neugebauer E, et al. The European Association for Endoscopic Surgery clinical prac-

- tice guideline on the pneumoperitoneum for laparoscopic surgery. *Surg Endosc* 2002; 16:1121–1143
- 329 Society of American Gastrointestinal Endoscopic Surgeons. Global statement on deep venous thrombosis prophylaxis during laparoscopic surgery. Available at: www.sages.org/sg_pub_c.html. Accessed August 17, 2003
 - 330 Bergqvist D, Lowe G. Venous thromboembolism in patients undergoing laparoscopic and arthroscopic surgery and in leg casts. *Arch Intern Med* 2002; 162:2173–2176
 - 331 NIH Consensus Conference. Prevention of venous thrombosis and pulmonary embolism. *JAMA* 1986; 256:744–749
 - 332 Turpie AGG, Levine MN, Hirsh J, et al. A randomized controlled trial of a low-molecular-weight heparin (enoxaparin) to prevent deep-vein thrombosis in patients undergoing elective hip surgery. *N Engl J Med* 1986; 315:925–929
 - 333 Beisaw NE, Comerota AJ, Groth HE, et al. Dihydroergotamine/heparin in the prevention of deep-vein thrombosis after total hip replacement: a controlled, prospective randomized multicenter trial. *J Bone Joint Surg Am* 1988; 70:2–10
 - 334 Haake DA, Berkman SA. Venous thromboembolic disease after hip surgery: risk factors, prophylaxis, and diagnosis. *Clin Orthop* 1989; 242:212–231
 - 335 Lassen MR, Borris LC, Christiansen HM, et al. Prevention of thromboembolism in 190 hip arthroplasties: comparison of LMW heparin and placebo. *Acta Orthop Scand* 1991; 62:33–38
 - 336 Hoek JA, Nurmohamed MT, Hamelynck KJ, et al. Prevention of deep vein thrombosis following total hip replacement by low molecular weight heparinoid. *Thromb Haemost* 1992; 67:28–32
 - 337 Eriksson BI, Kalebo P, Anthmyr BA, et al. Prevention of deep-vein thrombosis and pulmonary embolism after total hip or knee replacement: a meta-analysis of prospective studies investigating symptomatic outcomes. *J Bone Joint Surg Am* 1991; 73:484–493
 - 338 Warwick D, Bannister GC, Glew D, et al. Perioperative low-molecular-weight heparin: is it effective and safe? *J Bone Joint Surg Br* 1995; 77:715–719
 - 339 Mahomed NN, Barrett JA, Latz JN, et al. Rates and outcomes of primary and revision total hip replacement in the United States Medicare population. *J Bone Joint Surg Am* 2003; 85:27–32
 - 340 Phillips CB, Barrett JA, Losina E, et al. Incidence rates of dislocation, pulmonary embolism, and deep infection during the first six months after elective total hip replacement. *J Bone Joint Surg Am* 2003; 85:20–26
 - 341 Mohr DN, Silverstein MD, Ilstrup DM, et al. Venous thromboembolism associated with hip and knee arthroplasty: current prophylactic practices and outcomes. *Mayo Clin Proc* 1992; 67:861–870
 - 342 Murray DW, Britton AR, Bulstrode CJK. Thromboprophylaxis and death after total hip replacement. *J Bone Joint Surg Br* 1996; 78:863–870
 - 343 Colwell CW, Collis DK, Paulson R, et al. Comparison of enoxaparin and warfarin for the prevention of venous thromboembolic disease after total hip arthroplasty: evaluation during hospitalization and three months after discharge. *J Bone Joint Surg Am* 1999; 81:932–940
 - 344 Stulberg BN, Insall JN, Williams GW, et al. Deep-vein thrombosis following total knee replacement: an analysis of six hundred and thirty-eight arthroplasties. *J Bone Joint Surg Am* 1984; 66:194–201
 - 345 Lynch AF, Bourne RB, Rorabeck CH, et al. Deep-vein thrombosis and continuous passive motion after total knee arthroplasty. *J Bone Joint Surg Am* 1988; 70:11–14
 - 346 Stringer MD, Steadman CA, Hedges AR, et al. Deep vein thrombosis after elective knee surgery: an incidence study in 312 patients. *J Bone Joint Surg Br* 1989; 71:492–497
 - 347 Leclerc JR, Geerts WH, Desjardins L, et al. Prevention of deep vein thrombosis after major knee surgery: a randomized, double-blind trial comparing a low molecular weight heparin fragment [enoxaparin] to placebo. *Thromb Haemost* 1992; 67:417–423
 - 348 Levine MN, Gent M, Hirsh J, et al. Ardeparin (low-molecular-weight heparin) vs graduated compression stockings for the prevention of venous thromboembolism: a randomized trial in patients undergoing knee surgery. *Arch Intern Med* 1996; 156:851–856
 - 349 Warwick D, Harrison J, Whitehouse S. A randomised comparison of a foot pump and low-molecular-weight heparin in the prevention of deep-vein thrombosis after total knee replacement. *J Bone Joint Surg Br* 2002; 84:344–350
 - 350 Khaw FM, Moran CG, Pinder IM, et al. The incidence of fatal pulmonary embolism after knee replacement with no prophylactic anticoagulation. *J Bone Joint Surg Br* 1993; 75:940–941
 - 351 Ansari S, Warwick D, Ackroyd CE, et al. Incidence of fatal pulmonary embolism after 1,390 knee arthroplasties without routine prophylactic anticoagulation, except in high-risk cases. *J Arthroplasty* 1997; 12:599–602
 - 352 Snook GA, Chrisman OD, Wilson TC. Thromboembolism after surgical treatment of hip fractures. *Clin Orthop* 1981; 155:21–24
 - 353 Agnelli G, Cosmi B, DiFilippo P, et al. A randomised, double-blind, placebo-controlled trial of dermatan sulphate for prevention of deep vein thrombosis in hip fracture. *Thromb Haemost* 1992; 67:203–208
 - 354 Dahl OE, Andreassen G, Aspelin T, et al. Prolonged thromboprophylaxis following hip replacement surgery: results of a double-blind, prospective, randomised, placebo-controlled study with dalteparin (Fragmin). *Thromb Haemost* 1997; 77:26–31
 - 355 Seagroatt V, Tan HS, Goldacre M. Elective total hip replacement: incidence, emergency readmission rate, and postoperative mortality. *BMJ* 1991; 303:1431–1435
 - 356 Turpie AGG, Bauer KA, Eriksson BI, et al. Fondaparinux vs enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery: a meta-analysis of 4 randomized double-blind studies. *Arch Intern Med* 2002; 162:1833–1840
 - 357 Warwick DJ, Whitehouse S. Symptomatic venous thromboembolism after total knee replacement. *J Bone Joint Surg Br* 1997; 78:780–786
 - 358 Dahl OE, Gudmundsen TE, Haukeland L. Late occurring clinical deep vein thrombosis in joint-operated patients. *Acta Orthop Scand* 2000; 71:47–50
 - 359 Heit JA, Elliott CG, Trowbridge AA, et al. Ardeparin sodium for extended out-of-hospital prophylaxis against venous thromboembolism after total hip or knee replacement: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2000; 132:853–861
 - 360 Anderson DR, Wilson SJ, Blundell J, et al. Comparison of a nomogram and physician-adjusted dosage of warfarin for prophylaxis against deep-vein thrombosis after arthroplasty. *J Bone Joint Surg Am* 2002; 84:1992–1997
 - 361 Pellegrini VD, Clement D, Lush-Ehmann C, et al. Natural history of thromboembolic disease after total hip arthroplasty. *Clin Orthop* 1996; 333:27–40
 - 362 Ginsberg JS, Gent M, Turkstra F, et al. Postthrombotic syndrome after hip or knee arthroplasty: a cross-sectional study. *Arch Intern Med* 2000; 160:669–672
 - 363 Kim YH, Oh SH, Kim JS. Incidence and natural history of

- deep-vein thrombosis after total hip arthroplasty. *J Bone Joint Surg Br* 2003; 85:661–665
- 364 Buehler KO, D'Lima DD, Petersilge WJ, et al. Late deep venous thrombosis and delayed weight bearing after total hip arthroplasty. *Clin Orthop* 1999; 361:123–130
- 365 Lindahl TL, Lundahl TH, Nilsson L, et al. APC-resistance is a risk factor for postoperative thromboembolism in elective replacement of the hip or knee: a prospective study. *Thromb Haemost* 1999; 81:18–21
- 366 Westrich GH, Weksler BB, Glueck CJ, et al. Correlation of thrombophilia and hypofibrinolysis with pulmonary embolism following total hip arthroplasty: an analysis of genetic factors. *J Bone Joint Surg Am* 2002; 84:2161–2167
- 367 Wilson D, Cooke EA, McNally MA, et al. Altered venous function and deep venous thrombosis following proximal femoral fracture. *Injury* 2002; 33:33–39
- 368 Planes A, Vochelle N, Darmon JY, et al. Risk of deep-venous thrombosis after hospital discharge in patients having undergone total hip replacement: double-blind randomised comparison of enoxaparin versus placebo. *Lancet* 1996; 348:224–228
- 369 Salvati EA, Pellegrini VD, Sharrock NE, et al. Recent advances in venous thromboembolic prophylaxis during and after total hip replacement. *J Bone Joint Surg Am* 2000; 82:252–270
- 370 Warwick D, Williams MH, Bannister GC. Death and thromboembolic disease after total hip replacement: a series of 1162 cases with no routine chemical prophylaxis. *J Bone Joint Surg Br* 1995; 77:6–10
- 371 Gillespie W, Murray D, Gregg PJ, et al. Risks and benefits of prophylaxis against venous thromboembolism in orthopaedic surgery. *J Bone Joint Surg Br* 2000; 82:475–479
- 372 Wroblewski BM, Siney PD, Fleming PA. Fatal pulmonary embolism after total hip arthroplasty: diurnal variations. *Orthopedics* 1998; 21:1269–1271
- 373 Borris LC, Christiansen HM, Lassen MR, et al. Comparison of real-time B-mode ultrasonography and bilateral ascending phlebography for detection of postoperative deep vein thrombosis following elective hip surgery. *Thromb Haemost* 1989; 61:363–365
- 374 Heit J, Neemeh J, Hyers T, et al. Operating characteristics of cuff impedance plethysmography in the diagnosis of deep-vein thrombosis following total hip or knee arthroplasty [abstract]. *Blood* 1991; 78(suppl):214a
- 375 Agnelli G, Volpato R, Radicchia S, et al. Detection of asymptomatic deep vein thrombosis by real-time B-mode ultrasonography in hip surgery patients. *Thromb Haemost* 1992; 68:257–260
- 376 Crippa L, Ravasi F, D'Angelo SV et al. Diagnostic value of compression ultrasonography and fibrinogen-related parameters for the detection of postoperative deep vein thrombosis following elective hip replacement: a pilot study. *Thromb Haemost* 1995; 74:1235–1239
- 377 Magnusson M, Eriksson BI, Kalebo P, et al. Is colour Doppler ultrasound a sensitive screening method in diagnosing deep vein thrombosis after hip surgery? *Thromb Haemost* 1996; 75:242–245
- 378 Lensing AWA, Doris CI, McGrath FP, et al. A comparison of compression ultrasound with color Doppler ultrasound for the diagnosis of symptomless postoperative deep vein thrombosis. *Arch Intern Med* 1997; 157:765–768
- 379 Comp PC, Voegeli T, McCutchen JW, et al. A comparison of danaparoid and warfarin for prophylaxis against deep vein thrombosis after total hip replacement. *Orthopedics* 1998; 21:1123–1128
- 380 Barnes RW, Brand RA, Clarke W, et al. Efficacy of graded-compression antiembolism stockings in patients undergoing total hip arthroplasty. *Clin Orthop* 1978; 132:61–67
- 381 Nilsen DWT, Naess-Andresen KF, Kierulf P, et al. Graded pressure stockings in prevention of deep vein thrombosis following total hip replacement. *Acta Chir Scand* 1984; 150:531–534
- 382 Fordyce MJF, Ling RSM. A venous foot pump reduces thrombosis after total hip replacement. *J Bone Joint Surg Br* 1992; 74:45–49
- 383 Samama CM, Clergue F, Barre J, et al. Low molecular weight heparin associated with spinal anaesthesia and gradual compression stockings in total hip replacement surgery. *Br J Anaesth* 1997; 78:660–665
- 384 Paiement G, Wessinger SJ, Waltman AC, et al. Low-dose warfarin versus external pneumatic compression for prophylaxis against venous thromboembolism following total hip replacement. *J Arthroplasty* 1987; 2:23–26
- 385 Bailey JP, Kruger MP, Solano FX, et al. Prospective randomized trial of sequential compression devices vs low-dose warfarin for deep venous thrombosis prophylaxis in total hip arthroplasty. *J Arthroplasty* 1991; 6(suppl):S29–S35
- 386 Kaempffe FA, Lifeso RM, Meinking C. Intermittent pneumatic compression versus Coumadin: prevention of deep vein thrombosis in low-extremity total joint arthroplasty. *Clin Orthop* 1991; 269:89–97
- 387 Francis CW, Pellegrini VD, Marder VJ, et al. Comparison of warfarin and external pneumatic compression in prevention of venous thrombosis after total hip replacement. *JAMA* 1992; 267:2911–2915
- 388 Norgren L, Austrell C, Brummer R, et al. Low incidence of deep vein thrombosis after total hip replacement: an interim analysis of patients on low molecular weight heparin vs sequential gradient compression prophylaxis. *Int Angiol* 1996; 15(suppl):11–14
- 389 Ryan MG, Westrich GH, Potter HG, et al. Effect of mechanical compression on the prevalence of proximal deep venous thrombosis as assessed by magnetic resonance venography. *J Bone Joint Surg Am* 2002; 84:1998–2004
- 390 Sarmiento A, Goswami ADK. Thromboembolic prophylaxis with use of aspirin, exercise, and graded elastic stockings or intermittent compression devices in patients managed with total hip arthroplasty. *J Bone Joint Surg Am* 1999; 81:339–346
- 391 Eriksson BI, Ekman S, Baur M, et al. Regional block anaesthesia versus general anaesthesia: are different anti-thrombotic drugs equally effective in patients undergoing hip replacement?; retrospective analysis of 2354 patients undergoing hip replacement receiving either recombinant hirudin, unfractionated heparin or enoxaparin [abstract]. *Thromb Haemost* 1997; 77(suppl):487–488
- 392 Harris WH, Salzman EW, Athansoulis C, et al. Comparison of warfarin, low-molecular-weight dextran, aspirin, and subcutaneous heparin in prevention of venous thrombosis following total hip replacement. *J Bone Joint Surg Am* 1974; 56:1552–1562
- 393 Leyvraz PF, Richard J, Bachmann F, et al. Adjusted versus fixed-dose subcutaneous heparin in the prevention of deep-vein thrombosis after total hip replacement. *N Engl J Med* 1983; 309:954–958
- 394 Planes A, Vochelle N, Mazas F, et al. Prevention of postoperative venous thrombosis: a randomized trial comparing unfractionated heparin with low molecular weight heparin in patients undergoing total hip replacement. *Thromb Haemost* 1988; 60:407–410
- 395 Anderson DR, O'Brien BJ, Levine MN, et al. Efficacy and cost of low-molecular-weight heparin for the prevention of

- deep vein thrombosis after total hip arthroplasty. *Ann Intern Med* 1993; 119:1105–1112
- 396 Eriksson BI, Ekman S, Kalebo P, et al. Prevention of deep-vein thrombosis after total hip replacement: direct thrombin inhibition with recombinant hirudin, CGP 39393. *Lancet* 1996; 347:635–639
- 397 Eriksson BI, Ekman S, Lindbratt S, et al. Prevention of thromboembolism with use of recombinant hirudin: results of a double-blind, multicenter trial comparing the efficacy of desirudin (Revasc) with that of unfractionated heparin in patients having a total hip replacement. *J Bone Joint Surg Am* 1997; 79:326–333
- 398 Kakkur VV, Howes J, Sharma V, et al. A comparative, double-blind, randomised trial of a new second generation LMWH (bemiparin) and UFH in the prevention of post-operative venous thromboembolism. *Thromb Haemost* 2000; 83:523–529
- 399 Dechavanne M, Ville D, Berruyer M, et al. Randomized trial of a low-molecular-weight heparin (Kabi 2165) versus adjusted-dose subcutaneous standard heparin in the prophylaxis of deep-vein thrombosis after elective hip surgery. *Haemostasis* 1989; 19:5–12
- 400 Leyvraz PF, Bachmann F, Hoek J, et al. Prevention of deep vein thrombosis after hip replacement: randomised comparison between unfractionated heparin and low molecular weight heparin. *BMJ* 1991; 303:543–548
- 401 Rader CP, Kramer C, Konig A, et al. Low-molecular-weight heparin and partial thromboplastin time-adjusted unfractionated heparin in thromboprophylaxis after total knee and total hip arthroplasty. *J Arthroplasty* 1998; 13:180–185
- 402 Amstutz HC, Friscia DA, Dorey F, et al. Warfarin prophylaxis to prevent mortality from pulmonary embolism after total hip replacement. *J Bone Joint Surg Am* 1989; 71:321–326
- 403 Paiement GD, Wessinger SJ, Hughes R, et al. Routine use of adjusted low-dose warfarin to prevent venous thromboembolism after total hip replacement. *J Bone Joint Surg Am* 1993; 75:893–898
- 404 Janku GV, Paiement GD, Green HD. Prevention of thromboembolism in orthopaedics in the United States. *Clin Orthop* 1996; 325:313–321
- 405 Lieberman JR, Wollaeger J, Dorey F, et al. The efficacy of prophylaxis with low-dose warfarin for prevention of pulmonary embolism following total hip arthroplasty. *J Bone Joint Surg Am* 1997; 79:319–325
- 406 Gross M, Anderson DR, Nagpal S, et al. Venous thromboembolism prophylaxis after total hip or knee arthroplasty: a survey of Canadian orthopedic surgeons. *Can J Surg* 1999; 42:457–461
- 407 Mesko JW, Brand RA, Iorio RA, et al. Venous thromboembolic disease management patterns in total hip arthroplasty and total knee arthroplasty patients: a survey of the AAHKS membership. *J Arthroplasty* 2001; 16:679–688
- 408 RD Heparin Arthroplasty Group. RD heparin compared with warfarin for prevention of venous thromboembolic disease following total hip or knee arthroplasty. *J Bone Joint Surg Am* 1994; 76:1174–1185
- 409 Francis CW, Pellegrini VD, Totterman S, et al. Prevention of deep-vein thrombosis after total hip arthroplasty: comparison of warfarin and dalteparin. *J Bone Joint Surg Am* 1997; 79:1365–1372
- 410 Caprini JA, Arcelus JI, Motykie G, et al. The influence of oral anticoagulation therapy on deep vein thrombosis rates four weeks after total hip replacement. *J Vasc Surg* 1999; 30:813–820
- 411 German Hip Arthroplasty Trial Group (GHAT). Prevention of deep vein thrombosis with low molecular-weight heparin in patients undergoing total hip replacement: a randomized trial. *Arch Orthop Trauma Surg* 1992; 111:110–120
- 412 Colwell CW, Spiro TE, Trowbridge AA, et al. Use of enoxaparin, a low-molecular-weight heparin, and unfractionated heparin for the prevention of deep venous thrombosis after elective hip replacement: a clinical trial comparing efficacy and safety. *J Bone Joint Surg Am* 1994; 76:3–14
- 413 Hull R, Raskob GE, Pineo G, et al. A comparison of subcutaneous low-molecular-weight heparin with warfarin sodium for prophylaxis against deep-vein thrombosis after hip or knee implantation. *N Engl J Med* 1993; 329:1370–1376
- 414 Hamulyak K, Lensing AWA, van der Meer J, et al. Subcutaneous low-molecular weight heparin or oral anticoagulants for the prevention of deep-vein thrombosis in elective hip and knee replacement? *Thromb Haemost* 1995; 74:1428–1431
- 415 Hull RD, Pineo GF, Francis C, et al. Low-molecular-weight heparin prophylaxis using dalteparin in close proximity to surgery vs warfarin in hip arthroplasty patients: a double-blind, randomized comparison. *Arch Intern Med* 2000; 160:2199–2207
- 416 Colwell CW, Spiro TE, Trowbridge AA, et al. Efficacy and safety of enoxaparin versus unfractionated heparin for prevention of deep venous thrombosis after elective knee arthroplasty. *Clin Orthop* 1995; 321:19–27
- 417 Lassen MR, Bauer KA, Eriksson BI, et al. Postoperative fondaparinux versus preoperative enoxaparin for prevention of venous thromboembolism in elective hip-replacement surgery: a randomised double-blind comparison. *Lancet* 2002; 359:1715–1720
- 418 Turpie AGG, Bauer KA, Eriksson BI, et al. Postoperative fondaparinux versus postoperative enoxaparin for prevention of venous thromboembolism after elective hip-replacement surgery: a randomised double-blind trial. *Lancet* 2002; 359:1721–1726
- 419 Bauer KA, Eriksson BI, Lassen MR, et al. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. *N Engl J Med* 2001; 345:1305–1310
- 420 Eriksson BI, Bauer KA, Lassen MR, et al. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. *N Engl J Med* 2001; 345:1298–1304
- 421 Eriksson BI, Wille-Jørgensen P, Kalebo P, et al. A comparison of recombinant hirudin with a low-molecular-weight heparin to prevent thromboembolic complications after total hip replacement. *N Engl J Med* 1997; 337:1329–1335
- 422 Eriksson BI, Arfwidsson AC, Frison L, et al. A dose ranging study of the oral direct thrombin inhibitor, ximelagatran, and its subcutaneous form, melagatran, compared with dalteparin in the prevention of thromboembolism after hip or knee replacement: METHRO I. *Thromb Haemost* 2002; 87:231–237
- 423 Eriksson BI, Bergqvist D, Kalebo P, et al. Ximelagatran and melagatran compared with dalteparin for prevention of venous thromboembolism after total hip or knee replacement: the METHRO II randomised trial. *Lancet* 2002; 360:1441–1447
- 424 Eriksson BI, Agnelli G, Cohen AT, et al. The direct thrombin inhibitor melagatran followed by oral ximelagatran compared with enoxaparin for the prevention of venous thromboembolism after total hip or total knee replacement: the EXPRESS Study. *J Thromb Haemost* 2003; 1:2490–2496
- 425 Eriksson BI, Agnelli G, Cohen AT, et al. Direct thrombin inhibitor melagatran followed by oral ximelagatran in com-

- parison with enoxaparin for prevention of venous thromboembolism after total hip or total knee replacement: the METHRO III study. *Thromb Haemost* 2003; 89:288–296
- 426 Colwell CW, Berkowitz SD, Davidson BL, et al. Comparison of ximelagatran, an oral direct thrombin inhibitor, with enoxaparin for the prevention of venous thromboembolism following total hip replacement: a randomized, double-blind study. *J Thromb Haemost* 2003; 2003:2119–2130
- 427 Hull RD, Delmore TJ, Hirsh J, et al. Effectiveness of intermittent pulsatile elastic stockings for the prevention of calf and thigh vein thrombosis in patients undergoing elective knee surgery. *Thromb Res* 1979; 16:37–45
- 428 Haas SB, Insall JN, Scuderi GR, et al. Pneumatic sequential-compression boots compared with aspirin prophylaxis of deep-vein thrombosis after total knee arthroplasty. *J Bone Joint Surg Am* 1990; 72:27–31
- 429 Wilson NV, Das SK, Kakkar VV, et al. Thrombo-embolic prophylaxis in total knee replacement: evaluation of the A-V Impulse System. *J Bone Joint Surg Br* 1992; 74:50–52
- 430 Norgren L, Toksvig-Larsen S, Magyar G, et al. Prevention of deep vein thrombosis in knee arthroplasty: preliminary results from a randomized controlled study of low molecular weight heparin vs foot pump compression. *Int Angiol* 17: 93–96, 1998
- 431 Hui ACW, Heras-Palou C, Dunn I, et al. Graded compression stockings for prevention of deep-vein thrombosis after hip and knee replacement. *J Bone Joint Surg Br* 1996; 78:550–554
- 432 Fauno P, Suomalainen O, Rehnberg V, et al. Prophylaxis for the prevention of venous thromboembolism after total knee arthroplasty: a comparison between unfractionated and low-molecular-weight heparin. *J Bone Joint Surg Am* 1994; 76:1814–1818
- 433 Francis CW, Pellegrini VD, Leibert KM, et al. Comparison of two warfarin regimens in the prevention of venous thrombosis following total knee replacement. *Thromb Haemost* 1996; 75:706–711
- 434 Leclerc JR, Geerts WH, Desjardins L, et al. Prevention of venous thromboembolism after knee arthroplasty: a randomized, double-blind trial comparing enoxaparin with warfarin. *Ann Intern Med* 1996; 124:619–626
- 435 Heit JA, Berkowitz SD, Bona R, et al. Efficacy and safety of low molecular weight heparin (ardeparin sodium) compared to warfarin for the prevention of venous thromboembolism after total knee replacement surgery: a double-blind, dose-ranging study. *Thromb Haemost* 1997; 77:32–38
- 436 Fitzgerald RH, Spiro TE, Trowbridge AA, et al. Prevention of venous thromboembolic disease following primary total knee arthroplasty: a randomized, multicenter, open-label, parallel-group comparison of enoxaparin and warfarin. *J Bone Joint Surg Am* 2001; 83:900–906
- 437 Francis CW, Davidson BL, Berkowitz SD, et al. Ximelagatran versus warfarin for the prevention of venous thromboembolism after total knee arthroplasty: a randomized, double-blind trial. *Ann Intern Med* 2002; 137:648–655
- 438 Colwell CW, Berkowitz SD, Comp PC, et al. Randomized, double-blind comparison of ximelagatran, an oral direct thrombin inhibitor, and warfarin to prevent venous thromboembolism (VTE) after total knee replacement (TKR): EXULT B [abstract]. *Blood* 2003; 102:14a
- 439 Francis CW, Berkowitz SD, Comp PC, et al. Comparison of ximelagatran with warfarin for the prevention of venous thromboembolism after total knee replacement. *N Engl J Med* 2003; 349:1703–1712
- 440 Lieberman JR, Sung R, Dorey F, et al. Low-dose warfarin prophylaxis to prevent symptomatic pulmonary embolism after total knee arthroplasty. *J Arthroplasty* 1997; 12:180–184
- 441 Heit JA, Colwell CW, Francis CW, et al. Comparison of the oral direct thrombin inhibitor ximelagatran with enoxaparin as prophylaxis against venous thromboembolism after total knee replacement: a phase 2 dose-finding study. *Arch Intern Med* 2001; 161:2215–2221
- 442 Navarro-Quilis A, Castellet E, Rocha E, et al. Efficacy and safety of bemiparin compared with enoxaparin in the prevention of venous thromboembolism after total knee arthroplasty: a randomized, double-blind clinical trial. *J Thromb Haemost* 2003; 1:425–432
- 443 Howard AW, Aaron SD. Low molecular weight heparin decreases proximal and distal deep venous thrombosis following total knee arthroplasty: a meta-analysis of randomized trials. *Thromb Haemost* 1998; 79:902–906
- 444 Brookenthal KR, Freedman KB, Lotke PA, et al. A meta-analysis of thromboembolic prophylaxis in total knee arthroplasty. *J Arthroplasty* 2001; 16:293–300
- 445 Menzin J, Colditz GA, Regan MM, et al. Cost-effectiveness of enoxaparin vs low-dose warfarin in the prevention of deep-vein thrombosis after total hip replacement surgery. *Arch Intern Med* 1995; 155:757–764
- 446 Saltiel E, Shane R. Evaluation costs of a pharmacist-run thromboprophylaxis program. *Formulary* 1996; 31:276–290
- 447 Hull RD, Raskob GE, Pineo GF, et al. Subcutaneous low-molecular-weight heparin vs warfarin for prophylaxis of deep vein thrombosis after hip or knee implantation: an economic perspective. *Arch Intern Med* 1997; 157:298–303
- 448 Hawkins DW, Langley PC, Krueger KP. A pharmacoeconomic assessment of enoxaparin and warfarin as prophylaxis for deep vein thrombosis in patients undergoing knee replacement surgery. *Clin Ther* 1998; 20:182–195
- 449 Friedman RJ, Dunsworth GA. Cost analyses of extended prophylaxis with enoxaparin after hip arthroplasty. *Clin Orthop* 2000; 370:171–182
- 450 Hoppener MR, Ettema HB, Kraaijenhagen RA, et al. Day-care or short-stay surgery and venous thromboembolism. *J Thromb Haemost* 2003; 1:863–865
- 451 Small NC. Complications in arthroscopic surgery performed by experienced arthroscopists. *Arthroscopy* 1988; 4:215–221
- 452 Bamford DJ, Paul AS, Noble J, et al. Avoidable complications of arthroscopic surgery. *J R Coll Surg Edinb* 1993; 38:92–95
- 453 Durica S, Raskob G, Johnson C, et al. Incidence of deep-vein thrombosis after arthroscopic knee surgery [abstract]. *Thromb Haemost* 1997; 77(suppl):183
- 454 Demers C, Marcoux S, Ginsberg JS, et al. Incidence of venographically proved deep vein thrombosis after knee arthroscopy. *Arch Intern Med* 1998; 158:47–50
- 455 Williams JS, Hulstyn MJ, Fadale PD, et al. Incidence of deep vein thrombosis after arthroscopic knee surgery: a prospective study. *Arthroscopy* 1995; 11:701–705
- 456 Cullison TR, Muldoon MP, Gorman JD, et al. The incidence of deep venous thrombosis in anterior cruciate ligament reconstruction. *Arthroscopy* 1996; 12:657–659
- 457 Jaureguito JW, Greenwald AE, Wilcox JF, et al. The incidence of deep venous thrombosis after arthroscopic knee surgery. *Am J Sports Med* 1999; 27:707–710
- 458 Delis KT, Hunt N, Strachan RK, et al. Incidence, natural history and risk factors of deep vein thrombosis in elective knee arthroscopy. *Thromb Haemost* 2001; 86:817–821
- 459 Wirth T, Schneider B, Misselwitz F, et al. Prevention of venous thromboembolism after knee arthroscopy with low-molecular weight heparin (reviparin): results of a randomized controlled trial. *Arthroscopy* 2001; 17:393–399
- 460 Michot M, Conen D, Holtz D, et al. Prevention of deep-vein

- thrombosis in ambulatory arthroscopic knee surgery: a randomized trial of prophylaxis with low-molecular weight heparin. *Arthroscopy* 2002; 18:257-263
- 461 Borgstrom S, Greitz T, van der Linden W, et al. Anticoagulant prophylaxis of venous thrombosis in patients with fractured neck of the femur: a controlled clinical trial using venous phlebography. *Acta Chir Scand* 1965; 129:500-508
- 462 Hamilton HW, Crawford JS, Gardiner JH, et al. Venous thrombosis in patients with fracture of the upper end of the femur: a phlebographic study of the effect of prophylactic anticoagulation. *J Bone Joint Surg Br* 1970; 52:268-289
- 463 Lowe GD, Campbell AF, Meek DR, et al. Subcutaneous anecrod in prevention of deep-vein thrombosis after operation for fractured neck of femur. *Lancet* 1978; ii:698-700
- 464 Rogers PH, Walsh PN, Marder VJ, et al. Controlled trial of low-dose heparin and sulfipyrazone to prevent venous thromboembolism after operation on the hip. *J Bone Joint Surg Am* 1978; 60:758-762
- 465 Jorgensen PS, Strandberg C, Willie-Jorgensen P, et al. Early preoperative thromboprophylaxis with Klexane in hip fracture surgery: a placebo-controlled study. *Clin Appl Thromb Hemost* 1998; 4:140-142
- 466 Perez JV, Warwick DJ, Case CP, et al. Death after proximal femoral fracture: an autopsy study. *Injury* 1995; 26:237-240
- 467 Schroder HM, Andreassen M. Autopsy-verified major pulmonary embolism after hip fracture. *Clin Orthop* 1993; 293:196-203
- 468 Hefley WF, Nelson CL, Puskarich-May CL. Effect of delayed admission to the hospital on the preoperative prevalence of deep-vein thrombosis associated with fractures about the hip. *J Bone Joint Surg Am* 1996; 78:581-583
- 469 Zahn HR, Skinner JA, Porteous MJ. The preoperative prevalence of deep vein thrombosis in patients with femoral neck fractures and delayed operation. *Injury* 1999; 30:605-607
- 470 Sorenson RM, Pace NL. Anesthetic techniques during surgical repair of femoral neck fractures: a meta-analysis. *Anesthesiology* 1992; 77:1095-1104
- 471 Handoll HH, Farrar MJ, McBirmie J, et al. Heparin, low molecular weight heparin and physical methods for preventing deep vein thrombosis and pulmonary embolism following surgery for hip fractures. *Cochrane Database Syst Rev* (database online). Issue 1, 2003
- 472 Fisher CG, Blachut PA, Salvian AJ, et al. Effectiveness of leg compression devices for the prevention of thromboembolic disease in orthopaedic trauma patients: a prospective, randomized study of compression alone versus no prophylaxis. *J Orthop Trauma* 1995; 9:1-7
- 473 Monreal M, Lafoz E, Navarro A, et al. A prospective double-blind trial of a low molecular weight heparin once daily compared with conventional low-dose heparin three times daily to prevent pulmonary embolism and venous thrombosis in patients with hip fracture. *J Trauma* 1989; 29:873-875
- 474 Barsotti J, Gruel Y, Rosset P, et al. Comparative double-blind study of two dosage regimens low-molecular weight heparin in elderly patients with a fracture of the neck of the femur. *J Orthop Trauma* 1990; 4:371-375
- 475 TIFDED Study Group. Thromboprophylaxis in hip fracture surgery: a pilot study comparing danaparoid, enoxaparin and dalteparin. *Haemostasis* 1999; 29:310-317
- 476 Roberts TS, Nelson CL, Barnes CL, et al. The preoperative prevalence and postoperative incidence of thromboembolism in patients with hip fractures treated with dextran prophylaxis. *Clin Orthop* 1990; 255:198-203
- 477 Girasole GJ, Cuomo F, Denton JR, et al. Diagnosis of deep vein thrombosis in elderly hip-fracture patients by using the duplex scanning technique. *Orthop Rev* 1994; 23:411-416
- 478 Williams WE, Wisniewski TF. Pre-operative anticoagulant prophylaxis in elderly patients with proximal femur fractures [abstract]. *J Bone Joint Surg Br* 1994; 76:79
- 479 Raskob GE, Hirsh J. Controversies in timing of the first dose of anticoagulant prophylaxis against venous thromboembolism after major orthopedic surgery. *Chest* 2003; 124 (suppl):379S-385S
- 480 Kearon C, Hirsh J. Starting prophylaxis for venous thromboembolism postoperatively. *Arch Intern Med* 1995; 155:366-372
- 481 Hull RD, Brant RF, Pineo GF, et al. Preoperative vs postoperative initiation of low-molecular-weight heparin prophylaxis against venous thromboembolism in patients undergoing elective hip replacement. *Arch Intern Med* 1999; 159:137-141
- 482 Hull RD, Pineo GF, Francis C, et al. Low-molecular-weight heparin prophylaxis using dalteparin extended out-of-hospital vs in-hospital warfarin/out-of-hospital placebo in hip arthroplasty patients: a double-blind, randomized comparison. *Arch Intern Med* 2000; 160:2208-2215
- 483 Strebel N, Prins M, Agnelli G, et al. Preoperative or postoperative start of prophylaxis for venous thromboembolism with low-molecular-weight heparin in elective hip surgery? *Arch Intern Med* 2002; 162:1451-1456
- 484 Hull RD, Pineo GF, Stein PD, et al. Timing of initial administration of low-molecular-weight heparin prophylaxis against deep vein thrombosis in patients following elective hip arthroplasty: a systematic review. *Arch Intern Med* 2001; 161:1952-1960
- 485 Hull RD, Burke N, Mah AF, et al. Timing of initial administration of prophylaxis against deep vein thrombosis in patients following hip or knee surgery [abstract]. *J Thromb Haemost* 2003; 1:P2043
- 486 Berry DJ. Surveillance for venous thromboembolic disease after total knee arthroplasty. *Clin Orthop* 2001; 392:257-266
- 487 Schmidt B, Michler R, Klein M, et al. Ultrasound screening for distal vein thrombosis is not beneficial after major orthopedic surgery: a randomized controlled trial. *Thromb Haemost* 2003; 90:949-954
- 488 Verlato F, Bruchi O, Prandoni P, et al. The value of ultrasound screening for proximal vein thrombosis after total hip arthroplasty: a prospective cohort study. *Thromb Haemost* 2001; 86:534-537
- 489 Kearon C. Duration of venous thromboembolism prophylaxis after surgery. *Chest* 2003; 124 (suppl):386S-392S
- 490 Anderson FA Jr, White K, Hip and Knee Registry Investigators. Prolonged prophylaxis in orthopedic surgery: insights from the United States. *Semin Thromb Hemost* 2002; 28(suppl):43-46
- 491 Planes A, Samama MM, Lensing AWA, et al. Prevention of deep vein thrombosis after hip replacement: comparison between two low-molecular heparins, tinzaparin and enoxaparin. *Thromb Haemost* 1999; 81:22-25
- 492 Dahl OE, Aspelin T, Arnesen H, et al. Increased activation of coagulation and formation of late deep venous thrombosis following discontinuation of thromboprophylaxis after hip replacement surgery. *Thromb Res* 1995; 80:299-306
- 493 Arnesen H, Dahl OE, Aspelin T, et al. Sustained prothrombotic profile after hip replacement surgery: the influence of prolonged prophylaxis with dalteparin. *J Thromb Haemost* 2003; 1:971-975
- 494 Sikorski JM, Hampson WG, Staddon GE. The natural history and aetiology of deep vein thrombosis after total hip replacement. *J Bone Joint Surg Br* 1981; 63:171-177
- 495 Lotke PA, Steinberg ME, Ecker ML. Significance of deep

- venous thrombosis in the lower extremity after total joint arthroplasty. *Clin Orthop* 1994; 229:25–30
- 496 Trowbridge A, Boese CK, Woodruff B, et al. Incidence of posthospitalization proximal deep venous thrombosis after total hip arthroplasty: a pilot study. *Clin Orthop* 1994; 299:203–208
- 497 Bergqvist D, Benoni G, Bjorgell O, et al. Low-molecular-weight heparin (enoxaparin) as prophylaxis against venous thromboembolism after total hip replacement. *N Engl J Med* 1996; 335:696–700
- 498 White RH, Gettner S, Newman JM, et al. Predictors of rehospitalization for symptomatic venous thromboembolism after total hip arthroplasty. *N Engl J Med* 2000; 343:1758–1764
- 499 Heit JA, Silverstein MD, Mohr DN, et al. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. *Arch Intern Med* 2000; 160:809–815
- 500 Cohen AT, Bailey CS, Alikhan R, et al. Extended thromboprophylaxis with low molecular weight heparin reduces symptomatic venous thromboembolism following lower limb arthroplasty: a meta-analysis. *Thromb Haemost* 2001; 85:940–941
- 501 O'Donnell M, Linkins LA, Kearon C, et al. Reduction of out-of-hospital symptomatic venous thromboembolism by extended thromboprophylaxis with low-molecular-weight heparin following elective hip arthroplasty: a systematic review. *Arch Intern Med* 2003; 163:1362–1366
- 502 Lassen MR, Borris LC, Anderson BS, et al. Efficacy and safety of prolonged thromboprophylaxis with a low molecular weight heparin (dalteparin) after total hip arthroplasty—the Danish Prolonged Prophylaxis (DaPP) Study. *Thromb Res* 1998; 89:281–287
- 503 Comp PC, Spiro TE, Friedman RJ, et al. Prolonged enoxaparin therapy to prevent venous thromboembolism after primary hip or knee replacement. *J Bone Joint Surg Am* 2001; 83:336–345
- 504 Prandoni P, Bruchi O, Sabbion P, et al. Prolonged thromboprophylaxis with oral anticoagulants after total hip arthroplasty: a prospective controlled randomized study. *Arch Intern Med* 2002; 162:1966–1971
- 505 Samama CM, Vray M, Barre J, et al. Extended venous thromboembolism prophylaxis after total hip replacement: a comparison of low-molecular-weight heparin with oral anticoagulant. *Arch Intern Med* 2002; 162:2191–2196
- 506 Thaler HW, Roller RE, Greiner N, et al. Thromboprophylaxis with 60 mg enoxaparin is safe in hip trauma surgery. *J Trauma* 2001; 51:518–521
- 507 Bergqvist D, Jonsson B. Cost-effectiveness of prolonged administration of a low molecular weight heparin for the prevention of deep venous thrombosis following total hip replacement. *Value Health* 1999; 2:288–294
- 508 Davies LM, Richardson GA, Cohen AT. Economic evaluation of enoxaparin as postdischarge prophylaxis for deep vein thrombosis (DVT) in elective hip surgery. *Value Health* 2000; 3:397–406
- 509 Dahl OE, Pleil AM. Investment in prolonged thromboprophylaxis with dalteparin improves clinical outcomes after hip replacement. *J Thromb Haemost* 2003; 1:896–906
- 510 Heit JA. Low-molecular-weight heparin: the optimal duration of prophylaxis against postoperative venous thromboembolism after total hip or knee replacement. *Thromb Res* 2001; 101:V163–V173
- 511 Cogo A, Bernardi E, Prandoni P, et al. Acquired risk factors for deep-vein thrombosis in symptomatic outpatients. *Arch Intern Med* 1994; 154:164–168
- 512 Samama MMftSSG. An epidemiologic study of risk factors for deep vein thrombosis in medical outpatients: the Sirius study. *Arch Intern Med* 2000; 160:3415–3420
- 513 Catre MG. Anticoagulation in spinal surgery: a critical review of the literature. *Can J Surg* 1997; 40:413–419
- 514 West JL, Anderson LD. Incidence of deep vein thrombosis in major adult spinal surgery. *Spine* 1992; 17:S254–S257
- 515 Tetzlaff JE, Yoon HJ, O'Hara J et al. Influence of anesthetic technique on the incidence of deep venous thrombosis after elective lumbar spine surgery [abstract]. *Reg Anesth Pain Med* 1994; 19(suppl):28
- 516 Fujita T, Kostuik JP, Huckell CB, et al. Complications of spinal fusion in adult patients more than 60 years of age. *Orthop Clin North Am* 1998; 29:669–678
- 517 Oda T, Fuji T, Kato Y, et al. Deep venous thrombosis after posterior spinal surgery. *Spine* 2000; 25:2962–2967
- 518 Turner JA, Ersek M, Herron L, et al. Patient outcomes after lumbar spinal fusions. *JAMA* 1992; 268:907–911
- 519 Andreshak TG, An HS, Hall J, et al. Lumbar spine surgery in the obese patient. *J Spinal Disord* 1997; 10:376–379
- 520 Smith MD, Bressler EL, Lonstein JE, et al. Deep venous thrombosis and pulmonary embolism after major reconstructive operations on the spine. *J Bone Joint Surg Am* 1994; 76:980–985
- 521 Flinn WR, Sandager GP, Cerullo LJ, et al. Duplex venous scanning for the prospective surveillance of perioperative venous thrombosis. *Arch Surg* 1989; 124:901–905
- 522 Ferree BA, Stern PJ, Jolson RS, et al. Deep venous thrombosis after spinal surgery. *Spine* 1993; 18:315–319
- 523 Ferree BA, Wright AM. Deep venous thrombosis following posterior lumbar spinal surgery. *Spine* 1993; 18:1079–1082
- 524 Ferree BA. Deep venous thrombosis following lumbar laminotomy and laminectomy. *Orthopedics* 1994; 17:35–38
- 525 Flinn WR, Sandager GP, Silva MB, et al. Prospective surveillance for perioperative venous thrombosis: experience in 2643 patients. *Arch Surg* 1996; 131:472–480
- 526 Nelson LD, Montgomery SP, Dameron TB, et al. Deep vein thrombosis in lumbar spinal fusion: a prospective study of antiembolic and pneumatic compression stockings. *J South Orthop Assoc* 1996; 5:181–184
- 527 Rokito SE, Schwartz MC, Neuwirth MG. Deep vein thrombosis after major reconstructive spinal surgery. *Spine* 1996; 21:853–859
- 528 Wood KB, Kos PB, Abnet JK, et al. Prevention of deep-vein thrombosis after major spinal surgery: a comparison study of external devices. *J Spinal Disord* 1997; 10:209–214
- 529 Gallus AS, Hirsh J, O'Brien SE et al. Prevention of venous thrombosis with small, subcutaneous doses of heparin. *JAMA* 1976; 235:1980–1982
- 530 Macouillard G, Castagnera L, Claverie JP, et al. Prevention of deep venous thrombosis in spinal surgery: comparison of intermittent sequential pneumatic compression versus low molecular weight heparin [abstract]. *Thromb Haemost* 1993; 69:646
- 531 Macouillard G, Castagnera L, Claverie JP, et al. Comparative efficacy of two dosages of a low molecular weight heparin for prevention of deep venous thrombosis in spinal surgery [abstract]. *Thromb Haemost* 1995; 73:979
- 532 Leppilahti J, Orava S. Total Achilles tendon rupture: a review. *Sports Med* 1998; 25:79–100
- 533 Hjelmstedt A, Bergvall U. Incidence of thrombosis in patients with tibial fractures: a phlebographic study. *Acta Chir Scand* 1968; 134:209–218
- 534 Abelseth G, Buckley RE, Pineo GE, et al. Incidence of deep-vein thrombosis in patients with fractures of the lower extremity distal to the hip. *J Orthop Trauma* 1996; 10:230–235
- 535 Lassen MR, Borris LC, Nakov RL. Use of the low-molecu-

- lar-weight heparin reviparin to prevent deep-vein thrombosis after leg injury requiring immobilization. *N Engl J Med* 2002;347:726–730
- 536 Jorgensen PS, Warming T, Hansen K, et al. Low molecular weight heparin (Innohep) as thromboprophylaxis in outpatients with a plaster cast: a venographic controlled study. *Thromb Res* 2002; 105:477–480
- 537 Kock HJ, Schmit-Neuerburg KP, Hanke J, et al. Thromboprophylaxis with low-molecular-weight heparin in outpatients with plaster-cast immobilization of the leg. *Lancet* 1995; 346:459–461
- 538 Spannagel U, Kujath P. Low molecular weight heparin for the prevention of thromboembolism in outpatients immobilized by plaster cast. *Semin Thromb Haemost* 1993; 19(suppl):131–141
- 539 Hamilton MG, Hull RD, Pineo GF. Venous thromboembolism in neurosurgery and neurology patients: a review. *Neurosurgery* 1994; 34:280–296
- 540 Agnelli G. Prevention of venous thromboembolism after neurosurgery. *Thromb Haemost* 1999; 82:925–930
- 541 Chan AT, Atiemo A, Diran LL, et al. Venous thromboembolism occurs frequently in patients undergoing brain tumor surgery despite prophylaxis. *J Thromb Thrombolysis* 1999; 8:139–142
- 542 Van den Berg E, Bahr W, Hess J, et al. Duplex screening for quality assurance of postoperative thromboembolism prophylaxis in neurosurgery: Krefeld Study "Thrombo 2000" [abstract]. *J Thromb Haemost* 2003; 1(suppl):P1460
- 543 Valladares JB, Hankinson J. Incidence of lower extremity deep vein thrombosis in neurosurgical patients. *Neurosurgery* 1980; 6:138–141
- 544 Marras LC, Geerts WH, Perry JR. The risk of venous thromboembolism is increased throughout the course of malignant glioma: an evidence-based review. *Cancer* 2000; 89:640–646
- 545 Anderson FA, Huang W, Sullivan C, et al. The continuing risk of venous thromboembolism following operation for glioma: findings from the Glioma Outcomes Project [abstract]. *Haemost Thromb* 2001; 86(suppl):OC902
- 546 Walsh DC, Kakkar AK. Thromboembolism in brain tumors. *Curr Opin Pul Med* 2001; 7:326–331
- 547 Ruff RL, Posner JB. Incidence and treatment of peripheral venous thrombosis in patients with glioma. *Ann Neurol* 1983; 13:334–336
- 548 Brandes AA, Scelzi E, Salmistraro G, et al. Incidence and risk of thromboembolism during treatment of high-grade gliomas: a prospective study. *Eur J Cancer* 1997; 33:1592–1596
- 549 Anderson FA, Huang W, Bernstein M, et al. Practices in prevention of venous thromboembolism following operation for glioma: findings from the Glioma Outcomes Project [abstract]. *Haemost Thromb* 2001; 86(suppl):OC1016
- 550 Melon E, Keravel Y, Gaston A, et al. Deep venous thrombosis prophylaxis by low molecular weight heparin in neurosurgical patients [abstract]. *Anesthesiology* 1991; 75:A214
- 551 Nurmohamed MT, van Riel AM, Henkens CMA, et al. Low molecular weight heparin and compression stockings in the prevention of venous thromboembolism in neurosurgery. *Thromb Haemost* 1996; 75:233–238
- 552 Wautrecht JC, Macquaire V, Vandesteene A, et al. Prevention of deep vein thrombosis in neurosurgical patients with brain tumors: a controlled, randomized study comparing graded compression stockings alone and with intermittent sequential compression; correlation with pre- and postoperative fibrinolysis—preliminary results. *Int Angiol* 1996; 15(suppl):5–10
- 553 Agnelli G, Piovella F, Buoncristiani P, et al. Enoxaparin plus compression stockings compared with compression stockings alone in the prevention of venous thromboembolism after elective neurosurgery. *N Engl J Med* 1998; 339:80–85
- 554 Cerrato D, Ariano C, Fiacchino F. Deep vein thrombosis and low-dose heparin prophylaxis in neurosurgical patients. *J Neurosurg* 1978; 49:378–381
- 555 Goldhaber SZ, Dunn K, Gerhard-Herman M, et al. Low rate of venous thromboembolism after craniotomy for brain tumor using multimodality prophylaxis. *Chest* 2002; 122:1933–1937
- 556 Macdonald RL, Amidei C, Baron J, et al. Randomized, pilot study of intermittent pneumatic compression devices plus dalteparin versus intermittent pneumatic compression devices plus heparin for prevention of venous thromboembolism in patients undergoing craniotomy. *Surg Neurol* 2003; 59:362–372
- 557 Boeer A, Voth E, Henze T, et al. Early heparin therapy in patients with spontaneous intracerebral haemorrhage. *J Neurol Neurosurg Psychiatry* 1991; 54:466–467
- 558 Frim DM, Barker FG, Poletti CE, et al. Postoperative low-dose heparin decreases thromboembolic complications in neurosurgical patients. *Neurosurgery* 1992; 30:830–832
- 559 Macdonald RL, Amidei C, Lin G, et al. Safety of perioperative subcutaneous heparin for prophylaxis of venous thromboembolism in patients undergoing craniotomy. *Neurosurgery* 1999; 45:245–251
- 560 Constantini S, Kanner A, Friedman A, et al. Safety of perioperative minidose heparin in patients undergoing brain tumor surgery: a prospective, randomized, double-blind study. *J Neurosurg* 2001; 94:918–921
- 561 Dickinson LD, Miller LD, Patel CP, et al. Enoxaparin increases the incidence of postoperative intracranial hemorrhage when initiated preoperatively for deep venous thrombosis prophylaxis in patients with brain tumors. *Neurosurgery* 1998; 43:1074–1081
- 562 Raabe A, Gerlach R, Zimmermann M, et al. The risk of haemorrhage associated with early postoperative heparin administration after intracranial surgery. *Acta Neurochir (Wien)* 2001; 143:1–7
- 563 Meissner MH. Deep venous thrombosis in the trauma patient. *Semin Vasc Surg* 1998; 11:274–282
- 564 Rogers FB. Venous thromboembolism in trauma patients: a review. *Surgery* 2001; 130:1–12
- 565 Rogers FB, Cipolle MD, Velmahos G, et al. Practice management guidelines for the prevention of venous thromboembolism in trauma patients: the EAST Practice Management Guidelines Work Group. *J Trauma* 2002; 53:142–164
- 566 Kudsk KA, Fabian TC, Baum S, et al. Silent deep vein thrombosis in immobilized multiple trauma patients. *Am J Surg* 1989; 158:515–519
- 567 O'Malley KF, Ross SE. Pulmonary embolism in major trauma patients. *J Trauma* 1990; 30:748–750
- 568 Rogers FB, Shackford SR, Wilson J, et al. Prophylactic vena cava filter insertion in severely injured trauma patients: indications and preliminary results. *J Trauma* 1993; 35:637–641
- 569 Smith RM, Airey M, Franks AJ. Death after major trauma: can we affect it? The changing cause of death in each phase after injury [abstract]. *Injury* 1994; 25(suppl):SB23–SB24
- 570 Acosta JA, Yang JC, Winchell RJ, et al. Lethal injuries and time to death in a level I trauma center. *J Am Coll Surg* 1998; 186:528–533
- 571 Meissner MH, Chandler WL, Elliott JS. Venous thromboembolism in trauma: a local manifestation of systemic hypercoagulability? *J Trauma* 2003; 54:224–231
- 572 Velmahos GC, Kern J, Chan LS, et al. Prevention of venous thromboembolism after injury: an evidence-based report:

- Part II. Analysis of risk factors and evaluation of the role of vena caval filters. *J Trauma* 2000; 49:140–144
- 573 Knudson MM, Lewis FR, Clinton A, et al. Prevention of venous thromboembolism in trauma patients. *J Trauma* 1994; 37:480–487
- 574 Frezza EE, Siram SM, van Thiel DH, et al. Venous thromboembolism after penetrating chest trauma is not a cause of early death. *J Cardiovasc Surg* 1996; 37:521–524
- 575 Bauer G. Thrombosis following leg injuries. *Acta Chir Scand* 1944; 90:229–248
- 576 Geerts WH, Jay RM, Code KI, et al. A comparison of low-dose heparin with low-molecular-weight heparin as prophylaxis against venous thromboembolism after major trauma. *N Engl J Med* 1996; 335:701–707
- 577 Haentjens P. Thromboembolic prophylaxis in orthopaedic trauma patients: a comparison between a fixed dose and an individually adjusted dose of a low molecular weight heparin (nadroparin calcium). *Injury* 1996; 27:385–390
- 578 Knudson MM, Morabito D, Paiement GD, et al. Use of low molecular weight heparin in preventing thromboembolism in trauma patients. *J Trauma* 1996; 41:446–459
- 579 Cohn SM, Moller BA, Feinstein AJ, et al. Prospective trial of low-molecular-weight heparin versus unfractionated heparin in moderately injured patients. *Vasc Surg* 1999; 33:219–223
- 580 Elliott CG, Dudley TM, Egger M, et al. Calf-thigh sequential pneumatic compression compared with plantar venous pneumatic compression to prevent deep-vein thrombosis after non-lower extremity trauma. *J Trauma* 1999; 47:25–32
- 581 Montgomery KD, Geerts WH, Potter HG, et al. Practical management of venous thromboembolism following pelvic fractures. *Orthop Clin North Am* 1997; 28:397–404
- 582 Pasquale M, Fabian TC. Development atEAHCoPMG: practice management guidelines for trauma from the Eastern Association for the Surgery of Trauma. *J Trauma* 1998; 44:941–957
- 583 Shackford SR, Davis JW, Hollingsworth-Fridlund P, et al. Venous thromboembolism in patients with major trauma. *Am J Surg* 1990; 159:365–369
- 584 Napolitano LM, Garlapati VS, Heard SO, et al. Asymptomatic deep venous thrombosis in the trauma patient: is an aggressive screening protocol justified? *J Trauma* 1995; 39:651–659
- 585 Velmahos GC, Kern J, Chan LS, et al. Prevention of venous thromboembolism after injury: an evidence-based report: Part I. Analysis of risk factors and evaluation of the role of vena caval filters. *J Trauma* 2000; 49:132–139
- 586 Gearhart MM, Luchette FA, Proctor MC, et al. The risk assessment profile score identifies trauma patients at risk for deep vein thrombosis. *Surgery* 2000; 128:631–640
- 587 Huk M, Lynsky D, O'Callaghan T et al. Compliance of sequential compression device for deep vein thrombosis prophylaxis in the adult trauma patient: surgical intensive care unit vs. intermediate care [abstract]. *Crit Care Med* 1998; 26(suppl):A47
- 588 Geerts WH, Jay R, Code K, et al. Venous foot pump as thromboprophylaxis in major trauma [abstract]. *Thromb Haemost* 1999; 82(suppl):650–651
- 589 Upchurch GR, Demling RH, Davies J, et al. Efficacy of subcutaneous heparin in prevention of venous thromboembolic events in trauma patients. *Am Surg* 1995; 61:749–755
- 590 Devlin JW, Pettita A, Shepard AD, et al. Cost-effectiveness of enoxaparin versus low-dose heparin for prophylaxis against venous thrombosis after major trauma. *Pharmacotherapy* 1998; 18:1335–1342
- 591 Wade WE, Chisholm MA. Deep venous thrombosis prophylaxis in trauma: cost analysis. *Blood Coag Fibrinolysis* 2000; 11:101–106
- 592 Selby R, Geerts WH. Venous thromboembolism prophylaxis after trauma: dollars and sense. *Crit Care Med* 2001; 29:1839–1840
- 593 Shorr AF, Ramage AS. Enoxaparin for thromboprophylaxis after major trauma: potential cost implications. *Crit Care Med* 2001; 29:1659–1665
- 594 Burns GA, Cohn SM, Frumento RJ, et al. Prospective ultrasound evaluation of venous thrombosis in high-risk trauma patients. *J Trauma* 1993; 35:405–408
- 595 Brasel KJ, Borgstrom DC, Weigelt JA. Cost-effective prevention of pulmonary embolus in high-risk trauma patients. *J Trauma* 1997; 42:456–462
- 596 Headrick JR, Barker DE, Pate LM, et al. The role of ultrasonography and inferior vena cava filter placement in high-risk trauma patients. *Am Surg* 1997; 63:1–8
- 597 van den Berg E, Bathgate B, Panagakos E, et al. Duplex screening as a method of quality assurance of perioperative thromboembolism prophylaxis. *Int Angiol* 1999; 18:210–219
- 598 Satiani B, Falcone R, Shook L, et al. Screening for major deep vein thrombosis in seriously injured patients: a prospective study. *Ann Vasc Surg* 1997; 11:626–629
- 599 Piotrowski JJ, Alexander JJ, Brandt CP, et al. Is deep vein thrombosis surveillance warranted in high-risk trauma patients? *Am J Surg* 1996; 172:210–213
- 600 Hammers LW, Cohn SM, Brown JM, et al. Doppler color flow imaging surveillance of deep vein thrombosis in high-risk trauma patients. *J Ultrasound Med* 1996; 15:19–24
- 601 Stover MD, Morgan SJ, Boisse MJ, et al. Prospective comparison of contrast-enhanced computed tomography versus magnetic resonance venography in the detection of occult deep pelvic vein thrombosis in patients with pelvic and acetabular fractures. *J Orthop Trauma* 2002; 16:613–621
- 602 Spain DA, Richardson JD, Polk HC, et al. Venous thromboembolism in the high risk trauma patient: do risks justify aggressive screening and prophylaxis? *J Trauma* 1997; 42:463–469
- 603 Schwarcz TH, Quick RC, Minion DJ, et al. Enoxaparin treatment in high-risk trauma patients limits the utility of surveillance venous duplex scanning. *J Vasc Surg* 2001; 34:447–452
- 604 Khansarinia S, Dennis JW, Veldenz HC, et al. Prophylactic Greenfield filter placement in selected high-risk trauma patients. *J Vasc Surg* 1995; 22:231–236
- 605 Rogers FB, Shackford SR, Ricci MA, et al. Routine prophylactic vena cava filter insertion in severely injured trauma patients decreases the incidence of pulmonary embolism. *J Am Coll Surg* 1995; 180:641–647
- 606 Rodriguez JL, Lopez JM, Proctor MC, et al. Early placement of prophylactic vena caval filters in injured patients at high risk for pulmonary embolism. *J Trauma* 1996; 40:797–802
- 607 Langan EM, Miller RS, Casey WJ, et al. Prophylactic inferior vena cava filters in trauma patients at high risk: follow-up examination and risk/benefit assessment. *J Vasc Surg* 1999; 30:484–490
- 608 Sing RF, Cicci CK, Smith CH, et al. Bedside insertion of inferior vena cava filters in the intensive care unit. *J Trauma* 1999; 47:1104–1107
- 609 Tola JC, Holtzmann R, Lottenberg L. Bedside placement of inferior vena cava filters in the intensive care unit. *Am Surg* 1999; 65:833–837
- 610 Carlin AM, Tyburski JG, Wilson RF, et al. Prophylactic and therapeutic inferior vena cava filters to prevent pulmonary emboli in trauma patients. *Arch Surg* 2002; 137:521–527
- 611 Girard P, Stern JB, Parent F. Medical literature and vena cava filters: so far so weak. *Chest* 2002; 122:963–967

- 612 McMurty AL, Owings JT, Anderson JT, et al. Increased use of prophylactic vena cava filters in trauma patients failed to decrease overall incidence of pulmonary embolism. *J Am Coll Surg* 1999; 189:314–320
- 613 Becker DM, Philbrick JT, Selby JB. Inferior vena cava filters: indications, safety, effectiveness. *Arch Intern Med* 1992; 152:1985–1994
- 614 Patton JH, Fabian TC, Croce MA, et al. Prophylactic Greenfield filters: acute complications and long-term follow-up. *J Trauma* 1996; 41:231–236
- 615 Decousus H, Leizorovicz A, Parent F, et al. A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. *N Engl J Med* 1998; 338:409–415
- 616 Blebea J, Wilson R, Waybill P, et al. Deep venous thrombosis after percutaneous insertion of vena caval filters. *J Vasc Surg* 1999; 30:821–828
- 617 Greenfield LJ, Proctor MC, Michaels AJ, et al. Prophylactic vena cava filters in trauma: the rest of the story. *J Vasc Surg* 2000; 32:490–497
- 618 Wojcik R, Cipolle MD, Fearen I, et al. Long-term follow-up of trauma patients with a vena caval filter. *J Trauma* 2000; 49:839–843
- 619 Greenfield LJ. Discussion. *J Vasc Surg* 1995; 22:235–236
- 620 Rohrer MJ, Scheidler MG, Wheeler HB, et al. Extended indications for placement of an inferior vena cava filter. *J Vasc Surg* 1989; 10:44–50
- 621 Sekharan J, Dennis JW, Miranda FE, et al. Long-term follow-up of prophylactic Greenfield filters in multisystem trauma patients. *J Trauma* 2001; 51:1087–1091
- 622 Duperier T, Mosenthal A, Swan KG, et al. Acute complications associated with Greenfield filter insertion in high-risk trauma patients. *J Trauma* 2003; 54:545–549
- 623 Lorch H, Welger D, Wagner V, et al. Current practice of temporary vena cava filter insertion: a multicenter registry. *J Vasc Interv Radiol* 2000; 11:83–88
- 624 Ashley DW, Gamblin TC, S.T. B, et al. Accurate deployment of vena cava filters: comparison of intravascular ultrasound and contrast venography. *J Trauma* 2001; 50:975–981
- 625 Connors MS, Becker S, Guzman RJ, et al. Duplex scan-directed placement of inferior vena cava filters: a five-year institutional experience. *J Vasc Surg* 2002; 35:286–291
- 626 Maxwell RA, Chavarria-Aguilar M, Cockerham WT, et al. Routine prophylactic vena cava filtration is not indicated after acute spinal cord injury. *J Trauma* 2002; 52:902–906
- 627 Brathwaite CEM, O'Malley KF, Ross SE, et al. Continuous pulse oximetry and the diagnosis of pulmonary embolism in critically ill trauma patients. *J Trauma* 1992; 33:528–530
- 628 Dennis JW, Menawat S, von Thron J, et al. Efficacy of deep venous thrombosis prophylaxis in trauma patients and identification of high-risk groups. *J Trauma* 1993; 35:132–139
- 629 Norwood SH, McAuley CE, Berne JD, et al. A potentially expanded role for enoxaparin in preventing venous thromboembolism in high risk blunt trauma patients. *J Am Coll Surg* 2001; 192:161–167
- 630 Norwood SH, McAuley CE, Berne JD, et al. Prospective evaluation of the safety of enoxaparin prophylaxis for venous thromboembolism in patients with intracranial hemorrhagic injuries. *Arch Surg* 2002; 137:696–702
- 631 Consortium for Spinal Cord Medicine. Prevention of thromboembolism in spinal cord injury. *J Spinal Cord Med* 1997; 20:259–283
- 632 Attia J, Ray JG, Cook DJ, et al. Deep vein thrombosis and its prevention in critically ill adults. *Arch Intern Med* 2001; 161:1268–1279
- 633 Spinal Cord Injury Thromboprophylaxis Investigators. Prevention of venous thromboembolism in the acute treatment phase after spinal cord injury: a randomized, multicenter trial comparing low-dose heparin plus intermittent pneumatic compression with enoxaparin. *J Trauma* 2003; 54:1116–1126
- 634 Waring WP, Karunas RS. Acute spinal cord injuries and the incidence of clinically occurring thromboembolic disease. *Paraplegia* 1991; 29:8–16
- 635 DeVivo MJ, Krause JS, Lammertse DP. Recent trends in mortality and causes of death among persons with spinal cord injury. *Arch Phys Med Rehabil* 1999; 80:1411–1419
- 636 Kulkarni JR, Burt AA, Tromans AT, et al. Prophylactic low dose heparin anticoagulant therapy in patients with spinal cord injuries: a retrospective study. *Paraplegia* 1992; 30:169–172
- 637 Powell M, Kirshblum S, O'Connor KC. Duplex ultrasound screening for deep vein thrombosis in spinal cord injured patients at rehabilitation admission. *Arch Phys Med Rehabil* 1999; 80:1044–1046
- 638 Aito S, Pieri A, D'Andrea M et al. Primary prevention of deep venous thrombosis and pulmonary embolism in acute spinal cord injured patients. *Spinal Cord* 2002; 40:300–303
- 639 Lim AC, Roth EJ, Green D. Lower limb paralysis: its effect on the recanalization of deep-vein thrombosis. *Arch Phys Med Rehabil* 1992; 73:331–333
- 640 Kim SW, Charalal JT, Park KW, et al. Prevalence of deep venous thrombosis in patients with chronic spinal cord injury. *Arch Phys Med Rehabil* 1994; 75:965–968
- 641 Green D, Rossi EC, Yao JS, et al. Deep vein thrombosis in spinal cord injury: effect of prophylaxis with calf compression, aspirin, and dipyridamole. *Paraplegia* 1982; 20:227–234
- 642 Green D, Lee MY, Ito VY, et al. Fixed vs adjusted-dose heparin in the prophylaxis of thromboembolism in spinal cord injury. *JAMA* 1988; 260:1255–1258
- 643 Merli GJ, Herbison GJ, Ditunno JF, et al. Deep vein thrombosis: prophylaxis in acute spinal cord injured patients. *Arch Phys Med Rehabil* 1988; 69:661–664
- 644 Green D, Lee MY, Lim AC, et al. Prevention of thromboembolism after spinal cord injury using low-molecular-weight heparin. *Ann Intern Med* 1990; 113:571–574
- 645 Harris S, Chen D, Green D. Enoxaparin for thromboembolism prophylaxis in spinal injury: preliminary report on experience with 105 patients. *Am J Phys Med Rehabil* 1996; 75:326–327
- 646 Silver JR, Moulton A. Prophylactic anticoagulant therapy against pulmonary emboli in acute paraplegia. *BMJ* 1970; 2:338–340
- 647 Silver JR. The prophylactic use of anticoagulant therapy in the prevention of pulmonary emboli in one hundred consecutive spinal injury patients. *Paraplegia* 1974; 12:188–196
- 648 El Masri WS, Silver JR. Prophylactic anticoagulant therapy in patients with spinal cord injury. *Paraplegia* 1981; 19:334–342
- 649 Stambolis V, Shekhani NA, Wright RE. Warfarin for the prophylaxis of thromboembolism in patients with acute traumatic spinal cord injury [abstract]. *Arch Phys Med Rehabil* 1995; 76:1077–1078
- 650 Wilson JT, Rogers FB, Wald SL, et al. Prophylactic vena cava filter insertion in patients with traumatic spinal cord injury: preliminary results. *Neurosurgery* 1994; 35:234–239
- 651 Hadley MN. Deep venous thrombosis and thromboembolism in patients with cervical spinal cord injuries. *Neurosurgery* 2002; 50(suppl):S73–S80
- 652 Balshi JD, Cantelmo NL, Menzoian JO. Complications of caval interruption by Greenfield filter in quadriplegics. *J Vasc Surg* 1989; 9:558–562
- 653 Kinney TB, Rose SC, Valji K, et al. Does cervical spinal cord injury induce a higher incidence of complications after

- prophylactic Greenfield inferior vena cava filter usage? *J Vasc Interv Radiol* 1996; 7:907-915
- 654 Yehnik A, Dizien O, Bussel B, et al. Systematic lower limb phlebography in acute spinal cord injury in 147 patients. *Paraplegia* 1991; 29:253-260
- 655 Colachis SC, Clinchot DM. The association between deep venous thrombosis and heterotopic ossification in patients with acute traumatic spinal cord injury. *Paraplegia* 1993; 31:507-512
- 656 Gunduz S, Ogur E, Mohur H, et al. Deep vein thrombosis in spinal cord injured patients. *Paraplegia* 1993; 31:606-610
- 657 Deep K, Jigajinni MV, McLean AN, et al. Prophylaxis of thromboembolism in spinal injuries: results of enoxaparin used in 276 patients. *Spinal Cord* 2001; 39:88-91
- 658 Spinal Cord Injury Thromboprophylaxis Investigators. Prevention of venous thromboembolism in the rehabilitation phase after spinal cord injury: prophylaxis with low-dose heparin or enoxaparin. *J Trauma* 2003; 54:1111-1115
- 659 Chen D, Apple DF, Hudson LM, et al. Medical complications during acute rehabilitation following spinal cord injury: current experience of the Model Systems. *Arch Phys Med Rehabil* 1999; 80:1397-1401
- 660 Hull RD. Venous thromboembolism in spinal cord injury patients. *Chest* 1992; 102(suppl):658S-663S
- 661 Ball PA. Critical care of spinal cord injury. *Spine* 2001; 26(suppl):S27-S30
- 662 Kowal-Vern A, Gamelli RL, Walenga JM, et al. The effect of burn wound size on hemostasis: a correlation of the hemostatic changes to the clinical state. *J Trauma* 1992; 33:50-57
- 663 Wait M, Hunt JL, Purdue GF. Duplex scanning of central vascular access sites in burn patients. *Ann Surg* 1990; 211:499-503
- 664 Gnoyski JM, Keen ME, Gamelli RL, et al. Deep venous thrombosis and the association with burns involving the lower extremities [abstract]. *Arch Phys Med Rehabil* 1994; 75:1045
- 665 Harrington DT, Mozingo DW, Cancio L, et al. Thermally injured patients are at significant risk for thromboembolic complications [abstract]. *J Trauma* 2001; 50:495-499
- 666 Brischetto MJ, Brischetto MA, Auer A, et al. Venous thrombosis in burn patients [abstract]. *Am J Respir Crit Care Med* 1998; 157:A768
- 667 Harrington DT, Burke B, Bird P, et al. Thermally injured patients are at significant risk of thromboembolic complications [abstract]. *J Burn Care Rehabil* 1999; 20:S178
- 668 Wahl WL, Brandt MM, Ahrens KS, et al. Venous thrombosis incidence in burn patients preliminary results of a prospective study. *J Burn Care Rehabil* 2002; 23:97-102
- 669 Wibbenmeyer LA, Hoballah JJ, Amelon MJ, et al. The prevalence of venous thromboembolism of the lower extremity among thermally injured patients determined by duplex sonography. *J Trauma* 2003; 55:1162-1167
- 670 Coleman JB, Chang FC. Pulmonary embolism: an unrecognized event in severely burned patients. *Am J Surg* 1975; 130:697-699
- 671 Rue LW, Cioffi WG, Rush R, et al. Thromboembolic complications in thermally injured patients. *World J Surg* 1992; 16:1151-1155
- 672 Wahl WL, Brandt MM. Potential risk factors for deep venous thrombosis in burn patients. *J Burn Care Rehabil* 2001; 22:128-131
- 673 Sheridan RL, Rue LW, McManus WF, et al. Burns in morbidly obese patients. *J Trauma* 1992; 33:818-820
- 674 Sorensen B, Hall KV. Mortality and causes of death in burned patients treated by the exposure method. *Plast Reconstr Surg* 1973; 51:59-66
- 675 Warden GD, Wilmore DW, Pruitt BA. Central venous thrombosis: a hazard of medical progress. *J Trauma* 1973; 13:620-626
- 676 Evidence Based Guidelines Group American Burn Association. Deep venous thrombosis prophylaxis in burns. *J Burn Care Rehabil* 2001; 22(suppl):67S-69S
- 677 Bouthier J. The venous thrombotic risk in nonsurgical patients. *Drugs* 1996; 52(suppl):16-29
- 678 Goldhaber SZ, Dunn K, MacDougall RC, et al. New onset of venous thromboembolism among hospitalized patients at Brigham and Women's Hospital is caused more often by prophylaxis failure than by withholding treatment. *Chest* 2000; 118:1680-1684
- 679 Goldhaber SZ, Savage DD, Garison RJ, et al. Risk factors for pulmonary embolism: the Farmingham Study. *Am J Med* 1983; 74:1023-1028
- 680 Lindblad B, Sternby NH, Bergqvist D. Incidence of venous thromboembolism verified by necropsy over 30 years. *BMJ* 1991; 302:709-711
- 681 Alikhan R, Peters F, Wilmott R, et al. Epidemiology of fatal pulmonary embolism in non-surgical patients [abstract]. *Blood* 2002; 100:276a
- 682 Haas SK. Venous thromboembolic risk and its prevention in hospitalized medical patients. *Semin Thromb Haemost* 2002; 28:577-583
- 683 Gallus AS, Hirsh J, Tuttle RJ, et al. Small subcutaneous doses of heparin in prevention of venous thrombosis. *N Engl J Med* 1973; 288:545-551
- 684 Belch JJ, Lowe GDO, Ward AG, et al. Prevention of deep vein thrombosis in medical patients by low-dose heparin. *Scott Med J* 1981; 26:115-117
- 685 Cade JF. High risk of the critically ill for venous thromboembolism. *Crit Care Med* 1982; 10:448-450
- 686 Dahan R, Houlbert D, Caulin C, et al. Prevention of deep vein thrombosis in elderly medical in-patients by a low molecular weight heparin: a randomized double-blind trial. *Haemostasis* 1986; 16:159-164
- 687 Samama MM, Cohen AT, Darmon JY, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. *N Engl J Med* 1999; 341:793-800
- 688 Oger E, Bressollette L, Nonent M, et al. High prevalence of asymptomatic deep vein thrombosis on admission in a medical unit among elderly patients: the TADEUS Project. *Thromb Haemost* 2002; 88:592-597
- 689 Leizorovicz A, Cohen AT, Turpie AGG, et al. A randomized placebo controlled trial of dalteparin for the prevention of venous thromboembolism in 3706 acutely ill medical patients: the PREVENT medical thromboprophylaxis study [abstract]. *J Thromb Haemost* 2003; 1(suppl):OC396
- 690 Prescott SM, Richards KL, Tikoff G, et al. Venous thromboembolism in decompensated chronic obstructive pulmonary disease: a prospective study. *Am Rev Respir Dis* 1981; 123:32-36
- 691 Schonhofer B, Kohler D. Prevalence of deep-vein thrombosis of the leg in patients with acute exacerbation of chronic obstructive pulmonary disease. *Respiration* 1998; 65:173-177
- 692 Schuurman B, den Heijer M, Nijs AM. Thrombosis prophylaxis in hospitalised medical patients: does prophylaxis in all patients make sense? *Neth J Med* 2000; 56:171-176
- 693 Cohen AT. Venous thromboembolic disease management of the nonsurgical moderate-and high-risk patient. *Semin Hematol* 2000; 37(suppl):19-22
- 694 Bergmann JF, Mouly S. Thromboprophylaxis in medical patients: focus on France. *Semin Thromb Hemost* 2002; 28(suppl):51-55
- 695 Cohen AT, Alikhan R, Arcelus J, et al. Venous thromboem-

- bolism risk assessment in medical patients [abstract]. *Blood* 2002; 100:280a
- 696 Lutz L, Haas S, Hach-Wunderle V, et al. Venous thromboembolism in internal medicine: risk assessment and pharmaceutical prophylaxis: publication for the specialist platform. *Med Welt* 2002; 53:231–234
- 697 Howell MD, Geraci JM, Knowlton AA. Congestive heart failure and outpatient risk of venous thromboembolism: a retrospective, case-control study. *J Clin Epidemiol* 2001; 54:810–816
- 698 Tveit DP, Hypolite IO, Hshieh P, et al. Chronic dialysis patients have high risk for pulmonary embolism. *Am J Kidney Dis* 2002; 39:1011–1017
- 699 Muir KW, Watt A, Baxter G, et al. Randomized trial of graded compression stockings for prevention of deep-vein thrombosis after acute stroke. *Q J Med* 2000; 93:359–364
- 700 Alikhan R, Cohen AT, Combe S, et al. Benefit of enoxaparin in medical patients: a subgroup analysis [abstract]. *Blood* 2001; 98:266a
- 701 Bergmann JF, Neuhart E. A multicenter randomized double-blind study of enoxaparin compared with unfractionated heparin in the prevention of venous thromboembolic disease in elderly in-patients bedridden for an acute medical illness. *Thromb Haemost* 1996; 76:529–534
- 702 Harenberg J, Roebruck P, Heene DL, et al. Subcutaneous low-molecular-weight heparin versus standard heparin and the prevention of thromboembolism in medical inpatients. *Haemostasis* 1996; 26:127–139
- 703 Lechler E, Schramm W, Flosbach CW, et al. The venous thrombotic risk in non-surgical patients: epidemiological data and efficacy/safety profile of a low-molecular-weight heparin (enoxaparin). *Haemostasis* 1996; 26(suppl):49–56
- 704 Harenberg J, Schomaker U, Flosbach CW. Enoxaparin is superior to unfractionated heparin in the prevention of thromboembolic events in medical inpatients at increased thromboembolic risk [abstract]. *Blood* 1999; 94:(suppl)399a
- 705 Kleber FX, Witt C, Vogel G, et al. Randomized comparison of enoxaparin with unfractionated heparin for the prevention of venous thromboembolism in medical patients with heart failure or severe respiratory disease. *Am Heart J* 2003; 145:614–621
- 706 Gardlund BfHPSG. Randomised, controlled trial of low-dose heparin for prevention of fatal pulmonary embolism in patients with infectious diseases. *Lancet* 1996; 347:1357–1361
- 707 Bergmann JF, Caulin C. Heparin prophylaxis in bedridden patients [correspondence]. *Lancet* 1996; 348:205–206
- 708 Wade WE, Chisholm MA. Cost-effectiveness analysis of deep vein thrombosis prophylaxis in internal medicine patients. *Thromb Res* 1999; 94:65–68
- 709 Lloyd A, Anderson P, Quinlan DJ, et al. Economic evaluation of prophylaxis of venous thromboembolism in acute medical patients with enoxaparin in the U.K. [abstract]. *Blood* 2000; 96:847a
- 710 de Lissoyov G, Subedi P. Economic evaluation of enoxaparin as prophylaxis against venous thromboembolism in seriously ill medical patients: a US perspective. *Am J Manag Care* 2002; 8:1082–1088
- 711 Lamy A, Wang X, Kent R, et al. Economic evaluation of the MEDENOX trial: a Canadian perspective. *Can Respir J* 2002; 9:169–177
- 712 Alikhan R, Cohen AT. A safety analysis of thromboprophylaxis in acute medical illness. *Thromb Haemost* 2003; 89:590–591
- 713 Girolami B, Prandoni P, Stefani PM, et al. The incidence of heparin-induced thrombocytopenia in hospitalised medical patients treated with subcutaneous unfractionated heparin: a prospective cohort study. *Blood* 2003; 101:2955–2959
- 714 Cohen AT, Davidson BL, Gallus AS, et al. Fondaparinux for the prevention of VTE in acutely ill medical patients [abstract]. *Blood* 2003; 102:15a
- 715 Donati MB. Cancer and thrombosis. *Haemostasis* 1994; 24:128–131
- 716 Arkel YS. Thrombosis and cancer. *Semin Oncol* 2000; 27:362–374
- 717 Levitan N, Dowlati A, Remick SC, et al. Rates of initial and recurrent thromboembolic disease among patients with malignancy versus those without malignancy: risk analysis using Medicare claims data. *Medicine* 1999; 78:285–291
- 718 Sallah S, Wan JY, Nguyen NP. Venous thrombosis in patients with solid tumors: determination of frequency and characteristics. *Thromb Haemost* 2002; 87:575–579
- 719 Thodiyl PA, Kakkar AK. Variation in relative risk of venous thromboembolism in different cancers. *Thromb Haemost* 2002; 87:1076–1077
- 720 Lee AYY, Levine MN. Venous thromboembolism and cancer: risks and outcomes. *Circulation* 2003; 107:I-17–I-21
- 721 Gallus AS. Prevention of post-operative deep leg vein thrombosis in patients with cancer. *Thromb Haemost* 1997; 78:126–132
- 722 Kakkar AK, Williamson RCN. Prevention of venous thromboembolism in cancer patients. *Semin Thromb Haemost* 1999; 25:239–243
- 723 Bergqvist D. Venous thromboembolism and cancer: prevention of VTE. *Thromb Res* 2001; 102:V209–V213
- 724 Kakkar AK, Haas S, Walsh D, et al. Prevention of perioperative venous thromboembolism: outcome after cancer and non-cancer surgery [abstract]. *Thromb Haemost* 2001; 86(suppl):OC1732
- 725 Fisher B, Constantino J, Redmond C, et al. A randomized clinical trial evaluating tamoxifen in the treatment of patients with node-negative breast cancer who have estrogen-receptor-positive tumors. *N Engl J Med* 1989; 320:479–484
- 726 Fisher B, Dignan J, Wolmark N, et al. Tamoxifen and chemotherapy for lymph node-negative, estrogen receptor-positive breast cancer. *J Natl Cancer Inst* 1997; 89:1673–1682
- 727 Levine MN, Gent M, Hirsh J, et al. The thrombogenic effect of anticancer drug therapy in women with stage II breast cancer. *N Engl J Med* 1988; 318:404–407
- 728 Saphner T, Tormey DC, Gray R. Venous and arterial thrombosis in patients who received adjuvant therapy for breast cancer. *J Clin Oncol* 1991; 9:286–294
- 729 Levine M, Hirsh J, Gent M, et al. Double-blind randomized trial of very-low-dose warfarin for prevention of thromboembolism in stage IV breast cancer. *Lancet* 1994; 343:886–889
- 730 Rajan R, Gafni A, Levine M, et al. Very low-dose warfarin prophylaxis to prevent thromboembolism in women with metastatic breast cancer receiving chemotherapy: an economic evaluation. *J Clin Oncol* 1995; 13:42–46
- 731 Fisher B, Constantino JP, Wickerham DL. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst* 1998; 90:1371–1388
- 732 Pritchard KI, Paterson AHG, Paul NA, et al. Increased thromboembolic complications with concurrent tamoxifen and chemotherapy in a randomized trial of adjuvant therapy for women with metastatic breast cancer. *J Clin Oncol* 1996; 14:2731–2737
- 733 Bonnetere J, Buzdar A, Nabholz JMA, et al. Anastrozole is superior to tamoxifen as first-line therapy in hormone receptor positive advanced breast carcinoma: results of two

- randomized trials designed for combined analysis. *Cancer* 2001; 92:2247–2258
- 734 ATAC (Arimidex Tamoxifen Alone or in Combination) Trialists' Group. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. *Lancet* 2002; 359:2131–2139
- 735 Kakkar AK, Kadziola Z, Williamson RCN, et al. Low molecular weight heparin (LMWH) therapy and survival in advanced cancer [abstract]. *Blood* 2002; 100:148a
- 736 Bona RD. Thrombotic complications of central venous catheters in cancer patients. *Semin Thromb Haemost* 1999; 25:147–155
- 737 Randolph AG, Cook DJ, Gonzales CA, et al. Benefit of heparin in central venous and pulmonary artery catheters: a meta-analysis of randomized controlled trials. *Chest* 1998; 113:165–171
- 738 Bern MM, Lokich JJ, Wallach SR, et al. Very low doses of warfarin can prevent thrombosis in central venous catheters: a randomized prospective trial. *Ann Intern Med* 1990; 112:423–428
- 739 Couban S, Goodyear M, Burnell M, et al. A randomized double-blind placebo-controlled study of low dose warfarin for the prevention of symptomatic central venous catheter-associated thrombosis in patients with cancer [abstract]. *Blood* 2002; 100(suppl):703a
- 740 Heaton DC, Han DY, Inder A. Minidose (1 mg) warfarin as prophylaxis for central vein catheter thrombosis. *Intern Med* 2002; 32:84–88
- 741 Masci G, Magagnoli M, Zucali PA, et al. Minidose warfarin prophylaxis for catheter-associated thrombosis in cancer patients: can it be safely associated with fluorouracil-based chemotherapy? *J Clin Oncol* 2003; 21:736–739
- 742 Monreal M, Alastrue A, Rull M, et al. Upper extremity deep venous thrombosis in cancer patients with venous access devices: prophylaxis with a low molecular weight heparin (Fragmin). *Thromb Haemost* 1996; 75:251–253
- 743 Reichardt P, Kretzschmar A, Biakhov M, et al. A phase III double-blind, placebo-controlled study evaluating the efficacy and safety of daily low-molecular-weight heparin (dalteparin sodium, Fragmin) in preventing catheter-related complications in cancer patients with central venous catheters [abstract]. *Clin Oncol* 2002; 21:abstract 1474
- 744 Walshe LJ, Malak SF, Eagan J, et al. Complication rates among cancer patients with peripherally inserted central catheters. *J Clin Oncol* 2002; 20:3276–3281
- 745 Krauth D, Holden A, Knapic N, et al. Safety and efficacy of long-term oral anticoagulation in cancer patients. *Cancer* 1987; 59:983–985
- 746 Hutten BA, Prins MH, Gent M, et al. Incidence of recurrent thromboembolic and bleeding complications among patients with venous thromboembolism in relation to both malignancy and achieved International Normalized ratio: a retrospective analysis. *J Clin Oncol* 2000; 18:3078–3083
- 747 Prandoni P, Lensing AWA, Piccioli A, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. *Blood* 2002; 100:3484–3488
- 748 Geerts W, Cook D, Selby R, et al. Venous thromboembolism and its prevention in critical care. *J Crit Care* 2002; 17:95–104
- 749 Jain M, Schmidt GA. Venous thromboembolism: prevention and prophylaxis. *Semin Respir Crit Care Med* 1997; 18: 79–90
- 750 Cook D, Attia J, Weaver B, et al. Venous thromboembolic disease: an observational study in medical-surgical intensive care unit patients. *J Crit Care* 2000; 15:127–132
- 751 Cook DJ, Crowther M, Meade M, et al. Deep venous thrombosis in medical-surgical ICU patients: prevalence, incidence and risk factors [abstract]. *Crit Care* 2003; 7(suppl):S54
- 752 Goldberg SK, Lippmann ML, Walkenstein MD, et al. The prevalence of DVT among patients in respiratory failure: the role of DVT prophylaxis [abstract]. *Am J Respir Crit Care Med* 1996; 153:A94
- 753 Harris LM, Curl GR, Booth FV, et al. Screening for asymptomatic deep vein thrombosis in surgical intensive care patients. *J Vasc Surg* 1997; 26:764–769
- 754 Fraisse F, Holzapfel L, Couland JM, et al. Nadroparin in the prevention of deep vein thrombosis in acute decompensated COPD. *Am J Respir Crit Care Med* 2000; 161:1109–1114
- 755 Moser KM, LeMoine JR, Nachtwey FJ, et al. Deep venous thrombosis and pulmonary embolism: frequency in a respiratory intensive care unit. *JAMA* 1981; 246:1422–1424
- 756 Kapoor M, Kupfer YY, Tessler S. Subcutaneous heparin prophylaxis significantly reduces the incidence of venous thromboembolic events in the critically ill [abstract]. *Crit Care Med* 1999; 27(suppl):A69
- 757 Goldhaber SZ, Kett DH, Cusumano CJ, et al. Low molecular weight heparin versus minidose unfractionated heparin for prophylaxis against venous thromboembolism in medical intensive care unit patients: a randomized controlled trial [abstract]. *J Am Coll Cardiol* 2000; 35(suppl):325A
- 758 Hirsch DR, Ingenito EP, Goldhaber SZ. Prevalence of deep venous thrombosis among patients in medical intensive care. *JAMA* 1995; 274:335–337
- 759 Marik PE, Andrews L, Maini B. The incidence of deep venous thrombosis in ICU patients. *Chest* 1997; 111:661–664
- 760 Dorffler-Melly J, de Jonge E, de Pont AC, et al. Bioavailability of subcutaneous low-molecular-weight heparin to patients on vasopressors. *Lancet* 2002; 359:849–850
- 761 McDonald E, Landry F, Boudreau C, et al. Relationship between peak anti-Xa levels and calculated creatinine clearance in ICU patients receiving low molecular weight heparin [abstract]. *Crit Care* 2003; 7(suppl):S55
- 762 McDonald E, Landry F, Boudreau C, et al. Relationship between trough anti-Xa levels and calculated creatinine clearance in ICU patients receiving low molecular weight heparin [abstract]. *Crit Care Med* 2003; 31:A609
- 763 Geerts WH, Selby R. Prevention of venous thromboembolism in the ICU. *Chest* 2003; 124(suppl):357S–363S
- 764 Levi D, Kupfer Y, Seneviratne C, et al. Computerized order entry sets and intensive education improve the rate of prophylaxis for deep vein thrombophlebitis [abstract]. *Chest* 1998; 114(suppl):280S
- 765 Ferrari E, Chevallier T, Chapelier A, et al. Travel as a risk factor for venous thromboembolic disease: a case-control study. *Chest* 1999; 115:440–444
- 766 Kraaijenhagen RA, Haverkamp D, Koopman MMW, et al. Travel and risk of venous thrombosis. *Lancet* 2000; 356: 1492–1493
- 767 Bagshaw M. Traveller's thrombosis: a review of deep vein thrombosis associated with travel. *Aviat Space Environ Med* 2001; 72:848–851
- 768 Belcaro G, Geroulakos G, Nicolaidis AN, et al. Venous thromboembolism from air travel: the LONFLIT Study. *Angiology* 2001; 52:369–374
- 769 Dimberg LA, Mundt KA, Sulsky SI, et al. Deep venous thrombosis associated with corporate air travel. *J Travel Med* 2001; 8:127–132
- 770 Hirsh J, O'Donnell MJ. Venous thromboembolism after long flights: are airlines to blame? *Lancet* 2001; 357:1461–1462

- 771 Arya R, Barnes JA, Hossain U, et al. Long-haul flights and deep vein thrombosis: a significant risk only when additional factors are also present. *Br J Haematol* 2002; 116:653–654
- 772 Gallus AS, Goghlan DC. Travel and venous thrombosis. *Curr Opin Pulm Med* 2002; 8:372–378
- 773 Giangrande PLF. Air travel and thrombosis. *Br J Haematol* 2002; 117:509–512
- 774 Ten Wolde M, Kraaijenhagen RA, Schiereck J, et al. Travel and the risk of symptomatic venous thromboembolism. *Thromb Haemost* 2003; 89:499–505
- 775 Kesteven P, Robinson B. Incidence of symptomatic thrombosis in a stable population of 650,000: travel and other risk factors. *Aviat Space Environ Med* 2002; 73:593–596
- 776 Kelman CW, Kortt MA, Becker NG, et al. Deep vein thrombosis and air travel: record linkage study. *BMJ* 2003; 327:1072–1075
- 777 Lapostolle FK, Surget V, Borron SW, et al. Severe pulmonary embolism associated with air travel. *N Engl J Med* 2001; 345:779–783
- 778 Belcaro G, Cesarone MR, Shah SSG, et al. Prevention of edema, flight microangiopathy and venous thrombosis in long flights with elastic stockings: a randomized trial; the LONFLIT 4 Concorde Edema-SSL Study. *Angiology* 2002; 53:635–645
- 779 Cesarone MR, Belcaro G, Nicolaidis AN, et al. Venous thrombosis from air travel: the LONFLIT3 study: prevention with aspirin vs low-molecular-weight heparin (LMWH) in high-risk subjects; a randomized trial. *Angiology* 2002; 53:1–6
- 780 Hughes BJ, Hopkins RJ, Hill S, et al. Frequency of venous thromboembolism in low to moderate risk long distance travellers: the New Zealand Air Traveller's Thrombosis (NZATT) study. *Lancet* 2003; 362:2039–2044
- 781 Perez-Rodriguez E, Jimenez D, Diaz G, et al. Incidence of air travel-related pulmonary embolism at the Madrid-Barajas Airport. *Arch Intern Med* 2003; 163:2766–2770
- 782 Ansell JA. Air travel and venous thromboembolism: is the evidence in? *N Engl J Med* 2001; 345:828–829
- 783 Egermayer P. The "economy class syndrome": problems with the assessment of risk factors for venous thromboembolism. *Chest* 2001; 120:1047–1048
- 784 Bendz B, Rostrup M, Sevre K, et al. Association between acute hypocarbic hypoxia and activation of coagulation in human beings. *Lancet* 2000; 356:1657–1658
- 785 Hodkinson PD, Hunt BJ, Parmar K, et al. Is mild normobaric hypoxia a risk factor for venous thromboembolism? *J Thromb Haemost* 2003; 1:2131–2133
- 786 Rege KP, Bevan DH, Chitolie A, et al. Risk factors and thrombosis after airline flight. *Thromb Haemost* 1999; 81:995–996
- 787 Arfvidsson B, Elkof B, Kistner RL, et al. Risk factors for venous thromboembolism following prolonged air travel: coach class thrombosis. *Hematol Oncol Clin North Am* 2000; 14:391–400
- 788 Scurr JH, Machin SJ, Bailey-King S, et al. Frequency and prevention of symptomless deep-vein thrombosis in long-haul flights: a randomised trial. *Lancet* 2001; 357:1485–1489
- 789 Martinelli I, Taioli E, Battaglioli T, et al. Risk of venous thromboembolism after air travel: interaction with thrombophilia and oral contraceptives. *Arch Intern Med* 2003; 163:2771–2774
- 790 Schwarz T, Siegert G, Oettler W, et al. Venous thrombosis after long-haul flights. *Arch Intern Med* 2003; 163:2759–2764
- 791 Belcaro GV, Cesarone MR, Nicolaidis A, et al. Prevention of flight venous thrombosis in high risk subjects with stockings or one-dose enoxaparin [abstract]. *Circulation* 2002; 106(suppl):II-721
- 792 Cesarone MR, Belcaro G, Nicolaidis AN, et al. The LONFLIT4-Concorde-Sigvaris Traveno Stockings in Long Flights (EcoTraS) Study: a randomized trial. *Angiology* 2003; 54:1–9
- 793 Cesarone MR, Belcaro G, Errichi BM, et al. The LONFLIT4-Concorde Deep Venous Thrombosis and Edema Study: prevention with travel stockings. *Angiology* 2003; 54:143–154
- 794 Aviation Medicine Association Medical Guidelines Task Force. Medical guidelines for airline travel, 2nd ed. *Aviat Space Environ Med* 2003; 74:A1–A19

**Prevention of Venous Thromboembolism: The Seventh ACCP
Conference on Antithrombotic and Thrombolytic Therapy**
William H. Geerts, Graham F. Pineo, John A. Heit, David Bergqvist, Michael
R. Lassen, Clifford W. Colwell and Joel G. Ray
Chest 2004;126;338-400
DOI 10.1378/chest.126.3_suppl.338S

This information is current as of January 26, 2008

Updated Information & Services	Updated information and services, including high-resolution figures, can be found at: http://chestjournal.org/cgi/content/full/126/3_suppl/338S
References	This article cites 784 articles, 168 of which you can access for free at: http://chestjournal.org/cgi/content/full/126/3_suppl/338S#BIBL
Citations	This article has been cited by 56 HighWire-hosted articles: http://chestjournal.org/cgi/content/full/126/3_suppl/338S
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://chestjournal.org/misc/reprints.shtml
Reprints	Information about ordering reprints can be found online: http://chestjournal.org/misc/reprints.shtml
Email alerting service	Receive free email alerts when new articles cite this article sign up in the box at the top right corner of the online article.
Images in PowerPoint format	Figures that appear in CHEST articles can be downloaded for teaching purposes in PowerPoint slide format. See any online article figure for directions.

A M E R I C A N C O L L E G E O F

P H Y S I C I A N S[®]