Prevention of Venous Thromboembolism

The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy

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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) [≤ 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).

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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.

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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 study[42] 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 with considerable acute morbidity, substantial consumption of resources, and long-term sequelae of clinical and economic significance.[5,49]

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.

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 (≤ 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 trials[108] 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 metaanalysis[149] 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 randomized clinical trials in general surgery[71] 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 metaanalysis[77] 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 LMWHs[200] or different regimens of the same LMWH.[101,188,190,201–206] One metaanalysis[40] 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*, $\leq$ 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 study[174] 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 trial[214] 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 review[133] 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 study[219] 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 analysis[222] 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 ≤ 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 study[20] 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 evidence[226] 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 registry[239] 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 study[241] 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 trial[228] 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 study[243]

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 study[238] compared LDUH, 7,500 U bid, with enoxaparin, 40 mg daily, with each administered for $\leq$ 2 days, among 233 patients undergoing aortic or infrainguinal 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 thromboemobolic 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 study[205] 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 $\leq$ 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, ≤ 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 survey[311] 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 laparoscopies[315] observed a symptomatic VTE rate of only 2 per 10,000 patients. In a literature review of laparoscopic cholecystectomy[316] 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 Riempst 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 laparoscopy[321]; colon resection[324]; and various procedures.[320,323]

Contrast venography was the primary outcome in one trial[313] 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 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

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 aspirin[389] 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 LDUH[71] or aspirin[149] 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 administrated 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 trial[409] 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 study[415] 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 trials[422–425] 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 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

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 symptomatic 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 trial[438] 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 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

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 coworkers[346] 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 study[453] 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 Gallagher[68] > 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 audit[16] 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 metaanalysis[149] 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 HFS[471] 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 trial[465] 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 placebo[465] 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 trial[155] 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 trial[155] 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 coworkers[420] 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 review[480] 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 review[483] 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 LWMH 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 review[483] 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 1A**). For LMWH, there are only small differences between starting preoperatively or postoperatively, and both options are acceptable (**Grade 1A**).

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 1A**).

3.5.3 Duration of prophylaxis

An excellent review of the duration of thromboprophylaxis after surgery has recently been published.[489] Although 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/m^2, 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 trials[39] 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 trial[359] 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 trial[504] also confirmed the benefit of post-hospital discharge pophylaxis 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 trial[505] 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 TKA[503] 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 trial[52] 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 fusions[518] 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 trial[529] 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 trial[530] 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 study[531] from the same center, no DVTs were found in the 60 patients who were given either enoxaparin, 20 or 40 mg daily. Another randomized trial[528] 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 studies[533–536] routinely screened for asymptomatic DVT, using contrast venography, in patients with isolated lower extremity fractures who had not received thromboprophylaxis. Hjelmstedt and Bergvall[533] 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 study[536] 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	Venography ≥ 5 weeks	Placebo	Reviparin, 1,750 U daily	29/159 (18)	14/134 (10)
	Achilles tendon repair				6/28 (21)	3/48 (6)
Jorgensen et al[536]/2002	Below-knee fractures	Venography ≥ 5 weeks	No prophylaxis	Tinzaparin, 3,500 U daily	10/77 (13)	8/73 (11)
	Tendon ruptures				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 nonblinded 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 reviparin, 1,750 U self-administered by daily subcutaneous injection for at least 5 weeks. The DVT rates in the placebo and reviparin 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 trial[536] 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 colleagues[548] 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 Project[545] 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 al[127] 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 trial[554] 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 study[556] 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 study[542] 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 multisystem 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 metaanalysis[585] 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 trial[580] in which the rate of DVT was three times greater with these devices than with IPC, as well as by a cohort study[588] 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 metaanalysis[585] 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 trial[576] 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] Greenfield[619] 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. Others[602] 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,[624625] 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 incomplete 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 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*, 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 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

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 fracture[626]; 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 alone[641] is ineffective for prophylaxis in SCI patients, while adjusted-dose unfractionated heparin[642] and LMWH[576,644,645] are substantially more efficacious. The efficacy of LMWH is also supported by an uncontrolled study[645] 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 colleagues[659] 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 study[658] 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 LWMH (**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 VTE[499] 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 study[688] 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 study[697] identified heart failure as an independent risk factor for VTE in outpatients, with the risk rising with declining ejection fraction. An administrative database[698] 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 study[699] 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 Study[689] 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 patients[704] 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 ≥ 65 yr (83, 7%)	FUT × 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 ≥ 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 colleagues[70] 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 group[707] 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 review[712] 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 study[713] 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 assessed[714] 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 trial[733] 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 trial[743] 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 study[756] 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**

		Intervention		DVT†	
Study/Year	Method of Diagnosis	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 study[776] 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 literature[774] 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 study[780] 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)
				Enoxaparin, 4,000 U		0/102
Cesarone et al[779]/2002	High	> 10	None	Aspirin, 400 mg daily × 3	4/83 (4.8)	3/84 (3.6)
				Enoxaparin, 100 U/kg		0/82
Cesarone et al[792]/2003	Low–medium	7–12	None	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 ≤ 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, ≤ 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 LWMH (**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**).

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