Prevention of Venous Thromboembolism

William H. Geerts, MD, FCCP, Chair; John A. Heit, MD; † G. Patrick Clagett, MD; Graham F. Pineo, MD, FCCP;‡ Clifford W. Colwell, MD;§ Frederick A. Anderson, Jr., PhD;‖ and H. Brownell Wheeler, MD*

Abbreviations: ADH = adjusted dose heparin; CI = confidence interval; DVT = deep vein thrombosis; ES = elastic (graduated compression) stockings; FUT = fibrinogen uptake test; INR = international normalized ratio; IPC = intermittent pneumatic compression; IVC = inferior vena cava; LDUH = low-dose unfractionated heparin; LMWH = low-molecular-weight heparin; MI = myocardial infarction; PE = pulmonary embolism; q8h = every 8 h; q12h = every 12 h; SC = subcutaneous; SCI = spinal cord injury; THR = total hip replacement; TKR = total knee replacement; VTE = venous thromboembolism

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This chapter reviews the literature related to the risks of VTE and its prevention. For each patient group, literature searches have been conducted and *a priori* criteria for inclusion of studies have been applied to derive quantitative estimates of the baseline risks of thromboembolism and the efficacy of each of the prophylaxis interventions (Table 1). In the summary tables, the rates of deep vein thrombosis have been pooled from the eligible trials for each intervention and then compared with the rate among pooled, untreated, or placebo-treated control patients to determine the reduction in relative risk. Because comparisons among the interventions are indirect, the results of this pooling analysis provide an approximate guide to the relative efficacy of various prophylactic strategies. The final recommendations are based on the results of our pooled data as well as major randomized trials and/or formal, published meta-analyses. Although the recommendations are evidence-based, where possible, practical suggestions for prophylaxis are provided, particularly in situations where the evidence is inadequate.

The rationale for thromboprophylaxis is based on the high prevalence of of venous thromboembolism (VTE) among hospitalized patients, the clinically silent nature of the disease in the majority of patients, and the morbidity, costs, and potential mortality associated with unprevented thrombi. Both deep vein thrombosis (DVT) and pulmonary embolism (PE) produce few specific symptoms, and the clinical diagnosis is unreliable.[1,2] Since the first manifestation of the disease may be fatal PE, it is inappropriate to wait for symptoms and then rely on the diagnosis and treatment of established VTE. Unrecognized and untreated DVT may also lead to long-term morbidity from the postphlebitic syndrome and may predispose patients to future episodes of recurrent VTE.[3,4]

An alternative to prophylaxis would be the use of serial surveillance tests such as duplex ultrasonography in high-risk patients.[5,6] This approach is expensive and can be applied only to limited numbers of patients at risk. In addition, noninvasive screening tests, such as impedance plethysmography or duplex ultrasonography, have only moderate sensitivity and positive predictive value when used in asymptomatic, high-risk patients such as those undergoing major orthopedic surgery.[7–11] Routine screening has also not been demonstrated to reduce the frequency of clinically important outcomes, such as symptomatic VTE or fatal PE. Broad application of effective methods of prophylaxis has been more cost-effective and is probably safer than selective, intensive surveillance.[12–21]

Despite overwhelming evidence of the efficacy of an assortment of prophylactic modalities, surveys conducted in the United States,[22–24] Canada,[25] the United Kingdom,[26–30] Sweden,[31] Switzerland,[32] Spain,[33] and Australia/New Zealand[34,35] document wide practice variations among physicians, with 28 to 100% of respondents indicating that they routinely used prophylaxis. In a random survey of fellows of the American College of Surgeons, 86% claimed they used prophylaxis in 1993,[23] this proportion rising to 96% by 1997.[36] However, a US study of 2,000 patients, hospitalized at 16 acute-care hospitals, showed that only one third of these patients actually received prophylaxis despite the presence of multiple risk factors for VTE.[37] Use of prophylaxis was higher in teaching than in nonteaching hospitals. A records review of patients aged 65 years or older and undergoing abdominal or thoracic surgery at 20 Oklahoma hospitals showed that prophylaxis was used in only 38%.[38] Of patients considered to be at very high risk, with multiple risk factors for VTE, only 39%

Table 1—*Criteria for Inclusion of Studies*

- Patients identifiable as belonging to the group of interest and similar enough to current patients to be relevant
- Outcome assessment:
  A. Orthopedic studies: contrast venography only (bilateral or unilateral)
  B. Nonorthopedic studies: contrast venography or fibrinogen leg scanning
- Sample size: at least 10 patients per group
- Numerator: objectively demonstrated deep vein thrombosis
- Denominator: patients with adequate outcome assessments

I. Baseline Risks of Thrombosis
- Design: either prospective cohort studies or control groups of randomized trials
- Interventions: no prophylaxis used

II. Prophylaxis Efficacy
- Design: randomized trials only
- Interventions: clinically relevant, available options; for drugs, currently approved or utilized agents and doses

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

received prophylaxis, and one third of these received inappropriate prophylaxis according to published guidelines. In 1996, a Scottish study, entitled "Still Missing the Boat With Fatal Pulmonary Embolism," documented fatal PE in surgical patients during a 1-year period.[39] Fifty-six percent of the patients who died of PE did not receive prophylaxis despite having major risk factors and no contraindications to standard antithrombotic regimens.

Why isn't thromboprophylaxis used more widely?

Many physicians believe that the overall incidence of VTE among hospitalized and postoperative patients has decreased over the past decades, to a point where the incidence is too low to consider prophylaxis. These physicians frequently cite informal, retrospective surveys of their own clinical services (or their personal experience) and the rare occurrence of fatal PE diagnosed by autopsy at their hospital to bolster this argument. In fact, the incidence of VTE may have declined in recent years,[40] and this probably reflects the success of prophylaxis strategies as well as other aspects of surgical and postoperative care.[41–43] Even so, the incidence of this preventable condition remains too high; current estimates of the incidence of fatal PE, based on hospital discharge data, suggest the need for even wider application of prophylaxis.[44] Furthermore, the difficulty in establishing the antemortem diagnosis of PE is very common as is the low rate of autopsy in the United States. Data from countries where autopsies are carried out more commonly indicate that PE remains a significant problem.[42,44–46] A 25-year population-based study from the Rochester Epidemiology Project documents that, while the incidence of PE has decreased during this period, the incidence of DVT has remained unchanged for men and is increasing for older women.[47] Most epidemiologic studies document that the elderly are particularly vulnerable to PE.[46,47] With the increasing age of the population, VTE will become an escalating public health problem.

Another reason for failure to use prophylaxis, especially in surgical patients, is the concern about bleeding complications from anticoagulants. Countering this argument are abundant data from meta-analyses and placebo-controlled, double-blind, randomized trials that demonstrate either no increase or small increases in the absolute rates of major bleeding with the use of low-dose unfractionated heparin (LDUH) or low-molecular-weight heparin (LMWH).[48–54] Although wound hematomas are seen more frequently with these agents,[48,51] (and this may potentially increase the risk of wound infection, dehiscence, and infection of a prosthetic device placed at the time of operation), avoidance of LDUH or LMWH cannot generally be justified on these grounds alone. Alternatively, mechanical methods of prophylaxis carry no bleeding risk and have been efficacious in some patient groups.[48] Heparin-induced thrombocytopenia is also a potential concern with widespread use of heparin preparations.[55] The rate of thrombocytopenia with prophylactic use of heparin is 1 to 5%, and the incidence of clinically overt vascular thrombosis in postoperative patients with heparin-induced thrombocytopenia is approximately 50%.[55,56] LMWHs are much less likely to produce heparin-induced thrombocytopenia than unfractionated heparin.[56] The costs of thromboprophylaxis have also been used as an argument against its wider use; however, the studies addressing this issue have uniformly concluded that broad application of prophylaxis is highly cost-effective.[12–19]

The final major reason for not using prophylaxis has to do with subjective perceptions of the magnitude of the problem and the effects of prophylaxis in individual practices. Because VTE is most often clinically silent, the occurrence of overt VTE among an individual physician's patients is perceived as rare.[57] For example, extrapolation of data from meta-analyses suggests that fatal PE occurs in 0.5 to 0.8% of unprotected patients over the age of 40 years undergoing major abdominal surgery and, in many of these, the diagnosis and cause of death would not be known.[14,48,49] Similarly, although postoperative proximal DVT is present in 6 to 7% of general surgery patients, the majority do not have clinical manifestations and therefore would not be detected. As a consequence, a busy surgeon whose practice consists of a high volume of major abdominal surgery may not perceive VTE as a significant problem. More importantly, this physician would not be aware of a reduction in the incidence of fatal PE from 0.7 to 0.2% in his or her own practice that has been found in meta-analyses with the use of LDUH, for example.[48,49] Thus, from an individual practice perspective, it is difficult to appreciate the effectiveness of prophylaxis, whereas failures (patients developing clinically overt VTE despite prophylaxis) are readily apparent. In addition, bleeding complications are highly visible, not easily forgotten, and frequently attributed, inappropriately, to the use of prophylaxis.

Risk Factor Stratification

Knowledge of specific risk factors in patient groups or in individual patients forms the basis for the appropriate use of prophylaxis. Clinical risk factors include the following: increasing age; prolonged immobility, stroke, or paralysis; previous VTE; cancer and its treatment; major surgery (particularly operations involving the abdomen, pelvis, and lower extremities); trauma (especially fractures of the pelvis, hip, or leg); obesity; varicose veins; cardiac dysfunction; indwelling central venous catheters; inflammatory bowel disease; nephrotic syndrome; and pregnancy or estrogen use.[58–63] These risk factors are present, often in combination, in a high proportion of hospitalized patients.[64] For surgical patients, the incidence of DVT is affected by the preexisting factors just listed and by factors related to the procedure itself, including the site, technique, and duration of the procedure, the type of anesthetic, the presence of infection, and the degree of postoperative immobilization. The role of congenital and acquired thrombophilic disorders (hypercoagulable states) in potentiating the risk of VTE associated with clinical risk factors (especially hospitalization or surgery) remains to be clarified. The thrombophilic abnormalities include the following: activated protein C resistance (factor V Leiden); prothrombin variant 20210A; antiphospholipid antibodies (lupus anticoagulant and anticardiolipin antibody); defi-

ciency or dysfunction of antithrombin, protein C, protein S, or heparin cofactor II; dysfibrinogenemia; decreased levels of plasminogen and plasminogen activators; heparin-induced thrombocytopenia; hyperhomocystinemia; and myeloproliferative disorders such as polycythemia vera and primary thrombocytosis.[65–68]

In many patients, multiple risk factors may be present, and the risks are cumulative.[69,70] For example, elderly patients with hip fractures undergoing major orthopedic operations and who remain immobile in bed after operation are among the most susceptible to fatal PE. Formal risk assessment models for DVT have been proposed for surgical patients.[71–77] Awareness of the clinical settings in which the risk has been defined by epidemiologic studies is also important in the successful application of prophylaxis recommendations (Table 2). For example, the patients at greatest risk for VTE are those undergoing major lower extremity orthopedic surgery and those who experience major trauma or spinal cord injury.

Important Issues Related to Thromboprophylaxis Data

Although we have attempted to provide an unbiased overview of the available data about thromboprophylaxis, we recognize that there are important limitations of the evidence largely due to the number and quality of the studies that form the basis for our recommendations. These caveats include the following points.

Appropriate End Points for Studies of DVT Prophylaxis: Physicians differ in their views on the appropriate end points for studies of DVT prophylaxis. Some believe that very sensitive and specific diagnostic tests for all thromboembolic activity are essential. These outcomes are contrast venography for high-risk patients and fibrinogen leg scanning for moderate-risk patients. Others consider that evidence of reduction in deaths from all causes is required to convince them that an intervention is of benefit. Both of these approaches have limitations. The majority of the thrombi detected by sensitive screening methods for DVT are not clinically relevant (although only a small amount of data allows us to predict which thrombi will resolve and which will produce important adverse effects). However, insistence on death as the exclusive outcome dismisses the significant burden of disease due to symptomatic thromboembolic events as well as the cost inefficiency associated with the investigation and treatment of these complications. We suggest a middle ground based on large trials that use a clinically important VTE outcome, consisting of a composite of fatal PE, symptomatic, proven DVT or PE, and asymptomatic proximal DVT. These larger trials should be performed once smaller studies using an accurate test for all DVT have demonstrated the biological efficacy of the intervention.

Limitations of DVT Screening Methods Each of the DVT screening methods has limitations. Fibrinogen leg scanning, also called the fibrinogen uptake test (FUT), lacks specificity and sensitivity[78–80]; duplex ultrasonography has poor sensitivity as a screening test in asymptomatic patients[8–11]; and venography is associated with a significant rate of nondiagnostic studies, is no longer widely available, and the clinical relevance of many of the thrombi detected is questioned. Despite these limitations, the relative risk reductions when two prophylaxis choices are compared using these outcome measures are likely to be valid as long as systematic bias has been eliminated.[81]

Mechanical Methods of Prophylaxis: Special caution should specifically be exercised when interpreting the risk

Table 2—*Levels of Thromboembolism Risk in Surgical Patients Without Prophylaxis**

Level of Risk Examples	Calf DVT, %	Proximal DVT, %	Clinical PE, %	Fatal PE, %	Successful Prevention Strategies
Low risk Minor surgery in patients < 40 yr with no additional risk factors	2	0.4	0.2	0.002	No specific measures Aggressive mobilization
Moderate risk Minor surgery in patients with additional risk factors; nonmajor surgery in patients aged 40–60 yr with no additional risk factors; major surgery in patients < 40 yr with no additional risk factors	10–20	2–4	1–2	0.1–0.4	LDUH q12h, LMWH, ES, or IPC
High risk Nonmajor surgery in patients > 60 yr or with additional risk factors; major surgery in patients > 40 yr or with additional risk factors	20–40	4–8	2–4	0.4–1.0	LDUH q8h, LMWH, or IPC
Highest risk Major surgery in patients > 40 yr plus prior VTE, cancer, or molecular hypercoagulable state; hip or knee arthroplasty, hip fracture surgery; major trauma; spinal cord injury	40–80	10–20	4–10	0.2–5	LMWH, oral anticoagulants, IPC/ES + LDUH/LMWH, or ADH

*Modified from Gallus et al[60] and International Consensus Statement.[74]

reductions ascribed to mechanical methods of prophylaxis for three reasons. Most trials have not been able to blind the mechanical devices, leading to the potential for diagnostic suspicion bias. If fibrinogen leg scanning was the DVT screening method, the known 10 to 30% false positive rate of the FUT might have been reduced by the mechanical prophylaxis but not by the alternative option.[82] Finally, because of relatively poor compliance with all mechanical options, they may well not perform as well in routine clinical practice as in research studies where major efforts are made to optimize proper use.

Results May Not Apply to All Patients: Because most studies have excluded the patients at highest risk for both thromboembolic and adverse outcomes, the results may not apply to all patients, especially those with previous history of VTE, or to patients with a greater-than-average bleeding potential.

Prophylaxis Decisions for an Individual Patient: The prophylaxis recommendations contained herein are made for groups of patients, for whom the benefits appear to outweigh the risks. However, prophylaxis decisions for an individual patient are best made by combining knowledge of the literature (including the group recommendations provided herein and elsewhere) with clinical judgment (including detailed knowledge of that particular patient's unique risks for thrombosis, the potential for adverse consequences due to the prophylaxis, and the availability of various prophylaxis options locally). The recommendations that are best for the group may not be best for the individual.[83]

Antithrombotic Drugs and Regional Anesthesia: Perispinal hematoma after neuraxial blockade (spinal or epidural anesthesia or epidural analgesia) is a rare complication of anticoagulant therapy or prophylaxis.[84,85] Although rare, the seriousness of the complication mandates cautious use of antithrombotic medication in patients having neuraxial blockade. A 1997 US Food and Drug Administration Public Health Advisory called attention to safety reports describing 43 US patients who had developed perispinal hematoma after receiving the LMWH enoxaparin concurrently with spinal/epidural anesthesia.[86,87] Many of these patients suffered neurologic impairment, including permanent paralysis, despite decompressive laminectomy in 65%. The median age was 78 years (range, 28 to 90), and 78% of the patients were women. Some patients had preexisting spinal abnormalities, and a third received additional hemostasis-inhibiting medications. Nearly 90% of these complications occurred in patients receiving enoxaparin as prophylaxis after surgery, primarily total knee or hip replacement or spinal surgery. Factors suspected of predisposing patients to perispinal hematoma include the presence of an underlying hemostatic disorder, traumatic needle or catheter insertion, repeated insertion attempts or blood return, catheter insertion or removal in the presence of significant levels of anticoagulant, use of continuous epidural catheters, anticoagulant dosage, concurrent administration of medications known to increase bleeding, vertebral column abnormalities, older age, and female gender.[84,85,87] Unfortunately, the prevalence of this problem and the predictive value of potential risk factors are, at present, unknown. The problem has also been reported with LDUH, although with apparent lower frequency. Therefore, the benefit vs risk of any anticoagulant prophylaxis or therapy for patients with spinal/epidural anesthesia or analgesia is difficult to assess.

Critical reviews of this problem provide guidelines for LMWH use in patients with spinal/epidural anesthetic interventions.[85,88,89] We believe that neuraxial blockade and anticoagulant thromboprophylaxis, including LMWHs, can generally be used concomitantly. The following recommendations may improve the safety of neuraxial blockade in patients who have received or will receive anticoagulant prophylaxis: (1) neuraxial blockade should generally be avoided in patients with a clinical bleeding disorder; (2) in patients receiving drugs that may impair hemostasis (*eg*, aspirin, other platelet inhibitors, or anticoagulants), insertion of the spinal needle should be delayed until the anticoagulant effect of the medication is minimal (usually at least 8 to 12 h after a prophylactic LMWH or heparin injection); (3) anticoagulant prophylaxis should be avoided or delayed if there is a hemorrhagic aspirate ("bloody tap") during the initial spinal needle placement; (4) removal of epidural catheters should be done when the anticoagulant effect is at a minimum (usually just before the next scheduled subcutaneous [SC] injection); and (5) anticoagulant prophylaxis should be delayed for at least 2 h after spinal needle placement or catheter removal. All patients should be monitored carefully and frequently for the new onset of back pain and for symptoms or signs of cord compression (*eg*, progression of lower extremity numbness or weakness, bowel or bladder dysfunction). For patients in whom spinal hematoma is suspected, diagnostic imaging and definitive surgical therapy must be performed as rapidly as possible to reduce the risk of permanent paresis.

The sections that follow are based primarily on the hospital services to which patients are admitted. In each patient category, the risks of VTE and the effective methods of prophylaxis are detailed, if known. For most patient groups, sufficient numbers of randomized clinical trials are available to allow strong recommendations (grade 1A or 1B) to be made with regard to the benefits and risks of methods to prevent VTE. Standard antithrombotic regimens shown to be effective are summarized in Table 3.

General, Gynecologic, and Urologic Surgery

General Surgery

The overall incidence of thromboembolic end points in general surgical patients was calculated by pooling data from the control groups of published English-language trials of thromboprophylaxis (Table 4). In most studies, the majority of patients had elective GI surgery. However, some of the patient populations were more heterogeneous and included individuals also undergoing gynecologic, thoracic, urologic, or vascular operations. Almost all pa-

tients were older than 40 years. The overall incidence of DVT as assessed by the FUT was 25% in untreated patients. Trials in which the FUT was confirmed by contrast venography found DVT in 19% of the patients. In surgical patients with malignant disease, the incidence of DVT was 29%. Proximal (popliteal or higher) DVT was found in 7% of patients not given prophylaxis. Clinically recognized PE (fatal and nonfatal) was seen in 1.6% of patients, and fatal PE was diagnosed in 0.9% of patients. The rates of these more serious end points among control patients may underestimate what would be expected among surgical patients in whom prophylaxis is withheld, because most patients in the trials received therapeutic anticoagulation when serial FUT scans became abnormal.

In Table 5, the effects of commonly used prophylactic regimens in general surgery are tabulated. Among the antithrombotic drugs, LDUH and LMWH are the most effective in reducing the incidence of DVT as assessed by FUT. These agents have been the most completely studied and have been the subject of numerous meta-analyses in general surgery patients.[48–53,178] LDUH was the first antithrombotic agent investigated in large randomized trials and, because it was often compared with placebo, a beneficial effect on reducing serious end points such as proximal DVT and PE was consistently demonstrated. The effect of treatment with LMWH on proximal DVT and PE cannot be directly assessed because most investigators believed that placebo-controls were unethical and that new regimens should be compared with LDUH treatment or other active interventions. However, it is reasonable to assume that LMWH and other anticoagulants, shown as equivalent to or superior to LDUH in reducing total DVT, would have similar beneficial effects on proximal DVT and PE.

A large number of trials have randomized general surgery patients to control groups or low-dose heparin. Treatment with SC heparin (5,000 U) was usually started 2 h before operation and continued every 8 or 12 h after surgery, for 7 days or until patients were ambulatory or discharged from the hospital. Low-dose heparin was consistent in reducing the incidence of DVT assessed by FUT alone or FUT confirmed by venography. The overall incidence of DVT was reduced from 25 to 8%. Although, to our knowledge, there are no randomized trials compar-

Table 3—*Regimens to Prevent VTE*

Method	Description
LDUH	Heparin 5,000 U SC, given q8–12h starting 1–2 h before operation
ADH	Heparin SC, given q8h starting at approximately 3,500 U SC and adjusted by ± 500 U SC per dose, to maintain a midinterval aPTT at high normal values
LMWH and heparinoids*	General surgery, moderate risk:
	Dalteparin, 2,500 U SC 1–2 h before surgery and once daily postop
	Enoxaparin, 20 mg SC, 1–2 h before surgery and once daily postop
	Nadroparin, 2,850 U SC 2–4 h before surgery and once daily postop
	Tinzaparin, 3,500 U SC 2 h before surgery and once daily postop
	General surgery, high risk:
	Dalteparin, 5,000 U SC 8–12 h before surgery and once daily postop
	Danaparoid, 750 U SC 1–4 h before surgery and q12h postop
	Enoxaparin, 40 mg SC, 1–2 h preop and once daily postop
	Enoxaparin, 30 mg SC, q12h starting 8–12 h postop
	Orthopedic surgery
	Dalteparin, 5,000 U SC 8–12 h preop and once daily starting 12–24 h postop
	Dalteparin, 2,500 U SC 6–8 h postop; then 5,000 U SC once daily
	Danaparoid, 750 U SC 1–4 h preop and q12h postop
	Enoxaparin, 30 mg SC q12h starting 12–24 h postop
	Enoxaparin, 40 mg SC once daily starting 10–12 h preop
	Nadroparin, 38 U/kg SC 12 h preop, 12 h postop, and once daily on postop days 1, 2, and 3; then increase to 57 U/kg SC once daily
	Tinzaparin, 75 U/kg SC once daily starting 12–24 h postop
	Tinzaparin, 4,500 U SC 12 h preop and once daily postop
	Major trauma
	Enoxaparin, 30 mg SC q12h starting 12–36 h postinjury if hemostatically stable
	Acute spinal cord injury
	Enoxaparin, 30 mg SC q12h
	Medical conditions
	Dalteparin, 2,500 U SC once daily
	Danaparoid, 750 U SC q12h
	Enoxaparin, 40 mg SC once daily
	Nadroparin, 2,850 U SC once daily
Perioperative warfarin	Start daily dose with approximately 5–10 mg the day of or the day after surgery; adjust the dose for a target INR of 2.5 (range 2–3)
IPC/ES	Start immediately before operation, and continue until fully ambulatory

*Dosage expressed in anti-Xa units (for enoxaparin, 1 mg = 100 anti-Xa units). Postop = postoperative.

Table 4—*VTE in General Surgery Patients Without Thromboprophylaxis*

End Point	No. of Trials	References	No. of Patients (With End Point/ Total Screened)	Incidence, %	95% CI
DVT (FUT)	54	90–143	1,084/4,310	25	24–27
Confirmed DVT (FUT → venogram)	20	92, 94, 96–100, 102, 113, 117, 122, 125, 127, 129, 131–133, 136–138	288/1,507	19	17–21
DVT (FUT) (Malignant disease)	16	95, 96, 99–101, 107, 108, 111, 120, 124, 128, 131, 133, 134, 136, 140	159/546	29	25–33
Proximal DVT	16	91, 94, 96, 99, 100, 102–104, 109, 112, 113, 130, 133, 134, 139, 141	83/1,206	7	6–8
All PE	32	90–101, 104, 105, 107, 108, 111, 113, 114, 116, 118, 119, 121, 122, 125–127, 133, 134, 141, 142, 144	82/5,091	1.6	1.3–2.0
Fatal PE	33	90–102, 104, 105, 107, 108, 111, 113, 114, 116, 118, 119, 121, 122, 125–127, 133, 134, 141, 144, 145	48/5,547	0.9	0.6–1.2

ing twice daily dosing with 3 daily doses, one meta-analysis showed that LDUH given every 8 h was more efficacious.[48] The beneficial effect of LDUH was also observed in trials in which patients with malignant disease were studied. Data from meta-analyses show that LDUH also reduced the more serious end points of proximal DVT, clinically diagnosed PE, and fatal PE diagnosed at autopsy.[48,49] These studies showed a 50% reduction in fatal PE with LDUH prophylaxis. Three large studies were designed to test the efficacy of LDUH in preventing fatal PE, and all three demonstrated a significant beneficial effect (overall risk reduction for fatal PE with LDUH = 89%).[90,144,145]

The advantages and disadvantages of LMWH in general surgery have been clarified by a number of large trials, as well as by meta-analyses in which LMWH and LDUH were compared.[50,51,147–160] On balance, LMWH and LDUH appear to be equally efficacious in preventing DVT in general surgery patients. Some studies have reported significantly fewer wound hematomas and bleeding complications with LMWH,[51,157,159] while other well-designed trials have shown that LMWH causes more bleeding than LDUH.[149,153,160] The discrepant findings appear to be related to dosage; there is a clear dose-response effect of LMWH on bleeding complications (and probably also on the efficacy of prophylaxis). Higher doses of LMWH (> 3,400 anti-Xa units daily) in comparison to LDUH (5,000 U bid or tid) are associated with more bleeding.[53] In contrast, lower doses of LMWH (< 3,400 anti-Xa units daily) are equivalent to LDUH in preventing VTE in moderate-risk patients and have a lower rate of bleeding complications.[53] While one meta-analysis could not discern superior efficacy of higher doses of LMWH,[53] individual studies in high-risk general surgery patients suggest that this may be the case.[158,172,173] One distinct advantage of LMWH is that it can be administered once daily. LMWH is also less likely to cause heparin-induced thrombocytopenia and thrombosis than standard heparin preparations.[56] Optimal timing for the commencement of LMWH therapy (preoperatively or postoperatively) has been the subject of considerable interest. In orthopedic patients, anticoagulant treatment is often started 12 to 24 h after operation because of fear of bleeding and for convenience. In general surgery patients, there appear to be no adverse consequences of giving the first dose of LMWH (< 3,400 U) 2 h before operation,[177] and there may be an additional benefit in preventing DVT from developing during surgery or in the immediate postoperative period. When higher doses of LMWH are used in high-risk general surgery patients, treatment with the drug should generally be commenced 10 to 12 h before operation to avoid excessive intraoperative bleeding.

Given the approximate equivalence in efficacy and safety of LDUH and LMWH in general surgery patients,

Table 5—*Prevention of DVT After General Surgery**

Regimen	No. of Trials	No. of Patients	No. of Patients With DVT	Incidence, %	95% CI	Risk Reduction, %
Untreated controls[90–143]	54	4,310	1,084	25	24–27	—
Aspirin[110, 122–124, 146]	5	372	76	20	16–25	20
ES[120, 138, 141]	3	196	28	14	10–20	44
Low-dose heparin[90–92, 94, 95, 98–102, 104–111, 113, 114, 116, 117, 147–171]	47	10,339	784	8	7–8	68
LMWH[147–160, 170, 172–177]	21	9,364	595	6	6–7	76
IPC[129, 140]	2	132	4	3	1–8	88

*Pooled data from randomized trials using fibrinogen leg scanning as the primary outcome; superscript numbers are references.

cost becomes an important determinant in the choice between these drugs. In North America, LMWHs cost 2 to 10 times more than LDUH, and the cost-effectiveness analyses performed in abdominal and colorectal surgery patients concluded that prophylaxis with LDUH was more economical.[160,179] In countries where LMWHs are less expensive, these agents may be equivalent in overall costs and more appealing because of once daily administration.[19,180]

Intermittent pneumatic compression (IPC) is an attractive method of prophylaxis because there is no risk of hemorrhagic complications. However, IPC has not been studied as thoroughly as other methods in general surgery. Several small studies have demonstrated that IPC is effective in reducing DVT in general surgery patients and in surgical patients with malignant disease.[48,129,140] In trials comparing IPC with LDUH, both agents produced similar reductions in DVT.[161,162,171] It is not proven that IPC prevents PE (or even proximal DVT) in general surgery patients. Intermittent plantar compression, using the venous foot pump, produces hemodynamic effects on lower extremity emptying similar to that of IPC and, like IPC, it also stimulates fibrinolytic activity.[181] To our knowledge, there are no trials of these devices in general surgery patients.

Graded compression elastic stockings (ES) reduce the incidence of leg DVT[182] and enhance the protection provided by LDUH, but too few data are available to assess their effect on proximal DVT and PE. Patients with malignant disease and other high-risk general surgical conditions have not been evaluated in sufficient numbers to allow firm conclusions with regard to the efficacy of ES in these clinical settings. In some of the randomized trials, high-risk patients were specifically excluded.[119,120] Further clinical trials are needed to assess the effectiveness of ES in such patients. Another limitation is that some patients cannot effectively wear ES because of unusual limb size or shape.

Combining ES with other prophylactic agents, such as LDUH, appears to give better protection against VTE than either approach alone.[163,183] ES counteract venous stasis and augment venous return during abdominal insufflation for laparoscopic procedures.[184,185] A recent uncontrolled study demonstrated a 2% risk of DVT as detected by duplex ultrasonography in patients undergoing laparoscopic or minilaparotomy cholecystectomy when LMWH, intraoperative IPC, and ES were combined.[186]

Because of its low expense, ease of administration, and few side effects, aspirin would appear to be an ideal antithrombotic agent to prevent VTE. However, aspirin has generally been found to be ineffective in preventing VTE in general surgery patients, and we do not recommend it as an appropriate strategy.[75] This view has been challenged by the Antiplatelet Trialists' Collaboration meta-analysis, which concluded that perioperative antiplatelet treatment reduced the incidence of DVT in general surgery patients by 37% and PE by 71% in comparison to untreated control subjects.[187] These reductions were highly significant, and similar effects were also reported in patients undergoing orthopedic and other operations. However, the Antiplatelet Trialists' Collaboration group pooled >30 antiplatelet trials of variable scientific design.[188,189] Most individual trials demonstrate no significant benefit of aspirin or they show that aspirin is less effective than other agents.[110,122–124]

Despite the paucity of evidence, warfarin, given in full therapeutic doses, may be effective in preventing extensive DVT in general surgery patients.[115] However, the onset of action of warfarin is delayed, the treatment is cumbersome because it requires frequent laboratory monitoring, and it is subject to bleeding complications if not closely monitored. Because of these shortcomings and the availability of other effective options, there is little rationale for using warfarin in general surgery patients.

An appropriate preventive strategy in general surgery takes into account the risk of VTE, the effectiveness of the various agents, and the expense and possible complications incurred by their use (Table 2).[75] In low-risk patients undergoing minor or relatively short operations, who are <40 years of age and have no additional risk factors, no specific prophylaxis other than early ambulation is necessary. Two large-scale studies document a near zero risk for the development of clinical VTE after minor procedures in low-risk patients.[190,191] In moderate-risk patients who are >40 years of age or who are undergoing major operations, but who have no additional clinical risk factors, LDUH given every 12 h, LMWH once daily ($<3,400$ anti-Xa U), or properly used ES should be sufficient. IPC would be a reasonable alternative to these agents. In patients >40 years undergoing major surgery with additional risk factors, several effective prophylactic methods are available. LDUH given every 8 or 12 h and once-daily LMWH are effective. IPC would also be a consideration, especially if the patient is particularly prone to bleeding. Adding ES to any of these methods may give additional protection. In general surgery patients with multiple risk factors, combining the most effective pharmacologic methods with IPC or ES should offer excellent protection. Higher daily doses of LMWH ($>3,400$ U), as is often used in orthopedic surgery, would also be appropriate.

The issue of prophylaxis beyond the period of hospitalization was addressed in a single small, randomized study of high-risk patients undergoing major abdominal or thoracic surgery.[192] Prolonged prophylaxis with LMWH for 3 weeks after hospital discharge did not significantly reduce the incidence of DVT as assessed by bilateral venography performed 4 weeks after surgery, compared with 1 week of in-hospital LMWH (5% vs 10%). However, a total of only 118 patients had adequate venography. A cost-effectiveness analysis, based on event rates from the literature, concluded that postdischarge prophylaxis of general surgery patients was effective, but the marginal costs were too high to warrant its routine use.[193] The issue of duration of thromboprophylaxis in general surgery must now be reevaluated in the context of current short lengths of hospital stay.

Gynecologic Surgery

VTE is also an important and potentially preventable complication following gynecologic surgery.[194–198] The overall incidence of DVT is comparable to or slightly lower

than that associated with general surgery.[199] Using the FUT as the primary outcome measure, the reported frequency of postoperative DVT in 19 studies that included 2,268 patients who underwent gynecologic surgery without prophylaxis varied between 4% and 38%, with an average of 16%.[93,96,107,115,119,127,134,200–211] Fatal PE has been reported in 0.4% of a pooled sample, including > 1,000 unprotected patients.[96,107,119,133,202,208,209] The factors that appear to increase the thromboembolic risk following gynecologic surgery include older age, previous VTE, surgery for cancer, and abdominal (vs vaginal) procedure. Gynecologic oncology patients, in particular, have a substantially increased DVT risk because many of these patients are elderly; they all have cancer; in some there may be compression of major veins by a pelvic mass; they are prone to venous intimal injury during the procedure, especially when pelvic lymph node dissection is performed; the procedures are frequently lengthy; residual tumor may be left behind; postoperative mobility is often impaired; and chemotherapy itself is thrombogenic. As in other surgical patients, although thrombi generally begin to form at or shortly after surgery,[208] the majority of symptomatic events occur after hospital discharge.[212] Despite changes in surgical and postoperative care and the use of prophylaxis, few prospective studies have been carried out over the past 15 years. Therefore, contemporary data related to the risks and prevention of VTE in this patient group are lacking.[212]

Pooling of the rates of fatal PE in prospective studies of 7,000 gynecologic surgery patients demonstrates a 75% risk reduction with the use of thromboprophylaxis (from 0.4 to 0.1%). The results of randomized trials of prophylaxis on DVT rates in gynecologic surgery patients are displayed in Table 6.

A single study of patients undergoing elective gynecologic surgery for benign disease reported that ES provided protection against DVT compared with no prophylaxis.[119] Three randomized trials have assessed IPC in gynecology patients.[133,134,215] Use of IPC only during surgery and the first 24 h postoperatively was not efficacious,[133] while continuing IPC for at least 5 days after surgery was highly effective compared with controls and resulted in protection comparable to LDUH.[134,215]

The strongest evidence that thromboprophylaxis is of benefit in gynecologic surgery has been provided for the use of LDUH. In six randomized trials with untreated control groups, the relative risk reduction in DVT with LDUH treatment was 64% (20% vs 7%).[93,96,107,115,203,209] Patients having surgery for gynecologic cancers derive less protection from twice daily administration of LDUH than those with benign disease,[96,217] while a regimen of LDUH given three times daily appears to be more effective in these patients.[96,209,215] Increased bleeding complications have been described in some studies using LDUH,[215,220] but not in others.[209]

When compared with LDUH, aspirin and dextran have an efficacy rate 2 to 4 times lower in gynecologic surgery patients and are not recommended.[107,203,216,217] Treatment with oral anticoagulants in full doses or in mini doses, started at least a week before surgery, has been more efficacious than no prophylaxis in three small studies,[115,210,211] but LDUH is at least as effective and considerably easier to use.[115] To the best of our knowledge, there are no trials using LMWH that meet the inclusion criteria in Table 1, although LMWH appears to provide protection comparable to LDUH when either symptomatic VTE or screening with impedance plethysmography is employed.[221–226] In an uncontrolled case series of 2,030 patients who had major gynecologic surgery and who were given enoxaparin 20 mg once daily, there was one fatal PE, and only 7 patients (0.3%) had symptomatic VTE.[227]

The risk classification and prophylaxis recommendations in Table 2 are applicable to gynecologic surgery.[196,197,199] Patients who are otherwise well and who undergo brief procedures probably do not require any specific prophylaxis, but they should be encouraged to mobilize early after surgery. For patients having major gynecologic procedures for benign disease without additional risk factors, administration of LDUH twice daily is recommended. Alternatives include treatment once daily with LMWH or intraoperative IPC continued for at least several days after surgery. For higher-risk patients, one of the following options is recommended: LDUH + ES or IPC, LDUH three times daily, or LMWH given in daily doses of at least 3,400 anti-Xa U. An unresolved issue is the duration of antithrombotic therapy in gynecologic oncology patients. A recent study followed a large cohort of gynecologic cancer patients with serial IPGs postoperatively and during subsequent courses of chemotherapy.[228] The postoperative proximal DVT rate was 15%, but this increased to 20 to 30% when the events during follow-up were also counted. The occurrence of these thrombi predicted a sixfold increased risk of death during follow-up.

Table 6—*Prevention of DVT After Gynecologic Surgery

Regimen	No. of Trials	No. of Patients	Incidence of DVT, %	95% CI	Relative Risk Reduction, %
Untreated control subjects[93, 96, 107, 115, 119, 127, 134, 201, 203, 209–211]	12	945	16	14–19	—
Oral anticoagulants[115, 210, 211, 213, 214]	5	183	13	8–18	22
IPC[133, 134, 215]	3	253	9	6–13	44
LDUH[93, 96, 107, 115, 203, 209, 215–219]	11	1,092	7	6–9	56
ES[119]	1	104	0	0–3	"99"

*Pooled data from randomized trials that used routine FUT as the primary outcome; superscript numbers are references.

Urologic Surgery

Thromboembolic events are considered the most important nonsurgical complication of major urologic procedures.[229–231] Because most of the epidemiologic data were derived 10 to 30 years ago, changes in surgical care, more aggressive mobilization, and possibly greater use of prophylaxis have apparently resulted in decreased rates of VTE over time.[232,233] However, 1 to 5% of contemporary patients undergoing major urosurgery experience symptomatic VTE, and fatal PE is seen occasionally (risk $\leq$ 1/500).[232–240] Factors that have been demonstrated to increase the risk of DVT in these patients include open (vs transurethral) procedures, malignancy, increased age, general (vs regional) anesthetic, and duration of the procedure.

Over the past decade, to our knowledge, there have been no published studies in urology that meet the methodologic criteria in Table 1, and the optimal approach to thromboprophylaxis is not known for these patients.[241] LDUH and LMWH probably have similar efficacy in urology as in general surgery.[49,103,118,227,231,240] However, concerns have been raised about the potential for increased rates of pelvic hematoma and lymphocele in patients receiving anticoagulant prophylaxis for open urologic procedures.[231,233,240] Use of ES or IPC is likely to be efficacious in urosurgery,[97,236,242,243] but the high costs of IPC have been raised as a problem with this method.[244] It is also possible that the addition of IPC to inexpensive ES may not provide additional protection in these patients.[236,242] However, combining mechanical and pharmacologic prophylaxis may be more effective than either alone but will substantially increase the costs.[112,231,240]

For patients undergoing transurethral prostatectomy, the risks of VTE are low,[49,103,227] and there may be increased risk of bleeding with use of perioperative LDUH or LMWH.[245–247] Early postoperative mobilization is probably the only intervention warranted in these and other low-risk urosurgery patients. Routine prophylaxis is recommended for more extensive, open procedures, including radical prostatectomy, cystectomy, or nephrectomy. Until further data become available, the options to consider for these patients include LDUH, ES, IPC, LMWH, and combinations of mechanical and pharmacologic methods. For patients at particularly high risk, commencing treatment with ES plus or minus IPC just prior to surgery and then adding LDUH (or LMWH) postoperatively should be considered, although this approach has not been formally evaluated in urology patients (to our knowledge).

Orthopedic Surgery

Clinical trials and cohort studies have provided a clearer picture of the natural history of acute VTE associated with major orthopedic surgery of the lower extremity and have also provided considerable information to guide decisions about prophylaxis. Based on the results of contrast venography, performed on either control patients or patients randomized to receive placebo, the prevalence of total DVT at 7 to 14 days after total hip replacement (THR), total knee replacement (TKR), and hip fracture surgery is about 50 to 60% (Table 7),[248–272] with proximal DVT rates of about 25%, 15 to 20%, and 30%, respectively. While the operated-on leg is most commonly affected, the nonoperated-on leg is also affected in about 20% of THR patients[250,274–279] and in about 14% of TKR patients.[280] The incidence of asymptomatic PE is less certain. Intraoperative transesophageal echocardiography shows frequent "debris" transiting the right side of the heart, particularly during reaming of the bone.[281,282] This debris, which includes both fat and thromboemboli, often causes transient hypoxemia and pulmonary hypertension; however, serious clinical sequelae are uncommon. In studies in which a ventilation-perfusion lung scan was routinely performed, about 7 to 11% of THR and TKR patients had a high-probability scan within 7 to 14 days after surgery.[252,259,261,283,284] New DVT and PE after hospital discharge are also common. Venography studies show that, without postdischarge prophylaxis, 10 to 20% of patients develop new evidence of DVT within 4 to 5 weeks after hospital discharge,[284–286] and about 6% develop an intermediate- or high-probability lung scan.[284]

Compared with routine screening for asymptomatic VTE, the incidence of symptomatic, objectively documented DVT or PE is far less common. For example, among a cohort of 1,162 consecutive THR patients, for whom essentially the only prophylaxis was ES, the 6-month cumulative incidence of VTE was 3.4%; PE was seen in 1.6% (0.3% fatal), and DVT was diagnosed in a further 1.9%.[254] Similarly, among TKR patients receiving only ES prophylaxis, the 3-month cumulative incidence of PE was 1.5% (0.2% fatal).[262] Follow-up studies of in-hospital anticoagulant prophylaxis show that only 1.3 to 3% of patients develop symptomatic VTE during a 3-month follow-up period despite an expected 25 to 40% prevalence of asymptomatic DVT at the time of hospital discharge.[287–289] From these data, we conclude that most DVT that develop despite prophylaxis resolve without causing symptoms. One cohort study, comprised of 213 elective THR or hip fracture patients with normal venog-

Table 7—*VTE Prevalence After THR or TKR Surgery, or Surgery for Hip Fracture*

	DVT*		PE	
Procedure	Total, %	Proximal, %	Total, %	Fatal, %
THR	45–57[248–251]	23–36[248–251]	0.7–30[252–254]	0.1–0.4[253–257]
TKR	40–84[258–261]	9–20[258–261]	1.8–7[259,261]	0.2–0.7[253,262,263]
Hip fracture surgery	36–60[264–272]	17–36[269,271,272]	4.3–24[256]	3.6–12.9[259,273]

*Total or proximal DVT prevalence among control or placebo groups in clinical trials using mandatory postoperative venography. Superscript numbers are references.

raphy at hospital discharge, reported no subsequent episodes of symptomatic VTE over the next 1 to 2 months.[290] Similarly, an overview of 2,361 major orthopedic surgery patients with normal venography at the time of hospital discharge found a 1.3% cumulative incidence of VTE over the following 4 weeks.[291] Because the proportion of patients developing venous stasis syndrome after major hip or knee surgery is low (4 to 6%)[292,293] and does not appear to increase among patients with asymptomatic calf or proximal DVT, compared with patients with no DVT,[293] we conclude that most asymptomatic thrombi resolve without causing serious clinical sequelae.

Together, these data suggest the following hypothesis regarding the natural history of VTE after major orthopedic surgery. Asymptomatic VTE (including proximal DVT and even PE) is common and, in the absence of prophylaxis, affects at least half of these patients. The majority of these thrombi resolve spontaneously. For certain patients, however, the persistence of venous injury, stasis due to prolonged immobility,[294] an impaired natural anticoagulant[295] or fibrinolytic system, or some as yet unidentified factor, allows a thrombus to propagate and to become symptomatic due to either venous occlusion or embolization. At present, our ability to identify these high-risk patients is limited, and future research should be directed to determining the genetic, clinical, and biochemical characteristics that predispose to the development of clinically important postoperative VTE. Until we are able to stratify patients according to their individual risk and then target prophylaxis to those at highest risk, primary prophylaxis should be provided to all patients undergoing major orthopedic surgery of the lower extremity. While most DVT detected by venography will remain asymptomatic and will resolve without treatment, thrombosis detected by venography remains a credible outcome measure for comparing the efficacy of different prophylaxis regimens. Consequently, we have confined our review to English-language clinical trials that required either mandatory postoperative venography of the operated-on leg (or both legs) or objectively confirmed symptomatic VTE for determination of efficacy. Since we cannot predict which asymptomatic DVT will eventually become symptomatic,[296–300] we have analyzed the total DVT rates (proximal plus distal DVT). We report the pooled venography results (including 95% confidence intervals [CIs] and relative risk reductions) by type of surgery (THR, TKR, or hip fracture surgery) to allow cross-trial comparisons of different prophylaxis agents and regimens. Only results from single-modality prophylaxis regimens (excluding graded elastic compression stockings) are included. Finally, the benefits of any prophylaxis regimen should be weighed against the costs, including those resulting from bleeding complications, as well as the costs associated with failed prophylaxis (*eg*, VTE and death). This comparison is best performed using a formal cost-effectiveness analysis.[301] Although we report cost-effectiveness studies where available, they should be interpreted with caution, as most used risk reduction in asymptomatic DVT by venography to determine the potential benefit derived from each prophylaxis regimen.

Elective THR Surgery

Withholding primary prophylaxis in favor of case-finding by serial noninvasive screening for asymptomatic DVT is problematic in this patient population because the commonly available noninvasive tests (impedance plethysmography or compression or color duplex ultrasonography) are insensitive for asymptomatic calf and proximal DVT.[7–9,302–306] Moreover, clinical trials and cohort studies have found that a strategy of screening for proximal DVT with predischarge color duplex ultrasonography was ineffective.[287,307] While a similar strategy using predischarge venography appeared to be cost-effective in a single study,[300] routine venography is not widely available or generally acceptable. Radioisotope-based imaging of asymptomatic thrombus has not been shown to be bene-

Table 8—*Prevention of DVT After THR Surgery

Prophylaxis Regimen	No. of Trials	Combined Enrollment†	Total DVT Prevalence, % (95% CI)	Total DVT RRR, %	Proximal DVT‡ Prevalence, % (95% CI)	Proximal DVT‡ RRR, %
Placebo/control[82, 248, 249, 251, 269, 309–315]	12	626	54.2 (50–58)	—	26.6 (23–31)	—
ES[250, 254, 316, 317]	4	290	41.7 (36–48)	23	25.5 (21–31)	4
Aspirin[311, 318–322]	6	473	40.2 (35–45)	26	11.4 (8–16)	57
Low-dose heparin[168, 252, 276, 279, 318, 323–328]	11	1016	30.1 (27–33)	45	19.3 (17–22)	27
Warfarin[318, 322, 329–339]	13	1828	22.1 (20–24)	59	5.2 (4–6)	80
IPC[82, 249, 329–331, 340, 341]	7	423	20.3 (17–24)	63	13.7 (11–17)	48
Recombinant hirudin[327, 328, 342]	3	1172	16.3 (14–19)	70	4.1 (3–5)	85
LMWH[248, 250, 252, 275–277, 279, 315, 317, 321, 325, 333–337, 339, 341–353]	30	6216	16.1 (15–17)	70	5.9 (5–7)	78
Danaparoid[251, 278, 338]	3	441	15.6 (12–19)	71	4.1 (2–6)	85
Adjusted-dose heparin[275, 323, 343, 346]	4	293	14.0 (10–19)	74	10.2 (7–14)	62

*Pooled DVT rates (total and proximal) determined by routine contrast venography from randomized trials; superscript numbers are references; RRR = relative risk reduction.

†Patients with adequate venography.

‡The denominators for proximal DVT may be slightly different than for total DVT, since some studies did not report proximal DVT rates.

ficial in large studies.[308] Consequently, primary prophylaxis is recommended for all THR patients (Table 8).

Several nonpharmacologic prophylaxis methods have been studied in THR patients, including ES,[250,254,316,317,354,355] IPC,[82,249,329–331,340,341] and early ambulation.[356] All provide some benefit, with DVT risk reductions of 20 to 60%, but with little effect on proximal DVT rates. Two studies suggest that pneumatic plantar compression using foot pumps may be moderately effective at decreasing total DVT.[316,349] However, because the published experience with the foot pump in THR patients is small and the proximal DVT rates appear to be greater than with current anticoagulant prophylaxis, we cannot recommend this modality for primary prophylaxis. Compared to general anesthesia, regional anesthesia (spinal or epidural) is associated with a significantly reduced incidence of postoperative DVT for THR surgery in the absence or presence of other thromboprophylaxis interventions.[357–359] This is also true in surgery for hip fracture.[360] However, the VTE prevalence after regional anesthesia remains substantial and warrants additional primary prophylaxis.

Inferior vena cava (IVC) filter placement has been suggested as a prophylaxis option for patients at extremely high risk for both postoperative VTE and bleeding.[361–363] However, we are not aware of any randomized trials of prophylactic IVC filter insertion or of any studies that address the value of filters when added to recommended prophylaxis options. In a treatment study, patients with acute DVT who were judged to be at high risk for subsequent PE were randomly assigned to IVC filter placement or no filter placement in addition to concurrent anticoagulation.[364] The incidence of subsequent PE (symptomatic plus asymptomatic) was significantly reduced in the short-term among patients receiving an IVC filter. However, mortality was not reduced in the filter group, and filter patients had significantly more recurrent DVTs on follow-up. Extrapolating these data to high-risk orthopedic surgery patients, prophylactic IVC filter placement may reduce the immediate risk of post-operative PE at enormous cost, but it will increase the risk of future DVT.[365] Based on these issues, we believe that placement of an IVC filter as prophylaxis should be discouraged.

A number of anticoagulant-based prophylaxis regimens for THR surgery have been studied (Table 8). Although meta-analyses have shown LDUH[49] or aspirin[187] prophylaxis to be more effective than no prophylaxis, both are less effective than other prophylaxis regimens in high-risk patients.[276,321,323,327,328] Among 4,088 hip and knee arthroplasty patients randomized to treatment with aspirin or placebo (plus or minus other thromboprophylactic measures), there was no benefit associated with aspirin use for either venous or arterial thromboembolic events.[366] Preoperative LDUH followed by postoperative heparin, dose-adjusted to maintain the activated partial thromboplastin time at or just above the upper range of normal (adjusted-dose heparin), is safe and highly effective, and may be considered for patients at extremely high risk because of concomitant risk factors.[275,323,343,346] However, most surgeons consider adjusted-dose heparin prophylaxis to be impractical for routine use.

Adjusted-dose oral anticoagulation (*eg*, warfarin sodium) is, generally, a safe and effective prophylaxis and has been adopted by many orthopedic surgeons in North America.[25,253,329,333–335,367–369] Adjusted-dose warfarin has the potential advantage of allowing continued prophylaxis after hospital discharge (as long as the infrastructure is in place to do this effectively and safely). Oral anticoagulants should be administered at a dose sufficient to prolong the international normalized ratio (INR) to a target of 2.5 (range = 2.0 to 3.0). The initial oral anticoagulant dose should be administered either the evening prior to surgery or as soon after surgery as possible. However, even with early initiation of oral anticoagulant therapy, the INR usually does not reach the target range until at least the third postoperative day.[334,337,370]

LMWH and heparinoids have been studied extensively and are highly effective and generally safe as VTE prophylaxis after THR (Table 8). LMWH is more effective than LDUH,[50,276,279,325] and is at least as effective as ,[279] or superior[275] to, adjusted-dose unfractionated heparin.

Two clinical trials that have compared LMWH to adjusted-dose warfarin prophylaxis found no difference in either total or proximal DVT prevalence.[333,334] Among patients receiving LMWH prophylaxis, one trial showed a small increase in the number of bleeding complications,[333] while the other study found greater blood loss.[334] Another clinical trial found the total DVT prevalence to be significantly less with LMWH (started preoperatively) compared to adjusted-dose warfarin although, in this study, patients receiving LMWH prophylaxis had significantly greater bleeding at the operative site and greater transfusion requirements.[337] Finally, a study comparing LMWH (started at half the daily dose, either within 2 h before surgery or at least 4 h after surgery) with warfarin therapy started postoperatively revealed a significant reduction in both total and proximal DVT rates with LMWH.[339] The incidence of symptomatic, objectively documented DVT was also lower with preoperative LMWH, than with warfarin (1.5% vs 4.4%; $p = 0.024$).

Two meta-analyses of the various prophylaxis regimens concluded that LMWH was most effective, although the differences in efficacy between LMWH and either adjusted-dose warfarin or adjusted-dose heparin prophylaxis were small.[371,372] When the results from the five large studies that directly compared adjusted oral anticoagulation with LMWH in THR were pooled, the DVT rates were 20.7% (256/1,238) in the oral anticoagulant groups and 13.7% (238/1,741) in the patients who received LMWH.[333–335,337,339] The proximal DVT rates were 4.8% and 3.4%, respectively. The pooled rates for major bleeding (using somewhat different definitions in the five studies) were 3.3% in the oral anticoagulant patients and 5.3% in the LWMH groups. In a large, open-label clinical trial, THR patients were randomly assigned to in-hospital prophylaxis with either LMWH (enoxaparin 30 mg SC bid started postoperatively; N = 1,516) or adjusted-dose warfarin (INR = 2.0 to 3.0; N = 1,495).[288] Symptomatic, objectively documented VTE was the primary efficacy end point. The mean duration of prophylaxis was 7.5 days for LMWH and 7.0 days for warfarin. The cumulative in-

hospital incidence of symptomatic VTE was 0.3% among patients receiving LMWH, compared to 1.1% among patients receiving warfarin ($p = 0.008$). Major bleeding was seen in 1.2% of the LMWH patients and in 0.5% of the patients receiving warfarin ($p = 0.055$).

From these data, we conclude that LMWH is significantly more effective than warfarin in preventing asymptomatic and symptomatic in-hospital VTE. However, the risk of surgical site bleeding and wound hematoma is slightly greater with LMWH. These conclusions are consistent with the more rapid onset of anticoagulant activity with LMWH compared to warfarin. We suggest that the selection of LMWH or warfarin prophylaxis be made at the specific hospital level (and, on occasion, at the individual patient level) based on issues that include cost, convenience, availability of an infrastructure to provide safe oral anticoagulation, duration of planned prophylaxis, and potential bleeding and thrombosis risks. In a decision-analysis using Canadian health-care costs, LMWH was preferred over adjusted-dose warfarin anticoagulation.[373] However, a recent analysis based on US health-care costs found adjusted-dose warfarin to be more cost-effective compared to LMWH.[21]

Three clinical trials have found treatment with SC recombinant hirudin (15 mg SC bid, initiated preoperatively) to be more effective than LDUH[327,328] or LMWH,[342] with no difference in bleeding. While not approved for prophylaxis, recombinant hirudin (lepirudin, Refludan) is approved by the US Food and Drug Administration for therapy of heparin-induced thrombocytopenia.

Elective TKR Surgery

From the thromboembolism perspective, knee arthroplasty differs from THR in several important respects. Without prophylaxis, the total DVT rate is greater in TKR than in THR. The prophylaxis interventions, used successfully in THR, have significantly lower efficacy in TKR patients. Although major bleeding is not more common in TKR patients, awareness of and concerns about nonmajor bleeding and its potential consequences are greater after TKR. Finally, in TKR, LMWH clearly has greater efficacy than warfarin.

The results of four small studies suggest that IPC is effective prophylaxis in TKR patients[331,374–379] (Table 9).These devices are most effective when they are applied either intraoperatively or immediately postoperatively and are worn continuously, at least until the patient is fully ambulatory. The utility of IPC devices is limited by poor compliance and patient intolerance, significant costs, and the inability to continue prophylaxis after hospital discharge. IPC may be useful as an in-hospital adjunct to anticoagulant-based prophylaxis regimens. The venous foot compression pump has been shown to be efficacious in two small studies in TKR patients.[376,380] However, in two other trials, LMWH was considerably more efficacious than these devices.[385,386] Continuous passive motion devices have not reduced the DVT incidence in TKR patients compared with routine physiotherapy alone.[260]

Low-dose heparin[383,384] and aspirin[260,321,322,366,375,380] are associated with relatively small risk reductions for DVT and are not recommended in TKR. Six studies have compared adjusted-dose warfarin prophylaxis (INR = 2.0 to 3.0) with LMWH.[280,333–335,370,381] Based on postoperative venography, warfarin was only moderately effective, with total DVT rates ranging from 36 to 55%, and a pooled relative risk reduction of only 27%, compared with the rate from the pooled control patients. In addition, the proximal DVT prevalence ranged from 7 to 12%. However, in a clinical trial of 257 TKR patients receiving warfarin prophylaxis (target INR range = 1.8 to 2.5) for a mean duration of 10 days, the 3-month cumulative incidence of symptomatic VTE was only 0.8%.[370] Based on this study, we conclude that adjusted-dose warfarin is effective as prophylaxis after TKR.

LMWH has been studied extensively and is safe and effective prophylaxis after TKR surgery.[274,280,287,321,333–335,370,378,381,383–386] When the results from the six random-

Table 9—*Prevention of DVT After TKR Surgery

Prophylaxis Regimen	No. of Trials	Combined Enrollment†	Total DVT		Proximal DVT‡	
			Prevalence, % (95% CI)	Relative Risk Reduction, %	Prevalence, % (95% CI)	Relative Risk Reduction, %
Placebo/control[261, 274, 374–377]	6	199	64.3 (57–71)	—	15.3 (10–23)	—
ES[377, 378]	2	145	60.7 (52–69)	6	16.6 (11–24)	—
Aspirin[260, 321, 322, 375, 379, 380]	6	443	56.0 (51–61)	13	8.9 (6–12)	42
Warfarin[280, 322, 331, 333–335, 370, 381, 382]	9	1294	46.8 (44–49)	27	10.0 (8–12)	35
LDH[383, 384]	2	236	43.2 (37–50)	33	11.4 (8–16)	25
VFP[376, 380, 385, 386]	4	172	40.7 (33–48)	37	2.3 (1–6)	85
LMWH[274, 280, 321, 333–335, 370, 378, 381, 383–386]	13	1740	30.6 (29–33)	52	5.6 (5–7)	63
IPC[331, 374, 375, 379]	4	110	28.2 (20–38)	56	7.3 (3–14)	52

*Pooled DVT rates (total and proximal) determined by routine contrast venography from randomized trials; superscript numbers are references; VFP = venous foot pump.

†Patients with adequate venography.

‡The denominators for proximal DVT may be slightly different than for total DVT since some studies did not report proximal DVT rates.

ized trials that directly compared oral anticoagulants with LMWH in TKR were pooled, the DVT rates were 46.2% (505/1,094) in the oral anticoagulant groups and 31.5% (388/1,231) in the patients who received LMWH.[280,333–335,370,381] The proximal DVT rates were 10.2% and 6.7%, respectively. One study showed an increase in the incidence of major bleeding (0.9% vs 2.8%),[333] and three studies found a significant increase in blood loss and transfusion requirements among patients receiving LMWH.[280,370,381]

To our knowledge, there are no studies comparing LMWH to warfarin prophylaxis among patients undergoing TKR surgery in which symptomatic, objectively documented VTE was the primary efficacy outcome. Consequently, we cannot make firm recommendations regarding the preference of LMWH or warfarin as prophylaxis for this patient group. Based on the available data, we believe that LMWH is likely to be more effective than warfarin but probably causes more surgical-site bleeding and wound hematomas, especially if LMWH therapy is started within 24 h after surgery. Similar to THR, we suggest that the choice of LMWH or warfarin prophylaxis for TKR surgery be an institutional decision. The overall costs of utilizing warfarin or LMWH prophylaxis following lower extremity arthroplasty are similar.[21,387–389] In a recent analysis based on US health-care costs, adjusted-dose warfarin prophylaxis was slightly more cost-effective than LMWH.[21]

While the pooled risk reduction estimate is greatest for IPC (Table 9), the combined patient enrollment in the LMWH and warfarin prophylaxis trials is each 10 times greater than the combined enrollment in the IPC trials. Consequently, we have more confidence in the estimated risk reduction associated with LMWH and warfarin prophylaxis. In the absence of clinical trials directly comparing LMWH or warfarin prophylaxis to IPC, we cannot recommend one of these prophylaxis regimens over the other. For patients with additional risk factors for postoperative VTE, combined prophylaxis with IPC and either LMWH or adjusted-dose warfarin should be considered.

Hip Fracture Surgery

The rates of total and proximal DVT after hip fracture, derived from prospective studies in which contrast venography was routinely performed, are about 50% and 25%, respectively, without thromboprophylaxis (Table 7). These rates are comparable to those seen in hip and knee arthroplasty patients. However, fatal PE is more common in hip fracture patients than after elective arthroplasty. In a population-based autopsy study of 581 patients who died after hip fracture from from 1953 to 1992, PE was the fourth most common cause of death, accounting for 14% of all deaths.[390] Furthermore, the rate of PE was unchanged over the course of the 40-year study. These data supplement fatal PE rates of 4 to 12% reported in studies of other hip fracture populations.[256] Factors that further increase the VTE rates in hip fracture patients include age, delayed hospital admission or delayed surgery, and the use of a general (vs regional) anesthetic.[264,391] The site of the fracture (subcapital or intertrochanteric) does not appear to be important.[390,392]

In a multivariate analysis, the risk of death following hip fracture was significantly reduced among patients receiving pharmacologic thromboprophylaxis.[273] These data support the recommendation that routine VTE prophylaxis be provided for all patients undergoing surgery for hip fracture (Table 10). Even patients with major comorbidity or cognitive impairment should receive prophylaxis to reduce the morbidity associated with symptomatic VTE and to decrease the resource utilization associated with investigation and treatment when these frequent events arise.

In one clinical trial, the incidence of VTE was reduced among patients receiving postoperative IPC compared with placebo.[397] However, we are not aware of any studies comparing IPC to other prophylaxis regimens.

A meta-analysis has suggested that aspirin prophylaxis is effective in preventing postoperative VTE.[187] However, none of the studies included in this meta-analysis used routine contrast venography as an outcome measure, and, compared with other prophylaxis regimens, aspirin provides relatively little protection (Table 10). Interest in the use of antiplatelet agents in hip fracture patients has been fueled by the awareness that aspirin significantly reduces the incidence of stroke and myocardial infarction (MI),[398,399] both of which are common causes of death after hip fracture surgery.[390] In the Pulmonary Embolism Prevention (PEP) Trial, 13,356 hip fracture patients from 148 hospitals in five countries were randomly allocated to treatment with either 160 mg of enteric-coated aspirin or placebo, started before surgery (in 82%) and continued for 35 days.[366] Additional prophylaxis with LDUH, LMWH, or ES was used in 18%, 26%, and 30% of patients, respectively. Fatal PE and DVT were both significantly reduced by the addition of aspirin (each with an absolute

Table 10—*Prevention of DVT After Surgery for Hip Fracture

Prophylaxis Regimen	No. of Trials	Combined Enrollment†	Total DVT Prevalence, % (95% CI)	Relative Risk Reduction, %
Placebo/control[264–272]	9	381	48 (43–53)	—
Aspirin[270, 271, 393]	3	171	34 (27–42)	29
Low-dose heparin[269, 394]	2	59	27 (16–40)	44
LMWH/heparinoids[272, 393, 394, 400, 401]	5	437	27 (23–31)	44
Warfarin[264, 268, 271, 395, 396]	5	239	24 (19–30)	48

*Pooled total DVT rates determined by routine venography from randomized trials; superscript numbers are references.
†Patients with adequate venography.

risk reduction of 0.4%), while fatal and nonfatal arterial events (MI or stroke) and all-cause mortality were not. Wound-related and GI bleeding and transfusions were slightly, but significantly, more common in the aspirin-treated patients. Compared with placebo, for every 1,000 hip fracture patients given perioperative aspirin prophylaxis, one would expect 9 fewer venous thromboembolic events (including 4 fewer fatal PE). However, one would also expect 6 more fatal or nonfatal cardiac events and/or 10 more GI bleeds, 6 more bleeds requiring transfusion, or 6 more wound bleeds. Based on the results of this trial, we cannot recommend the routine use of aspirin as thromboprophylaxis in hip fracture patients.

Two trials have suggested substantial protection by LDUH, but the sample sizes of both studies were small with correspondingly broad CIs.[269,394] The pooled results from five studies of adjusted-dose oral anticoagulant prophylaxis show moderate reductions in relative risk.[264,268,271,395,396] The reported bleeding rates for oral anticoagulant prophylaxis range from 2 to 47%,[264,268,271,395,396] with the most recent trial finding no difference in bleeding compared with placebo.[271] The results of five studies of LMWH/heparinoids also demonstrate important risk reductions for DVT,[272,393,394,400,401] but unfortunately, to our knowledge, there are no trials that directly compare LMWH and warfarin in this patient group. Two studies found no significant difference in bleeding with LMWH compared with placebo[272] or LDUH,[394] although the sample sizes were too small to exclude a true difference. Based on current data, either LMWH or oral anticoagulant prophylaxis is recommended. Because the risk of VTE begins immediately after the fracture, prophylaxis should commence preoperatively if surgery is to be delayed, or as soon as hemostasis has been demonstrated after surgery. Clearly, more high-quality trials are required in this important patient group.

Other Prophylaxis Issues in Major Orthopedic Surgery

Comparisons Between LMWHs: Currently, four LMW heparins (dalteparin, enoxaparin, nadroparin, tinzaparin) and one heparinoid (danaparoid) are available in the United States or Canada (Table 3). At the appropriate LMWH-specific dose and dosing schedule, all are safe and effective as prophylaxis after major orthopedic surgery.[280,285,325,333,335,337,348,351,353,386,402] Few studies have directly compared two LMWHs.[351,353] To date, the limited available data suggest that any observed differences between the LMWHs are similar to the variability between different trials using the same LMWH.[351,353] LMWH are clearly effective and safe when administered at a fixed dose and without laboratory monitoring or dose adjustment. Whether LMWH would be more effective and safe if administered at a weight-adjusted dose or with laboratory monitoring and dosage adjustment has not been adequately studied.

Preoperative or Postoperative Initiation of LMWH Therapy: In North America, the initial LMWH dose is generally administered 12 to 24 h after surgery. However, in Europe, the first LMWH dose is usually administered the evening (10 to 12 h) before surgery. One review suggested that any difference in efficacy between preoperative and postoperative commencement of LMWH prophylaxis was likely to be small,[403] while a recent meta-analysis concluded that preoperative-initiated LMWH was significantly more effective than postoperative-initiated LMWH.[404] This issue has been addressed directly in a recent clinical trial in which THR patients were randomly allocated to one of three groups: preoperative LMWH (dalteparin 2,500 U SC started about 1 h before surgery, with a second 2,500 U dose given about 7 h after surgery, followed by 5,000 U daily); postoperative LMWH (dalteparin 2,500 U given about 7 h after surgery, then 5,000 U daily); or postoperative adjusted-dose warfarin.[286,339] Based on predischarge venography, the total and proximal DVT rates among the preoperative (10.7% and 0.8%, respectively) and postoperative (13.1% and 0.8%, respectively) LMWH groups did not differ significantly, while the prevalence in the warfarin group (24.0% and 3.0%, respectively) was significantly greater than either of the two LMWH regimens. Preoperative LMWH caused significantly more major bleeding compared with warfarin, and there was a nonsignificant trend toward more bleeding when compared with postoperative LMWH. However, there was no increased bleeding with the postoperative regimen of LMW compared to warfarin. We conclude that, for most patients receiving LMWH prophylaxis, the initial dose may be administered either before or after surgery. For patients at high risk for bleeding, the initial LMWH dose should be delayed until 12–24 h after surgery. Regardless of the timing of the initial LMWH dose, the first postoperative dose should be delayed until hemostasis is assured (based on examination of the limb and drainage volumes).

Duration of Thromboprophylaxis: The optimal duration of postoperative prophylaxis after hip and knee arthroplasty and hip fracture surgery has been under intense debate in recent years and remains uncertain. In previous trials, thromboprophylaxis was continued for the duration of postoperative hospitalization and generally ranged from 7 to 14 days. Currently, the duration of hospitalization is often ≤5 days, which may provide an inadequate duration of prophylaxis. Several studies suggest that the risk for DVT may persist for up to 2 months after total hip replacement surgery.[300,405–407] Six randomized, double-blind trials have addressed the need for out-of-hospital LMWH prophylaxis after THR surgery, using venographic DVT as the efficacy outcome measure (Table 11).Each of these trials compared in-hospital prophylaxis (range, 6 to 14 days) with approximately 5 weeks of postoperative LMWH treatment (range, 30 to 35 days). The in-hospital prophylaxis groups received placebo injections after hospital discharge. The most recent trial compared in-hospital warfarin prophylaxis with extended LMWH.[286,339] All of the studies found that the incidence of asymptomatic DVT after hospital discharge was substantial (range, 12 to 37%) and was significantly reduced by out-of-hospital LMWH prophylaxis (range, 4 to 19%). Extended prophylaxis reduced total and proximal DVT by at least 50%. Symptom-

atic, objectively confirmed VTE was reported in only one of these trials, and this outcome developed in 10 patients given in-hospital prophylaxis (7.6%) and in 2 patients who received extended prophylaxis (1.5%).[408] There were no major bleeding events in any of the 495 patients who received postdischarge LMWH.

In the most recent double-blind trial, THR and TKR patients with no clinical evidence of VTE after 4 to 10 days of postoperative LMWH prophylaxis (ardeparin, 50 anti-Xa U/kilogram BID) were randomly allocated to treatment with either continued LMWH (ardeparin, 100 anti-Xa U/kg) or placebo, injected as a single daily dose for 6 weeks after surgery.[289] After a mean 7.3 days of in-hospital LMWH prophylaxis, 1.5% of 607 patients receiving extended out-of-hospital LMWH and 1.9% of 588 patients receiving placebo developed symptomatic DVT or PE, or died, during the interval from hospital discharge to 12 weeks after surgery (odds ratio = 0.7, 95% CI: 0.3 to 1.7; p = 0.5).

Symptomatic VTE in Large Orthopedic Trials: A large cohort study of THR and TKR patients who received LMWH (enoxaparin 30 mg SC bid, starting postoperatively) for a mean duration of 9.5 days, found the 90-day incidence of symptomatic VTE and fatal PE to be 4.3% and 0%, respectively, for THR patients, and 3.9% and 0.4%, respectively, for TKR patients[287] (Table 12).Similarly, two large cohort studies of THR patients, receiving adjusted-dose warfarin prophylaxis for 10 to 15 days, found a 90-day symptomatic VTE incidence of 0.9 to 1.2% and fatal PE incidence of 0 to 0.1%.[307,369] In a randomized trial (N = 3,011) comparing LMWH (enoxaparin) to warfarin prophylaxis for an average of 7.3 days after THR, the incidence of symptomatic VTE from hospital discharge to 12 weeks later was 3.6% for the group receiving enoxaparin and 3.7% for the group receiving warfarin (p = 0.9).[288]

Despite the low risks of symptomatic VTE seen in these follow-up studies, 45 to 80% of all symptomatic DVT and PE that are seen in hip and knee arthroplasty patients occur after hospital discharge.[254,287–289,411] The estimated median time from arthroplasty to VTE was 17 days for THR patients and 7 days after TKR.[411] Although the optimal duration of prophylaxis following major orthopedic surgery has not yet been defined, we recommend prophylaxis with LWMH or warfarin for at least 7 to 10 days. More prolonged prophylaxis should be considered, at least in patients with ongoing risk factors (*eg*, continued immobilization, obesity) or a history of VTE. For these patients, SC LMWH (once daily without laboratory monitoring or dose adjustment) is safe and effective for extended out-of-hospital prophylaxis.[284–286,408,409] Based primarily on VTE treatment trials, we believe that adjusted-dose warfarin (target INR = 2.5, range 2.0 to 3.0) may also be safe and effective for prolonged prophylaxis and may be an acceptable alternative to LMWH.[412–414] However, LMWH is significantly more effective than warfarin as early (in-hospital) prophylaxis after THR and TKR, the risk of bleeding associated with extended out-of-hospital warfarin prophylaxis (INR 2.0 to 3.0) may be greater than with LMWH, and patient self-injection of LMWH is considerably simpler than arranging safe outpatient warfarin supervision. Additional studies addressing the cost-benefit and cost-effectiveness of extended out-of-hospital thromboprophylaxis after THR, TKR, and hip fracture surgery are needed.

Predischarge Screening for DVT: Routine screening for asymptomatic DVT using duplex ultrasonography has not been shown to be useful in two large studies of THR and TKR patients.[287,307] Only 3 of 1,936 arthroplasty patients (0.15%) who received in-hospital LMWH prophylaxis and had predischarge ultrasonography were found to have asymptomatic DVT.[287] In a trial that randomized hip and knee arthroplasty patients to predischarge duplex ultrasound or a sham ultrasound procedure, the screening test detected DVT in 2.5% of patients, but this was not associated with any reduction in the rate of symptomatic VTE.[307]

Elective Spine Surgery: The incidence of thromboembolic complications after elective spine surgery is unknown.[415] Most of the available studies are retrospective, small, and of poor methodologic quality.[415] Symptomatic VTE and fatal PE are occasionally observed in these patients despite the use of aggressive mobilization and prophylaxis with IPC and/or ES.[416–418] Duplex ultrasound

Table 11—*Postdischarge LMWH Following In-hospital Prophylaxis After THR**

		DVT†		Proximal DVT†	
Author, yr	No. of Patients	In-hospital Prophylaxis, %	Extended LMWH, %	In-hospital Prophylaxis, %	Extended LMWH, %
Bergqvist et al, 1996[408]	223	37	18	24	7
Planes et al, 1996[285]	173	19	7	8	6
Dahl et al, 1997[284]	218	32	19	13	9
Spiro et al, 1997[409]	435	23	8	13	3
Lassen et al, 1998[410]	215	12	4	5	1
Hull et al, 2000[286]	533	37	20	9	3
Combined	1797	27	14	12	4

*In each of these trials, in-hospital prophylaxis with LMWH (in five studies) or warfarin (in the study by Hall et al) followed by postdischarge placebo was compared with in-hospital plus extended, postdischarge LMWH prophylaxis; superscript numbers are references.
†All patients underwent contrast venography day 30 to 35.

Table 12—*Symptomatic VTE After In-hospital Prophylaxis for THR and TKR

Author, year	Operation	No.	Prophylaxis	Duration of Prophylaxis, d	Symptomatic VTE, No. (%)	Fatal PE, No. (%)
Robinson et al, 1997[307]	THR	506	Warfarin	9.8	6 (1.2)	0
	TKR	518	Warfarin	9.8	3 (0.6)	1 (0.2)
Leclerc et al, 1998[287]	THR	1,142	LMWH	9.0	49 (4.3)	0
	TKR	842	LMWH	9.0	33 (3.9)	3 (0.4)
Colwell et al, 1999[288]	THR	1,516	LMWH	7.5	55 (3.6)	2 (0.1)
	THR	1,495	Warfarin	7.0	56 (3.7)	2 (0.1)
Heit et al, 2000[289]	THR/TKR	588	LMWH	7.3	11 (1.9)	3 (0.5)†

*Superscript numbers are references.
†Sudden death in 3 patients with known heart disease; no autopsies were performed; PE was not excluded.

identified DVT in 3% of 554 patients from six prospective studies, all of which routinely used mechanical prophylaxis.[416–422] It is not known whether or not mechanical prophylaxis has any protective effect on the rate of DVT in this patient group, since none of the studies were controlled. In one small clinical trial, no symptomatic thromboembolic events or abnormal duplex scans were found in any of the 110 patients who were randomized to receive prophylaxis with ES alone, ES plus IPC, or ES plus warfarin.[423] Laminectomy patients formed a subgroup of a randomized trial that compared LDUH with no prophylaxis and used the FUT to screen for DVT.[100] Thrombi were detected in 5 of 20 control patients and in none of the 18 LDUH patients. Since there are so little data related to thromboprophylaxis following spinal surgery, we cannot make any firm recommendations. However, it is reasonable to use ES alone, LDUH alone, or the combination of the two for these patients; intraoperative plus postoperative IPC may also be effective. Certainly, for spine surgery patients with additional thromboembolic risk factors, prophylaxis with one of these options is suggested.

Isolated Lower Extremity Fractures: Although lower extremity fractures are very common, the risk of VTE has been poorly studied in this patient group. Among 76 patients with tibial fractures, Hjelmstedt and Bergvall[424] found a 45% incidence of DVT overall, with extensive DVT in 16% of patients and proximal DVT in 8% of patients. DVT was seen in 71% of patients treated surgically and in 39% managed conservatively. Abelseth and colleagues[425] performed venography in 102 patients who had early operative fixation of isolated lower extremity fractures distal to the hip. Overall and proximal DVT rates were 28% and 4%, respectively. The risk of chronic leg swelling after these fractures and its association with postinjury DVT are also unknown. To our knowledge, there are no randomized trials of prophylaxis in patients with isolated lower extremity fractures, although two prospective studies have evaluated prophylaxis with LMWH in outpatients with lower extemity injuries managed with plaster casts.[426,427] In both trials, patients self-adminstered the LMWH until routine duplex scanning was performed at the time of cast removal, 2 to 10 weeks later. The study by Kujath et al[426] showed a significant reduction in overall DVT from 16.5 to 4.8% with LMWH (nadroparin 2,850 U once daily) in 253 patients. The rates in the subgroup of patients with fractures (N = 77) were 29% and 10%, respectively, for control subjects and LMWH patients ($p < 0.05$). A similar risk reduction was seen in the study reported by Kock et al[427] using certoparin 3,000 U daily in 391 patients. Among the 72 fracture patients, DVT was diagnosed in 6% of the control group, while none was detected in the LMWH group. Unfortunately, both studies have major limitations, including the small proportion of patients with fractures, nonoperative management of all cases, unblinded design, lack of disclosure of the patient selection process or the methods of randomization, high rates of postrandomization dropouts (17% and 31%), and the marked variation in study duration (1 to 72 days). Although DVT appears to occur with moderate frequency after isolated lower extremity fractures, there are few prospective studies available, and none have reported the incidence of clinically important VTE. Limited data demonstrate that DVT rates can be reduced by routine administration of LMWH in these patients, but this approach cannot currently be recommended because of uncertainty about whether the benefits of prophylaxis outweigh the risks and whether prophylaxis is cost-effective. As a minimum, all patients with lower extremity fractures or injuries should be warned to promptly seek medical attention if symptoms of possible DVT or PE arise. Clearly, more research is required in this area.

Neurosurgery, Trauma, Acute Spinal Cord Injury, and Burns

Neurosurgery

Patients undergoing elective neurosurgical procedures are known to be at increased risk of postoperative DVT and PE.[428–430] The control groups of randomized trials, which include a broad spectrum of neurosurgery patients, found that 22% of these patients had FUT evidence of DVT (Table 13) and 5% had proximal DVT.[431–437] Risk factors that appear to increase DVT rates in neurosurgery patients include intracranial (vs spinal) surgery, malignant (vs benign) tumors, duration of surgery, the presence of leg weakness, and increased age.[429,442,443] Patients with malignant brain tumors are at particularly high risk for VTE, both perioperatively and during subsequent follow-

up.[430,444,445] Among 264 patients with glioma, 31% developed symptomatic DVT, confirmed by venography, within 5 weeks of surgery.[444] Brandes and colleagues[446] effectively prevented postoperative VTE with aggressive use of perioperative LDUH but, by 1 year after surgery, 21% of brain tumor patients had experienced symptomatic, objectively proven DVT or PE.

Physical methods of prophylaxis have frequently been recommended in neurosurgery because of concerns about intracranial or spinal bleeding. IPC appears to be highly effective at preventing DVT in these patients, with an average risk reduction of 68% compared with controls (from 21 to 7% incidence in randomized trials).[431,433,434,436–438] Routine postoperative surveillance, using serial duplex scanning, of 2,643 neurosurgery patients who had undergone prophylaxis with ES and IPC, found DVT in 6%.[442] The rate in similar patients without prophylaxis is unknown. Although Turpie et al[437] found comparable DVT rates for patients receiving ES alone and those who had the combination of ES and IPC (both options were more effective than no prophylaxis), concerns about the efficacy of ES alone are raised by recent studies.[439–441,447]

The two largest prophylaxis trials in neurosurgery patients have compared the use of ES alone with a combination of ES and LMWH, started postoperatively.[440,441] Both studies used routine venography as the efficacy outcome and both showed significant risk reductions with the combined prophylaxis. In the trial by Nurmohamed et al, [440] the DVT and proximal DVT rates for the patients given ES alone were 26% and 12%, while the rates in those given ES plus LMWH were 19% and 7%, respectively. In the double-blind study by Agnelli and colleagues,[441] the DVT and proximal DVT rates for the ES group were 33% and 13%, compared with 17% and 5%, respectively, for the group that received the combined prophylaxis. The only randomized trial (to our knowledge) of LDUH in craniotomy patients found a reduction in DVT rate from 34% in control subjects to 6% in the group receiving heparin.[432]

Prospective studies have not demonstrated an increased risk of intracranial bleeding in neurosurgery patients who had prophylaxis with LDUH.[432,448–451] In a partially randomized trial in patients admitted to the hospital with spontaneous intracerebral hemorrhage, treatment with heparin 5,000 U tid started on the second day, did not result in more bleeding (and was more efficacious) than the same dose of heparin started on day 4 or day 10. [448] Pending further information, caution should be exercised with routine early use of LMWH in craniotomy patients.[440,441,447–452] In an unblinded, randomized trial comparing IPC alone, LMWH alone, and the combination in patients undergoing craniotomy or stereotactic biopsy for brain tumor, symptomatic intracranial hemorrhage occurred in 5 of 38 patients treated with LMWH and in none of the 19 patients given IPC alone.[452] In this study, LMWH therapy was started just before surgery, and four of the five bleeds occurred within 12 h of receiving the first dose.

In summary, IPC (plus or minus ES) can be recommended for prophylaxis of DVT in patients undergoing elective neurosurgery. Other options that may also be acceptable include LDUH and postoperative LMWH. The combination of LMWH and ES is more efficacious than ES alone, while the combination of LDUH and mechanical prophylaxis may also be more effective than either method alone.

Trauma

VTE is a common, life-threatening complication of major trauma.[425,453–461] Unfortunately, despite the presence of a large body of literature related to the topic of VTE in trauma, few studies meet the minimum methodology criteria presented in Table 1. Without prophylaxis, patients with multisystem or major trauma have a risk for DVT that exceeds 50%,[458,459] (Table 14) and fatal PE occurs in approximately 0.4 to 2.0%.[453,459,462,463] PE is the third most common cause of death in trauma patients who survive beyond the first day.[453,459,462,464,465] Thromboembolic complications are costly, accounting for 9% of the readmissions to hospital following trauma.[466] These observations clearly place trauma patients among the other high-risk groups for thromboembolism, including hip and knee arthroplasty or hip fracture repair.

In a prospective study of 443 patients with major trauma who did not receive any thromboprophylaxis, the incidence of DVT, using routine bilateral contrast venography, was 58%; 18% of patients had proximal DVT.[459] Among trauma subgroups, the expected high rates of DVT were seen in patients with lower extremity (69%) and spine (62%) fractures and in patients with major head injuries (54%). This study also documented a 40% DVT

Table 13—*Prevalence and Prevention of DVT in Neurosurgical Patients**

Prophylaxis Regimen	No. of Trials	No. of Patients	Pooled DVT Prevalence, %	95% CI	Relative Risk Reduction, %
Using fibrinogen leg scanning					
Untreated controls[431–437]	7	415	22	18–26	—
ES[437]	1	80	9	4–17	60
LDUH[432]	1	50	6	1–17	73
IPC[431,433,434,436–438]	6	434	7	5–10	66
Using routine venography					
ES[439–441]	3	367	28	24–33	—
ES + LMWH[439–441]	3	360	18	14–22	38

*Randomized trials with objective outcomes. Superscript numbers are references.

rate for patients whose only major injury involved their face, chest, or abdomen. Two prospective cohort studies, using serial duplex ultrasound scanning rather than venography, found that the proximal DVT rate in 187 patients not receiving prophylaxis was 10%.[467,468]

Trauma patients with single-system, nonorthopedic injuries have a lower risk of VTE than those with multiple injuries or with lower extremity fractures.[425,456,457,459] From a variety of trauma studies, the specific risk factors that were independently associated with an increased incidence of thromboembolism include the following: spinal cord injury, lower extremity or pelvic fracture, the need for a surgical procedure, increasing age, femoral venous line or major venous repair, prolonged immobility, and duration of hospital stay.[458,459] Although the risk of DVT increases with age, young trauma patients may develop major DVT and fatal PE. Therefore, thromboprophylaxis should not be withheld simply because of youth. Limited data suggest that patients with primarily penetrating injuries have a lower risk of thrombosis than those who sustain blunt trauma.[469,470]

Routine use of thromboprophylaxis in trauma was first recommended 50 years ago.[471] Unfortunately, there are still few randomized trials of prophylaxis in this patient group; all of these have been published in the past 5 years,[397,472–476] and only one has used contrast venography as the efficacy end point.[472] Research in this area has been so limited because of the inherent heterogeneity of the trauma population in terms of the spectrum of injuries and injury severity as well as patient stability and lengths of stay, the widespread belief (and reality) that clinical trials are more difficult in trauma patients, concerns about bleeding risks with the use of anticoagulants, and reliance on an insensitive screening test, duplex scanning, as the efficacy end point. Nevertheless, because of the high thrombosis risks in trauma, recommendations for prophylaxis have been made using information from the limited studies in this specific group combined with extrapolation from other high-risk groups.[75,461,477]

Mechanical prophylaxis methods are widely used in trauma because they can generally be applied early after hospital admission, and risk of bleeding is not increased. To our knowledge, ES have never been evaluated in trauma patients. The best evidence for the protection of IPC devices comes from a recent trial of 149 trauma patients without lower extremity fracture who were randomized to receive either thigh-length sequential compression devices or venous foot pumps.[476] Using a single duplex ultrasound examination on day 8 as the principal outcome, DVT was detected in 6.5% of the IPC group and in 21.0% of those who had foot pumps applied ($p = 0.009$). In two studies, IPC seemed to be effective in patients with head injuries.[468,474] However, a large number of other studies have reported that IPC provides equal or less protection than LDUH,[468,478–484] and some studies report no benefit of IPC compared with no prophylaxis.[397,468,478,479,483] In addition to suboptimal protection, other important problems with the use of IPC include its inability to be used in approximately one third of trauma patients (due to lower extremity fractures, casts, or dressings),[479] poor compliance with proper use of the devices by patients and nursing staff,[485,486] and relatively high cost. Although ES and IPC cannot be recommended as routine prophylaxis in trauma, they may be beneficial in patients with intracranial bleeding and possibly as the initial prophylaxis for patients currently at high risk for bleeding, until anticoagulants can be given later.

The venous foot pump has been considered as prophylaxis in trauma patients since there are few contraindications to its use. However, the efficacy of this device is called into question by a randomized trial showing DVT rates three times greater with the foot pump than with IPC[476] and by the results of a recent cohort study in which venographic DVT was found in 57% of 100 major trauma patients who had undergone prophylaxis with bilateral venous foot pumps.[487] Compliance with these devices in trauma patients is also poor.[488] At the present time, therefore, foot pumps cannot be recommended in trauma patients.

Although SC administration of LDUH is also a commonly used method of prophylaxis in trauma, it is not particularly effective in these patients.[461,489] While low-risk trauma patients might benefit from LDUH, evidence against its routine use in higher-risk patients comes from a pooled analysis that demonstrated that LDUH was no better than no prophylaxis and from a large trial comparing LDUH to LMWH.[472,489]

LMWH was assessed in a randomized, double-blind

Table 14—*Incidence of DVT in Trauma Patients (No Prophylaxis Used)**

Author, yr	Patients	No.	LE Fractures, %	DVT (%)	Proximal DVT (%)
Autopsy studies					
Sevitt and Gallagher, 1961[453]	Trauma deaths; patients with PE were excluded	92	61	61 (66)	(> 50)
Eeles and Sevitt, 1967[454]	Trauma deaths; majority had head injuries	42	29	27 (64)	NS
Venography studies					
Freeark et al, 1967[455]	Injuries leading to bedrest ≥ 3 wks	42	33	12 (29)	NS
Hjelmstedt and Bergvall, 1968[456]	Tibial fractures	76	100	34 (45)	6 (8)
Nylander and Semb, 1972[457]	Tibial fractures	14	100	8 (57)	NS
Kudsk et al, 1989[458]	Multisystem trauma; bedrest ≥ 10 d	38	55	24 (63)	12 (32)
Geerts et al, 1994[459]	Major trauma; injury severity score ≥ 9	349	52	201 (58)	63 (18)
Abelseth et al, 1996[425]	Isolated lower extremity fractures treated surgically	102	100	29 (28)	4 (4)

*Superscript numbers are references; NS = not stated.

trial that compared LDUH (5,000 U bid) with enoxaparin 30 mg bid; prophylaxis was started within 36 h after injury in 344 major trauma patients without frank intracranial bleeding.[472] Bilateral contrast venography was performed between day 10 and 14. The DVT rate was 44% in the patients who received LDUH and 31% in those given LMWH (risk reduction, 30%; $p = 0.01$). More importantly, the corresponding rates for proximal DVT were 15% and 6%, respectively (risk reduction with LMWH, 58%; $p = 0.01$). The overall rate of major bleeding was $< 2\%$ with no significant differences between the groups for bleeding events, transfusions, or changes in hematocrit. This study demonstrates the efficacy and safety of LMWH in high-risk trauma patients, as well as its superiority over LDUH.

A series of prospective trials, performed by Knudson et al,[468,474,481] employed serial duplex ultrasonography of the proximal leg veins as the primary outcome measure. In the first study, 113 patients received either LDUH or sequential compression devices plus ES . The rates of VTE were similar in the two groups, 8% and 12%, respectively.[481] The second trial compared LDUH, IPC, and no prophylaxis in 251 trauma patients.[468] The DVT rates with LDUH were no different than with no prophylaxis. DVT was detected more frequently when IPC was used than with no prophylaxis, except for patients with neurotrauma, in whom IPC seemed to be highly effective. In the most recent study, trauma patients who were able to receive prophylactic anticoagulants were randomized to LMWH (enoxaparin 30 mg bid) or mechanical prophylaxis with either IPC or the venous foot pump.[474] Patients unable to receive anticoagulants were given either IPC or the foot pump. When the results in the two subsets of patients were combined, the DVT rates for the foot pump, IPC, and LMWH groups were 7%, 2%, and 1%, respectively.

Although combinations of mechanical and pharmacologic methods of prophylaxis, used either simultaneously or sequentially, may provide additive protection, this has not been studied in trauma (to our knowledge) and would be associated with increased costs.

The high risk for clinically important VTE in trauma and the limited effectiveness of most prophylaxis modalities has led to recommendations that high-risk patients be screened for asymptomatic DVT with duplex ultrasound.[467,474,484,490,491] However, the sensitivity of noninvasive testing for silent proximal DVT is considerably lower than for symptomatic thrombi.[11,492] Duplex scanning will, therefore, fail to detect even proximal DVT in a significant proportion of trauma patients and may not result in fewer PE. At least 25% of trauma patients are unable to have a complete ultrasound study of their proximal deep venous system because of local injuries, dressings and casts, or poor patient cooperation.[484,493] There are also considerable costs involved.[463,490,492–494] Furthermore, reliance on screening has the potential to delay the initiation of prophylaxis. Although routine screening for DVT cannot be justified in trauma patients, selective screening might be beneficial in patients who are transferred from another hospital where effective prophylaxis was not utilized, prior to a major surgical procedure if the patient has not received aggressive prophylaxis, or in high-risk patients in whom early prophylaxis has not been possible.

Prophylactic vena caval filter insertion has been recommended by some investigators for trauma patients at very high risk for thromboembolic complications.[495–499] To our knowledge, there are no randomized trials demonstrating an incremental benefit of IVC filter insertion when added to the most effective prophylaxis modality appropriate for the patient's clinical status. Furthermore, IVC filter use may be associated with short- and long-term complications, there may be a tendency to inappropriately delay effective prophylaxis, and there is an increased incidence of thrombosis at the insertion site as well as late development of symptomatic DVT.[364,365,500,501] Greenfield[502] has estimated the cost of prophylactic IVC filter insertions to be $900,000,000 per year if they were placed in only 1% of disabling trauma patients. Finally, PE and occasional fatal PE still occur despite the presence of a filter.[497,498,503–505] When LMWH is used as prophylaxis, the addition of screening with duplex scanning or the insertion of a vena caval filter has been estimated to cost $>$ $100,000 per PE prevented.[490] Another analysis concluded that routine screening or prophylactic vena caval filter insertion would not prevent any deaths or otherwise benefit trauma patients.[506] There is insufficient evidence to recommend the prophylactic insertion of IVC filters in trauma patients, even in those at high risk for VTE, and a more conservative approach to its use is emerging.[477,490,506,507] IVC filter insertion is primarily indicated for patients with proven proximal DVT and who have absolute contraindications to full anticoagulation or require major surgery in the near future.

Every trauma unit should develop a management guideline for the prevention of thromboembolism, and every trauma patient should be assessed for his or her thromboembolic risk and for appropriate prophylaxis. It is important to select a method of propylaxis that is effective and to start as soon as possible, since symptomatic DVT and PE and fatal PE occur when suboptimal prophylaxis methods are used.[462,463,480,484,491,506,508]

The use of LMWH, started when primary hemostasis has occurred, is the simplest and most efficacious option for most high-risk trauma patients. Current contraindications to early initiation of LMWH prophylaxis include the following: (1) intracranial bleeding; (2) incomplete spinal cord injury associated with perispinal hematoma; (3) ongoing, uncontrolled bleeding; and (4) uncorrected coagulopathy. These conditions occur in up to one quarter of patients with major trauma on hospital admission. The presence of head injury without frank hemorrhage, complete spinal cord injuries (SCIs), lacerations or contusions of internal organs such as the lungs, liver, spleen, or kidneys, or the presence of retroperitoneal hematoma associated with pelvic fracture do not by themselves contraindicate the use of LMWH prophylaxis, as long as the patient has no evidence of active bleeding. Most trauma patients can be started on a regimen of LMWH within 36 h of injury, although short delays in commencement are appropriate when necessary to establish hemostatic stability.

For patients with contraindications to LMWH prophy-

laxis, mechanical modalities (ES, IPC) should be considered. After an initial period of mechanical prophylaxis, during which primary hemostasis becomes established, these patients can usually be started on a regimen of LMWH. Although the optimal duration of prophylaxis is not known for these patients, it should generally continue until discharge from hospital. If hospital stay (including rehabilitation) continues beyond 2 weeks, and if there is an ongoing risk for thromboembolism, continuing inpatient prophylaxis with oral anticoagulants should be considered, as long as there is no longer a major risk of bleeding and no further surgical procedures are planned. Although many trauma patients are not yet fully mobile at discharge from hospital, and the potential for delayed symptomatic thromboembolic events exists, to our knowledge, there are no data to quantify this risk. Unless such evidence becomes available in the future, we cannot recommend routine postdischarge prophylaxis for any trauma subgroup. However, we do recommend that all patients with major trauma undergo aggressive prophylaxis while in hospital, and we suggest that, on hospital discharge, patients with ongoing risk factors at least be warned to seek prompt medical attention if symptoms develop that might indicate DVT or PE.

Acute SCI

Acute SCI patients have the highest risk of DVT among all hospital admissions.[509] This results in both acute morbidity and mortality as well as considerable long-term disability.[510–512] Despite increased awareness of VTE as a complication of SCI, PE remains the third most common cause of death in these patients[513–515] A database that has followed >28,000 SCI patients since 1973 found that the risk of fatal PE has not fallen between 1973 to 1977 and 1992 to 1998.[515] In a multicenter review of 1,419 patients hospitalized with acute SCI, Waring and Karunas[514] reported a 15% incidence of symptomatic DVT and a 5% incidence of clinically recognized PE. Prospective screening studies show a 67 to 100% incidence of objectively proven DVT in this patient population[459,516–520] (Table 15).In a large study of thromboembolism in major trauma, SCI was the risk factor most strongly associated with the development of DVT (odds ratio 8.6 compared with trauma patients without SCI).[459] Among SCI patients, the factors that have been associated with an increased frequency of DVT are complete vs incomplete injury, paraplegia vs tetraplegia, and first 3 months after injury vs beyond 3 months.

Several small, randomized trials of prophylaxis have been performed in SCI patients (Table 16).Green et al conducted two randomized trials in which LDUH was compared with adjusted-dose heparin[521] or with a LMWH.[522] In the first study, the assessment for DVT was by IPG and Doppler flow studies. In the second trial, IPG was combined with duplex scanning. These screening tests, therefore, primarily detected proximal DVT. All positive or borderline test results were confirmed with venography. In the LDUH vs adjusted-dose heparin study, adjusted-dose heparin was significantly more effective than LDUH (DVT rates of 7% and 31%, respectively).[521] The second study demonstrated significant superiority of LMWH over LDUH (DVT rates 0% vs 26%, respectively).[522] A large randomized, double-blind trial compared LDUH and LMWH in a variety of major trauma patients.[472] Among the 15 SCI patients receiving LDUH, DVT and proximal DVT were detected in 10 (67%) and 2 (13%), respectively, while the comparable values for the 8 LMWH patients were 4 (50%) and 0. The use of LMWH as prophylaxis for DVT following acute SCI is also supported by an uncontrolled study of 60 patients given enoxaparin 30 mg q12h, in whom no DVT were detected by duplex scanning.[524]

In the only study that has assessed the efficacy of IPC in SCI patients, the residual proximal DVT rates were unacceptably high both with IPC alone (40%) and with IPC plus acetylsalicylic acid and dipyridamole (25%).[523] It thus appears that neither LDUH nor IPC provides adequate protection against VTE in SCI, while both adjusted-dose heparin and LMWH are more effective prophylaxis options than LDUH. Four uncontrolled studies with oral anticoagulants suggested a significant reduction in symptomatic VTE rates with the use of routine oral anticoagulation started shortly after hospital admission, compared with patients who did not have anticoagulation.[525–528]

Although the period of greatest risk for VTE is the acute-care phase,[513,515,517,519,529] symptomatic DVT, PE, and fatal PE also occur in the rehabilitation phase.[511,519,530–537] Chen et al[538] found that 10% of 1,649 patients admitted to 18 SCI rehabilitation units developed DVT, and 3% had PE. Gunduz and colleagues[531] reported

Table 15—*Incidence of DVT in Patients With Acute SCI (No Prophylaxis Used)

Author, yr	End Point	No. of Patients	DVT, No. (%)	Proximal DVT, No. (%)
Brach et al, 1977[516]	FUT/IPG	10	9 (90)	NS
Rossi et al, 1980[517]	FUT	18	13 (72)	3 (17)
Myllynen et al, 1985[518]	FUT	9	9 (100)	NS
Merli et al, 1988[519]	FUT/IPG	8	42 (48)	NS
Petaja et al, 1989[520]	FUT	9	6 (67)	NS
Geerts et al, 1994[459]	Venography	26	21 (81)	9 (35)

*FUT = fibrinogen leg scan, confirmed by venography; IPG = impedance plethysmography; NS = not stated; superscript numbers are references.

Table 16—*Randomized Studies of DVT Prevention After Acute SCI

Regimen	First Author, yr	End Points	DVT, No. (%)
Low-dose heparin	Green, 1988[521]	IPG	9/29 (31)
	Green, 1990[522]	IPG, DUS	5/19 (26)
	Geerts, 1996[472]	Venography	10/15 (67)
Intermittent pneumatic compression	Green, 1982[523]	FUT, IPG	6/15 (40)
Adjusted-dose heparin	Green, 1988[521]	IPG	2/29 (7)
LMWH	Green, 1990[522]	IPG, DUS	0/16 (0)
	Geerts, 1996[472]	Venography	4/8 (50)
Combinations (IPC, ASA, dipyridamole)	Green, 1982[523]	FUT, IPG	3/12 (25)

*IPG = impedance plethysmography; DUS = duplex ultrasound; ASA = acetylsalicylic acid; FUT = fibrinogen leg scan; superscript numbers are references.

venographic evidence of DVT in 53% of 30 patients admitted to a SCI rehabilitation unit (none had received prior DVT prophylaxis). In a study by Yelnik et al,[532] SCI patients with normal venography on admission to the rehabilitation unit underwent a second venogram approximately 1 month later. A further 14% of these patients developed new DVT during the first month of their rehabilitation program, despite continuation of thromboprophylaxis. The thromboembolic risk remains increased in part because of the very high incidence of DVT early after injury and the slow rate of resolution of DVT in these patients.[510] Based on this evidence, it has been recommended that DVT prophylaxis be continued for a minimum of 3 months (or at least until the completion of the rehabilitation phase) in patients with an acute SCI.[509,539]

Although to our knowledge no large, well-controlled studies of DVT prophylaxis following acute SCI have been published, the very high risk of DVT and PE, combined with the results of currently available studies, support the aggressive use of early prophylaxis in all SCI patients.[509,540] LMWH seems particularly promising, but further trials are needed. LDUH, IPC, or ES do not provide adequate protection when used alone, and to our knowledge, there are no data confirming significant benefit using these modalities in combination.[533,541]

Studies have not addressed the value of routine screening of SCI patients with duplex scanning, although this is a reasonable consideration for patients in whom prophylaxis has been delayed for several days. After the acute injury phase, continuing LMWH therapy or conversion to full-dose warfarin (target INR 2.5, range 2.0 to 3.0) for the duration of the rehabilitation phase may protect patients from delayed thromboembolic events and is recommended.[509] For patients with motor incomplete SCI, initiation of LMWH therapy should probably be delayed for 24 to 72 h if there is evidence of perispinal hematoma on CT scan or MRI, and longer-term, full anticoagulation with warfarin should probably be delayed until about 2 weeks after injury in such patients.

Burns

One would expect that burn patients would be at significant risk for VTE because of the presence of a systemic hypercoagulable state,[542] prolonged bedrest, and repeated surgical procedures, frequent sepsis, the common use of central venous lines, and premorbid risk factors. A number of autopsy studies have demonstrated that burn patients commonly have DVT[453,454] and PE[453,543–545] at the time of death, although fatal PE has been described in only 0.1 to 0.5% of patients.[545–548] Symptomatic VTE has been reported in only 0.4% to 0.9% of burn patients in large retrospective case reviews.[546,548,549] Among the few prospective screening studies, the DVT rates varied between 12% and 53%.[455,550–552] Central venous line-related thrombosis is common in burn patients and is associated with an increased risk of sepsis.[543,553]

To our knowledge, there are no thromboprophylaxis trials in this group of patients, and currently, there is insufficient evidence to justify the routine use of thromboprophylaxis in burn patients. However, it is reasonable to use prophylaxis in patients who have additional risk factors including concomitant lower extremity trauma, increased age,[547,548] extensive burns,[544,548] morbid obesity,[554] prolonged bedrest,[553] and central venous lines.[543,553]

Medical Conditions

In contrast to surgical patients, prevention of VTE has been less well studied in hospitalized medical patients.[555–558] Although the trials are generally limited in number and smaller in size, there are now sufficient data to make recommendations about prophylaxis for many nonsurgical patient groups (Table 17).

Myocardial Infarction

Prophylactic antithrombotic therapy in patients with MI can be used to prevent VTE as well as mural thrombosis and systemic arterial embolism.[580,581] The overall incidence of DVT is approximately 24% among MI patients not treated with antithrombotic therapy[559–561] (Table 17). Three trials have evaluated different LDUH regimens (5,000 U bid or tid, and 7,500 U bid)[559–561]; two found a reduction in the incidence of DVT using the FUT.[560,561] Two studies evaluated high-dose IV heparin (40,000 U/d) and also found a beneficial effect in reducing leg DVT, with no increase in bleeding complications.[562,563]

Several older randomized trials have demonstrated that full anticoagulation with heparin and oral anticoagulation after MI resulted in reduced rates of clinically diagnosed

DVT and PE compared with either no prophylaxis or low-dose anticoagulants.[582–584] In a study by Kierkegaard and Norgren,[585] 80 patients with acute MI wore ES on one leg, with the contralateral extremity serving as control. There were eight control legs with an abnormal FUT, compared with no abnormalities for legs on which ES were worn ($p = 0.003$).

From the available data, LDUH and full anticoagulation reduce the incidence of VTE in patients with acute MI. Presumably, mechanical methods of prophylaxis (ES, IPC) would also be useful in patients with acute MI when antithrombotic agents are contraindicated. However, the current aggressive therapy of MI with thrombolytics, unfractionated heparin, LMWH, antiplatelet agents, or combinations of these drugs has made the prevention of DVT a secondary aim in these patients. The effect of thrombolytic therapy or short-term, full-dose heparin or LMWH on the development of VTE after MI is not known.

Ischemic Stroke

Stroke patients have a high risk of DVT in the paretic or paralyzed lower extremity with a pooled DVT incidence of 55% (Table 17).[564–571] Approximately 5% of early deaths following stroke are attributed to PE. Among 421 patients admitted to a stroke rehabilitation unit, routine duplex ultrasonography detected proximal DVT in 14% at entry to the unit, and an additional 5% of patients without prophylaxis were subsequently found to have proximal DVT during the rehabilitation stay.[586]

To date, nine randomized trials have evaluated LDUH or LMWH in acute stroke patients.[564,566,568,570–574] In two separate trials, LDUH (5,000 U bid) was associated with a 71% risk reduction in DVT relative to control patients.[564,568] Similarly, two trials compared LMWH prophylaxis to placebo.[570,571] One study demonstrated significant efficacy for LMWH, while the other did not. The pooled DVT rates in these two trials were 40% for the placebo patients and 26% for the LMWH patients. Two recent trials have directly compared LMWH (enoxaparin 40 mg once daily) to LDUH (5,000 U tid) using routine contrast venography as the primary outcome.[572,579] Both studies found that LMWH provided greater protection than LDUH (relative risk reductions favoring LWMH of 29% and 43%) without more bleeding. The heparinoid, danaparoid, has been assessed as thromboprophylaxis in four stroke trials.[566,569,573,574] In the two danaparoid vs placebo studies, the combined relative risk reduction for the active agent was 78%,[566,569] while in the two danaparoid vs LDUH trials, there was a 44% risk reduction with the use of danaparoid.[573,574] In a nonrandomized, prospective study of 681 ischemic stroke patients, the combination of LDUH, ES, and IPC was associated with fewer symptomatic DVT and PE than LDUH plus ES.[587]

Two recent trials evaluated the effectiveness of heparin, aspirin, and danaparoid in reducing the neurologic deficit following acute ischemic stroke.[588,589] The incidence of clinical PE and DVT was also assessed. In the International Stroke Trial, a study of 19,435 patients with acute ischemic stroke, there was a significant reduction in the frequency of fatal and nonfatal PE with heparin (0.5% in the heparin-treated patients and 0.8% in the nontreated group; $p = 0.02$).[588] The heparin group randomly received either 5,000 U or 12,500 U, given SC q12h. There was no difference in the incidence of PE between these two heparin groups, but an increased bleeding risk was noted in the patients receiving the higher-dose regimen. Aspirin (300 mg) was ineffective in reducing fatal and nonfatal PE. In the Trial of ORG 10172 (danaparoid) in Acute Stroke Treatment (TOAST), IV danaparoid, adjusted to maintain an anti-Xa level between 0.6 to 0.8 for 7 days, was compared with placebo in the reduction of neurologic deficit following acute ischemic stroke ($N = 1,281$).[589] The clinical incidence of VTE was 0.4% in the placebo

Table 17—*Prevention of DVT in Patients With Medical Conditions

Condition Regimen	No. of Trials	No. of Patients	DVT, %	95% CI	Relative Risk Reduction, %
MI					
Control[559–561]	4	214	24	18–30	—
LDUH[559–561]	4	165	7	3–12	71
High-dose heparin[562,563]	2	70	4	1–12	86
Ischemic stroke					
Control[564–571]	8	346	55	49–60	—
LDUH[564,568,572–574]	5	364	24	20–29	56
LMWH[570–572]	3	158	23	17–30	58
Danaparoid[566,569,573,574]	4	203	10	6–15	82
Medical patients					
Control[566,575–577]	4	528	16	13–19	—
LDUH (FUT)[575,576,578]	3	327	6	4–9	61
LDUH (veno)[579†]	1	303	22	18–27	—
LMWH (FUT)[566,578]	2	339	4	2–6	76
LMWH (veno)[577,579†]	2	817	9.5	8–12	39

*Pooled results of randomized trials in which either the FUT or contrast venography were the primary efficacy outcomes. Superscript numbers are references.

†For reference 579, the outcome measure was venographic DVT plus death, probably accounting for the relatively high event rates.

group compared with none in those receiving danaparoid. This trial used therapeutic doses of danaparoid and cannot be compared with the trial using prophylactic dosing mentioned above.

From these studies, LDUH, LMWH, and danaparoid can be recommended in patients with acute stroke. Using asymptomatic DVT as the outcome, both LMWH and danaparoid are more efficacious than LDUH. In the trials, these prophylactic agents were maintained for 10 to 14 days following the cerebrovascular event. Continued use of prophylaxis would depend on the presence of ongoing risk factors such as paresis, bed rest, atrial fibrillation, and congestive heart failure. We are not aware of any thromboprophylactic trials for patients with hemorrhagic stroke. Use of ES or IPC is recommended for such patients if they are being actively treated.

Other Medical Conditions

Patients other than those with MI or ischemic stroke, who are admitted to medical wards, are at moderate risk for the development of VTE.[555,556] Most patients in the prospective clinical trials have had congestive heart failure, COPD, or infections. Using either the FUT or venography as routine screening tests, the DVT rates in the absence of prophylaxis have been reported to be approximately 16%[566,575–577] (Table 17) and autopsy-proven fatal PE was found in 2.5% of 200 medical patients followed up prospectively without prophylaxis.[590]

Studies for the prevention of VTE in medical patients have compared LDUH or LMWH with placebo[566,575–577] or LDUH with LMWH.[577–579,591–594] In earlier studies, LDUH 5,000 U, bid or tid, was compared with no prophylaxis or placebo for 10 to 14 days.[575,576] Rates of leg scan-detected DVT were reduced by 67% (from 27.5 to 9%), and bleeding complications were rare.

Two studies have compared LMWH with placebo.[566,577] In the first trial, enoxaparin 60 mg once daily or placebo was given to elderly medical patients for 10 days.[566] The DVT rates diagnosed by FUT were 4 of 132 (3%) vs 12 of 131 (9%) in the patients receiving LMWH or placebo, respectively ($p = 0.03$). Major bleeding was reported in one patient on LMWH and in two patients receiving placebo. In the recent Prophylaxis in Medical Patients with Enoxaparin (MEDENOX) study, enoxaparin (either 20 mg or 40 mg, once daily) was compared with placebo in 1,102 hospitalized patients, most of whom had congestive heart failure, acute respiratory failure, or acute infectious diseases.[577] The primary outcome was DVT detected by bilateral venography or duplex ultrasonography between days 6 and 14, or documented PE. The incidence of VTE was 14.9% (43/288) for the patients receiving placebo, 15% (43/287) for patients receiving enoxaparin 20 mg, and 5.5% (16/291) for patients receiving enoxaparin 40 mg ($p < 0.001$ for LMWH 40 mg vs placebo). Major bleeding occurred in 1.1% of patients receiving placebo, 0.3% of patients receiving enoxaparin 20 mg, and 1.7% of those in the 40-mg group. There was no difference in the death rates among the three groups.

LMWH has been compared with LDUH in six randomized trials.[578,579,591–594] Bergmann and Neuhart[578] compared enoxaparin 20 mg daily with LDUH 5,000 U bid in 959 hospitalized elderly patients with acute medical illness and found no significant differences for thromboembolic outcomes or bleeding. In a study of 877 medical patients, using routine venography to screen for DVT, the composite end point of VTE and death occurred in 22% of LDUH patients and in 15% of the patients who were randomized to LMWH ($p = 0.04$).[579] The remaining four comparative studies screened patients with other modalities including serial impedance plethysmography,[591] duplex scanning,[592,593] or plasma markers of thrombosis confirmed by objective tests, if positive.[594] In each of these trials, LMWH was either comparable or superior to LDUH.

In the Thromboembolism Prophylaxis in Internal Medicine with Enoxaparin (PRIME) Study, enoxaparin 40 mg once daily was compared with LDUH 5,000 U tid in 959 immobilized medical patients.[593] The primary end point was VTE, diagnosed by routine duplex ultrasonography and confirmed by venography or by objectively demonstrated PE. Thromboembolic events were detected in 1 of 393 (0.3%) patients receiving LMWH and 5 out of 377 (1.3%) patients receiving LDUH ($p = 0.2$). Major bleeding was seen in two patients receiving LMWH (0.4%) and in 7 receiving LDUH (1.5%), two of which resulted in death. There was no difference in the death rates (7 receiving LMWH and 11 receiving LDUH). In the PRINCE study, 665 patients with severe respiratory diseases or congestive heart failure were randomized to receive enoxaparin 40 mg/d or LDUH 5,000 U tid for 10 ± 2 days.[594] Patients with elevated levels of D-dimer or soluble fibrin underwent venography. Thromboembolic events were detected in 8.4% of patients receiving LMWH prophylaxis and 10.4% of those treated with LDUH ($p = 0.6$). Bleeding occurred in 1.5% of patients receiving LMWH and in 3.6% of patients receiving LDUH.

Two randomized trials assessed the effect of low-dose heparin on mortality. Halkin et al[595] gave 1,358 consecutive general medical patients LDUH 5,000 U bid or no treatment for the duration of hospitalization or until they were fully mobile. Randomization was based on the hospital record number. The all-cause mortality rate was 10.9% in the control group and 7.8% for patients randomized to LDUH ($p < 0.05$). Thromboembolic events were not reported. Six Swedish hospitals randomized 11,693 patients admitted to the hospital with acute infections to either treatment with LDUH 5,000 U bid or no prophylaxis until discharge.[596] In the intention-to-treat analysis, mortality rates were similar in the heparin and control groups (5.3% vs 5.6%; $p = 0.4$). Autopsy-proven PE rates were also similar, but the median time from randomization to fatal PE was 28 days in the heparin group and 12.5 days in the control group, the difference corresponding to the duration of heparin prophylaxis. There were fewer nonfatal thromboembolic events in the heparin group (116 vs 70; $p = 0.001$).

Two randomized clinical trials have also assessed the effect of LMWH on mortality.[566,597] In a small study by Dahan et al,[566] 4.4% of patients died in both the LMWH and placebo groups. In a letter to the editor, Bergmann and Caulin[597] described a study in which 2,472 patients,

admitted to hospital with acute medical conditions, were randomized to receive LMWH or placebo for up to 21 days. The overall hospital mortality was 10% in both groups.

It can be concluded from these studies that either LDUH or LMWH significantly decreases the incidence of thromboembolic events when compared with no prophylaxis in medical patients.[555,558,598] A recent meta-analysis of randomized trials, which compared LDUH to LMWH in medical inpatients, found that there was no significant difference in the incidence of thromboembolic events or death, while LMWH was associated with a 52% lower incidence of major bleeding.[558]

Cancer Patients

VTE is one of the most common complications seen in cancer patients and may be due to the hypercoagulable state of malignancy[599] and/or to its treatment including surgery, chemotherapy, radiotherapy, and central venous lines. In cancer patients, the prevention of thromboemboli is an even greater priority than in patients without malignancy, because the diagnoses of DVT and PE are often more difficult, and because the treatment of overt VTE is less successful and is associated with more bleeding complications.

Cancer patients undergoing surgical procedures have at least twice the risk of postoperative DVT and more than 3 times the risk of fatal PE than noncancer patients undergoing similar procedures.[600] Thromboprophylaxis with LDUH is effective in reducing DVT and fatal PE in patients having cancer surgery.[48,90,100] Furthermore, a large study randomized medical patients to receive LDUH or no prophylaxis, with in-hospital death as the primary outcome.[595] Among the subgroup of patients with cancer, mortality was 32% in the control group and 19% in the group who were allocated to LDUH.

Chemotherapy itself is strongly associated with thromboembolic complications.[601] The risk of thromboembolism in women with stage II breast cancer receiving chemotherapy is 7 to 11%, falling dramatically when the course of chemotherapy has been completed.[602,603] The antiestrogen, tamoxifen, increases the thrombotic risk of chemotherapy twofold to sixfold in breast cancer patients.[604] In a randomized trial of adjuvant tamoxifen in stage I breast cancer, the risk of thromboembolism was six times greater in the tamoxifen-treated group, compared with the placebo-treated patients.[605] Tamoxifen used for the prevention of breast cancer is associated with increased rates of DVT (relative risk = 1.6) and PE (relative risk = 3.0).[606] The other advanced cancers that are associated with a high risk of thromboembolism include brain tumors and adenocarcinoma (including colorectal, pancreatic, lung, renal cell, and ovarian cancers).

Levine et al[607] randomized 311 women with metastatic breast cancer receiving chemotherapy to treatment with either very low dose warfarin (n = 152) or placebo (n = 159). The warfarin dose was 1 mg/d for 6 weeks, and then the dose was adjusted to maintain the INR between 1.3 and 1.9. The average INR was 1.5, and the average dose of warfarin to maintain the INR within the target range was 2.6 mg. There were seven thromboembolic events in the placebo group compared with one in the warfarin group ($p = 0.03$). Major bleeding occurred in two placebo-treated patients and in one patient receiving warfarin. Rajan et al[608] performed a cost-effectiveness analysis using the results of this trial and showed that very low dose warfarin can be provided to women with metastatic breast cancer receiving chemotherapy without an increase in health-care costs.

Cancer patients with indwelling central venous catheters frequently develop thrombosis of the axillary/subclavian veins.[609] Bern et al[610] conducted a trial in which 82 patients with central vein catheters were randomized either to prophylaxis with warfarin 1 mg/d or no treatment. All patients underwent upper extremity venography at 90 days, or sooner if they developed symptoms of thrombosis. Patients who received warfarin had a 9.5% rate of venous thrombosis compared with 37.5% in the control patients ($p < 0.001$). In a subsequent study, Monreal and colleagues[611] randomized cancer patients with central venous catheters to treatment with LMWH (dalteparin 2,500 anti-Xa U daily) or no treatment for 90 days, whereupon upper extremity venography was performed. This study was stopped early after 8 of 13 control patients developed thrombosis, compared with one LMWH-treated patient ($p = 0.002$). Reducing catheter-related central venous thrombosis and line malfunction are important advantages of prophylaxis in these patients, but the most compelling benefit is a decrease in catheter-related sepsis.[612] Based on these observations, it is suggested that 1 mg/d of warfarin or LMWH be administered once daily to cancer patients with indwelling central venous catheters.

In summary, cancer patients undergoing major surgical procedures are at high risk for VTE and should receive aggressive prophylaxis as recommended above in the sections on general, gynecologic, and urologic surgery, and in Tables 2 and 3.[600] Cancer patients who are immobile or at bedrest for acute medical illnesses should be considered for thromboprophylaxis using the guidelines above for medical patients. Patients with long-term central lines for chemotherapy should also receive prophylaxis with either warfarin 1 mg daily or subcutaneous LMWH to prevent axillary-subclavian vein thrombosis. Prophylaxis with low-intensity warfarin (or other anticoagulants) in the ambulatory cancer patient to prevent VTE warrants further evaluation. Finally, the potential benefits of anticoagulants on the course of some cancers also requires intense study.[613,614]

Critical Care

Most critical care patients have at least one risk factor for VTE and most have multiple factors.[615] Although there is a paucity of critical care-specific data about thromboembolism, the information presented above for groups that constitute the majority of ICU patients (especially general surgery, trauma, and medical patients) is highly relevant to those in ICUs. Fibrinogen leg scanning discovered DVT in 29% of 59 medical ICU patients not receiving any prophylaxis.[576] A recent double-blind trial of medical ICU patients used duplex scanning every 72 h

until discharge from the unit and found DVT in 31% of the 390 control patients.[616] In another prospective trial, contrast venography detected DVT in 28% of 85 patients, with exacerbations of chronic obstructive lung disease requiring mechanical ventilation.[617]

We are aware of only three published randomized trials of DVT prophylaxis in the ICU.[576,616,617] In the first, medical ICU patients received either LDUH or placebo.[576] The DVT rates by FUT were 29% and 13% in the control and LDUH groups, respectively ($p < 0.05$). Serial duplex scanning was used to screen 791 medical ICU patients in the second study, which also compared LDUH to placebo.[616] DVT was detected in 31% of the placebo-treated patients and in 11% of the LDUH group ($p = 0.001$). In the third study, chronic obstructive lung disease patients receiving mechanical ventilation were randomized to treatment with placebo or the LMWH, nadroparin, given in a body weight-adjusted dose of approximately 65 U/kg daily.[617] Routine venography detected DVT in 28% of control subjects and 16% of treated patients ($p = 0.045$).

All ICU patients should be assessed for their risk of thromboembolism, and prophylaxis should be utilized in most. A written policy for prophylaxis combined with preprinted or computerized ICU admission orders is desirable.[618] In these patients, it is important to make individual decisions regarding the initiation of prophylaxis and the modalities used based on the their specific clinical picture. In general, for ICU patients at high risk for bleeding, mechanical prophylaxis with either ES alone or combined with IPC until the bleeding risk decreases is reasonable. For the others, anticoagulant prophylaxis with LDUH or LMWH, depending on the population under consideration, is suggested.

Prophylaxis Implementation Strategies

VTE is an important health-care problem, resulting in significant mortality, morbidity, and resource expenditures. Despite the need for additional data, we believe that there is sufficient evidence to recommend the routine use of thromboprophylaxis for many hospitalized patient groups. These include patients undergoing major general, gynecologic, and urologic surgery, lower extremity arthroplasty and hip fracture repair, neurosurgery, patients admitted with major trauma or SCI, and medical patients with risk factors for thromboembolism. The implementation of evidence-based and thoughtful prophylaxis strategies provides benefit to patients and should also protect their caregivers and the hospitals from legal liability, while the lack of such strategies may be criticized.

There are two general approaches to the implementation of thromboprophylaxis in patients at risk. The first approach involves identifying the patients at greatest risk for thromboembolic complications, and then targeting preventive measures in these but not in the others. The second strategy involves implementation of prophylaxis routinely for all patients who belong to each of the target groups. Because we currently have limited ability to identify which individual patients, belonging to the clinical groups discussed above, do not require prophylaxis,[619] we strongly support the concept of providing prophylaxis for every member of the group (unless there are specific contraindictions).

Publication of consensus conference recommendations alone are insufficient to ensure the routine use of these recommendations in clinical practice.[620] Educational programs are important in supporting the use of appropriate prophylaxis programs and in countering misperceptions about these recommendations. A 1994 prospective study documented a nearly twofold increase in prophylaxis (from 29 to 52%) among hospitalized patients at risk, with the use of educational strategies designed to increase awareness of the problem of VTE.[621] Prophylaxis use was significantly greater in hospitals whose physicians participated in the formal education programs. One key factor that motivated clinicians to change practice was the provision of hospital-specific data demonstrating the potential benefits of prophylaxis strategies. Further improvements in the use of VTE prophylaxis may be possible through other formal physician education programs.[622,623] Automated reminder systems also increase the appropriate use of thromboprophylaxis.[624] Increasingly, hospitals are adopting direct computer order-entry for drugs and other interventions. These same systems can easily be adapted to provide prophylaxis recommendations based on simple risk factor assessment, similar to the proven effectiveness of these programs in selecting antimicrobial therapy, in reducing adverse drug reactions, and in the management of acute respiratory failure.[625–630]

Recommendations

General Recommendations

1. 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.
2. For all patient groups, we do **not** recommend aspirin for prophylaxis, because other measures are more efficacious (grade 1A).
3. In all patients having spinal puncture or epidural catheters placed for regional anesthesia or analgesia, we recommend that antithrombotic therapy or prophylaxis be used with caution (grade 1C+).

General, Gynecologic, and Urologic Surgery

General Surgery

1. In low-risk general surgery patients (Table 2) who are undergoing minor procedures, are < 40 years of age, and have no additional risk factors, we recommend the use of no specific prophylaxis other than early ambulation (grade 1C).
2. Moderate-risk general surgery patients are those undergoing minor procedures but have additional thrombosis risk factors, those having

nonmajor surgery between the ages of 40 and 60 years with no additional risk factors, or those undergoing major operations who are younger than 40 years with no additional clinical risk factors. We recommend prophylaxis with LDUH, LMWH, ES, or IPC (all grade 1A in comparison to no prophylaxis).

3. Higher-risk general surgery patients are those having nonmajor surgery over the age of 60 years or with additional risk factors or patients undergoing major surgery over the age of 40 years or with additional risk factors. We recommend thrombosis prophylaxis with LDUH, LMWH, or IPC (all grade 1A in comparison to no prophylaxis).

3.1 In higher-risk general surgery patients with a greater than usual risk of bleeding, we recommend the use of mechanical prophylaxis with ES or IPC, at least initially (grade 1C).

4. In very-high-risk general surgery patients with multiple risk factors, we recommend that effective pharmacologic methods (LDUH or LMWH) be combined with ES or IPC (grade 1C based on small studies and on extrapolation of data from other patient groups).

5. 1 In selected very-high-risk general surgery patients, we recommend that clinicians consider postdischarge LMWH or perioperative warfarin (INR 2.0 to 3.0) (grade 2C).

Gynecologic Surgery

1. For gynecologic surgery patients undergoing brief procedures for benign disease, we recommend early mobilization alone (grade 1C).
2. We recommend that patients having major gynecologic surgery for benign disease, without additional risk factors, receive twice daily LDUH (grade 1A). Alternatives include once daily LMWH or IPC, started just before surgery and continued for at least several days postoperatively (grade 1C+).
3. For patients undergoing extensive surgery for malignancy, we recommend routine prophylaxis with three daily doses of LDUH (grade 1A). Alternative considerations include the combination of LDUH plus mechanical prophylaxis with ES or IPC, or higher doses of LMWH, sincethese options may provide additional protection (grade 1C).

Urologic Surgery

1. In patients undergoing transurethral or other low-risk urologic procedures, we recommend that no specific prophylaxis other than prompt ambulation be used (grade 1C).
2. For patients with major, open urologic procedures, we recommend routine prophylaxis with LDUH, ES, IPC, or LMWH (all grade 1B in comparison to no prophylaxis).
3. For patients at the highest risk, we recommend combining ES plus or minus IPC, with LDUH or LMWH (grade 1C).

Major Orthopedic Surgery

Elective Hip Replacement

1. For patients undergoing elective THR surgery, we recommend either SC LMWH therapy (started 12 h before surgery, 12 to 24 h after surgery, or 4–6 h after surgery at half the usual high-risk dose and then continuing with the usual high-risk dose the following day), or adjusted-dose warfarin (INR target = 2.5, range 2.0 to 3.0; started preoperatively or immediately after surgery) (all grade 1A).
2. Adjusted-dose heparin therapy (started preoperatively) is an acceptable but more complex alternative (grade 2A).
3. Adjuvant prophylaxis with ES or IPC may provide additional efficacy (grade 2C).
4. Although other agents such as LDUH, aspirin, dextran, and IPC alone may reduce the overall incidence of VTE, they are less effective, and we do **not** recommend that these options be used.

Elective Knee Replacement

1. For patients undergoing elective TKR surgery, we recommend either LMWH or adjusted-dose warfarin (grade 1A).
2. Optimal use of IPC is an alternative option (grade 1B recommendation because of the few trials and small sample sizes).
3. LDUH is **not** recommended (grade 1C+).

Hip Fracture Surgery

1. For patients undergoing hip fracture surgery, we recommend either LMWH or adjusted-dose warfarin prophylaxis (grade 1B because the available data are limited).
2. The use of LDUH may be an alternative option, but this is a grade 2B recommendation based on the very limited available data.
3. We do not recommend the use of aspirin alone because it is less efficacious than other approaches (grade 2A).

Other Prophylaxis Issues for Major Orthopedic Surgery

1. The optimal duration of anticoagulant prophylaxis after THR or TKR surgery is uncertain, although at least 7 to 10 days of prophylaxis is recommended (grade 1A).
2. Extended out-of-hospital LMWH prophylaxis (beyond 7 to 10 days after surgery) may reduce the incidence of clinically important thromboembolic events, and we recommend this approach at least for high-risk patients (grade 2A because of uncertainty regarding cost-effectiveness).
3. We do **not** recommend routine duplex ultrasonography screening at the time of hospital

discharge or during outpatient follow-up in asymptomatic THR or TKR patients (grade 1A).

Neurosurgery, Trauma, and Acute SCI

Neurosurgery

1. We recommend the use of IPC with or without ES in patients undergoing intracranial neurosurgery (grade 1A).
2. LDUH or postoperative LMWH are acceptable alternatives (grade 2A because of concerns about clinically important intracranial hemorrhage).
3. The combination of physical (ES or IPC) and pharmacologic (LMWH or LDUH) prophylaxis modalities may be more effective than either modality alone in high-risk patients (grade 1B).

Trauma

1. Trauma patients with an identifiable risk factor for thromboembolism should receive prophylaxis if possible. If there is no contraindication, we recommend that clinicians use LMWH, starting treatment as soon as it is considered safe to do so (grade 1A).
2. We recommend that initial prophylaxis with a mechanical modality (ES and/or IPC) be used if LMWH prophylaxis will be delayed or is contraindicated because of concerns about the patient's risk of bleeding (grade 1C).
3. In patients at high risk for thromboembolism who have received suboptimal prophylaxis, consideration should be given to screening with duplex ultrasound (grade 1C).
4. We recommend that IVC filter insertion be used if proximal DVT is demonstrated and anticoagulation is contraindicated (grade 1C+). We do **not** recommend the use of IVC filter insertion for primary prophylaxis (grade 1C).

Acute SCI

1. In patients with acute SCI, we recommend prophylaxis with LMWH (grade 1B).
2. LDUH, ES, and IPC appear to be relatively ineffective when used alone, and we do **not** recommend these modalities (grade 1C).
3. ES and IPC might have benefit if used in combination with LMWH or LDUH or if anticoagulants are contraindicated early after injury (grade 2B).
4. In the rehabilitation phase of acute SCI, we recommend the continuation of LMWH therapy or conversion to full-dose oral anticoagulation (INR target 2.5, range 2.0 to 3.0) (grade 1C).

Medical Conditions

Acute MI

1. We recommend that most patients with acute MI receive prophylactic or therapeutic anticoagulant therapy with SC LDUH or IV heparin (grade 1A).

Ischemic Stroke

1. For patients with ischemic stroke and impaired mobility, we recommend the routine use of LDUH, LMWH, or the heparinoid, danaparoid (all grade 1A).
2. If anticoagulant prophylaxis is contraindicated, we recommend mechanical prophylaxis with ES or IPC (grade 1C+).

Other Medical Conditions

1. In general medical patients with risk factors for VTE (including cancer, bedrest, heart failure, severe lung disease), we recommend LDUH or LWMH (grade 1A).

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