Chapter 31. Prevention of Venous Thromboembolism

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Background

Venous thromboembolism (VTE) refers to occlusion within the venous system. It includes deep vein thrombosis (DVT), typically of the lower extremities, and embolism to the pulmonary vasculature. Distal DVT is occlusion confined to the deep calf veins, while thrombosis at or above the popliteal vein is considered proximal DVT. A distal DVT becomes clinically important if it extends proximally, where the chance of pulmonary embolization (PE) is clinically significant.

In hospitalized patients, VTE occurs with relatively high frequency. A patient's risk of VTE varies depending on multiple factors including age, medical condition, type of surgery, duration of immobilization, and the presence of an underlying hypercoagulable state such as malignancy. Measures to prevent VTE have been widely studied for many reasons, including VTE's high incidence, its associated mortality and morbidity, its cost of treatment, and its treatment-related complications.

VTE is often clinically silent. As a result, studies evaluating the efficacy of preventive measures generally screen patients who are asymptomatic. As widespread screening is not recommended in general practice, the incidence of VTE in most studies appears higher than that encountered in clinical practice. The importance of clinically undetected VTE is not fully understood.

Practice Description

Both mechanical and pharmacologic interventions have been evaluated for prevention of VTE (Table 31.1). Mechanical devices include graduated elastic stockings (ES) and intermittent pneumatic compression (IPC); pharmacologic measures include low dose unfractionated heparin (LDUH), low molecular weight heparin (LMWH), warfarin, and aspirin .

Prevalence and Severity of the Target Safety Problems

There are over 23 million surgeries performed each year in the United States.[1] The frequency of DVT and PE varies by type of procedure and specific patient risk factors, as set forth below. In general, without prophylaxis DVT occurs after approximately 20% of all major surgical procedures and PE in 1-2%. Over 50% of major orthopedic procedures are complicated by DVT and up to 30% by PE if prophylactic treatment is not instituted.[2]

In addition, of the more than 31 million patients admitted each year for medical conditions, up to 16% of patients will develop DVT in the absence of prophylaxis.[1,2]

Opportunities for Impact

Despite the frequency with which VTE occurs in hospitalized patients, and the well-established efficacy and safety of preventative measures, prophylaxis is often underused or used inappropriately. One survey of general surgeons found that 14% did not use VTE prophylaxis.[3] Another survey of orthopedic surgeons found that only 55% placed all hip fracture patients on VTE prophylaxis, and 12% never used prophylaxis.[4] When performing total hip replacement (THR) and total knee replacement (TKR), 81-84% of surgeons placed all patients on prophylaxis, and 3-5% used no prophylaxis. Taken together, these data imply that VTE prophylaxis is used in 92% of THR patients, 89% of TKR patients, and 73% of hip fracture repairs. For spinal procedures, 21-38% of surgeons used prophylaxis with all patients, while 46-64% did not use prophylaxis with any patients, an overall rate of prophylaxis of 25-44%.[4] A more recent chart review of Medicare patients over age 65 undergoing major abdominothoracic surgery from 20 Oklahoma hospitals found that only 38% of patients were given VTE prophylaxis.[5] Of patients considered at very high risk for VTE, the same percentage received some form of prophylaxis, but only 66% of those received appropriate preventive measures.[5]

Another chart review of high-risk patients at 10 acute care US hospitals found that some type of VTE prophylaxis was used in 94% of orthopedic patients and 75% of abdominal surgery patients.[6] However, the 1995 American College of Chest Physician grade A recommendations[7] (those therapies supported by the most rigorously designed studies) were followed in only 84% of THRs, 76% of TKRs, 45% of hip fracture repairs, and 50% of abdominal surgery patients. Compliance with grade A recommendations was no better in the 3 hospitals that had critical pathways, pocket guides, or a policy for VTE prophylaxis.[6]

Inadequate VTE prophylaxis among medical patients may be even more prevalent. In one study, only 33% of patients admitted to a medical intensive care unit received VTE prophylaxis. Eighty-seven percent of these patients had one risk factor, and over 50% had multiple risks for VTE.[8] Another study found that of patients who developed VTE during admission or within 30 days of discharge, 48% had not received prophylaxis during hospitalization. Most of these were medical patients.[9]

Study Designs and Outcomes

There are a large number of randomized control trials (RCTs) and high quality meta-analyses that examine the efficacy of VTE prophylaxis. Most studies considered surgical rather than medical patients. Several differences in study design may account for heterogeneity among these studies, including differences in patients or procedures, the intervention (type, duration, or dose of prophylaxis), the method used to diagnosis VTE, the outcome measured (distal or proximal DVT, fatal or nonfatal PE), and whether the endpoint was a clinical event or one found by routine screening.

The "gold standard" for diagnosis of DVT is contrast venography, which is generally used in studies screening high-risk patients. Venography may detect a significant number of clots that are not clinically important, and is often technically limited.[10] Other common screening methods are fibrinogen leg scanning (fibrinogen uptake test, FUT) and duplex ultrasonography, both of which have low sensitivity for calf vein thrombosis.[11,12] Meta-analysis of studies using the FUT in orthopedic patients showed a sensitivity of 55% for calf vein thrombosis and 45% for all DVT, with a specificity of 92%.[11] For detection of calf vein thrombosis, duplex ultrasonography had a sensitivity and specificity of 39% and 98% in symptomatic hospitalized patients, and of 13% and 92% in patients undergoing arthroplasty.[12] In studies of general surgery

patients, the incidence of DVT was 25% when diagnosis was made by FUT, and 19% when confirmed by venogram.[2] However, in trials of VTE prophylaxis using elastic stockings in neurosurgical patients, the study using FUT found a DVT rate of 9%, while 3 others using venography found the rate of DVT to be 28%.[2]

In many studies, all patients are screened for DVT, although several studies only tested for DVT if clinical signs or symptoms occurred. Clearly, in the latter a number of DVT are missed; however, the clinical importance of these asymptomatic clots is unknown.

The gold standard for diagnosis of pulmonary embolus is pulmonary angiography. However, reliable evidence confirms that combining clinical probability with results of ventilation-perfusion scanning is an accurate and less invasive method of making this diagnosis.[13] Most studies report the incidence of symptomatic or fatal PE. Studies rarely screen for PE in asymptomatic patients. Silent pulmonary embolism may occur in up to 50% of patients with proximal DVT, however, the clinical importance of these emboli is unclear.[14]

Evidence for Effectiveness of the Practice

Studies of VTE prophylaxis are best grouped by the population at risk (Table 31.2). The sections that follow describe the prevalence of thromboembolism in patients in each category and discuss the efficacy of various prophylactic strategies.

General Surgery

For general surgery patients not receiving VTE prophylaxis, the incidence of DVT confirmed by venogram is 19%. Proximal DVT occurs in 7% of patients, PE in 1.6%, and fatal PE in 0.9%.[2]

In general surgery patients, the risk of VTE is highest in those undergoing major surgery who are over the age of 40 and have an underlying hypercoagulable state, prior VTE, or cancer. (Patients with spinal cord injury, trauma, and those undergoing hip or knee arthroplasty or hip fracture surgery also fall in this risk group and are discussed separately below). Incidence rates for patients in this "very high" risk group are as follows: calf DVT, up to 80%; proximal DVT, 20%; PE, 10%; and up to 5% may suffer a fatal PE if no prophylaxis is provided.[2] The risk of VTE is lowest in those surgical patients who are young, otherwise healthy, and whose surgeries are "minor." Such patients have incident rates as follows: calf DVT, 2%; proximal DVT, 0.4%, PE , 0.2%; and fatal PE , 0.002%.

Numerous studies show that both LDUH and LMWH reduce the risk of proximal DVT, PE, and fatal PE in patients undergoing general surgery. Pooled results from 46 randomized trials show that prophylaxis of general surgical patients with LDUH compared with placebo reduced the risk of DVT (diagnosed by FUT or FUT confirmed with venography) by 68%, (from 25% [95% CI: 24-27%] to 8% [95% CI: 7-8%]).[2] LMWH has comparable efficacy to LDUH for prevention of VTE, and may be more effective for preventing proximal DVT and PE.[2,15,16] Pooled results (though heterogeneity was present) from 26 studies showed that high dose LMWH (>3400 anti-Xa units) does not reduce DVT more than low dose LMWH does ($\leq$3400 anti-Xa units), but it does increase wound hematomas.[16] Both IPC and ES significantly reduce overall incidence of DVT, but have not been shown to diminish the incidence of proximal DVT or PE in general surgical patients.[17-20]

Orthopedic Patients

All studies included in the evaluation of prophylaxis for orthopedic patients used venography to diagnose DVT.

Total Hip Replacement

Within 7-14 days after total hip replacement (THR), patients not receiving prophylaxis have an incidence of total and proximal DVT of 54% and 25%, respectively. Asymptomatic PE may occur in 5-15%, symptomatic PE in 1-2%, and fatal PE in 0.1-0.4%.[2,21] In patients undergoing THR, many RCTs have shown that both mechanical and pharmacologic measures are highly effective in the prevention of VTE.

A meta-analysis of 52 RCTs showed that patients receiving prophylaxis with LMWH, LDUH, warfarin, aspirin or IPC had fewer total DVTs (proximal plus distal).[21] IPC and ES reduce distal DVT but do not significantly reduce proximal DVT in these patients.[2,17] Compared with placebo, prophylaxis with warfarin or LMWH resulted in the greatest reduction in proximal DVT: a reduction of 70-80% with either method (risk of proximal DVT with warfarin 5-6%, RR 6.3% [95% CI: 4.7-8.4%]; with LMWH 6–8%, RR 7.7% [95% CI: 5.7-10.3%]).[2,21] Both LMWH and warfarin resulted in significantly fewer proximal DVTs compared with LDUH or IPC ($p<0.006$ for each comparison).[21] Pooled data from 5 trials that directly compared LMWH with warfarin showed rates of proximal DVT of 3.4% and 4.8%, respectively.[2]

Following THR, symptomatic PE occurs significantly less frequently with warfarin (0.16%, 95% CI: 0.002-0.59) and LMWH (0.36%, 95% CI: 0.22-0.57) than with placebo (1.51%, 95% CI: 0.81-2.57). IPC, LDUH and aspirin do not reduce the risk of symptomatic PE more than placebo. Fatal PE did not occur in any control patients in these trials, and occurred in only 0.04-0.16% of those receiving prophylaxis with LMWH or warfarin.[21]

Recombinant hirudin, not approved in the United States for VTE prophylaxis, was found more effective than LDUH or LMWH in reducing VTE in 3 trials of patients undergoing THR. Bleeding did not increase.[2]

Hip Fracture Repair

Surgery for hip fracture carries a risk of DVT comparable to THR, however, the incidence of PE is higher, with fatal PE occurring in 4-12% of patients.[2] As with hip replacement surgery, LMWH and warfarin are the most effective agents for VTE prophylaxis for patients undergoing hip fracture repair.[2] In a trial of over 13,000 hip fracture patients, aspirin significantly reduced the risk of VTE, but with an absolute reduction of only 0.5% and a greater increase in adverse events, particularly major bleeds.[22] LDUH has been less well studied.

Total Knee Replacement

Compared to THR, knee replacement surgery carries a higher overall risk of DVT, but lower risk of proximal DVT, with a prevalence of approximately 64% and 15%, respectively. Total DVT and PE occur with the following frequencies in patients receiving prophylaxis: aspirin, 53% and 12%; warfarin, 45% and 8%; and IPC, 17% and 6%. DVT occurs in 29% of those treated with LMWH.[23] While IPC reduces total DVT compared to aspirin and warfarin, it does not significantly reduce proximal DVT.[2,23]

LMWH is the most effective method to prevent proximal DVT in patients undergoing TKR. Data from 13 trials with 1740 patients show a 63% decreased risk of proximal DVT with LMWH compared with placebo, 6% (95% CI: 5%-7%) vs. 15% (95% CI: 10%-23%).[2] Pooled

data show that aspirin (6 studies, 443 patients), warfarin (9 studies, 1294 patients), and LDUH (2 studies, 172 patients) do not significantly reduce proximal DVT following TKR.[2] Patients given warfarin prophylaxis who were routinely screened with venography had an 8–12% risk of proximal DVT. However, one study that followed patients for 3 months following TKR found that patients who received warfarin had a rate of *symptomatic* VTE of only 0.8%.[24]

The incidence of PE is low in TKR patients. Studies in which PE was diagnosed by lung scan or angiography showed the rate of symptomatic and asymptomatic PE in patients treated with aspirin to be 1.3% and 11.7%, respectively, with warfarin 0.4% and 8.2%, and with IPC 0.5% and 6.3%. Symptomatic PE occurred in none of 177 patients receiving LMWH. No studies of LMWH used routine lung scanning.[23]

Initiation of Therapy

Meta-analysis of patients undergoing THR found that LMWH initiated preoperatively resulted in a lower risk of VTE than LMWH started postoperatively (10% vs. 15%, p=0.02).[25] Major bleeding occurred less frequently in the group receiving preoperative LMWH (0.9% vs. 3.5%, p=0.01).

Duration of Therapy

The appropriate duration of VTE prophylaxis following orthopedic surgery is not clearly established. However, it is clear that the increased risk of DVT persists post-discharge. In the largest randomized trial of post-discharge LMWH, 533 patients received either 35 days of dalteparin or 6 days of warfarin followed by placebo. Patients treated with extended LMWH had significantly fewer total and proximal DVTs from day 6 to day 35 (for all DVT, dalteparin 4.8% vs. placebo 10.5%, p=0.03; for proximal DVT, dalteparin 1% vs. placebo 4.8%, p=0.02), as well as from day 1 to day 35 (dalteparin 2.6% vs. warfarin/placebo 9.2%, p=0.002). Seventy five percent of these DVTs were asymptomatic. Symptomatic thrombi occurred in approximately 1-2%. No patient had symptomatic, objectively documented pulmonary embolism.[26] Pooled data from this study and 5 others that compared in-hospital LMWH followed by LMWH or placebo found that prolonged LMWH resulted in a 66% reduction in total DVT (14% vs. 27%) and a 66% reduction in proximal DVT (4% vs. 12%) by 35 days.[2]

Neurosurgery

Patients undergoing neurosurgical procedures carry a risk of developing DVT of approximately 22%, and a risk of proximal DVT of 5%.[2] The risk of DVT is increased in patients undergoing intracranial surgery compared to spinal surgery. Among patients undergoing intracranial surgery, those with malignant tumors have a higher risk of DVT than those with benign tumors. Increasing age and increasing duration of neurosurgery further increase the risk of VTE. Meta-analysis of randomized studies comparing LMWH to placebo (one study) or LMWH plus ES to ES alone (2 studies) in neurosurgical patients found that LMWH was associated with a 38% reduction in total DVT (18% vs. 28%, p<0.001). Results in the two studies evaluating proximal DVT found a 50% reduction with LMWH compared with placebo (6% vs. 12%, p=0.008). There was no increase in major bleeding. All studies used venography to assess DVT.[27] The one randomized trial using LDUH (5000 U every 8 hours) found an 82% reduction in all DVT (6% vs. 34%, p=0.005). In this trial, DVT was diagnosed with FUT.[28] Two meta-analyses evaluating IPC for VTE prophylaxis showed a 66% reduction in all DVT compared with untreated controls (7% vs. 18-22%, p<0.001).[2,17] Compared with placebo, IPC also significantly reduced proximal DVTs in neurosurgical patients (6% vs. 17%, p<0.001).[17]

Trauma

Trauma patients, especially those with orthopedic injuries, are at very high risk for VTE. DVT occurs in over 50% of these patients, proximal DVT in approximately 20%, and fatal PE in up to 2%.[2] Few randomized trials have studied VTE prophylaxis in trauma patients. Meta-analysis shows that VTE prophylaxis, either with LDUH (4 randomized trials, OR 0.97, 95% CI: 0.35-2.6 for LDUH vs. control) or ES (3 randomized trials, OR 0.77, 95% CI: 0.27-2.2), did not reduce DVT in trauma patients compared with placebo.[29] Heterogeneity was present for all comparisons due to differences in methods used to diagnose DVT and differences in trauma populations. Pooled data from 4 studies (2 randomized and 2 nonrandomized) of LDUH versus mechanical prophylaxis found no difference in risk of DVT (OR 1.16, 95% CI: 0.5-2.7).[29] One randomized trial comparing LDUH with LMWH in trauma patients screened with venography found that DVT was reduced by 30% with enoxaparin (31% vs. 44%, p=0.01).[30] Of the 265 patients randomized, only one patient (in the LMWH group) suffered a PE.

Acute Spinal Cord Injury

The risk of DVT (diagnosed by FUT or impedance plethysmography) in patients with acute spinal cord injury ranges from 40-90%.[2] The only trial using screening venography in patients with acute spinal cord injury who were not receiving prophylaxis found DVT in 81% and proximal DVT in 35%.[31]

Prophylaxis in acute spinal cord injury has not been well studied. In the only study evaluating use of IPC, proximal DVT occurred in 40% of patients with IPC alone, and in 25% of patients with IPC combined with aspirin and dipyridamole.[32] One randomized trial with 35 patients found that LMWH (tinzaparin 3500U daily) compared to LDUH (5000U three times a day) reduced DVT from 16% to 0%, a reduction that did not reach statistical significance.[33] However, a later prospective cohort study diagnosed DVT in 13% of 48 patients prophylactically treated with LMWH.[34] In both studies, screening for DVT was done with ultrasound or ultrasound plus impedance plethysmography, with confirmation by venography. Of 15 acute spinal cord injury patients from a randomized trial of major trauma patients, DVT was detected in 67% of those given LDUH and 50% with LMWH. Proximal DVT occurred in 13% receiving LDUH and none prophylaxed with LMWH.[30]

Medical Patients

VTE prevention in hospitalized medical patients has not been studied as extensively as in surgical patients. DVT occurs in 24% of patients with myocardial infarction, and is reduced by 71% with LDUH compared with placebo with no increase in bleeding (4 studies with 165 patients).[2] However, most patients with acute myocardial infarction receive full anticoagulation for treatment of the acute coronary syndrome.

After ischemic stroke, 55% of untreated patients develop DVT. Prophylaxis with either LDUH or LMWH given for 10-14 days reduces DVT by 56%, from 55% (95% CI: 49%-60%) to 24% (95% CI: 20%-29%). Two studies directly comparing LDUH (5000 U three times daily) to LMWH (enoxaparin 40 mg once daily), using venography for diagnosis, found greater reduction in DVT with LMWH.[2]

Among hospitalized patients with other medical conditions, the rate of DVT is approximately 16%.[2] A meta-analysis of studies of hospitalized patients with conditions other than myocardial infarction or ischemic stroke given VTE prophylaxis with unfractionated or low molecular weight heparin showed a 56% reduction in DVT (RR 0.44, 95% CI: 0.29-0.64) and a 52% reduction in PE (RR 0.48, 95% CI: 0.34-0.68). No significant difference was found between LMWH and LDUH in incidence of DVT, PE, or mortality; however, major hemorrhage was lower with LMWH than with LDUH (RR 0.48, 95% CI: 0.23-1.00).[35]

Another randomized trial comparing enoxaparin with placebo in 866 medical patients found a 63% reduction in overall VTE risk with enoxaparin (40 mg) compared with placebo in the first 14 days (5.5% vs. 15%, RR 0.37, 95% CI 0.22-0.63). Proximal DVT was reduced by 65% (1.7% vs. 4.9%, RR 0.40, 95% CI 0.23-0.69). Significant reductions in total and proximal DVT persisted at 110 days. VTE was not reduced in the group receiving 20 mg of enoxaparin. The most common medical conditions were acute infectious disease, acute respiratory failure, New York Heart Association Class III or IV congestive heart failure.[36]

The risk of VTE is higher in patients with malignant disease, especially those with adenocarcinoma or brain tumors. Factors associated with increased VTE in cancer patients include chemotherapy, surgery, and indwelling central venous catheters. Breast cancer patients treated with tamoxifen also have higher rates of VTE. In patients with indwelling central venous catheters who received low dose warfarin (1 mg per day), upper extremity DVT was reduced by 75% (9.5% vs. 37.5%).[37]

In summary, for general surgery patients who are at moderate risk or greater for VTE, LDUH and LMWH are the most effective methods for prophylaxis. IPC also provides effective DVT prevention, but in very high risk patients should only be used in conjunction with heparin. For orthopedic procedures, LMWH and warfarin are the most effective preventive measures. Neurosurgical patients should receive LMWH or LDUH, while in acute spinal cord injury or trauma, LMWH provides the largest reduction in VTE. For stroke or medical patients, LMWH and LDUH show the greatest benefit for VTE prevention (see Table 31.2).

Summary of Prophylaxis Recommendations

For general surgery patients at moderate to high risk, LDUH and LMWH have comparable effectiveness for prevention of VTE, with similar bleeding risks. LDUH is generally more cost-effective. For high risk patients, IPC has not been consistently shown to prevent proximal DVT (See Table 31.3).

For major orthopedic procedures (THR, TKR, hip fracture repair), prophylaxis with LMWH or warfarin results in the greatest benefit, with a small increase in bleeds compared with

no prophylaxis, but no difference between the two agents. Warfarin may be more cost-effective, but necessitates monitoring and dose adjustment. This should be considered in choosing between the two agents.

IPC, LMWH, and LDUH are all acceptable methods of prophylaxis for neurosurgical patients. Each effectively reduces proximal DVT with no increase in major bleeding. There are no data on cost-effectiveness of prophylaxis for these patients.

Data for prophylaxis of trauma patients does not show conclusive VTE reduction with any agent. However, the risk of VTE among these patients is high and prophylaxis should be considered, especially for those with orthopedic injuries. LMWH is a safe method of prophylaxis and has not been shown to increase major bleeds in blunt trauma patients. However if a patient is at high risk for major bleeding, IPC should be considered.

For medical patients, LDUH and LMWH are both effective for reducing VTE. LDUH may result in slightly more bleeding, but is more cost-effective. Patients at high risk for bleeding should be given prophylaxis with ES or IPC.

Potential for Harm

There is no documented risk associated with mechanical devices, although there is a potential risk that patients' legs will be examined less frequently. The major risk of pharmacologic prophylaxis is bleeding. Bleeding is typically considered major when the hemoglobin decreases by at least 2 g/dL, when red blood cell transfusion is necessary, when intracranial or retroperitoneal bleeding occurs, or when bleeding requires surgical intervention. Another consequence of heparin therapy may be thrombocytopenia.

For general surgery, there is no difference in the risk of major bleeding between LMWH and LDUH, although fewer minor bleeds may occur with LMWH (RR 0.64, 95% CI 0.58-0.70).[15] However, when evaluated according to dose of LMWH, compared with LDUH, low-dose LMWH (<3400 anti-Xa units) resulted in a significant decrease in wound hematomas, while high-dose LMWH carries a significant increase.[16]

Bleeding related to VTE prophylaxis is uncommon after orthopedic surgery. The greatest risk of bleeding occurs with LDUH (3.4% vs. 0.56% with placebo, RR 3.46, $p<0.0001$).[21] The risk of bleeding with LMWH is significantly greater than with placebo, but the absolute risk increase (ARI) is small (for TKR, 2.8% vs. 0.9%, ARI 1.7%; for THR, 1.2% vs. 0.9%, ARI 0.3%).[21] With warfarin, bleeding occurs in 0.5% of patients following THR.[2] Studies comparing LMWH to warfarin for THR found no difference in major bleeding.[21,26]

Among neurosurgical patients treated with LMWH, there was a two-fold increase in all bleeding compared with controls (6% vs. 3%, $p=0.02$), however, there was no significant difference in major bleeds.[27] Similar results were found in a study using LDUH.[28]

Blunt trauma patients who received enoxaparin 30mg q12h started within 24 hours of hospitalization had no bleeding events attributed to this treatment. This included patients with closed head injury, grade III liver injury, and grade IV splenic injury.[38]

Prophylaxis of medical patients with enoxaparin 40 mg/d did not increase the risk of bleeding compared to placebo. Of 711 patients treated with LMWH, there were no cases of severe thrombocytopenia (platelet count less than 50,000 per cubic millimeter).[36] Compared with LDUH, prophylaxis with LMWH results in fewer major bleeds (RR 0.48, 95% CI: 0.23-1.00).[35]

Costs and Implementation

A Swedish study evaluating general surgery patients at moderate risk for VTE and hip surgery patients found LDUH and LMWH were more cost-effective than no prophylaxis, and

LMWH was more cost-effective than LDUH.[39] An economic evaluation using decision analysis compared LDUH and LMWH for patients undergoing colorectal surgery. There was no difference in risk of VTE between groups. Per 1000 patients treated, prophylaxis with enoxaparin compared with LDUH resulted in 12 excess major bleeds and an additional cost of $145,667.[40] This supports LDUH as a more cost-effective measure for patients undergoing general surgery.

Meta-analysis of studies of the cost-effectiveness of VTE prophylaxis for patients undergoing hip arthroplasty found that with a 2.6 to 1 price ratio between LMWH and LDUH, use of LMWH would save the health care system approximately $50,000 per 1000 patients treated.[41] For VTE prophylaxis after TKR, LMWH was more cost-effective than warfarin, saving $2401 per 100 patients ($9197 vs. $11,598 per 100 patients).[42] This study was done in Canada, where LMWH is less costly than in the United States. Another meta-analysis of THR patients found that LDUH would decrease the cost of care related to DVT by $200 per patient. Compared with warfarin, LMWH would be more effective in preventing DVT (expected DVT rate 420/10,000 with warfarin and 250/10,000 with LMWH), and death from VTE (110/10,000 with warfarin and 70/10,000 with LMWH). However, preventing one death with LMWH use instead of warfarin would cost approximately $12,000.[43]

In medical patients, LDUH given 3 times daily was found to be more cost-effective than LMWH, with a savings per 1000 patients of $10,753 compared with enoxaparin 40 mg/d, and $15,000 compared with enoxaparin 20 mg/d.[44] The higher cost associated with enoxaparin 20 mg/d results from the higher incidence of complications with this regimen. This supports use of LDUH as the preferred method of prophylaxis for medical patients at the present time, though this is an area of active investigation. No studies were found evaluating the cost of DVT prophylaxis in neurosurgery patients.

Comment

As noted earlier, despite the clear evidence of effectiveness, DVT prophylaxis is underused. The reasons for this underuse have not been completely elucidated, nor have the optimal strategies for improving prophylaxis been fully identified. Various strategies have been tried in an effort to improve physician utilization of appropriate VTE prophylaxis. One hospital studied the impact of educational programs promoting guidelines for prophylaxis. It found that presentations to staff, distributions of cards with the hospital's guidelines, and posters increased prophylaxis of surgical patients from 59% to 70%, and to 77% for high-risk patients (see also Chapters 51 and 54).[45]

In another study, a computer-based clinical decision support system (CDSS) (see Chapter 53) providing information pertaining to VTE prophylaxis was used in an orthopedic surgery department of a teaching hospital. The investigators monitored the impact of CDSS use in 1971 patients undergoing orthopedic surgery. Compliance with guidelines was 83% during control periods and 95% during intervention periods. Inappropriate practice decisions occurred almost 4 times more frequently during control versus intervention periods.[46]

A third study evaluating methods to improve VTE prophylaxis among intensive care unit patients found that staff education improved use of appropriate prophylaxis from 38% to 62%. When required computerized order sets were added to education, appropriate prophylaxis increased to 97%.[47]

These studies suggest that either a knowledge gap or lack of awareness may exist among practitioners. For institutions or groups attempting to improve appropriate use of measures to prevent VTE, guidelines made available via computerized support systems or order sets provide

the most effective means of implementing appropriate VTE prophylaxis, especially when these systems are linked to effective educational programs.

Table 31.1. Mechanical and pharmacologic preventative measures for VTE

Practice	Type	Description	Comment
Graduated Elastic Stockings (ES)	Mechanical	Fitted hose that extend above the knee	Fitted hose are more efficacious than non-fitted
Intermittent pneumatic compression (IPC)	Mechanical	Devices fitted over lower extremities that sequentially inflate and deflate	
Aspirin	Pharmacologic	Usually 325 mg/d	
Warfarin	Pharmacologic	5-10 mg started the day of or after surgery; adjust to achieve an INR of 2-3	Monitoring of INR needed
Low-dose unfractionated heparin (LDUH)	Pharmacologic	Generally 5000 U subcutaneous bid or tid, though some studies have adjusted dose to maintain PTT at high end of normal	Contraindicated if active bleeding or history of thrombocytopenia; no need to follow coagulation studies (unless adjusted dose is used)
Low Molecular Weight Heparin (LMWH)	Pharmacologic	Dose depends on type of surgery and VTE risk*	No need to monitor coagulation studies

* LMWH dosing: Enoxaparin 20 mg SC daily (moderate risk surgery) or 40 mg SC daily (can go up to 30 mg SC q12h for high risk general surgery, major trauma or acute spinal cord injury); dalteparin 2500–5000 U SC daily; nadroparin 2500 U SC daily; tinzaparin 3500-4500 U SC daily (may be dosed 75U/kg/d for orthopedic surgery).

Table 31.2. Summary of DVT risk and prophylactic methods providing significant risk reduction*

Surgery/ Condition	Risk of all DVT in untreated patients	Type of Prophylaxis	Risk Reduction with Prophylaxis	Number of Studies
General Surgery[2]	25%	ES	44%	3
		LDUH	68%	47
		LMWH	76%	21
		IPC	88%	2
THR[2]	54%	LMWH	70%	30
		warfarin	59%	13
TKR[2,23]	64%	LMWH	52%	13
		IPC	73%	6
Neuro-surgery[27,28]	28%	LMWH	38%	3
		LDUH	72%	1†
Trauma[2,30]	30-60%	LMWH	30% (compared to LDUH)	1
Acute Spinal Cord Injury[2]	80%	Not established		
Ischemic stroke[2]	55%	LDUH	56%	5
		LMWH	58%	3
		Danaparoid	82%	4
Medical conditions[2]	16%	LMWH	76%	2†
			39%	2
		LDUH	61%	3†

* DVT indicates deep venous thrombosis; ES, graduated elastic stockings; IPC, intermittent pneumatic compression; LDUH, low-dose unfractionated heparin; LMWH, low molecular weight heparin; THR, total hip replacement; and TKR, total knee replacement.

† DVT diagnosed by fibrinogen uptake test (FUT)

Table 31.3. Recommended VTE prophylaxis for surgical procedures and medical conditions*

Surgery/Condition	Recommended Prophylaxis	Comments
General Surgery – low-risk: minor procedures, <40 years old, no additional risks	None	Early ambulation
General Surgery – moderate risk: minor procedure but with risk factor, nonmajor surgery age 40-60 with no risks, or major surgery <40 years with no risks	LDUH, LMWH, ES, or IPC	
General Surgery – high risk: nonmajor surgery over age 60 or over age 40 with risks.	LDUH, LMWH	
General Surgery – very high risk: major surgery over age 40 plus prior VTE, cancer or hypercoagulable state	LDUH or LMWH combined with ES or IPC	May consider postdischarge LMWH or perioperative warfarin
Elective Hip Replacement	LMWH or warfarin	May combine with ES or IPC; start LMWH 12 hours before surgery, 12-24 hours after surgery, or 4-6 hours after surgery at half the dose for initial dose. Start warfarin preoperatively or immediately after surgery, target INR 2.0-3.0.
Elective Knee Replacement	LMWH or warfarin	
Hip Fracture Surgery	LMWH or warfarin	
Neurosurgery	IPC, LDUH or LMWH	Start LMWH post-surgery
Trauma	LMWH with ES or IPC	If high risk of bleeding, may use ES and/or IPC alone.
Acute Spinal Cord Injury	LMWH	Continue LMWH during rehabilitation or convert to warfarin (target INR 2.5)
Ischemic Stroke	LDUH, LMWH, or danaparoid	If contraindication to anticoagulant, use ES or IPC.
Medical Conditions	LDUH or LWMH	

* Adapted with permission from Geerts WH, Heit JA, Clagett GP, Pineo GF, Colwell CW, Anderson FA, et al. Prevention of venous thromboembolism. Table: Regimens to prevent VTE, pp. 156S-158S. *Chest* 2001. Sixth ACCP Consensus Conference on Antithrombotic Therapy.[2] ES indicates graduated elastic stockings; INR, international normalized ratio; IPC, intermittent pneumatic compression; LDUH, low-dose unfractionated heparin; LMWH, low molecular weight heparin; and VTE, venous thromboembolism.

References

1. US Bureau of the Census. Statistical Abstract of the United States: 2000. 120th edition. Washington, DC. 2000.
2. Geerts WH, Heit JA, Clagett GP, Pineo GF, Colwell CW, Anderson FA, et al. Prevention of venous thromboembolism. *Chest*. 2001;119:132S-175S.
3. Caprini JA, Arcelus JI, Hoffman K, Mattern T, Laubach M, Size GP, et al. Prevention of venous thromboembolism in North America: results of a survey among general surgeons. *J Vasc Surg*. 1994;20:751-758.
4. Janku GV, Paiement GD, Green HD. Prevention of venous thromboembolism in orthopaedics in the United States. *Clin Ortho & Related Research*. 1996:313-321.
5. Bratzler DW, Raskob GE, Murray CK, Bumpus LJ, Piatt DS. Underuse of venous thromboembolism prophylaxis for general surgery patients: physician practices in the community hospital setting. *Arch Intern Med*. 1998;158:1909-1912.
6. Stratton MA, Anderson FA, Bussey HI, Caprini J. Prevention of venous thromboembolism: adherence to the 1995 American College of Chest Physicians Consensus Guidelines for Surgical Patients. *Arch Intern Med*. 2000;160:334-340.
7. Clagett GP, Anderson FAJ, Levine MN, Wheeler HB. Prevention of venous thromboembolism. *Chest*. 1995;108S:312S-334S.
8. Keane MG, P IE, Goldhaber SZ. Utilization of venous thromboembolism prophylaxis in the medial intensive care unit. *Chest*. 1994;106:13-14.
9. Goldhaber SZ, Dunn K, MacDougall RC. New onset of venous thromboembolism among hospitalized patients at Brigham and Women's Hospital is caused more often by prophylaxis failure than by withholding treatment. *Chest*. 2000;118:1680-1684.
10. Heijboer H, Cogo A, Buller HR. Detection of deep vein thrombosis with impedance plethysmography and real-time compression ultrasonography in hospitalized patients. *Arch Intern Med*. 1992;152:1901-1903.
11. Lensing AW, Hirsh J. 1251-fibrinogen leg scanning: reassessment of its role for the diagnosis of venous thrombosis in post-operative patients. *Thromb Heamost*. 1993;69:2-7.
12. Eskandari MK, Sugimoto H, Richardson T. Is color-flow duplex a good diagnostic test for detection of isolated calf vein thrombosis in high-risk patients? *Angiology*. 2000;51:705-710.
13. Perrier A, Miron MJ, Desmarais S, de Moerloose P. Using clinical evaluation and lung scan to rule out suspected pulmonary embolism. *Arch Intern Med*. 2000;160:512-516.
14. Meignan M, Rosso J, Gauthier H, Brunengo F. Systematic lung scans reveal a high frequency of silent pulmonary embolism in patients with proximal deep venous thrombosis. *Arch Intern Med*. 2000;160:159-164.
15. Palmer AJ, Schramm W, Kirchhof B, Bergemann R. Low molecular weight heparin and unfractionated heparin for prevention of thrombo-embolism in general surgery: a meta-analysis of randomised clinical trials. *Haemostasis*. 1997;27:65-74.
16. Koch A, Bouges S, Ziegler S, Dinkel H, Daures JP, Victor N. Low molecular weight heparin and unfractionated heparin in thrombosis prophylaxis after major surgical intervention: update of previous meta-analyses. *Br J Surg*. 1997;84:750-759.

17. Vanek VW. Meta-analysis of effectiveness of intermittent pneumatic compression devices with a comparison of thigh-high to knee-high sleeves. *American Surgeon*. 1998;64:1050-1058.
18. Wells PS, Lensing AW, Hirsh J. Graduated compression stockings in the prevention of postoperative venous thromboembolism. A meta-analysis. *Arch Intern Med*. 1994;154:67-72.
19. Agu O, Hamilton G, Baker D. Graduated compression stockings in the prevention of venous thromboembolism. *Br J Surg*. 1999;86:992-1004.
20. Amarigiri SV, Lees TA. Elastic compression stockings for prevention of deep vein thrombosis. In: *The Cochrane Library*, Issue1, 2001.
21. Freedman KB, Brookenthal KR, Fitzgerald RH, Jr., Williams S, Lonner JH. A meta-analysis of thromboembolic prophylaxis following elective total hip arthroplasty. *J Bone Joint Surg*. 2000;82-A:929-938.
22. Pulmonary Embolism Prevention (PEP) Trial Collaborative Group. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. *Lancet*. 2000;355:1295-1302.
23. Westrich GH, Haas SB, Mosca P, Peterson M. Meta-analysis of thromboembolic prophylaxis after total knee arthroplasty. *J Bone Joint Surg*. 2000;82-B:795-800.
24. Heit JA, Berkowitz SD, Bona R, Cabanas V, Corson JD, Elliott CG, et al. Efficacy and safety of low molecular weight heparin compared to warfarin for the prevention of VTE after total knee replacement surgery: a double-blind, dose-ranging study. *Thromb Haemost*. 1997;77:32-38.
25. Hull RD, Brant RF, Pineo GF, Stein PD. Preoperative vs postoperative initiatin of low-molecular-weight heparin prophylaxis against venous thromboembolism in patients undergoing elective hip replacement. *Arch Intern Med*. 1999;159:137-141.
26. Hull RD, Pineo GF, Francis C, Bergqvist D, Fellenius C, Soderberg K, et al. Low-molecular-weight heparin prophylaxis using dalteparin extended out-of-hospital placebo in hip arthroplasty patients. *Arch Intern Med*. 2000;160:2208-2215.
27. Iorio A, Agnelli G. Low-molecular-weight and unfractionated heparin for prevention of venous thromboembolism in neurosurgery: a meta-analysis. *Arch Intern Med*. 2000;160:2327-2332.
28. Cerrato D, Ariano C, Fiacchino F. Deep vein thrombosis and low-dose heparin prophylaxis in neurosurgical patients. *J Neurosurg*. 1978;49:378-381.
29. Velmahos GC, Kern J, Chan LS, Oder D, Murray JA, Shekelle P. Prevention of venous thromboembolism after injury: an evidence-based report–part I: analysis of risk factors and evaluation of the role of vena caval filters. *J Trauma*. 2000;49:132-138.
30. Geerts WH, Jay RM, Code KI. A comparison of low dose heparin with low molecular weight heparin as prophylaxis against venous thromboembolism after major trauma. *N Engl J Med*. 1996;335:701-707.
31. Geerts WH, Code KI, Jay RM, Chen E. A prospective study of venous thromboembolism after major trauma. *N Engl J Med*. 1994;331:1601-1606.
32. Green D, Rossi EC, Yao JS. Deep vein thrombosis in spinal cord injury: effect of prophylaxis with calf compression, aspirin and dipyridamole. *Paraplegia*. 1982;20:227-234.
33. Green D, Lee MY, Lim AC. Prevention of thromboembolism after spinal cord injury using low molecular weight heparin. *Ann Intern Med*. 1990;113:571-574.

34. Green D, Chen D, Chmiel JS. Prevention of thromboembolism in spinal cord injury: role of low molecular weight heparin. *Arch Phys Med Rehabil*. 1994;75:290-292.
35. Mismetti P, Laporte-Simitsidis S, Tardy B, Cucherat M, Buchmuller A, Juillard-Delsart D, et al. Prevention of venous thromboembolism in internal medicine with unfractionated or low-molecular-weight heparins: a meta-analysis of randomised clinical trials. *Thromb Haemost*. 2000;83:14-19.
36. Samama MM, Cohen AT, Darmon JY, Desjardins L, Eldor A, Janbon C, et al. A comparison of enoxaparin with placebo for the prevention of VTE in acutely ill medical patients. *N Engl J Med*. 1999;341:793-800.
37. Bern MM, Lokich JJ, Wallach SR. Very low doses of warfarin can prevent thrombosis in central venous catheters: a randomized prospective trial. *Ann Intern Med*. 1990;112:423-428.
38. Norwwod SH, McAuley CE, Berne JD, Vallina VL, Kerns DB, Grahm TW, et al. A potentially expanded role for enoxaparin in preventing venous thromboembolism in high risk blunt trauma patients. *J Am Coll Surg*. 2001;192:161-167.
39. Bergqvist D, Lindgren B, Matzsch T. Comparison of the cost of preventing postoperative deep vein thrombosis with either unfractionated or low molecular weight heparin. *Br J Surg*. 1996;83:1548-1552.
40. Etchells E, McLeod RS, Geerts W, Barton P, Detsky AS. Economic analysis of low-dose heparin vs the low-molecular-weight heparin enoxaparin for prevention of venous thromboembolism after colorectal surgery. *Arch Intern Med*. 1999;159:1221-1228.
41. Anderson DR, O'Brien BJ, Levine MN, Roberts R, Wells PS, Hirsh J. Efficacy and cost of low-molecular-weight heparin compared with standard heparin for the prevention of deep vein thrombosis after total hip arthroplasty. *Ann Intern Med*. 1993;119:1105-1112.
42. Hull RD, Raskob GE, Pineo GF, Feldstein W. Subcutaneous low-molecular-weight heparin vs warfarin for prophylaxis of deep vein thrombosis after hip or knee implantation: an economic perspective. *Arch Intern Med*. 1997;157:293-303.
43. Menzin J, Colditz GA, Regan MM, Richner RE, Oster G. Cost-effectiveness of enoxaparin vs low-dose warfarin in the prevention of deep-vein thrombosis after total hip replacement surgery. *Arch Intern Med*. 1995;155:757-764.
44. Wade WE. Cost-effectiveness analysis of deep vein thrombosis prophylaxis in internal medicine patients. *Thrombrosis Research*. 1999;94:65-68.
45. Peterson GM, Drake CI, Jupe DM, Vial JH, Wilkinson S. Educational campaign to improve the prevention of postoperative venous thromboembolism. *J Clin Pharm Therapeutics*. 1999;24:279-287.
46. Durieux P, Nizard R, Ravaud P, Mounier N, Lepage E. A clinical decision support system for prevention of venous thromboembolism. *JAMA*. 2000;283:2816-2821.
47. Levi D, Kupfter Y, Seneviratne C, Tessler S. Computerized order entry sets and intensive education improve the rate of prophylaxis for deep vein thrombophlebitis. *Chest*. 1998;114S:280S.