



Venous thromboembolism prophylaxis in the medically ill patient

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Venous thromboembolism (VTE), which includes the entities of deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common disease that affects more than 2 million people each year and may be responsible for up to 200,000 deaths annually [1]. Almost all PEs originate from existing clots in the deep venous system of the legs, of which more than half are clinically silent [2]. In fact, the first manifestation of the disease may be fatal PE. Identifying patients at risk and applying preventive measures is the only way to decrease VTE-related morbidity and mortality.

Scope of the problem

Venous thromboembolism accounts for 10% of all in-hospital mortality, with a long-term case fatality rate of 19% at 1 year [3]. In elderly patients, PE is associated with a 1-year mortality rate of 39%. Approximately three of four fatal PEs occur in medical patients, and autopsy series demonstrate that, over the past 2 decades, the incidence of fatal PE has remained constant for nonsurgical patients [4]. VTE survivors are at increased risk for VTE recurrence and for chronic postthrombotic syndrome (PTS). PTS is characterized by chronic pain, edema, skin induration, and ulceration of the lower extremities and is estimated to occur in one-third of VTE survivors within 10 years [5]. In economic terms, the cost of a primary DVT is similar to that of an acute myocardial infarction or stroke [6]. The additional long-term health care cost of PTS is approximately 75% of the cost of a primary DVT.

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The need for prophylaxis

Prevention of VTE has become widely accepted as an effective and worthwhile strategy. Nevertheless, most protocols for VTE prophylaxis have primarily addressed surgical patients, because the assessment of the prevention of VTE is less developed in medical populations. Nearly 100,000 surgical patients have been included in trials concerning the prevention of VTE, whereas only 15,000 patients receiving medical care have been included in such trials [7]. Medically ill patients accounted for fewer than 10% of patients identified as prophylaxis candidates in the 2001 American College of Chest Physicians (ACCP) recommendations for anticoagulation [8]. Unfortunately, even when guidelines exist, the use of preventive measures remains highly variable. A recent survey found that 28% of medical inpatients with risk factors for VTE were receiving prophylaxis [9]. General medical patients represent a heterogeneous group and are thought to have a lower incidence of VTE than surgical patients; however, evidence is mounting that all hospitalized patients, medical as well as surgical, should be protected from VTE. In another recent study, factors associated with institutionalization independently accounted for more than half of all cases of VTE in the community [10]. Hospitalization for surgery accounted for no more than 24% of cases, and 74% of patients had risk factors other than hospitalization or surgery.

Clinical risk factors

Knowledge of the clinical risk factors for VTE forms the basis for the appropriate use of prophylaxis.

As early as 1856, Virchow described the well-known triad of factors that predisposes patients to VTE—venous stasis, endothelial injury, and hypercoagulability. Numerous other independent risk factors have been identified [8] and are summarized in Box 1.

Cancer is a common comorbidity in the medically ill population. Patients with cancer, patients receiving chemotherapy, and patients with a history of cancer in remission are at increased risk for VTE. Hemostatic abnormalities are often associated with malignancy. In addition to the hypercoagulability seen in cancer, the presence of indwelling central venous catheters increases the risk for VTE.

Many aspects of cardiovascular disease represent independent risk factors for VTE. Acute myocardial infarction, ischemic and nonischemic cardiomyopathy, congestive heart failure secondary to valvular disease, and chronic idiopathic dilated cardiomyopathy increase the risk for VTE. The risk for VTE is especially high in patients with stages III to IV New York Heart Association heart failure.

Acute respiratory failure also increases the risk for VTE. Several conditions can produce, or are associated with, respiratory failure, including acute exacerbations of chronic obstructive pulmonary disease, adult respiratory distress syndrome, community acquired or nosocomial pneumonia, lung cancer, interstitial lung disease, and pulmonary hypertension [11].

Most hospitalized patients are aged more than 40 years, and this factor represents an independent risk for VTE. Patients aged 60 years and older are at the highest risk. Hospitalized elderly patients are often frail, immobile, or have restricted mobility. Advancing age also predisposes patients to venous stasis and the presence of venous varicosities. As the population ages, the number of cases of VTE can be expected to increase.

Restricted mobility can range from limited ambulation to bed rest and represents one of the most important risk factors for VTE. In a study of primarily medical patients, patients confined to bed rest for fewer than 5 days had a 21% occurrence rate of VTE compared with a 36% occurrence rate for patients restricted to bed rest for more than 10 days [12]. Patients with a lower limb paralysis associated with ischemic stroke have a DVT incidence of more than 50% in the paralyzed limb [8]. Patients with spinal cord injuries are similarly at high risk owing to immobility. Nevertheless, complete bed rest or paralysis is not needed to increase greatly the risk of VTE owing to restricted mobility. Medical patients who simply have restricted mobility seem to be at risk.

Most serious systemic infections increase the risk for VTE, including pneumonia and urinary tract, skin,

Box 1. Risk factors for venous thromboembolism

- Venous stasis
 - Advanced age (>40 years)
 - Immobilization/reduced mobility
 - Varicose veins
 - Acute myocardial infarction
 - Congestive heart failure
 - Stroke
 - Paralysis
 - Spinal cord injury
 - Hyperviscosity syndromes
 - Polycythemia
 - Anesthesia
 - Severe chronic obstructive pulmonary disease
- Endothelial injury
 - Surgery
 - Previous VTE
 - Trauma
 - Central venous catheters
- Hypercoagulability
 - Cancer
 - Obesity
 - Estrogens (contraceptives, hormone replacement therapy)
 - Pregnancy/postpartum
 - Family history
 - Inflammatory bowel disease
 - Systemic infections
 - Nephrotic syndrome
 - Thrombophilia
 - Activated protein C resistance
 - Prothrombin gene 20210A mutation
 - Antithrombin deficiency
 - Protein C and S deficiency
 - Heparin-induced thrombocytopenia
 - Antiphospholipid syndrome
 - Homocysteinemia
 - Lupus anticoagulant

and abdominal infections [11]. Seriously ill medical patients admitted to the intensive care unit (ICU) are at increased risk; this setting is also an independent risk factor for VTE.

Disorders of coagulation regulation predispose patients to VTE. These disorders can be inherited or acquired and include deficiencies in protein C and S, antithrombin, and plasminogen. Purely inherited disorders, such as the presence of factor V Leiden or

resistance to activated protein C, also increase VTE risk. The prevalence of the Leiden genetic mutation is 5% in the general population, making it the most common inherited disorder associated with VTE [13]. The risk for recurrent VTE is approximately 40% in heterozygotes compared with 18% in persons without the mutation. Another inherited risk factor recently described is the prothrombin gene mutation, which leads to elevated prothrombin levels and an increased risk for VTE in heterozygous carriers. This gene mutation occurs in 2% to 4% of the general population, with a southern European ethnic predominance [14]. An abnormality in the metabolism of homocysteine resulting in increased serum and urine levels of this product is another recognized clinical risk factor for VTE [15].

In the current hospital environment, virtually all medical patients are acutely ill and compromised by restricted mobility. Most patients have multiple risk factors, and the risks are cumulative [16]. A history of previous VTE confers risk for a future event, because approximately 20% of patients with confirmed VTE have had prior DVT or PE [17]. Anderson et al [18] demonstrated that one of five hospitalized patients had at least three VTE risk factors a decade ago. Currently, medical inpatients are older, sicker, and more complex, and as many as 90% or more of medical patients may be eligible for prophylaxis [19].

Nonpharmacologic prevention strategies

The use of nonpharmacologic VTE prevention strategies, such as elastic stockings (ES) or intermittent pneumatic compression (IPC) devices, has not been studied in heterogeneous medical populations and is not recommended for routine prophylaxis. Nevertheless, disease-specific trials have used ES or IPC alone or in combination with pharmacologic approaches. In a study by Kierkegaard and Norgren [20], 80 patients with acute myocardial infarction wore ES on one leg, with the contralateral extremity serving as a control. Eight of the control legs had an abnormal fibrinogen uptake scan, whereas there were no abnormalities in the legs on which ES were worn ($P = 0.003$). In a nonrandomized prospective study of 681 ischemic stroke patients, the combination of low-dose unfractionated heparin (LDUH), ES, and IPC was associated with fewer symptomatic VTEs when compared with LDUH plus ES [21]. Nevertheless, Hirsch et al [22] demonstrated in the medical ICU that IPC was no better than no prophylaxis at all. Upper- or lower-limb DVT was diagnosed in 32% of patients receiving no prophylaxis versus

33% of patients using IPC devices. Marik et al [23] also found IPC to be ineffective in the ICU setting. Lower-limb DVT was diagnosed by Doppler ultrasonography in 25% of patients receiving no prophylaxis versus 19% of patients using IPC ($P = 0.42$). Extrapolating further from the data obtained in trials in surgical patients, ES and IPC will most likely modulate the risk for VTE and carry no risk for hemorrhage [8]. Nevertheless, ES alone are unlikely to be helpful, because they yield only modest risk reductions in low-risk surgical populations. IPC has produced satisfactory risk reduction in high-risk surgical groups, but these devices have several significant limitations in the medically ill population. First, the mechanical devices must be worn continuously to maintain a protective effect, and this requirement increases VTE risk from immobility. Second, the devices may be uncomfortable to wear, thereby destroying sleep hygiene. Poor sleep hygiene has been associated with episodes of delirium in hospitalized elderly patients [24]. Third, the devices have not been studied adequately to recommend their use in place of pharmacologic strategies that have established efficacy. The use of ES or IPC strategies for the prevention of VTE in the medically ill population should be limited to situations in which the risk for bleeding is believed to exceed the risk for thrombosis.

Pharmacologic strategies

The most comprehensively studied patients with medical conditions have sustained myocardial infarction or ischemic stroke. Nevertheless, in myocardial infarction, the current use of fibrinolytics, systemic anticoagulation with heparins, antiplatelet agents, or combinations of these drugs has made the prevention of VTE a secondary goal. In general medical patients with risk factors for VTE, the ACCP recommends either LDUH twice or three times per day or low molecular weight heparin (LMWH) [8]. The following sections review the major trial evidence that supports this recommendation.

Low-dose unfractionated heparin versus placebo

Most data comparing LDUH with placebo are decades old. In ischemic stroke patients, two separate trials demonstrated a 71% risk reduction in DVT relative to control patients [25,26]. Belch et al [27] compared LDUH given every 8 hours with placebo in 100 patients with heart failure and respiratory disease and found a significant reduction in DVT by fibrino-

gen uptake scanning (4% versus 26%, $P = 0.01$). There was no increase in major bleeding. Cade [28] compared LDUH given every 12 hours with placebo in 250 medical and ICU patients and demonstrated a significant reduction in DVT by fibrinogen uptake scanning (13% versus 29%, $P < 0.05$). Safety endpoints were not evaluated. Ibarra-Perez and Sandset [29] compared given LDUH every 12 hours with placebo in 85 ICU patients and showed a significant reduction in DVT by venography (26% versus 3%, $P < 0.002$) with no increase in major hemorrhage. More recent work has been less clear in the medical ICU setting. Hirsh and colleagues [22] found LDUH given twice daily to be no better than no prophylaxis by Doppler ultrasonography (40% versus 32%). Marik et al [23] found that LDUH given twice daily significantly reduced the risk for VTE by Doppler ultrasonography (7% versus 25%, $P < 0.05$). No safety endpoints were evaluated in either of the previous studies. Kupfer et al [30] compared LDUH given every 8 hours with placebo and demonstrated a significant reduction in VTE in the LDUH group by serial duplex scanning (11% versus 31%, $P = 0.001$).

Two randomized trials assessed the effect of LDUH on mortality. Halkin et al [31] gave 1358 consecutive general medical patients LDUH twice daily versus no prophylaxis for the duration of hospitalization or until the patients were fully mobile. The primary outcome was all-cause mortality without reporting of thromboembolic events. The mortality rates were significantly lower in the LDUH group (7.8% versus 10.9%, $P < 0.05$). Garlund and colleagues [32] randomized 11,693 patients with acute infections who were admitted to six Swedish hospitals to treatment with LDUH twice daily or no prophylaxis until discharge. In the intention-to-treat analysis, mortality rates were similar in the LDUH and placebo groups (5.3% versus 5.6%, $P = 0.4$); however, there were fewer nonfatal VTE events in the LDUH group (70 versus 116, $P = 0.001$).

Low molecular weight heparin versus placebo

Two early studies performed on ischemic stroke patients compared dalteparin with placebo [33,34]. One study demonstrated significant efficacy for dalteparin, whereas the other did not. The pooled DVT rates in these two trials were 40% for placebo patients and 26% for the dalteparin group. More recently, two randomized and blinded trials have compared enoxaparin with placebo in the medically ill population. Dahan et al [35] compared 60 mg of enoxaparin daily with placebo in 270 medically ill patients and found a significant reduction in DVT by fibrinogen scanning

(10% versus 3%, $P = 0.04$) with no increase in major bleeding. The mortality rate was 4.4% in the enoxaparin and placebo groups. Samama and colleagues [36] compared two different doses of enoxaparin (20 or 40 mg) daily with placebo in the Comparison of Enoxaparin with Placebo for the Prevention of Venous Thromboembolism in Acutely Ill Medical Patients (MEDENOX) trial. The trial evaluated thromboprophylaxis in 1102 acutely ill medical patients who were at risk for thromboembolic complications owing to severely restricted mobility. The trial included general medical patients with acute disorders (average of 2.3 clinical risk factors) who were believed to have a moderate risk for DVT and who were older than age 40 years, had a projected hospital stay of less than 6 days, and had been immobilized previously for fewer than 3 days. Patients were randomized to placebo; enoxaparin, 20 mg daily; or enoxaparin, 40 mg daily for 6 to 14 days. The overall incidence of venographically detectable VTE was 14.9% in the placebo group (5% proximal DVT) versus 5.5% in the enoxaparin group ($P < 0.001$). In this patient population, the 40-mg dose reduced the risk of VTE by 63%. No significant differences were found in the enoxaparin 20-mg dose and placebo groups with regard to efficacy. There was no increase in major bleeding or thrombocytopenia with either dose of enoxaparin when compared with placebo. Mortality was not significantly different in any of the treatment groups; however, there was a 2.5% absolute risk reduction in the overall risk of death at 3 months in the group assigned to 40 mg of enoxaparin (Fig. 1).

Low-dose unfractionated heparin versus low molecular weight heparin

Several randomized trials have been performed comparing LDUH with dalteparin or enoxaparin. Harenburg et al [37] compared 2500 U of dalteparin daily with LDUH given every 8 hours in 166 medical patients and found no significant difference in DVT by serial plethysmography and Doppler ultrasound scanning (4.8% versus 3.4%; P , not significant). Nevertheless, LDUH was associated with significantly more episodes of major bleeding.

Bergmann and Neuhart [38] compared enoxaparin, 20 mg daily, with LDUH given every 12 hours in 442 hospitalized elderly patients and demonstrated no significant difference in VTE by fibrinogen scanning (4.8% versus 4.6%; P , not significant) with a similar safety profile. This result is intriguing, because Samama found the 20-mg enoxaparin dose to be no better than placebo.

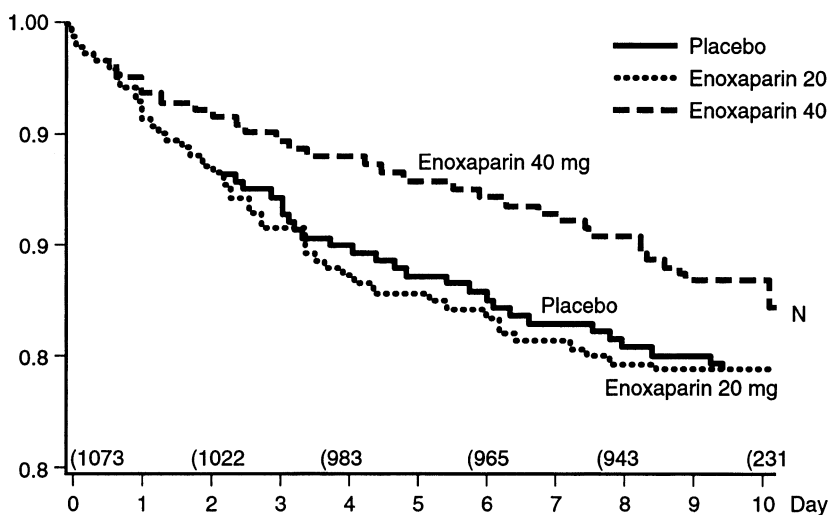


Fig. 1. Kaplan-Meier estimate of the probability of survival in the MEDENOX trial (log-rank test; $P = 0.31$; hazard ratio, 0.90; confidence interval, 0.7 to 1.1). The risk of death was lower in the group assigned to 40 mg of enoxaparin than in the group assigned to placebo. (Adapted from Samama MM, Cohen AT, Darmon J-Y, 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; with permission.)

Lechler et al [39] compared 40 mg of enoxaparin daily with LDUH given every 8 hours in the Prophylaxis in Internal Medicine with Enoxaparin (PRIME) study. This multicenter, randomized, double-blind controlled trial was performed on 959 patients who were immobilized for 7 days in addition to having another risk factor for VTE (ie, congestive heart failure, malignancy, obesity, or age over 60 years). There was no significant difference in the two strategies on duplex ultrasonography (0.2% versus 1.4%; P , not significant); however, there was more bleeding in the LDUH group.

Kleber et al [40] compared 40 mg of enoxaparin once daily with LDUH given every 8 hours in 665 patients with severe respiratory disease or congestive heart failure. Patients with elevated levels of D-dimer or soluble fibrin underwent venography. Thromboembolic events were detected in 8.4% of patients receiving enoxaparin and 10.4% of those treated with LDUH ($P = 0.6$). Substudy analysis found the enoxaparin strategy to be significantly more effective in reducing VTE in the setting of congestive heart failure when compared with LDUH (9.7% versus 16.1%, $P = 0.01$). In addition, overall bleeding occurred significantly more in the LDUH group when compared with the enoxaparin group (3.6% versus 1.5%, $P < 0.05$).

Using venographic endpoints, Harenburg et al [41] compared 40 mg of enoxaparin daily with LDUH given every 8 hours in 877 medically ill patients and found a significant reduction in a com-

posite endpoint of VTE and death with enoxaparin (15% versus 22%, $P = 0.04$). Also using venographic endpoints, Hillbom et al [42] compared 40 mg of enoxaparin daily with LDUH given every 8 hours in 212 ischemic stroke patients and found a significant reduction in DVT with enoxaparin without an increase in bleeding.

Mismetti et al [7] recently performed a meta-analysis of nine trials comparing LMWH with unfractionated heparin ($n = 4669$) and demonstrated no significant difference in DVT, clinical PE, or mortality. Nevertheless, LMWH was associated with significantly less bleeding (0.4% versus 1.2%, $P = 0.049$), representing a 52% risk reduction.

Evidence-based recommendations

The intensity of the prophylaxis should match the VTE risk in the general medical patient. Patients with medical conditions are thought to be at moderate risk for VTE based on epidemiologic data revealing DVT in 10% to 26% of general medical patients [8]. The MEDENOX trial found a 5% rate of proximal DVT in a heterogeneous cohort of general medical patients with an average of more than two clinical risk factors. Extrapolating from epidemiologic data obtained in surgical populations, the average medical patient would be at high risk for VTE. Autopsy-proven fatal PE was found in 2.5% of medical patients observed prospectively without prophylaxis [43]. Using epide-

miologic data obtained in surgical populations, the general medical patient would be in the very high-risk category for VTE. Understanding the true level of VTE risk in the medical patient is critical in attempts to apply the appropriate pharmacologic prevention strategy. LDUH given twice daily is not efficacious enough in high-risk surgical populations; LDUH every 8 hours is recommended [8]. In very high-risk surgical populations, LDUH is not recommended at all owing to the lack of efficacy data.

Using surgical evidence as a guide, LDUH given every 12 hours does not seem to be efficacious enough to prevent VTE in general medical patients who are at high to very high risk for VTE. Most of the studies suggesting the efficacy of LDUH given twice daily when compared with placebo were completed 20 years ago [27,28]. Given the increased acuity seen in hospitals today, it is unclear whether the earlier data remain applicable. The Bergmann data raised further questions by demonstrating that LDUH given twice daily was equivalent to a placebo

dose of LMWH [38]. All other direct comparisons between LDUH and LMWH used a regimen of LDUH three times daily. In each comparison, LMWH was at least as efficacious and was safer to administer. Harenberg [41], Hillbom [42], and Kleber [40] and their colleagues all found the LMWH strategy to be superior to LDUH three times daily in the specific medical conditions of ischemic stroke and heart failure. Indirect data also question the efficacy of LDUH. Goldhaber et al [12] demonstrated in a recent case series (n = 384) of secondary DVT at Brigham and Women's Hospital that 52% of the study population had received some form of prophylaxis. Almost two thirds of the group receiving prophylaxis was given unfractionated heparin with or without mechanical devices.

A proposed algorithm presents a rational approach to the use of prophylactic anticoagulation in medical patients (Fig. 2). Patients should be assessed for VTE risk. If two or more clinical risk factors are present, the patient is probably at high to very high risk for

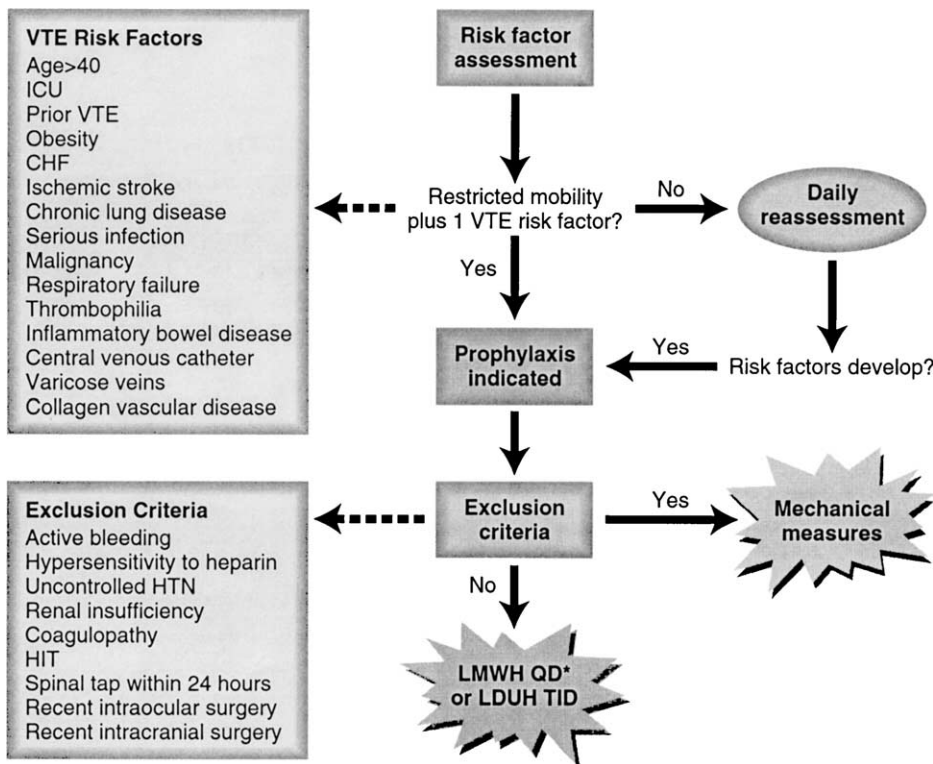


Fig. 2. Venous thromboembolism prophylaxis in the hospitalized medical patient. All patients should be screened and considered for VTE prophylaxis. LMWH is the preferred strategy owing to superior efficacy and safety. CHF, congestive heart failure; HIT, heparin-induced thrombocytopenia; HTN, hypertension; ICU, intensive care unit; LDUH, low-density unfractionated heparin; LMWH, low molecular weight heparin; VTE, venous thromboembolism. (Adapted from American Health Consultants and DVT-Free Clinical Consensus Panel, Victor Tapson, MD, Panel Chairman; with permission.)

VTE. In this setting, for the purpose of efficacy and safety, LMWH is the preferred pharmacologic preventive approach. Of the LMWH preparations, only enoxaparin is currently approved by the United States Food and Drug Administration for VTE prevention in the medically ill population with restricted mobility.

Low molecular weight heparin has not been studied adequately in clinical trials in several important patient populations. These special groups include patients with morbid obesity (>150 kg) and those with severe renal insufficiency (creatinine clearance <30 mL/minute). Morbidly obese patients are at increased risk for VTE [8]. Fixed doses of LMWH administered once daily may not be sufficient in morbidly obese patients. In addition, patients with severe renal insufficiency may be at increased risk for bleeding with pharmacologic prophylaxis when compared with non-renal impaired patients. LMWH is cleared by the kidneys, and patients with renal impairment experience a prolonged elimination of the drug that can lead to unintended high heparin levels over time, increasing the risk for hemorrhage. Ultimately, in all patient assessments, the risk for bleeding must be weighed against the risk for thrombosis. Patients with a high to very high risk for hemorrhage should probably not receive pharmacologic VTE prevention strategies; nonpharmacologic approaches would be preferred.

In most VTE prevention trials, study patients have received prophylaxis for at least 7 to 10 days [8]; however, shorter or longer durations of prophylaxis may be appropriate depending on clinical factors or the length of hospitalization. Many patients are still at risk for VTE at the time of hospital discharge. The convalescent phase of medical illness is often accompanied by limited mobility. Extending VTE prophylaxis out of the hospital following recent acute illness is being investigated in the Extended VTE Prophylaxis in Acutely Ill Medical Patients with Prolonged Immobilization trial. This double-blind, placebo-controlled, parallel multicenter study is being performed on acutely ill medical patients with prolonged immobilization.

Pharmacoeconomic data

Pharmacoeconomic data suggest that the increased initial cost of LMWH is more than offset by the benefits of lower morbidity and reduced hospitalization costs owing to a reduction in VTE complications, recurrence, or adverse events related to prophylaxis [43,44]. A recently proposed cost-analytic model indicates that thromboprophylaxis

with 40 mg of enoxaparin daily is cost-effective in acutely ill medical patients when compared with no prophylaxis [44]. The effectiveness analysis in this model is consistent with the large body of clinical evidence demonstrating a better risk-to-benefit ratio when using LMWH versus unfractionated heparin for VTE prevention. Moreover, when compared with thromboprophylaxis using unfractionated heparin, enoxaparin prophylaxis was found to be cost neutral.

Summary

All general medical patients should be assessed for clinical risk factors for VTE. The ACCP has recommended that general medical patients with clinical risk factors receive either LDUH twice or three times daily or once-daily LMWH. Current evidence suggests that twice-daily LDUH may not be efficacious enough in the acutely ill medical inpatient. LDUH three times daily may be efficacious in most medical patients; however, it is associated with an increased risk for bleeding. The preferred strategy for prevention in the medically ill population at high to very high risk for VTE is LMWH. For patients who have a high to very high risk for bleeding, nonpharmacologic strategies such as ES or IPC devices are recommended.

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