Preventing Venous Thromboembolism in Medical Patients

Alain Leizorovicz, MD; Patrick Mismetti, MD, PhD

Abstract—Given the increased number of patients hospitalized for acute medical illnesses and the associated risk of venous thromboembolism (VTE), the use of prophylaxis has become a public health matter. Thromboprophylaxis is not widely practiced in acutely ill medical patients, due in part to the heterogeneity of this group and the perceived difficulty in assessing those who would most benefit from treatment. Nevertheless, the results of recent well-conducted clinical trials support the evidence-based recommendations for more widespread systematic use of low-dose low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) in this population. Three large well-controlled studies (MEDENOX, PREVENT, and ARTEMIS) in acutely ill medical patients confirm previous findings that different at-risk patient populations show a consistent 50% reduction in VTE events with LMWH and fondaparinux. A meta-analysis in nearly 5000 patients in internal medicine comparing UFH and LMWH revealed a trend for reduction of deep vein thrombosis and pulmonary embolism with LMWH. Based on duration of use in clinical trials in acutely ill medical patients, prophylactic treatment with UFH and LMWH is recommended for 2 weeks. (Circulation. 2004;110[suppl IV]:IV-13–IV-19.)

Key Words: venous thromboembolism ■ thromboprophylaxis ■ unfractionated heparin ■ low-molecular-weight heparin ■ stroke ■ ICU ■ medical patients

Epidemiological studies show that venous thromboembolism (VTE) remains a major cause of morbidity and mortality in hospitalized patients.1–7 Although venous thromboprophylaxis in surgical patients is widely practiced, this approach has not been broadly implemented in hospitalized medical patients. A number of reasons may account for this discrepancy. The apparent greater heterogeneity of medical patients compared with surgical patients may limit accurate assessment of the overall burden of VTE in medical patients; for some practitioners, identifying individual medical patients at high risk for VTE may seem difficult. Finally, the evidence from randomized clinical trials supporting use of VTE prophylaxis in medical patients is perceived by some physicians as less solid than that in surgical patients. The results of large randomized studies in medical patients provide an opportunity to review the evidence supporting a reappraisal of current practices.

Epidemiology and the Burden of Venous Thromboembolism

VTE is a prevalent disorder that is projected to increase; it is a cause of mortality in the short term and morbidity over the long term. In the United States and in Europe, VTE commonly occurs and is associated with a high risk of death. It has been estimated that almost 300,000 cases of VTE occur each year in the United States, corresponding to an incidence of 1 per 1000.8 The early mortality rate can be as high as 3.8% in patients with deep vein thrombosis (DVT) and 38.9% in those with pulmonary embolism (PE).9

The development of noninvasive reliable methods for the diagnosis of DVT and PE has facilitated recognition of VTE. Nevertheless, fatal PE can be the first manifestation of the disease. Furthermore, because older age is a major risk factor for VTE and its secondary complications, the increased proportion of elderly people in the population is likely to contribute to high morbidity and mortality in the future.9

Besides age, population studies have identified other major risk factors for VTE; these include obesity, chronic heart failure, chronic lung disease, malignancy, ischemic stroke, birth control pills, and postmenopausal hormone replacement therapy.7,8

Hospitalized Medical Patients

Autopsy studies confirm the high number of deaths due to or associated with PE in hospitalized patients; time trends show relative stability in the rates of fatal PE in this group. Thus, the population of hospitalized patients is of particular interest with respect to VTE and its potential prophylaxis.

Hospitalized patients are at particular risk for VTE and its complications because of the combination of chronic risk factors (eg, advanced age, heart failure, prior VTE) and an acute transient increased risk associated with the condition leading to the hospitalization. An acute medical condition such as acute stroke or acute myocardial infarction (MI), or...
exacerbation of heart failure or pulmonary failure, or infectious disease may create the need for elective or emergency surgery. All of these acute medical conditions are strong independent risk factors for VTE\textsuperscript{10–12} and often a cause of prolonged immobilization, which in itself is an independent risk factor.\textsuperscript{8,9}

Because the number of patients hospitalized for nonsurgical reasons is greater than the number of patients admitted for surgery, it is not surprising that about 75% of VTE cases occur in acutely ill nonsurgical patients.\textsuperscript{10,11}

### Need for Risk Stratification in Patients Hospitalized for Acute Medical Conditions

There is a need for systematic assessment of risk in patients hospitalized for acute medical conditions. Quantifying a patient’s risk permits selection of those for whom the benefits of prophylaxis exceed its dangers. This assessment should be based on predisposing risk factors, inherited or acquired, as well as the transient risk associated with hospitalization. Predisposing risk factors include increasing age, cancer (past or active), history of VTE, chronic heart failure, chronic lung disease, obesity, varicose veins, active collagen vascular disorders, and thrombophilia (Table 1).

Transient excess risk for VTE in medical patients is conferred by most conditions that require prolonged (several days) immobilization of the patient. The following acute medical conditions are considered particularly high risk in this regard: acute stroke, acute MI, acute heart failure, acute respiratory failure, infectious disease, and inflammatory disease. It is not always possible to separate the risk of condition from that attributable to immobilization.\textsuperscript{12–13} The following medical interventions are associated with increased risk for VTE: anti-cancer treatments, central venous lines, hospitalization in the intensive care unit (ICU), and the need for respiratory assistance. There are great variations of risk among patients, depending on the nature of the acute illness and preexisting risk factors; therefore, an individual assessment is warranted (Figure 1).\textsuperscript{11}

### TABLE 1. Risk Factors for VTE

<table>
<thead>
<tr>
<th>Acute Medical Illness</th>
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<tbody>
<tr>
<td>Stroke</td>
<td></td>
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<tr>
<td>Myocardial infarction</td>
<td></td>
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<tr>
<td>Illness requiring ICU</td>
<td></td>
</tr>
<tr>
<td>Other acute illnesses requiring immobilization for at least 3 days</td>
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<table>
<thead>
<tr>
<th>Clinical Risk Factors</th>
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<tbody>
<tr>
<td>Previous PE or DVT</td>
<td></td>
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<tr>
<td>Cancer</td>
<td></td>
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<tr>
<td>Congestive heart failure</td>
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<tr>
<td>Chronic obstructive pulmonary disease</td>
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<tr>
<td>Diabetes mellitus</td>
<td></td>
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<tr>
<td>Inflammatory bowel disease</td>
<td></td>
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<tr>
<td>Antipsychotic drug use</td>
<td></td>
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<tr>
<td>Chronic in-dwelling central venous catheter</td>
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<tr>
<td>Permanent pacemaker</td>
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<tr>
<td>Collagen vascular disorders</td>
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<tr>
<td>Internal cardiac defibrillator</td>
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<tr>
<td>Stroke with limb paresis</td>
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<tr>
<td>Nursing-home confinement, current or repeated hospital admission</td>
<td></td>
</tr>
<tr>
<td>Varicose veins</td>
<td></td>
</tr>
<tr>
<td>Hormone replacement therapy</td>
<td></td>
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<tr>
<td>Obesity</td>
<td></td>
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<tr>
<td>Cancer chemotherapy</td>
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### Thrombophilia

| Factor V Leiden mutation                      |  |
| Prothrombin gene mutation                     |  |
| Hyperhomocysteinemia (including mutation in methylene tetrahydrofolate reductase) |  |
| Antiphospholipid antibody syndrome            |  |
| Deficiency of antithrombin II, protein C, or protein S |  |
| High concentrations of factor VIII, IX, or XI |  |
| Increased lipoprotein(a)                     |  |

ICU indicates intensive care unit; PE, pulmonary embolism.

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**Figure 1.** Risk of DVT with no prophylaxis in various groups of hospitalized patients. (Adapted from Geerts WH et al. Chest. 2001;119:132S–175S.)
Evidenced-Based Review of the Benefit and Risk of Thromboprophylaxis in Medical Patients

Although hundreds of thousands of surgical patients have been included in clinical trials for the evaluation of thromboprophylaxis, far fewer medical patients have been enrolled in such trials and fewer agents have been evaluated in this population. Nevertheless, there is solid and consistent evidence of benefit from thromboprophylaxis in medical patients at risk for VTE.

Before reviewing the VTE prophylactic effect of different antithrombotic drugs, it is important to evaluate evidence with mechanical prophylactic devices. A few randomized trials have been performed to evaluate graduated compression stockings and intermittent pneumatic compression in a limited number of patients, mainly surgical and neurological patients. A meta-analysis of the studies performed in absence of other prophylactic treatment showed an odds ratio (OR) of 0.34 (95% CI 0.25 to 0.46) favoring compression stockings over control. The meta-analysis of the studies evaluating compression stockings in patients receiving pharmacological prophylaxis showed that the stockings conferred additional benefit (OR 0.24, 95% CI 0.15 to 0.37).

Medical Patients at Permanent Risk for VTE

Medical patients who are candidates for prophylaxis include those with limited mobility who live in nursing homes, those needing long-term hospitalization for chronic conditions such as paraplegia, and those requiring permanent respiratory assistance. However, the true long-term risk of VTE in these patients is not well known; no studies have been performed that evaluate the benefit of prophylaxis with an appropriate duration of treatment.

Acute Myocardial Infarction

Patients hospitalized for an acute MI are at high risk of VTE. In a meta-analysis reviewing placebo-controlled studies of antithrombotic therapy in patients with suspected acute MI, the rate of PE was 3.9% (91 of 2335). The authors of the study acknowledged that this rate might be underestimated. These studies were performed before the use of fibrinolytic treatments and the introduction of aspirin as a systematic treatment for acute-phase MI.

Preventing VTE is not the primary therapeutic objective in acute MI patients. These patients usually receive combinations of antithrombotic treatments, including fibrinolitics, antiplatelet agents (aspirin, clopidogrel, glycoprotein Ib/IIa antagonists), as well as a full dose of heparin. Nevertheless, heparin confers additional benefit on top of other antithrombotic treatment for the prevention of VTE.

Stroke

In the absence of prophylaxis, the incidence of DVT in patients with acute hemiplegic stroke is ~50% within 2 weeks. Pulmonary emboli are frequent in stroke patients; 13% to 25% of early stroke deaths have been attributed to PE, most often between the second and fourth weeks. Aspirin, given as soon as the diagnosis of ischemic stroke is confirmed, reduces the risk of recurrent stroke, improves survival, and prevents PE (1 PE avoided per 1000 patients treated).

Unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and heparinoids have been evaluated in acute-stroke patients. Although this review did not show an improvement in survival with anticoagulants in these patients, their use did prevent ~4 PE events per 1000 patients. A meta-analysis of smaller trials designed to evaluate the prevention of asymptomatic DVT concluded that treatment with LMWH compared with placebo reduced the rate of DVT (OR 0.27, 95% CI 0.08 to 0.96) and symptomatic PE (OR 0.34, 95% CI 0.17 to 0.69). However, there was increased risk of major bleeding (OR 2.17, 95% CI 1.10 to 4.28).

LMWH and heparin may not be equivalent for VTE prevention in stroke patients. A review of studies comparing UFH, LMWH, and heparinoids included 5 trials involving 705 patients. Standard UFH was compared with a heparinoid (danaparoid) in 4 trials and with LMWH (enoxaparin) in 1 study. Overall, 13% (55 of 414) of the patients allocated to danaparoid or enoxaparin had DVT compared with 22% (65 of 291) of those allocated to UFH. This reduction was significant (OR 0.52, 95% CI 0.56 to 0.79). However, the authors concluded that “the number of major events (PE, death, intracranial or extracranial hemorrhage) was too small to provide a reliable estimate of more important benefits and risks.”

Intensive Care Unit

Admission to a medical ICU is associated with a high risk of VTE. There is a paucity of randomized studies in this setting. Only 1 early trial comparing UFH with control (119 patients) and a more recent trial comparing LMWH with placebo (223 patients), which included patients requiring mechanical ventilation, have been published. Both showed a decrease of ~50% in asymptomatic DVT.

The lack of solid evidence for thromboprophylaxis in the ICU may explain the varying recommendations for its use and practice disparities in this setting; the ICU has been termed “the last frontier for prophylaxis.” On the other hand, in institutions where the staff is especially concerned about risk for VTE, physiotherapy and other preventive measures are applied more often.

Other Acute Illnesses

The principal reasons for limited use of thromboprophylaxis in patients with acute medical illnesses may include: lack of awareness of the risk of VTE in this group, including that for asymptomatic DVT; concern about bleeding; uncertain cost-
to-benefit ratio; and lack of convenient risk-stratification tools for selecting patients for treatment.

Since 1982, 9 randomized studies have compared a low-dose regimen of UFH or LMWH to control or placebo in patients with acute medical illnesses. A meta-analysis\(^3\) of the 7 trials (including 15 095 patients) that were available in 2000 concluded that heparins significantly reduced the risk of asymptomatic DVT by 56\% (relative risk: 0.44, 95\% CI 0.29 to 0.64; \(P<0.001\)) and the risk of PE by 52\% (relative risk: 0.48, 95\% CI 0.34 to 0.68; \(P<0.001\)). There was a nonsignificant (\(P=0.08\)) adverse trend for major bleedings and a neutral effect for total mortality (Figure 2).\(^3\)

The 2 largest studies, which recruited 2474 patients\(^3\) and 11 693 patients,\(^3\) respectively, were designed primarily as mortality assessments. They did not demonstrate a reduction in total mortality or in fatal PE with anticoagulation therapy. The open design of the largest study could have led to biases that the authors themselves acknowledged. The final conclusion of the study was to recommend against use of prophylactic heparin. This resulted in inconsistent recommendations and variable interpretation and application of guidelines for thromboprophylaxis.\(^1\) In fact, despite results favoring prophylaxis and recommendations for anticoagulation therapy from expert groups, the use of UFH or LMWH for thromboprophylaxis has remained low.\(^1,3\)

Three studies with more solid methodology have been completed (Tables 2 and 3) in medical patients.\(^3\) All were placebo-controlled studies with objective systematic assessment of the primary end point, VTE, defined as asymptomatic DVT or symptomatic VTE. The MEDENOX (prophylaxis in Medical patients with ENOXaparin) study had 1102 patients randomized in 3 arms, 2 doses of enoxaparin (40 mg and 20 mg) and placebo. PREVENT (Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized Patients) trial compared dalteparin with placebo. PREVENT (Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized Patients) trial compared dalteparin with placebo. The sample size of PREVENT, 3681 patients, was tailored to look primarily at proximal asymptomatic DVT or symptomatic VTE. ARTEMIS (ARixtra for ThromboEmbolism Prevention

### Table 2. Design Features of MEDENOX, PREVENT, and ARTEMIS\(^3\)–\(^\text{38}\)

<table>
<thead>
<tr>
<th>MEDENOX</th>
<th>PREVENT</th>
<th>ARTEMIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatments</td>
<td>Enoxaparin 40 mg, enoxaparin 20 mg, placebo</td>
<td>Dalteparin 5000 IU, placebo</td>
</tr>
<tr>
<td>Once daily for 14 days</td>
<td>Once daily for 14 days</td>
<td>Once daily for 14 days</td>
</tr>
<tr>
<td>Eligibility Criteria</td>
<td>Age ≥ 40 y&lt;br&gt;Expected hospital stay ≥ 6 days, recent immobilization (≥ 3 days), and CHF (NYHA III/IV) or acute respiratory illness, infection, bone/joint, or inflamed bowel, if ≥ 1 added risk for VTE (eg, &gt; 75 y, cancer, previous VTE, obesity, varicose veins, hormones, or chronic heart or lung failure)</td>
<td>Age ≥ 40 y&lt;br&gt;Expected hospital stay ≥ 4 days, recent immobilization (≥ 3 days), and CHF (NYHA III/IV) or acute respiratory illness, infection, bone/joint, or inflamed bowel, if ≥ 1 added risk for VTE (eg, &gt; 75 y, cancer, previous VTE, obesity, varicose veins, hormones, or chronic heart or lung failure)</td>
</tr>
<tr>
<td>Primary Efficacy</td>
<td>Distal &amp; proximal&lt;br&gt;Venographic DVT&lt;br&gt;Symptomatic VTE&lt;br&gt;Fatal PE&lt;br&gt;Safety</td>
<td>Distal &amp; proximal&lt;br&gt;Proximal ultrasonographic DVT&lt;br&gt;Symptomatic VTE&lt;br&gt;Fatal PE&lt;br&gt;Safety</td>
</tr>
<tr>
<td>At Day 14</td>
<td>At Day 21</td>
<td>At Day 14</td>
</tr>
</tbody>
</table>

### Table 3. Results of MEDENOX, PREVENT, ARTEMIS: Incidence of Proximal DVT or Symptomatic VTE at Day 14–21

<table>
<thead>
<tr>
<th>MEDENOX</th>
<th>PREVENT</th>
<th>ARTEMIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin 2.1%</td>
<td>Dalteparin 2.6%</td>
<td>Fondaparinux 1.5%</td>
</tr>
<tr>
<td>Placebo 6.6%</td>
<td>Placebo 5.0%</td>
<td>Placebo 3.4%</td>
</tr>
<tr>
<td>(P=0.037)</td>
<td>(P=0.002)</td>
<td>(P=0.085)</td>
</tr>
</tbody>
</table>
in a Medical Indications Study) compared a low dose of an anti-Xa agent (fondaparinux 2.5 mg) with placebo in 849 patients.

There were some differences in the designs of these studies (Table 2).36–38 In PREVENT, the major component of the primary end point, asymptomatic proximal DVT, was assessed by systematic screening with compression ultrasound (CUS), whereas venography was used in the other studies. There is ample evidence that the noninvasive technique of CUS is as reliable as venography for diagnosing asymptomatic proximal DVT. Compression ultrasound is more practical and is now accepted as a diagnostic method for evaluating proximal DVT in prophylaxis studies by drug agencies.39 In addition, in PREVENT, all CUS exams were recorded and centrally read by a core laboratory.

All 3 studies showed consistent results: a reduction of VTE in the range of 50%. The relative risks are as follows: MEDENOX, 0.37 (95% CI 0.22 to 0.63), PREVENT, 0.55 (95% CI 0.38 to 0.80), and ARTEMIS, 0.53 (95% CI 0.31 to 0.92). The overall estimate of the relative risk for proximal DVT or symptomatic VTE from these 3 trials is 0.50 (95% CI 0.38 to 0.66) (Table 3).36–38

In all 3 trials, the active treatments were given for a maximum of 14 days. Despite this short duration, the relative effect observed at the end of the treatment period persisted at 3 months in MEDENOX and PREVENT and at 1 month in ARTEMIS.36–38

A nonsignificant trend was observed in favor of enoxaparin in MEDENOX for total mortality but was not observed in the other studies; this is consistent with the results of previous studies. Patients included in the 3 studies had different risks of death, which was reflected in the higher total mortality rate in the placebo group of the MEDENOX study, 14% at 3 months, compared with ∼6% in PREVENT at 3 months and 6% at 1 month in ARTEMIS.36–38

These 3 studies confirm the efficacy of LMWH and fondaparinux in reducing the risk of VTE. The risk of major bleeding was minimal. In all 3 studies there was a nonsignificant excess (<1%) of major bleedings in active treatment groups.36–38

### Practical Questions and Recommendations

Answers to practical questions and recommendations for anticoagulation in patients hospitalized for acute medical illnesses are explicated below.

#### A. Which Treatment Should Be Used—UFH or LMWH—and at What Dose?

The meta-analysis31 of all studies comparing UFH and LMWH included 9 trials for a total of 4669 patients (Figure 3).

<table>
<thead>
<tr>
<th>Reason for admission</th>
<th>Risk factors</th>
</tr>
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<tbody>
<tr>
<td>Congestive heart failure NYHA class III/IV</td>
<td>Age 60 y</td>
</tr>
<tr>
<td>Acute lung disease</td>
<td>Cancer</td>
</tr>
<tr>
<td>Acute infectious disease</td>
<td>Previous VTE</td>
</tr>
<tr>
<td>Inflammatory disease</td>
<td>Obesity</td>
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<tr>
<td></td>
<td>Varicose veins</td>
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<tr>
<td></td>
<td>Chronic heart disease</td>
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<td></td>
<td>Chronic pulmonary disease</td>
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<tr>
<td></td>
<td>Hormone therapy</td>
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<tr>
<td></td>
<td>Thrombophilia</td>
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</table>

**Table 4. Thromboprophylaxis for Acutely Ill Medical Patients**

**STEP 1: Systematically assess all cases**

- Hospitalized patients with acute medical illness
- Projected immobilization of 3 or more days

**STEP 2: Consider thromboprophylaxis in particular if reason for admission and/or risk factors are among the following lists**

**STEP 3: Give thromboprophylaxis for 2 weeks (if no contraindications)**

- Enoxaparin 40 mg daily or dalteparin 5000 U daily or UFH 5000 U 3× daily
- Graduated compression stockings or intermittent pneumatic compression devices for patients with contraindications to anticoagulation
- Combined LMWH or UFH plus graduated compression stockings or intermittent pneumatic compression devices for patients at very high risk
3). There was a trend in favor of LMWH for the reduction of DVT (relative risk 0.83, 95% CI 0.56 to 1.24) and of PE (relative risk 0.74, 95% CI 0.29 to 1.80). Major bleeding was marginally less frequent in the LMWH group (relative risk 0.48, 95% CI 0.23 to 1.0; P=0.049).

Considering LMWH, it is advisable to use those specific compounds that have demonstrated efficacy in placebo-controlled studies and only in the tested doses (ie, 40 mg of enoxaparin or 5000 IU of dalteparin).

B. Which Patients Should Be Selected for Treatment?

All patients admitted in the hospital for an acute medical illness—including those who develop such a condition after admission for another reason and for whom there is a projected stay of a few days with immobilization—should be considered for prophylaxis with UFH or LMWH. Estrogen-containing products must be discontinued in these immobilized patients because of their contribution to higher risk for DVT. Subgroup analyses of studies have confirmed that a wide range of moderate- to high-risk medical patients, in particular elderly patients and patients with heart failure or respiratory failure, benefit from thromboprophylaxis. Parameters for selecting the appropriate patients to treat are shown in Table 4.

Renal function should be assessed before prescribing LMWH. If renal function is severely altered (ie, creatinine clearance is <30 mL/min) there is a risk of accumulation of LMWH and UFH might be considered as an alternative.

Although a number of patients, in particular the elderly, already may have asymptomatic DVT when admitted to hospital, it is not necessary to screen all patients for this sequelae. The clinical trials, which showed benefits with anticoagulants, were done without preliminary screening for DVT.

C. Could Low-Dose UFH or LMWH Be Given to Patients Already Receiving Other Potentially Effective Prophylactic Treatments?

Patients already receiving full doses of UFH, LMWH, or oral anticoagulants are obviously not eligible for low-dose UFH or LMWH unless their original treatments have to be discontinued during the hospital stay. On the other hand, patients receiving antiplatelet treatment (eg, those with coronary disease) benefit from the addition of UFH or LMWH. Similarly, pharmacological thromboprophylaxis seems to be additive to the use of mechanical prevention such as compression stockings.

D. For How Long Should Treatment Be Given?

Typically, in the clinical trials performed thus far in medical patients, UFH or LMWH regimens did not exceed 2 weeks. Thus, treatment duration should not exceed this length.

Conclusion

There is an ever-growing population of patients who are hospitalized for acute medical illnesses with an associated risk of VTE. The use of prophylaxis has not been widely used because of difficulty identifying at-risk patients and lack of solid clinical trials; however, the results of recent, well-conducted clinical trials support the evidence-based recommendations for more widespread systematic use of low-dose LMWH or UFH.

Through risk stratification and timely treatment, the risk of VTE in patients hospitalized for acute medical illnesses can be greatly reduced.

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