

## CLINICAL PRACTICE

# Prophylaxis for Thromboembolism in Hospitalized Medical Patients

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*This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

**A 62-year-old man is admitted with fever, cough, and dyspnea. He is weak, appears to be dehydrated, and has purulent sputum. His temperature is 39.2°C, respirations 22, and blood pressure 128/69 mm Hg. There are crackles over the left lower lung field, and chest radiography shows a density in the left lower lobe that is consistent with pneumonia. Should thromboprophylaxis be provided? If so, in what form?**

## THE CLINICAL PROBLEM

Venous thromboembolism is a frequent cause of preventable illness and death in hospitalized patients. About 25% of all cases of venous thromboembolism are associated with hospitalization,<sup>1,2</sup> and 50 to 75% of cases of venous thromboembolism in hospitalized patients occur in those on the medical service.<sup>3-5</sup> In prospective studies of hospitalized patients at high risk who were not receiving prophylaxis, deep-vein thrombosis was found by means of venography in 10.5%<sup>6</sup> to 14.9%<sup>7</sup> of patients and by means of ultrasonography in 5.0% of patients.<sup>8</sup> In these studies, pulmonary embolism occurred in 0.3 to 1.5% of cases, and proximal deep-vein thrombosis in 2.0 to 4.9% of cases. Thrombosis was asymptomatic in over 70% of cases, probably because most patients spent much of the day in bed, with little ambulation. Pulmonary embolism is thought to be associated with 5 to 10% of deaths of hospitalized patients,<sup>9-12</sup> but this diagnosis is not suspected clinically in the vast majority of cases.

## STRATEGIES AND EVIDENCE

For patients presenting with symptoms of venous thromboembolism, accurate diagnosis and treatment are essential. However, diagnosis and treatment alone are inadequate for hospitalized patients who are at high risk, in whom asymptomatic deep-vein thrombosis is common and death from pulmonary embolism usually occurs rapidly, before the diagnosis is suspected. In such patients, primary prophylaxis with the use of a highly effective intervention that carries a low risk of adverse effects is the best approach.

## ASSESSMENT OF RISK

The risk of venous thromboembolism is related to the presence or absence of specific risk factors (Table 1), and it increases if multiple risk factors are present, as is the case in most hospitalized patients. Because decisions regarding prophylaxis depend on the baseline risk, all patients should undergo a risk assessment on admission to the hospital and a reassessment when their status changes, such as after transfer to the intensive care unit or after surgery. Systems to estimate risk on the basis of the number

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and type of risk factors present in an individual hospitalized patient have been proposed,<sup>13,14</sup> but none have been prospectively validated. Although data are not available to inform specific recommendations for prophylaxis that are based on the patient's age and the expected duration of hospitalization, prophylaxis is generally considered reasonable for patients on the medical service who are older than 40 years, have limited mobility for 3 days or more, and have at least one risk factor.

#### PROPHYLAXIS

The pathogenesis of venous thrombosis is related primarily to hypercoagulability and venous stasis. Available prophylactic treatments improve venous flow or reduce blood coagulability.

#### Nonpharmacologic Therapies

Both ambulation and exercises involving foot extension improve venous flow and should be encouraged. Graduated compression stockings and pneumatic compression devices also reduce venous stasis and are effective in reducing the risk of postoperative venous thromboembolism.<sup>15,16</sup> A Cochrane Review showed that the use of graduated compression stockings reduced venous thromboembolism in hospitalized patients after surgery by about 50%.<sup>16</sup> However, no data are available from large studies of hospitalized medical patients, and the reliability of information from clinical studies is limited by the lack of blinding. Nonpharmacologic prophylaxis is a logical choice for patients at high risk for bleeding with anticoagulant prophylaxis, including patients with active or recent gastrointestinal bleeding, patients with hemorrhagic stroke, and those with hemostatic defects such as severe thrombocytopenia. Removal of graduated compression stockings because of discomfort, transport within the hospital, or visits to the bathroom can limit their effectiveness.

#### Anticoagulant Prophylaxis

Effective prophylaxis can be provided with unfractionated heparin, low-molecular-weight heparins, or fondaparinux (Table 2). The initial information about the value of prophylaxis in hospitalized patients came from clinical trials involving patients undergoing surgery.<sup>17</sup> A single large trial showed that the use of low-dose unfractionated heparin was associated with a decrease in the incidence of fatal pulmonary embolism after general surgery.<sup>18</sup> A subsequent meta-analysis of 74 trials showed

**Table 1. Risk Factors for Venous Thromboembolism in Hospitalized Patients.**

Condition
Acute infectious disease
Congestive heart failure*
Acute myocardial infarction
Acute respiratory disease
Stroke
Rheumatic disease (e.g., acute arthritis)
Inflammatory bowel disease
Clinical characteristic
Previous venous thromboembolism
Older age (especially >75 yr)
Recent surgery or trauma
Immobility or paresis
Obesity (BMI >30)†
Central venous catheterization
Inherited or acquired thrombophilic states
Varicose veins
Estrogen therapy

\* Congestive heart failure is defined as New York Heart Association class III or IV disease.

† The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

that low doses of heparin reduced the rates of postoperative venous thromboembolism and total and fatal pulmonary embolism by 67%, 47%, and 64%, respectively.<sup>19</sup> Heparin therapy resulted in a 2% absolute increase in the incidence bleeding complications, most of which occurred at the surgical site.<sup>19</sup> Most of these studies identified thrombosis by means of noninvasive vascular testing, and the presence of asymptomatic thrombi was the most common end point. Although the clinical significance of such thrombi is questionable, studies of the natural history of venous thromboembolism indicate direct relations among calf-vein thrombi, larger proximal thrombi, and pulmonary embolism.<sup>20-23</sup>

There have been fewer trials involving hospitalized medical patients, but the results have provided support for the use of anticoagulant prophylaxis. One meta-analysis<sup>24</sup> included four studies of 5256 patients with deep-vein thrombosis as the end point, five studies of 7355 patients with death as the end point, nine studies of 19,958 patients with pulmonary embolism as the end point, and

**Table 2. Medications and Doses for Prophylaxis of Venous Thromboembolism in Hospitalized Medical Patients.\***

Drug†	Dose	Comment
Unfractionated heparin	5000 U subcutaneously, every 8 hr‡	
Low-molecular-weight heparins		
Enoxaparin (Lovenox)	40 mg subcutaneously, once daily	More expensive than heparin; 20 mg daily not effective
Dalteparin (Fragmin)	5000 U subcutaneously, once daily	More expensive than heparin
Fondaparinux (Arixtra)§	2.5 mg subcutaneously, once daily	More expensive than heparin

\* Anticoagulant prophylaxis should not be used if there is a risk of excessive bleeding, such as in patients with active or recent gastrointestinal bleeding, hemorrhagic stroke, or hemostatic defects such as severe thrombocytopenia.

† Unfractionated heparin and low-molecular-weight heparins should not be used in patients with current or previous heparin-induced thrombocytopenia.

‡ A dose of 5000 U given subcutaneously every 12 hours has also been used. Expert opinion favors 8-hour dosing, although the 8- and 12-hour regimens have not been directly compared.

§ Fondaparinux is approved by the Food and Drug Administration for prophylaxis in surgical patients, but the same regimen has been used in medical patients.

seven studies of 19,510 patients with fatal pulmonary embolism as the end point. The use of anticoagulant prophylaxis resulted in significant reductions in the relative risks of pulmonary embolism (0.43; 95% confidence interval [CI], 0.26 to 0.71) and fatal pulmonary embolism (0.38; 95% CI, 0.21 to 0.69) and a nonsignificant reduction in the relative risk of deep-vein thrombosis (0.47; 95% CI, 0.22 to 1.00), with no effect on overall mortality and a nonsignificant increase in the relative risk of major bleeding (1.32; 95% CI, 0.73 to 2.37).

In another trial, hospitalized patients receiving unfractionated heparin (5000 U every 8 hours) had lower mortality than those receiving no treatment (7.8% vs. 10.9%,  $P=0.03$ ).<sup>25</sup> However, there was no placebo group, and treatment was assigned according to the medical-record number, a method that is subject to bias. An open-label study in Sweden involving 11,693 patients with infectious diseases showed no significant differences in mortality during hospitalization or in autopsy-verified fatal pulmonary embolism among patients randomly assigned to receive either unfractionated heparin (5000 U every 12 hours) or no prophylactic treatment.<sup>26</sup>

Three large randomized, double-blind, placebo-controlled trials have provided further support for the value of prophylaxis in hospitalized patients (Fig. 1). The Prophylaxis in Medical Patients with Enoxaparin (MEDENOX) study compared two doses of enoxaparin (20 mg or 40 mg once daily) with placebo in 1102 nonsurgical patients who were more than 40 years old and were hospitalized for at least 6 days.<sup>7</sup> Most patients had congestive heart

failure, non-ventilator-dependent respiratory failure, or acute infectious disease, as well as multiple risk factors for venous thromboembolism. The primary end point was deep-vein thrombosis or pulmonary embolism. Patients underwent bilateral venography, or compression ultrasonography if venography could not be performed, between days 6 and 14. The group randomly assigned to receive 40 mg of enoxaparin daily (but not the 20-mg enoxaparin group) had a significantly lower rate of thromboembolism than the placebo group (5.5% vs. 14.9%,  $P<0.001$ ) and a significantly lower rate of proximal deep-vein thrombosis (4.9% vs. 1.7%,  $P=0.04$ ); there were no significant differences among the groups in mortality at day 10 or in bleeding complications.

Similar results were reported for another low-molecular-weight heparin, dalteparin. The Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized Patients Trial (PREVENT) was a placebo-controlled, randomized trial involving 3706 patients who, at entry, were similar to those in the MEDENOX study.<sup>8</sup> Patients randomly assigned to dalteparin (5000 U once daily for 14 days) had significantly lower rates of venous thromboembolism (the primary end point, which included symptomatic deep-vein thrombosis, pulmonary embolism, and asymptomatic deep-vein thrombosis on ultrasonography) by day 21 than patients randomly assigned to placebo (2.8% vs. 5.0%,  $P=0.002$ ). The rate of proximal deep-vein thrombosis was also significantly reduced in the dalteparin group, but there were no significant differences between the dalteparin

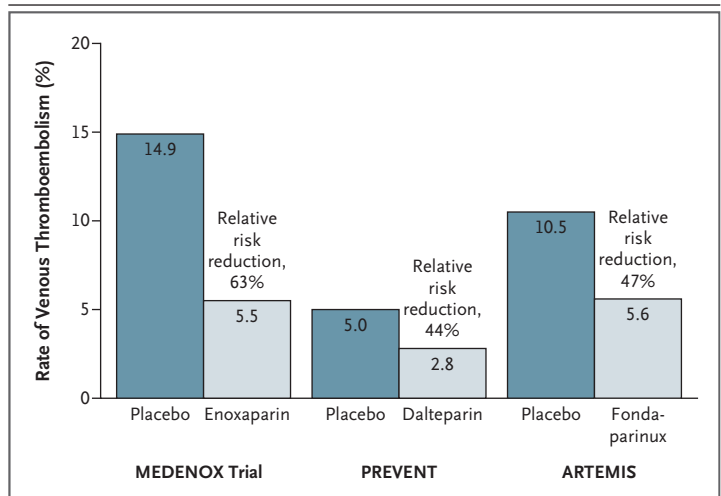
group and the placebo group in the rate of a combined end point that included pulmonary embolism, death, and major bleeding (0.49% and 0.16%, respectively).

The third placebo-controlled, randomized trial assessed prophylaxis with fondaparinux, a synthetic pentasaccharide with inhibitory activity specific for activated factor X that is sold under the trade name of Arixtra. The Arixtra for Thromboembolism Prevention in a Medical Indications Study (ARTEMIS)<sup>6</sup> involved 849 hospitalized patients, with entry criteria similar to those in the MEDENOX trial and PREVENT. Patients randomly assigned to fondaparinux (2.5 mg once daily for 6 to 14 days) had a significant reduction in the incidence of venous thromboembolism (symptomatic or asymptomatic, detected by means of venography) as compared with those randomly assigned to placebo (5.6% vs. 10.5%; relative risk reduction, 47%;  $P=0.03$ ). Fatal pulmonary embolism occurred in five patients in the placebo group and in none in the fondaparinux group; mortality at 1 month was 6.0% and 3.3%, respectively ( $P=0.06$ ). Major bleeding occurred in one patient in each group.

All these trials involved hospitalized patients considered to be at high risk for thromboembolism because of the reason for admission (including congestive heart failure, acute respiratory failure, and infectious disease) and other underlying medical conditions and characteristics. The benefit of prophylaxis is expected to be smaller among lower-risk patients. Also, many of the studies had as an end point the presence of asymptomatic distal thrombi diagnosed by means of screening venography, although two trials also showed significant reductions in proximal-vein thrombosis among patients receiving prophylaxis.

#### Comparison of Anticoagulant Regimens

A meta-analysis of eight trials comparing unfractionated heparin with low-molecular-weight heparins for prophylaxis in hospitalized patients<sup>27</sup> showed no significant differences between the two treatment groups in the rates of venous thromboembolism, but patients receiving low-molecular-weight heparins had a lower rate of major bleeding (relative risk, 0.48; 95% CI, 0.23 to 1.00).<sup>27</sup> No studies have directly compared different commonly used regimens of unfractionated heparin (i.e., 5000 U every 8 hours and 5000 U every 12 hours), nor has fondaparinux been directly com-



**Figure 1. Results of Trials of Prophylaxis for Venous Thromboembolism in High-Risk Hospitalized Patients.**

In three randomized, double-blind trials, enoxaparin, dalteparin, or fondaparinux was compared with placebo for the prevention of venous thromboembolism. The use of the anticoagulant resulted in significantly decreased rates of thromboembolism in the Prophylaxis in Medical Patients with Enoxaparin (MEDENOX) trial ( $P<0.001$ ),<sup>7</sup> the Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized Patients Trial (PREVENT) ( $P=0.002$ ),<sup>8</sup> and the Arixtra for Thromboembolism Prevention in a Medical Indications Study (ARTEMIS) ( $P=0.03$ ).<sup>6</sup> Relative risk reductions are shown for patients receiving each prophylactic drug as compared with those receiving placebo.

pared with unfractionated or low-molecular-weight heparins.

#### Patients with Cancer

Hospitalized patients with active cancer are at particularly high risk for thromboembolism. In a large administrative database of patients with cancer and neutropenia due to chemotherapy, the rate of diagnostically coded symptomatic venous thromboembolism during a single hospital stay was 5.4%.<sup>28</sup> Data from large randomized trials specifically focused on prophylaxis in hospitalized patients with cancer are not available.

#### Patients with Stroke

Patients with acute stroke, particularly when associated with leg paralysis, have a risk of deep-vein thrombosis of about 60%,<sup>1,29</sup> and several studies have evaluated prophylaxis in this population.<sup>29,30</sup> A Cochrane Review of studies including 22,544 patients found that the use of anticoagulants reduced the rates of pulmonary embolism by 40% and deep-vein thrombosis by 79%.<sup>31</sup> However, the rate of intracranial bleeding was also in-

creased; this finding appears to be largely attributable to the inclusion of one large study that involved a high dose of heparin. In studies that involved low-molecular-weight heparins, the rate of pulmonary embolism was significantly reduced, with no increase in the rate of bleeding.<sup>31</sup>

#### *Patients with Other Critical Illnesses*

Critically ill patients typically have multiple risk factors for and a high rate of venous thromboembolism. Limited evidence from small randomized trials indicates that prophylaxis with either unfractionated or low-molecular-weight heparins is effective in such patients.<sup>17</sup> A systematic review of 26 studies involving 73,000 patients who had had acute myocardial infarction showed a significant reduction of about 50% in the rate of pulmonary embolism among patients who received heparin therapy at any dose and nearly the same reduction in 7 trials involving low-dose heparin.<sup>32</sup>

#### *Strategies to Increase the Use of Anticoagulation in At-Risk Hospitalized Patients*

Evidence indicates that prophylaxis for venous thromboembolism is underused in hospitalized patients.<sup>3,5,33-35</sup> A community-wide study of 16 hospitals in Massachusetts showed that prophylaxis was provided for only 32% of patients at high risk.<sup>3</sup> A prospective study of patients in the intensive care unit showed that only 33% received prophylaxis, which was administered after an average delay of 2 days.<sup>35</sup> Data from one registry showed that only 42% of 2726 patients with symptomatic deep-vein thrombosis in whom thrombosis developed during hospitalization had received any form of prophylaxis,<sup>5</sup> and in a survey of 106 oncologists, about 80% reported that they did not routinely provide prophylaxis for inpatients undergoing active treatment for cancer.<sup>36</sup>

Hospital-based interventions may increase the use of prophylactic anticoagulation. Evidence-based educational programs that provide hospital-specific data demonstrating the problem of venous thromboembolism can be successful in increasing the use of prophylaxis by clinicians, as shown in a study that evaluated the use of prophylaxis in 15 community hospitals before and after a targeted continuing medical education program was conducted.<sup>37</sup> In large randomized trials, computer prompts that remind physicians, through order-entry systems, to consider the appropriate use of prophylaxis have been shown to increase its actual

use.<sup>38,39</sup> In a trial that assessed the effects of a computerized reminder system on both the use of heparin and outcomes among 2501 inpatients identified by the computer program to be at high risk (on the basis of the presence of cancer, previous venous thromboembolism, hypercoagulability, major surgery, advanced age, obesity, bed rest, or the use of postmenopausal hormone therapy or oral contraceptives), the intervention group received prophylactic treatment at a higher rate than the control group (34% vs. 15%,  $P < 0.001$ ) and also had a lower incidence of clinically diagnosed, objectively confirmed deep-vein thrombosis or pulmonary embolism at 90 days (4.9% vs. 8.2%,  $P < 0.001$ ).<sup>39</sup>

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#### AREAS OF UNCERTAINTY

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There is strong evidence from well-conducted clinical trials that anticoagulant prophylaxis reduces the risk of asymptomatic deep-vein thrombosis and proximal deep-vein thrombosis in hospitalized patients. Less information is available regarding the effects of treatment on the most important outcomes — fatal and nonfatal pulmonary embolism — but findings from a meta-analysis also suggest improvement in these outcomes. Because the entry criteria in clinical trials have selected for high-risk patients, the generalizability of the findings to heterogeneous populations of hospitalized patients is uncertain. Risk-stratification models have been developed primarily for surgical patients, and there is limited information regarding their applicability to hospitalized patients.

Uncertainty also remains regarding the best prophylactic treatment. Evidence in surgical patients indicates that graduated compression stockings and pneumatic compression devices are effective, but no data from large studies of hospitalized medical patients are available. These interventions are particularly important for patients in whom anticoagulant prophylaxis may carry excessive risk because of coexisting conditions. Additional uncertainty remains regarding the relative effectiveness and safety of unfractionated heparin, low-molecular-weight heparins, and fondaparinux.

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#### GUIDELINES

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The American College of Chest Physicians has published guidelines for the use of prophylaxis against thromboembolism in hospitalized pa-

tients.<sup>17</sup> These guidelines strongly recommend the use of either unfractionated or low-molecular-weight heparins in acutely ill hospitalized patients with heart failure, severe respiratory disease, acute stroke, immobility, or multiple risk factors (listed in Table 1). Mechanical methods of prophylaxis are recommended for patients at increased risk for bleeding. Similar recommendations have been published by the Thromboembolic Risk Factors Consensus Group.<sup>40</sup> The recommendations given here are consistent with the published guidelines.

## CONCLUSIONS AND RECOMMENDATIONS

Venous thromboembolism is a common but preventable serious complication in hospitalized patients. The patient described in the vignette has several risk factors, including his age and the pres-

ence of acute infectious disease, and prophylaxis is warranted. In the absence of a contraindication, I would recommend prophylaxis with unfractionated heparin, a low-molecular-weight heparin, or fondaparinux at the doses listed in Table 2. Unfractionated heparin is less expensive but must be given three times daily, whereas low-molecular-weight heparins and fondaparinux are more expensive but can be given once daily. All three agents have been shown to be effective in reducing the risk of venous thromboembolism in randomized trials. For patients who have active gastrointestinal or intracranial bleeding or who are at high risk for bleeding, the use of graduated compression stockings or the intermittent use of pneumatic compression devices is a reasonable alternative.

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**CORRECTION**

**Prophylaxis for Thromboembolism in Hospitalized Medical Patients**

Prophylaxis for Thromboembolism in Hospitalized Medical Patients .  
The fourth sentence of the sixth paragraph under the Anticoagulant Prophylaxis heading (page 1441) should have read "Fatal pulmonary embolism occurred in five patients in the placebo group and in none in the fonaparinux group; mortality at 1 month was 6.0% and 3.3%, respectively (P=0.06)" rather than "mortality at 1 month was 3.3% and 6.0%." The text has been corrected on the *Journal's* Web site at [www.nejm.org](http://www.nejm.org).