Prevention of Venous Thromboembolism Among Hospitalized Medical Patients

Samuel Z. Goldhaber, MD; Alexander G.G. Turpie, MD

Case presentation: A 79-year-old woman was noted by staff at her skilled nursing facility to have increasing shortness of breath during the previous 24 to 48 hours. She had been receiving daily physical therapy, occupational therapy, and 6 prescription medications to manage underlying congestive heart failure with preserved systolic function. The woman was hospitalized. After being transferred to the emergency department, she underwent further workup, which showed no pulmonary embolism on chest CT scan. The chest x-ray, however, revealed a new right lobar infiltrate and consolidation, which are consistent with pneumonia. On examination, she was alert, with a respiratory rate of 24 per minute, heart rate of 96 bpm, blood pressure of 154/76 mm Hg, temperature of 38°C, distended neck veins, right lower lung zone posterior musical rales, regular heart rhythm, normal S1, single S2, and grade II/VI systolic murmur at the left lower sternal border. The diagnosis of pneumonia was made, and levofloxacin was initiated in the emergency department. Specific evaluation of her medical regimen, including furosemide, potassium chloride, metoprolol, candesartan, simvastatin, and baby aspirin, was recommended.

The Problem

Prevention of venous thromboembolism has been neglected in hospitalized patients with medical illnesses such as congestive heart failure, chronic lung disease, cancer, and infectious diseases. In the Medical Intensive Care Unit (MICU) at Brigham and Women’s Hospital, we found a combination of omitted and ineffective prophylaxis. When we performed venous ultrasound examinations on 100 patients admitted to the MICU with an anticipated stay of >48 hours, we detected deep vein thrombosis (DVT) in 33%.1 Almost 50% of the patients with DVT had proximal leg DVT. The remainder had calf DVT or upper-extremity DVT.

In a subsequent audit of 384 patients who developed in-hospital DVT or pulmonary embolism after admission to Brigham and Women’s Hospital, 52% had received ineffective prophylaxis, and 48% had received no prophylaxis whatsoever.2 Of the 183 patients who received no prophylaxis, 110 (60%) were medical patients and 73 (40%) were surgical patients. Overall, pulmonary embolism caused or was a major contributor to 13 (3.4%) deaths in this cohort of 384 patients. Of the 13 deaths from pulmonary embolism, 11 patients were on the medical service and 2 were on the thoracic surgical service.

The problem of inadequate and omitted prophylaxis in hospitalized patients with medical illness appears to be widespread throughout North America. In a prospective registry of 5451 patients with ultrasound-confirmed DVT conducted at 183 US hospitals, 3894 (71%) had not received prophylaxis before they developed DVT.3 Of these 3894 patients, 2295 (59%) were nonsurgical. The most common medical comorbidities were hypertension (50%), immobility (34%), cancer (32%), previous DVT (22%), and neurological disease (22%).

It remains frustrating that effective and safe prophylaxis measures exist but are not universally implemented in hospitalized medical patients. The majority of DVT that develops in hospitalized patients occurs in medical rather than in surgical or trauma patients, who benefit from higher rates of effective preventive measures.

Straightforward Solutions

Medical patients have available to them mechanical, pharmacological,
and combined mechanical-plus-pharmacological strategies that can markedly reduce the frequency of DVT or pulmonary embolism with a low rate of complications.

**Mechanical Prophylaxis**
Mechanical measures include graduated compression stockings and intermittent pneumatic compression (IPC) devices. Both graduated compression stockings and IPC devices increase venous blood flow and decrease venous stasis. In addition, IPC devices stimulate endogenous fibrinolytic activity by causing gentle trauma to the vascular endothelial cells of the lower leg and by altering rheological characteristics and perfusion pressure.

**Pharmacological Prophylaxis**
The greatest advances in prophylaxis of medical patients have emerged from 3 large, rigorously conducted randomized double-blind placebo-controlled trials (Table): (1) MEDENOX (Prophylaxis in Medical Patients with Enoxaparin), (2) PREVENT (Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized Patients Trial), and (3) ARTEMIS (Arixtra for ThromboEmbolism Prevention in a Medical Indications Study). The 3 trials share an important common theme: once-daily fixed low doses of 2 low-molecular-weight heparins (enoxaparin 40 mg in MEDENOX [enoxaparin 20 mg was no more effective than was placebo] and dalteparin 5000 U in PREVENT) and a once-daily fixed low dose of pentasaccharide (fondaparinux 2.5 mg in ARTEMIS) are effective and safe. All 3 pharmacological regimens approximately halved the DVT rate as compared with placebo, without increasing the major bleeding complication rate.

These 3 trials have demonstrated that pharmacological prophylaxis should be a “default admission order” for most medical patients who are hospitalized for >1 or 2 days. In the MEDENOX trial, independent risk factors that predicted the development of venous thromboembolism included age ≥75 years, cancer, previous venous thromboembolism, acute infectious disease, and chronic respiratory disease. In the ARTEMIS trial, fondaparinux showed a trend toward reducing overall mortality from 6.0% in the placebo group to 3.3% in the fondaparinux group. The weight of evidence now favors pharmacological prophylaxis of medical patients at risk and precludes further placebo-controlled randomized trials in this patient population.

Before the development of low-molecular-weight heparins, “mini-dose” unfractionated heparin, 5000 U 3 times daily, was the standard pharmacological preventive regimen for medical patients. In a multicenter European trial (THE-PRINCE, The Thromboembolism-Prevention in Cardiac or Respiratory Disease with Enoxaparin), 665 patients were enrolled in 64 German hospitals. Half had heart failure and half had severe respiratory disease. In THE-PRINCE study, which was designed as an equivalence trial, patients were randomized to receive open-label heparin 5000 U 3 times daily versus enoxaparin 40 mg once daily; DVT was diagnosed with contrast venography. There was no difference in efficacy or safety with these 2 prophylactic strategies.

**Aspirin**
In a meta-analysis of trials of antiplatelet therapy, the risk of symptomatic pulmonary embolism was reduced with antiplatelet therapy from 0.61% to 0.46%. Nevertheless, antiplatelet therapy is not the standard of care for the prevention of venous thromboembolism in medical patients. Aspirin is warranted, however, for the prevention of heart attack and stroke.

**Implementing Contemporary Guidelines for Prophylaxis**
Despite multiple educational initiatives for healthcare providers, venous thromboembolism prophylaxis remains underused. Often, ineffective preventive regimens are prescribed. Some clinicians continue to perceive pharmacological prophylaxis as excessively risky because of the possibility of bleeding complications. Others find established guidelines to be too cumbersome for practical everyday use. A minority believe that small asymptomatic DVT is simply not worth the effort to prevent because these tiny thrombi cannot directly cause clinically significant pulmonary embolism.

Information technology should help to improve the safety of patients at risk for DVT and pulmonary embolism. Computer technology will allow the identification of patients at high risk for venous thromboembolism. Future programming may permit electronic alerts to the physicians responsible for high-risk patients and may suggest appropriate prophylaxis modalities. So far, however, computer reminder systems have demonstrated only the ability to increase the frequency of prophylaxis orders without causing a decline in the rate of DVT or pulmonary embolism.

In the future, prompt identification of hospitalized medical patients at risk for DVT and pulmonary embolism is expected to improve the safety of these patients.

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**Large-Scale Randomized Placebo-Controlled Trials of Venous Thromboembolism Prophylaxis in Hospitalized Medical Patients**

<table>
<thead>
<tr>
<th>MEDENOX</th>
<th>PREVENT</th>
<th>ARTEMIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. randomized</td>
<td>1102</td>
<td>3706</td>
</tr>
<tr>
<td>Drug</td>
<td>Enoxaparin</td>
<td>Dalteparin</td>
</tr>
<tr>
<td>DVT diagnosis</td>
<td>Venogram</td>
<td>Ultrasound</td>
</tr>
<tr>
<td>Primary end point</td>
<td>VTE</td>
<td>VTE, SCD</td>
</tr>
<tr>
<td>Follow-up</td>
<td>3 mo</td>
<td>90 d</td>
</tr>
<tr>
<td>Reduction primary end point, %</td>
<td>63</td>
<td>45</td>
</tr>
<tr>
<td>Major bleeding (drug), %</td>
<td>1.7</td>
<td>0.5</td>
</tr>
<tr>
<td>Major bleeding (placebo), %</td>
<td>1.1</td>
<td>0.2</td>
</tr>
</tbody>
</table>

VTE indicates venous thromboembolism; SCD, sudden cardiac death.
of venous thromboembolism will facilitate the institution of mechanical and pharmacological prophylaxis modalities. The foundation of preventive strategies should be the completed large pharmacological trials (Table), as well as consensus guidelines for prophylaxis.15

The cardiovascular specialist will focus on the cause and immediate management of congestive heart failure in people like the 79-year-old woman presented in our case study. She appears to have diastolic dysfunction, underlying systemic arterial hypertension, and a new pneumonia. The cardiologist will make sure that left ventricular function is still well preserved and will work with the referring physician to optimize heart rate and blood pressure control. With 7 active medication orders (including the antibiotic), it would be easy to overlook DVT prevention, although this patient is in a high-risk group for developing DVT. In the absence of overt bleeding, she will benefit from an eighth medication: once-daily prophylactic injections of 40 mg enoxaparin or 5000 U daily dalteparin. This incremental strategy should decrease her risk of developing DVT, with no appreciable increase in major bleeding, by 50%.

References