What is the best choice for prophylaxis against VTE in medical inpatients?

By Joshua D. Lenchus, DO, RPh, FACP, and Amir K. Jaffer, MD

Case
A 76-year-old gentleman is admitted for progressively worsening dyspnea, cough, and bilateral leg edema. Upon admission, his blood pressure is 150/90 mmHg, pulse 90 beats per minute, and respiration is 24 per minute.

Pertinent physical findings include jugular venous distension, bilateral cracks, S3 gallop, and 2+ bilateral lower extremity edema. The chest radiograph shows cardiomegaly and pulmonary edema. He is admitted to the hospital with a diagnosis of acute decompensated heart failure and starts aggressive medical therapy.

Overview
Approximately 2 million cases of deep-vein thrombosis (DVT) occur annually in the United States. Based on studies utilizing ventilation-perfusion scanning, half these patients likely have a silent pulmonary embolism (PE); of these, approximately 250,000 die.

The spectrum of venous thromboembolism (VTE), which includes DVT and PE, can vary from being asymptomatic to sudden death. Autopsy studies suggest a leading cause of sudden death in hospitalized medical patients is often a PE. There also are sequelae, such as chronic pulmonary hypertension, occurring in approximately 5% of PE cases, and post-thrombotic syndrome, occurring in approximately 40% of patients with DVT at two years.

A recent study suggests DVT occurs three times more commonly in the outpatient setting. However, more than half of these patients were hospitalized in the three months prior. This is likely due to inadequate in-hospital prevention because of absence of prophylaxis, use of an unsuitable modality, insufficient dose of the drug, or ineffective duration of therapy. Inadequate and omitted VTE prophylaxis for medical patients was clearly demonstrated in the DVT Free Registry. This registry was created by 183 U.S. hospitals and included 5,451 patients, inpatients, and outpatients with ultrasound-confirmed DVT.

The number of medical inpatients who received prophylaxis in the 30 days prior to diagnosis was 28%—lower than the 48% of surgical patients. In a recent international registry, IMPROVE, only approximately 50% of hospitalized patients received prophylaxis.

Vinchow’s triad describes three underlying etiologic factors for thrombosis: stasis of blood flow, endothelial injury, and hypercoagulability. Established VTE risk factors reflect these underlying pathophysiologic processes. Important risk factors for VTE include increasing age, prolonged immobility, malignancy, major surgery, multiple trauma, prior VTE, and chronic heart failure.

However, the magnitude of risk conferred by these and other risk factors varies (see Table 1, p. 35). It is not known how these factors interact to determine a patient’s individual VTE risk, but there is evidence it increases in proportion to the number of predisposing factors present.

In a recent systematic review of nine studies, including approximately 20,000 patients, prophylaxis reduced the rate of symptomatic VTE in at-risk hospitalized medical patients without increasing major bleeding.

Multiple healthcare organizations, such as the National Quality Forum (NQF), Joint Commission on Accreditation of Healthcare Organizations (JCAHO), and Agency for Healthcare Research and Quality (AHRQ) have identified VTE as a preventable condition in hospitalized patients. Formal risk assessment must be conducted as a first step, followed by the initiation of timely prophylaxis to improve patient safety.

Review of the Data
Mechanical forms of prophylaxis, such as graduated compression stockings, have been evaluated in patients with stroke and myocardial infarction. Intermittent pneumatic compression stockings and venous foot pumps have not been studied in randomized controlled trials (RCTs) in general medical patients.

Although there is data supporting the efficacy of these devices in surgical patients, the American College of Chest Physicians’ (ACCP) guidelines recommend against the use of mechanical forms of prophylaxis in medical patients unless there is a contraindication to pharmacologic prophylaxis.

The ideal prophylactic agent is cost-effective and has no side effects. Available pharmacologic options for prevention of VTE in medical patients include unfractionated heparin (UFH), low molecular weight heparins (LMWHs), and the synthetic pentasaccharide, fondaparinux. Oral anticoagulants, e.g., vitamin K antagonists (VKAs), have not been adequately studied in medical inpatients. Since VKA take several days to achieve therapeutic anticoagulation, we do not recommend using them de novo as VTE prophylaxis.

However, patients taking an oral VKA in the outpatient setting who have a therapeutic international normalized ratio (INR) during hospitalization probably are adequately protected from VTE.

KEY CLINICAL QUESTIONS

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The ideal prophylactic agent is cost-effective and has no side effects. Available pharmacologic options for prevention of VTE in medical patients include unfractionated heparin (UFH), low molecular weight heparins (LMWHs), and the synthetic pentasaccharide, fondaparinux. Oral anticoagulants, e.g., vitamin K antagonists (VKAs), have not been adequately studied in medical inpatients. Since VKA take several days to achieve therapeutic anticoagulation, we do not recommend using them de novo as VTE prophylaxis.

However, patients taking an oral VKA in the outpatient setting who have a therapeutic international normalized ratio (INR) during hospitalization probably are adequately protected from VTE.
and do not need additional pharmacologic prophylaxis. Newer anticoagu-
lants in phase III testing for prevention of VTE in medically ill patients include oral direct thrombin inhibitors and anti-Xa inhibitors. ACCP guidelines recommend either low-dose UFH or LMWH as first-line agents for VTE prevention in medical inpatients.

**Unfractionated heparin:** UFH is a heterogeneous mixture of repeating polysaccharide chains of varying sizes, averaging about 15,000 Daltons. It binds anti-thrombin III (AT-III) and facilitates AT-III-mediated inactivation of factor Xa, factor IXa, and XIa; of these, Xa and Xa are most responsive to inhibition.

Due to its large size, UFH only is partially absorbed from subcutaneous (SC) tissue, and it has a variable anticoagulant response due to interactions with plasma proteins, macroglobulins, and endothelial cells. However, in prophyla-
lactic SC doses (5,000 units two or three times daily), monitoring of the activated partial thromboplastin time (aPTT) is recommended (e.g., frail or elderly patients), prophyla-
lactic SC doses may slightly prolong the aPTT.

UFH also binds to platelets and platelet factor 4 (PF4), which may precip-
itate heparin-induced thrombocytope-
nia (HIT). At least three clinical trials have evaluated the efficacy of SC UFH with a placebo and found prophylactic doses of UFH decrease the relative risk of DVT as detected by fibrinogen uptake test by about 70% without increasing the risk of bleeding.14

**Low molecular weight heparins:** LMWHs are derived from UFH through a chemical depolymeriza-
tion, or fractionation, process. They are about one-third the size of UFH, with a molecular weight of approximately 5,000 Daltons. These smaller molecules are readily absorbed through the skin, eliciting the SC tissue, and it has a variable antico-
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**Synthetic pentasaccharide:** Fondaparinux is a synthetic analogue of the unique pentasaccharide sequence that mediates the interaction of heparin with antithrombin. It inhibits both free and platelet-bound factor Xa. It binds antithrombin with high affinity, has close to 100% bioavailability, and has a plasma half-life of 17 hours that permits once-daily administration.

This drug is excreted unchanged in the urine and therefore contraindicated in patients with severe renal impairment (e.g., creatinine clearance less than 20 mL/min). It does not bind PF4 in vitro and thus should not cause HIT.15

Fondaparinux has been evaluated in medical inpatients in a randomized placebo controlled trial, ARTEMIS. Fondaparinux 2.5 mg SC once daily decreased the rate of venographically-
confirmed DVT from 10.5% to 5.6% (p=0.029); there was also a decrease in major bleeding from 1.7% to 0.7% (p=0.029). A reduction in overall mortality from 6% to 3.3% (P=NS) was observed.

**Table 1. Risk Factors for VTE in Medically Ill Patients**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immobility</td>
<td>Yes</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Yes</td>
</tr>
<tr>
<td>Cancer therapy</td>
<td>No</td>
</tr>
<tr>
<td>Hormonal therapy, chemotherapy, radiotherapy</td>
<td>Yes</td>
</tr>
<tr>
<td>Previous VTE</td>
<td>Yes</td>
</tr>
<tr>
<td>Increasing age</td>
<td>Yes</td>
</tr>
<tr>
<td>Pregnancy and postpartum period</td>
<td>No</td>
</tr>
<tr>
<td>Estrogen containing oral contraceptation, hormone replacement therapy</td>
<td>No</td>
</tr>
<tr>
<td>or selective estrogen receptor modulators</td>
<td>Yes</td>
</tr>
<tr>
<td>Infections (e.g., urinary tract infection, pneumonia);</td>
<td>No</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Yes</td>
</tr>
<tr>
<td>Decompensated heart failure</td>
<td>Yes</td>
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<tr>
<td>Respiratory failure</td>
<td>Yes</td>
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<tr>
<td>Inflammatory bowel disease</td>
<td>Yes</td>
</tr>
<tr>
<td>Neutrophilic syndromes</td>
<td>No</td>
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<tr>
<td>Myeloproliferative disorders</td>
<td>No</td>
</tr>
<tr>
<td>Obesity</td>
<td>Yes</td>
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<tr>
<td>Smoking</td>
<td>Yes</td>
</tr>
<tr>
<td>Varicose veins</td>
<td>Yes</td>
</tr>
<tr>
<td>Central venous catheterization</td>
<td>No</td>
</tr>
<tr>
<td>Inherited or acquired thrombophilia</td>
<td>No</td>
</tr>
</tbody>
</table>

**Table 2. Various Pharmacologic Agents for Medical Prophylaxis**

<table>
<thead>
<tr>
<th>Class</th>
<th>UFH</th>
<th>LMWH</th>
<th>LMWH</th>
<th>Synthentic pentasaccharide Factor Xa inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA approved for medical prophylaxis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Approved dose</td>
<td>5,000 units SC three times daily</td>
<td>45 mg SC once daily</td>
<td>5,000 units SC once daily</td>
<td>2.5 mg SC once daily*</td>
</tr>
<tr>
<td>Dosing in renal insufficiency (creatinine clearance 10 to 30 mL/min)</td>
<td>Consider UFH 6,000 units SC twice daily</td>
<td>Adjust to 30 mg SC once daily</td>
<td>Not indicated</td>
<td>Comment outlined</td>
</tr>
<tr>
<td>Reversal agent</td>
<td>Pentamine Sulfate (complete reversal)</td>
<td>Pentamine sulfate (50-75% reversal)</td>
<td>Pentamine sulfate (50-75% reversal)</td>
<td>Recombinant Factor Xa</td>
</tr>
</tbody>
</table>

*Fondaparinux is not FDA approved for medical prophylaxis.
enoxaparin reduced the relative risk of VTE by 44% (2.8% vs. 4.9%; p=0.0011). There was major bleeding in 12 subjects who received extended-duration enoxaparin and three subjects receiving placebo (0.6% vs. 0.1%; p=0.0192).

There was no difference in all-cause mortality between the extended-duration enoxaparin and placebo groups at six months (10.1% vs. 8.9%, p=0.179). The authors concluded 38 days of enoxaparin 40 mg SC once daily significantly reduced the overall incidence of VTE compared with a 10-day regimen in acutely ill medical patients with reduced mobility. This reduction in overall risk for VTE was consistent in patients with prior history of VTE or with active cancer. In those older than 75 years with prior history of VTE, we recommend five weeks of prophylaxis for VTE.

For many patients, this will mean prophylaxis after discharge from the hospital. All clinical trials discussed above included similar patients and support the use of pharmacologic prophylaxis. All hospitalized medical patients should undergo VTE risk assessment and implementation of pharmacologic prophylaxis in the absence of contraindications.

References

Back to the Case
Our patient has acute decompensated heart failure and likely will be limited in his ability to ambulate. All the clinical trials discussed above included similar patients and support the use of pharmacological prophylaxis. All hospitalized medical patients should undergo VTE risk assessment and implementation of pharmacologic prophylaxis in the absence of contraindications.