KEY CLINICAL QUESTIONS

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

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KEY POINTS

1. All hospitalized medical patients should undergo VTE risk assessment upon admission.
2. Patients at risk for VTE should receive pharmacologic prophylaxis for seven to 14 days in the absence of any contraindications. Extended prophylaxis for five weeks may be indicated in patients older than 75 and/or those with prior history of VTE or cancer..
3. Mechanical forms of prophylaxis should only be used if anticoagulants are contraindicated.

THE BOTTOM LINE

All medical inpatients should be assessed for VTE prophylaxis upon admission, and prescribed pharmacologic prophylaxis with LMWH for seven to 14 days in the absence of contraindications. If risk factors do not mandate prophylaxis, patients should be assessed daily for any change in clinical status and prophylaxis should be employed as warranted.

ADDITIONAL READING

■ Francis CW. Prophylaxis for thromboembolism in hospitalized medical patients. *N Engl J Med.* 2007;356: 1438-1444.
■ Hirsh J, Raschke R. The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence-Based Guidelines. *Chest.* 2004;126,3 (suppl):163S-697S.

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 mm/Hg, pulse 90 beats per minute, and respiration is 24 per minute.

Pertinent physical findings include jugular venous distension, bilateral crackles, 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.[1]

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.[2] 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.[3] In a recent international registry, IMPROVE, only approximately 50% of hospitalized patients received prophylaxis.[4]

Virchow'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.[5]

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.[6]

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

An example of deep-vein thrombosis.

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.[7]

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 [VKA]), 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 anticoagulants 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 factors IIa, IXa, Xa, and XIIa; of these, IIa 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, macrophages, and endothelial cells.[8] However, in prophylactic SC doses (5,000 units two or three times daily), monitoring of the activated partial thromboplastin time (aPTT) is not required. In some cases, (e.g., frail or elderly patients), prophylactic SC doses may slightly prolong the aPTT.

UFH also binds to platelets and platelet factor 4 (PF4), and may precipitate heparin-induced thrombocytopenia (HIT). At least three clinical trials have compared 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.[9-11]

Low molecular weight heparins: LMWHs are derived from UFH through a chemical depolymerization, 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 from the SC tissue, eliciting a more predictable anticoagulant response than UFH. Unlike UFH, LMWHs have only minimal nonspecific binding to plasma proteins, endothelial cells, and monocytes, resulting in a predictable dose response. This obviates the need for lab monitoring, even when used in full, therapeutic dosing.

Compared with UFH, these agents have a longer plasma half-life, allowing them to be dosed SC once or twice daily. Also, they don't bind platelets as readily as UFH resulting in a lower risk of HIT. Because they're smaller, LMWHs tend to preferentially inhibit factor Xa, whereas UFH tends to inhibit factors Xa and IIa equally.

LMWHs have been evaluated in two large, placebo-controlled clinical trials for the prevention of VTE in medical inpatients.

In the first trial, MEDENOX, almost half the patients were older than 75 (mean age approximately 73). Inclusion criteria were NYHA class 3 or 4 heart failure, acute respiratory failure without mechanical ventilation, acute infection without septic shock, acute rheumatic disease, or inflammatory bowel disease. The primary outcome was assessed in 866 patients. Enoxaparin 40 mg SC once daily

decreased the rate of VTE by two-thirds, from 15% to 5% (p=0.0002), without increased bleeding or thrombocytopenia compared with placebo.[12] Enoxaparin 40 mg SC once daily is approved by the Food and Drug Administration (FDA) for VTE prophylaxis in medically ill patients.

PREVENT was an international, multicenter, randomized, double-blind, placebo-controlled trial evaluating dalteparin's efficacy and safety. The inclusion criteria in this trial were acute congestive heart failure, non-ventilator-requiring acute respiratory failure, infection without septic shock, acute rheumatologic disorders, or inflammatory bowel disease. It studied 2,991 patients, and the primary outcome was VTE incidence and sudden death at day 21.

Dalteparin at 5,000 units decreased the rate of VTE, as detected by compression ultrasound, from 5% in the placebo group to 2.8%, a relative risk reduction of 45% (p=0.0015). The authors concluded the use of dalteparin reduced the incidence of VTE without increased risk of bleeding.[13] Dalteparin is FDA approved for VTE prophylaxis in medical inpatients.

At least two meta-analyses have evaluated LMWHs compared with UFH. In the first, nine trials comparing LMWH to UFH (4,669 patients) were included. No significant effect was observed on DVT, clinical PE, or mortality. However, LMWH reduced the risk of major hemorrhage by 52% (p=0.049).[14]

In a more recent meta-analysis, 36 studies were included comparing placebos with UFH and LMWH. Both agents were associated with a reduced risk of VTE. A UFH dosage of 5,000 units three times daily was more effective in preventing DVT than a dosage of 5,000 units twice daily when compared with the control (risk ratio [RR], 0.27; 95% confidence interval [CI], 0.20-0.36; vs. RR, 0.52; 95% CI, 0.28-0.96). Neither UFH nor LMWH reduced mortality. When directly compared with UFH, LMWH was associated with a lower risk of DVT (RR, 0.68; 95% CI, 0.52-0.88) and injection-site hematoma (RR, 0.47; 95% CI, 0.36-0.62), but no difference was seen between the two agents in the risk of bleeding or thrombocytopenia.

This contemporary meta-analysis clearly illustrates that UFH and LMWH reduce VTE risk in hospital-ized medical patients, but neither agent alters mortality. When directly compared, LMWH is more effective in preventing DVT.[15]

Despite the higher drug acquisition costs, LMWHs are more cost-effective than UFH for prophylaxis in medical patients because of their lower complication rates of HIT. LMWH reduces incremental costs by $13.88 per day compared with UFH.[16, 17]

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.

The drug is excreted unchanged in the urine and therefore contraindicated in patients with severe renal impairment (e.g., creatinine clearance less than 30 mL/min). It does not bind PF4 in vitro and thus should not cause HIT.

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 fatal PE from 1.7% to 0.7% (p=0.029). A reduction in overall mortality from 6% to 3.3% (P=NS) was observed.

Major bleeding occurred in 0.2% of patients in both groups. The drug is not FDA approved to prevent VTE in medical inpatients.[18]

Duration of therapy: Most clinical trials have used prophylaxis for seven to 14 days. The Extended Clinical Prophylaxis in Acutely Ill Medical Patients (EXCLAIM) trial evaluated duration of therapy, the results of which were presented recently at the 21st Congress of the International Society on Thrombosis and Haemostasis (ISTH).

Of the 5,105 patients who met inclusion criteria, 5,049, or 99%, received open-label prophylaxis with enoxaparin (10 ± four days); 2,013 patients subsequently received extended-duration enoxaparin; and 2,027 received placebo (each for 28 ± four days). Subjects were at least 40 years old, had been recently immobilized (for at least 3 days) and had a predefined acute medical illness. Mobility was defined as level 1 (total bed rest or sedentary) or level 2 (bathroom privileges). After a planned blinded interim analysis, the trial's data safety monitoring board recommended an amendment to the inclusion criteria, changing level 2 mobility to include age >75 years, and/or prior VTE, and/or diagnosed cancer.

When compared with placebo, extended-duration enoxaparin following the open-label, standard-duration

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Table 1. Risk Factors for VTE in Medically Ill Patients

- Immobility;
- Malignancy;
- Cancer therapy;
- Hormonal therapy, chemotherapy, or radiotherapy;
- Previous VTE;
- Increasing age;
- Pregnancy and postpartum period;
- Estrogen containing oral contraception, hormone replacement therapy, or selective estrogen receptor modulators;
- Infections (e.g., urinary tract infection, pneumonia);
- Sepsis;
- Decompensated heart failure;
- Respiratory failure;
- Inflammatory bowel disease;
- Nephrotic syndrome;
- Myeloproliferative disorders;
- Obesity;
- Smoking;
- Varicose veins;
- Central venous catheterization; and
- Inherited or acquired thrombophilia.

Source: Geerts WH, Pineo GF, Heit JA, Bergqvist D, Lassen MR, Colwell CW, Ray JG. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest.* 2004 Sep;126(3 Suppl):338S-400S.

Table 2. Various Pharmacologic Agents for Medical Prophylaxis

	Unfractionated heparin	Enoxaparin	Dalteparin	Fondaparinux
Class	UFH	LMWH	LMWH	Synthetic pentasaccharide, Factor Xa inhibitor
FDA approved for medical prophylaxis	Yes	Yes	Yes	No
Approved dose	5,000 units SC three times daily	40 mg SC once daily	5,000 units SC once daily	2.5 mg SC once daily*
Dosing in renal insufficiency (creatinine clearance 10 to 30 mL/min)	Consider UFH 5,000 units SC twice daily	Adjust to 30 mg SC once daily	Not indicated	Contraindicated
Reversal agent	Protamine Sulfate (complete reversal)	Protamine sulfate (60-75% reversal)	Protamine sulfate (60-75% reversal)	Recombinant Factor VIIa

*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 with a reduction in risk for asymptomatic proximal DVT and symptomatic VTE.

Based on this trial, we would recommend five weeks of prophylaxis for those older than 75 years with prior history of VTE or with active cancer. In the absence of these criteria, we recommend up to 14 days of therapy.

For many patients, this will mean prophylaxis after discharge from the hospital. While this represents a change in practice for many and may significantly complicate some discharge care plans we believe the significant burden of post-hospital VTE mandates a more aggressive approach to peri-hospitalization prophylaxis.

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. **TH**

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