

Prevention of venous thromboembolism in the hospitalized medical patient

■ ABSTRACT

Hospitalized acutely ill medical patients are at high risk for venous thromboembolism (VTE), and clinical trials clearly demonstrate that pharmacologic prophylaxis of VTE for up to 14 days significantly reduces the incidence of VTE in this population. Guidelines recommend use of low-molecular-weight heparin (LMWH) or unfractionated heparin (5,000 U three times daily) for VTE prophylaxis in hospitalized medical patients with risk factors for VTE; in patients with contraindications to anticoagulants, mechanical prophylaxis is recommended. All hospitalized medical patients should be assessed for their risk of VTE at admission and daily thereafter, and those with reduced mobility and one or more other VTE risk factors are candidates for aggressive VTE prophylaxis. Based on results from the recently reported EXCLAIM trial, extended post-discharge prophylaxis with LMWH for 28 days should be considered for hospitalized medical patients with reduced mobility who are older than age 75 or have a cancer diagnosis or a history of VTE.

The need for prophylaxis of venous thromboembolism (VTE) in hospitalized acutely ill medical patients is well established. Without prophylaxis, hospitalized medical patients develop VTE at a rate of 5% to 15%.¹⁻³ Moreover, pulmonary embolism (PE) occurs more frequently in hospitalized medical patients than in nonmedical patients, and is a leading cause of sudden death in hospitalized medical patients.^{4,5} Without appropriate prophylaxis, 1 in 20 hospitalized medical patients may suffer a fatal PE.⁴

■ PROPHYLAXIS IN MEDICAL PATIENTS: UNDERUSED AND OFTEN INAPPROPRIATE

Despite these risks and the clear indications for VTE prophylaxis in hospitalized medical patients, prophylaxis of VTE is omitted more often in these patients

than in hospitalized surgical patients.⁵ Even when prophylaxis is given, it is often used inappropriately in the medical population. So concludes a recent analysis of data from 196,104 patients with acute medical conditions who were discharged from 227 US hospitals from January 2002 to September 2005.⁶ Criteria for inclusion in the analysis were patient age of 40 years or older, a hospital stay of 6 days or greater, and an absence of contraindications to anticoagulation. Appropriate prophylaxis was defined in accordance with the Sixth American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy.⁷

The analysis revealed an overall VTE prophylaxis rate of 61.8%, but the rate of appropriate prophylaxis was only 33.9%, meaning that two-thirds of discharged patients did not receive prophylaxis in accordance with ACCP guidelines. When temporal trends were analyzed according to groups based on patients' diagnosis at admission (acute myocardial infarction, severe lung disease, ischemic stroke, cancer, heart failure, or trauma), the rate of appropriate prophylaxis remained essentially flat from the beginning to the end of the study period for virtually all diagnosis groups.⁶

Similar findings have emerged from the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE), an ongoing international registry of acutely ill medical patients.⁸ Data from the first 15,156 patients, enrolled from July 2002 through September 2006, reveal that 50% of patients received pharmacologic and/or mechanical VTE prophylaxis in the hospital, and only 60% of patients who met established criteria for VTE prophylaxis actually received it.

Analysis of the US portion of the IMPROVE data shows that 54% of the US patient sample received some form of VTE prophylaxis; 22% of US patients received intermittent pneumatic compression, 21% received unfractionated heparin (UFH), 14% received

See contents page for author affiliations. See end of article for author disclosures.

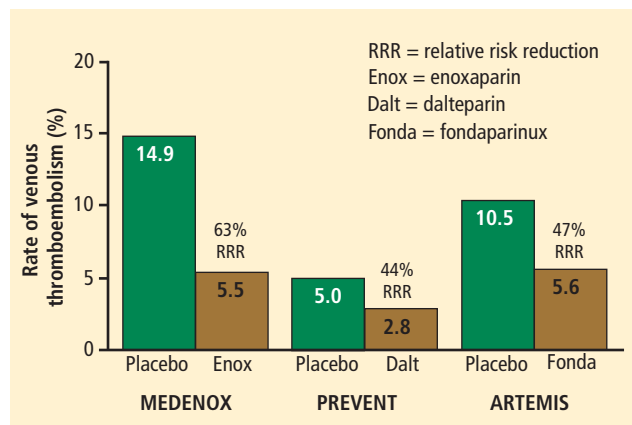


FIGURE 1. Rates of venous thromboembolism (VTE) in three large double-blind, placebo-controlled studies of pharmacologic prophylaxis of VTE in high-risk hospitalized medical patients.

Reprinted, with permission, from *New England Journal of Medicine* (Francis CW. Prophylaxis for thromboembolism in hospitalized medical patients. *N Engl J Med* 2007; 356:1438–1444). Copyright © 2007 Massachusetts Medical Society. All rights reserved.

low-molecular-weight heparin (LMWH), and 3% wore compression stockings.⁸ Thus, despite a paucity of data supporting a benefit of intermittent pneumatic compression in this population,⁹ it was the most frequently used form of prophylaxis in US patients.

CLINICAL TRIALS OF PHARMACOLOGIC PROPHYLAXIS IN MEDICAL PATIENTS

The evidence in support of pharmacologic prophylaxis of VTE in high-risk hospitalized medical patients is considerable. Three large double-blind, placebo-controlled trials of anticoagulants currently available in the United States have been reported in this patient population (Figure 1).^{1–3}

The Prophylaxis in Medical Patients with Enoxaparin (MEDENOX) trial¹ randomized 1,102 hospitalized patients to one of two doses of the LMWH enoxaparin (20 mg or 40 mg once daily subcutaneously) or placebo for 6 to 14 days. Compared with placebo, the 40-mg dose of enoxaparin was associated with a 63% reduction in risk of VTE over 3 months of follow-up ($P < .001$) (Figure 1).

The Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized Patients Trial (PREVENT)² was a multicenter, randomized, double-blind study comparing the LMWH dalteparin (5,000 IU daily given subcutaneously for 14 days) with placebo in 3,706 acutely ill medical patients. Over 90 days of follow-up, the risk of VTE was reduced by 44% in patients assigned to dalteparin compared with those assigned to placebo ($P = .0015$) (Figure 1).

The Arixtra for Thromboembolism Prevention in a Medical Indications Study (ARTEMIS)³ randomized 849 medical patients 60 years or older to 6 to 14 days of therapy with the selective factor Xa inhibitor fondaparinux (2.5 mg once daily subcutaneously) or placebo. Compared with the placebo group, fondaparinux recipients had a 47% lower risk of developing VTE by day 15 ($P = .029$) (Figure 1).

Fewer events and fatal PEs, but no effect on all-cause mortality

A recent meta-analysis by Dentali et al¹⁰ further demonstrates the efficacy of anticoagulant therapy for preventing symptomatic VTE in hospitalized medical patients. This analysis included several other trials in addition to the three reviewed above,^{1–3} for a total of nine randomized studies (seven of which were double-blind) comprising 19,958 patients. Across the nine studies, anticoagulant prophylaxis was clearly superior to placebo in preventing fatal PE (relative risk, 0.38 [95% CI, 0.21 to 0.69]). There was a strong trend toward a reduction in symptomatic deep vein thrombosis (DVT) with prophylaxis but no effect on all-cause mortality. The meta-analysis also provided reassurance that prophylaxis does not increase the rate of major bleeding.

HOW DO THE PROPHYLAXIS OPTIONS STACK UP?

What the ACCP recommends

Current ACCP guidelines recommend the use of either LMWH or low-dose UFH (5,000 U subcutaneously two or three times daily) as a Grade 1A recommendation for VTE prophylaxis in patients with medical conditions and risk factors for VTE.⁹ This represents the guidelines' highest level of recommendation, ie, one that is based on randomized controlled trials (RCTs) without important limitations. In contrast, the 2006 International Consensus Statement, developed as a collaborative effort among expert bodies on VTE, specified a more narrow dosing recommendation for UFH in this patient population (5,000 U three times daily, not twice daily) as well as specifying 40 mg once daily as the recommended dose of enoxaparin and 5,000 IU once daily as the recommended dose of dalteparin.¹¹

For medical patients with risk factors for VTE who have a contraindication to anticoagulant prophylaxis, the ACCP guidelines recommend the use of graduated compression stockings or intermittent pneumatic compression devices as a Grade 1C+ recommendation ("no RCTs but strong RCT results can be unequivocally extrapolated, or overwhelming evidence from observational studies").

Current ACCP guidelines do not address the use of fondaparinux in their recommendations for VTE prophylaxis in medical patients.

Getting a handle on bleeding risk

Patient characteristics that exclude pharmacologic thromboprophylaxis due to bleeding risk are generally limited to active bleeding or coagulopathy, as demonstrated by a platelet count less than 50,000 cells/ μ L or an international normalized ratio greater than 1.5. Additionally, bleeding risk should be carefully assessed if an invasive procedure is planned during a patient's hospital stay.

It is worth noting that the anticoagulant doses used for VTE prophylaxis are a fraction of those used for treatment of VTE. Thus, if a patient would be treated with full-dose anticoagulation if VTE developed, then that patient should be eligible for VTE prophylaxis.

Because the use of mechanical forms of prophylaxis in medical patients is not truly evidence-based, mechanical prophylaxis should be reserved for medical patients who have a contraindication to anticoagulants, or for use in combination with anticoagulants in patients at very high risk of VTE.

UFH vs LMWH

Two meta-analyses have compared UFH with LMWH for VTE prevention in medical patients.^{12,13} In a recent analysis that included 10 trials directly comparing the two therapies, 14 trials comparing UFH with control, and 11 trials comparing LMWH with control, Wein et al found a lower risk of DVT with LMWH than with UFH (relative risk, 0.68 [95% CI, 0.52 to 0.88]) but no difference between the therapies in mortality or bleeding risk.¹² In an earlier and smaller analysis, Mismetti et al found no significant differences between UFH and LMWH in preventing DVT or death but did find a significant reduction in major bleeding episodes with LMWH versus three-times-daily UFH (52% relative reduction; $P = .049$).¹³

Randomized trials also reveal that enoxaparin 40 mg once daily is as efficacious as UFH 5,000 U three times daily for VTE prevention in medical patients.^{14,15} The above analysis by Wein et al¹² and an additional meta-analysis by King and colleagues¹⁶ found that three-times-daily dosing of UFH is more efficacious than twice-daily dosing of UFH, but at the expense of more bleeding, including major bleeding.

Economic considerations

Because of differences in drug acquisition costs between UFH and the LMWH agents, several economic evaluations have compared the use of these therapies for prophylaxis in medical patients at risk of VTE.

In an analysis of hospital costs for medical patients receiving VTE prophylaxis from more than 330 US hospitals for the period 2001–2004, Burleigh et al found that mean total hospital costs were higher for patients who received UFH than for those who received LMWH (\$7,615 vs \$6,866) even though mean drug costs were higher for LMWH (\$791 vs \$569 for UFH).¹⁷ A reduction in hospital length of stay appeared to contribute to the overall savings with LMWH; other contributors may have included costs associated with heparin-induced thrombocytopenia (HIT) in UFH recipients or the extra nursing time required for administering UFH in two or three daily doses.

Leykum et al used a decision analysis model to estimate the economic effect of substituting enoxaparin for UFH in hospitalized medical patients for whom VTE prophylaxis is indicated.¹⁸ Cost data were based on Medicare reimbursement rates as well as drug and laboratory costs for a multi-institutional health system. The model assumed HIT incidence rates of 2.7% with UFH and 0.3% with enoxaparin. It also assumed the cost of a daily dose to be \$4 for UFH versus \$84 for enoxaparin. From the payer perspective, the model showed that substituting enoxaparin for UFH would reduce the overall cost of care by \$28.61 per day on a per-patient basis, despite enoxaparin's higher acquisition cost, and would save \$4,550 per quality-adjusted life-year by reducing the incidence of HIT.

Another cost analysis confirms the association between HIT and increased hospital costs. Creekmore et al retrospectively analyzed data from 10,121 adult medical patients who received VTE prophylaxis at the University of Utah Hospital in Salt Lake City from August 2000 to November 2004.¹⁹ They found that an admission during which HIT developed incurred a mean cost of \$56,364, compared with \$15,231 for an admission without HIT. Because LMWH was associated with a lower incidence of HIT compared with UFH (0.084% vs 0.51%, respectively), LMWH reduced the incremental cost of VTE prophylaxis by \$13.88 per patient compared with UFH.

■ THE EXCLAIM TRIAL: IS THERE A ROLE FOR EXTENDED PROPHYLAXIS?

Although the previously discussed studies have clearly demonstrated the benefit of in-hospital VTE prophylaxis for acutely ill medical patients, none has rigorously examined extended-duration out-of-hospital prophylaxis in these patients. This represents an important gap in the literature, since a substantial

TABLE 1**Primary efficacy outcomes in EXCLAIM trial at end of extended-duration prophylaxis period²¹**

	Incidence		Relative reduction	P for difference
	Placebo	Enoxa-parin		
Overall VTE events	4.9%	2.8%	44%	.0011
Asymptomatic proximal DVT	3.7%	2.5%	34%	.0319
Symptomatic VTE	1.1%	0.3%	73%	.0044
PE	0.2%	0%	—	NS
Fatal PE	0.1%	0%	—	NS

VTE = venous thromboembolism; DVT = deep vein thrombosis;
PE = pulmonary embolism; NS = not significant

proportion of VTE develops in the outpatient setting within 3 months of a hospitalization, and most outpatient VTE episodes occur within 1 month of a preceding hospitalization.²⁰

To begin to fill this gap, the Extended Clinical Prophylaxis in Acutely Ill Medical Patients (EXCLAIM) trial was conducted to compare extended-duration LMWH prophylaxis with a standard LMWH prophylaxis regimen in acutely ill medical patients using a prospective, multicenter, randomized, double-blind, placebo-controlled design.²¹

Patients and study design

Patients were eligible for enrollment if they were aged 40 years or older and had recent immobilization (≤ 3 days), a predefined acute medical illness, and either level 1 mobility (total bed rest or sedentary state) or level 2 mobility (level 1 with bathroom privileges). The predefined acute medical illnesses consisted of New York Heart Association class III/IV heart failure, acute respiratory insufficiency, or other acute medical conditions, including post-acute ischemic stroke, acute infection without septic shock, and active cancer.

All patients received open-label enoxaparin 40 mg subcutaneously once daily for 10 ± 4 days, after which they were randomized to either enoxaparin 40 mg subcutaneously once daily or placebo for an additional 28 ± 4 days.

The primary efficacy end point was the incidence of VTE events, defined as asymptomatic DVT documented by mandatory ultrasonography at the end of

the double-blind treatment period (28 ± 4 days) or as symptomatic DVT, symptomatic PE, or fatal PE at any time during the double-blind period. Symptomatic DVT was confirmed by objective tests; PE was confirmed by ventilation-perfusion scan, computed tomography, angiography, or autopsy.

Secondary efficacy end points were mortality at the end of the double-blind period, at 3 months, and at 6 months, as well as the incidence of VTE at 3 months.

The primary safety outcome measure was the incidence of major hemorrhage during the double-blind period; secondary safety measures were rates of major and minor hemorrhage, minor hemorrhage, HIT, and serious adverse events.

Population amended at planned interim analysis

After approximately half of the patients were enrolled, a planned and blinded interim analysis for futility concluded that the study was unlikely to show a statistically significant advantage of enoxaparin over placebo. The trial's steering committee followed the suggestion of its data safety monitoring board to redefine the inclusion criteria to refocus enrollment on patients with a high risk of VTE. A blinded analysis was performed to identify this subgroup.

The resulting amended inclusion criteria were the same as above except that level 2 mobility had to be accompanied by at least one of three additional high-risk criteria: (1) age greater than 75 years, (2) history of prior VTE, or (3) diagnosis of cancer.

The trial's main exclusion criteria were evidence of active bleeding, a contraindication to anticoagulation, receipt of prophylactic LMWH or UFH more than 72 hours prior to enrollment, treatment with an oral anti-coagulant within 72 hours of enrollment, major surgery within the prior 3 months, cerebral stroke with bleeding, and persistent renal failure (creatinine clearance < 30 mL/min).

Results

The amended study population included 5,105 patients, 5,049 of whom received open-label enoxaparin. Of this group, 2,013 were randomized to active extended prophylaxis with enoxaparin and 2,027 to placebo. Baseline characteristics, including level of mobility, were similar between the two groups.

Efficacy. As detailed in Table 1, VTE events occurred at a statistically significantly higher rate in the placebo arm than in the extended-duration enoxaparin arm, as did asymptomatic proximal DVT and symptomatic VTE. Rates of PE and fatal PE were also lower with enoxaparin than with placebo, but the number of events was so small that the between-

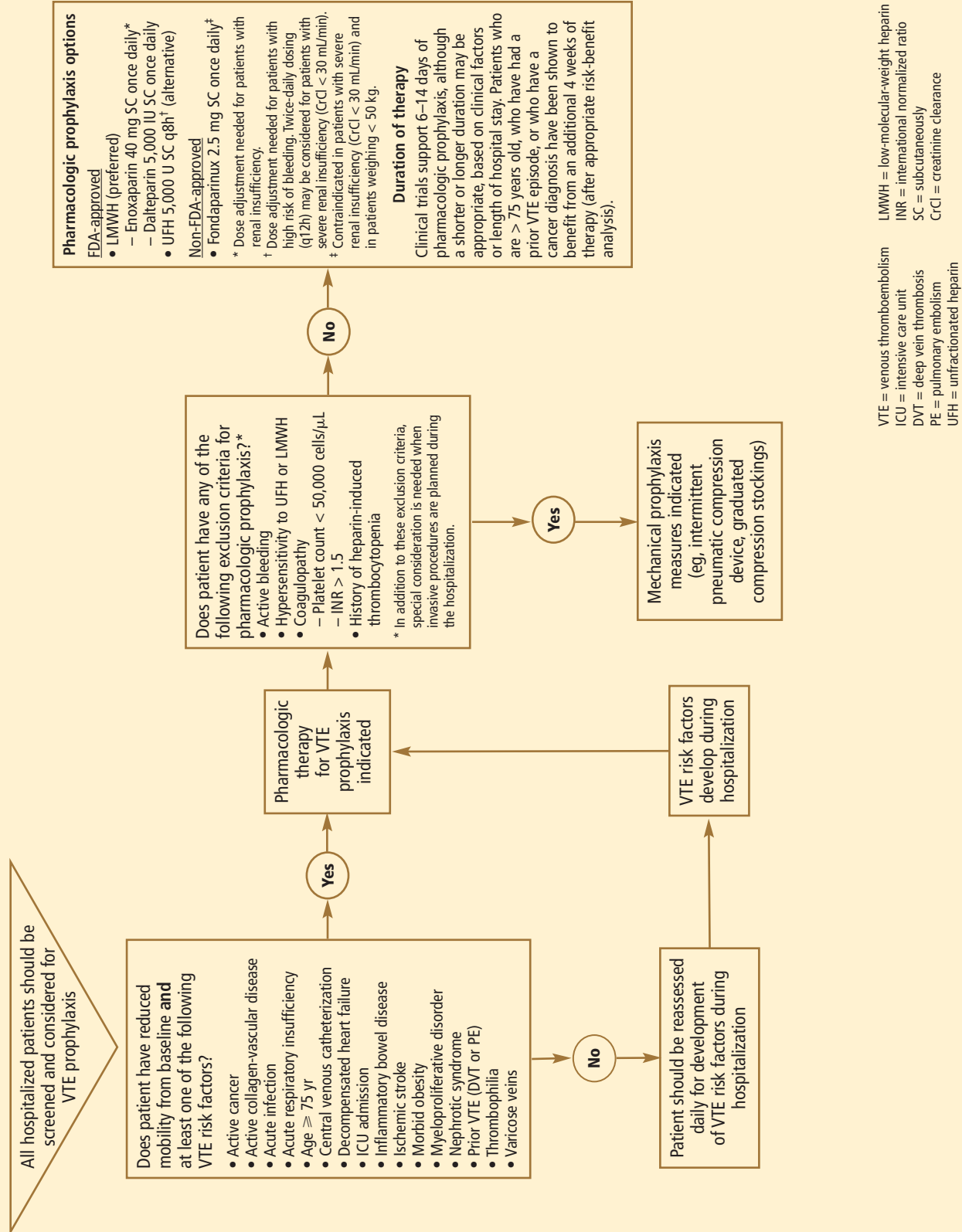


FIGURE 2. Algorithm for VTE prophylaxis in the hospitalized medical patient.

Case study: A 76-year-old woman with sepsis and heart failure

A 76-year-old woman is admitted and treated in the hospital for sepsis from a urinary source. She is sedentary while in the hospital but has no known risk factors for bleeding.

Her medical history consists of congestive heart failure (ejection fraction of 20% based on an echocardiogram obtained 1 month ago). She has no surgical history.

Her medications prior to admission were furosemide 20 mg twice daily, benazepril 40 mg/day, and carvedilol 12.5 mg/day. She has no known allergies. She reports no history of tobacco, alcohol, or illicit drug use.

Her laboratory values, which include platelets, hemoglobin, hematocrit, and creatinine, are all within the normal range except for an elevated white blood cell count of 15 on admission, which improves to normal over the course of her hospital stay.

She recovers well after 4-day treatment for urinary sepsis and heart failure with appropriate antibiotics and properly titrated fluids. She is ready for safe discharge on the fifth day of hospitalization but is still not at her baseline level of activity.

■ IS THIS PATIENT AT RISK FOR VTE?

Risk-factor assessment reveals that this patient has four risk factors for VTE:

- **Age greater than 75 years.** Older age, even on its own, is a significant risk factor for VTE. After the second decade of life, the risk of VTE increases exponentially in both men and women.²⁵

- **History of congestive heart failure (CHF).** In a retrospective case-control study, an ejection fraction less than 20% was associated with an odds ratio for VTE of 38.3.²⁶

- **Infectious etiology for her hospitalization (sepsis from urinary source).** In the first 2 weeks following an acute urinary tract infection, the risk of DVT is doubled.²⁷

- **Sedentary state in the hospital and at discharge.** In the MEDENOX trial, immobilized patients who received no prophylaxis (placebo) had a VTE incidence rate of 20.3%.²⁸

The presence of multiple VTE risk factors in hospitalized patients is becoming the norm. The risk for VTE increases as the number of risk factors increases, such

that nearly all hospitalized patients with five or more risk factors will have the potential to develop DVT if adequate prophylaxis is not used.²⁹

Without prophylaxis, the incidence of VTE in subjects enrolled in the MEDENOX trial who had the individual risk factors seen in this patient ranged from 14.6% (for acute heart failure) to 15.5% (for acute infectious disease) to 18.4% (for age > 75 years) to 20.3% (for immobility).²⁸ Therefore, this patient has, at minimum, a 15% to 20% likelihood of developing VTE without prophylaxis, based on any single risk factor, and most likely a much higher risk given her multiple risk factors.

■ WHAT IS THE APPROPRIATE PROPHYLAXIS?

The FDA-approved options for prevention of VTE in this setting are LMWH, UFH, and mechanical devices. As noted in the main text, current ACCP guidelines give preference to LMWH and low-dose UFH for VTE prophylaxis in medical patients; for patients with a contraindication to anticoagulants (see Figure 2), graduated compression stockings or intermittent pneumatic compression devices are recommended.⁹

Our patient has CHF and an infectious etiology for her hospital admission. In the MEDENOX trial, prophylaxis with LMWH significantly reduced the 14-day incidence of VTE compared with placebo in patients with acute heart failure ($P = .02$) or acute infectious disease ($P = .01$).^{1,28} The risk of major bleeding with pharmacologic prophylaxis in medical patients is minimal, according to the meta-analysis of Dentali et al.¹⁰ Our patient, therefore, seems likely to benefit from pharmacologic prophylaxis given that she has no known contraindications.

Choice of anticoagulant

In choosing between LMWH and UFH, the efficacy of each in preventing DVT and the risks of bleeding and development of HIT must be considered.

As reviewed in the main text, two meta-analyses comparing UFH and LMWH for prophylaxis in medical

group differences were not statistically significant.

The efficacy of extended prophylaxis with enoxaparin was enduring, as the cumulative incidence of VTE events at day 90 was significantly lower in enoxaparin recipients than in placebo recipients (3.0% vs 5.2%; relative reduction of 42%; $P = .0115$).

There was no difference in all-cause mortality at 6 months between the enoxaparin and placebo groups (10.1% vs 8.9%, respectively; $P = .179$).

Safety. Major hemorrhage was significantly more frequent in the enoxaparin arm, occurring in 0.60% of

enoxaparin recipients compared with 0.15% of placebo recipients ($P = .019$). Minor bleeding was also more common with enoxaparin (5.20% vs 3.70%; $P = .024$).

Conclusions

The EXCLAIM trial found that an extended-duration (38-day) enoxaparin regimen significantly reduced the overall incidence of VTE relative to a 10-day enoxaparin regimen in acutely ill medical patients with reduced mobility. At the same time, the extended regimen was associated with a significant increase in the

patients yielded results favorable to LMWH: Wein et al found significantly lower rates of DVT with LMWH but no difference in bleeding risk,¹² and Mismetti et al found a nonsignificant reduction in DVT rates but a significantly lower risk of bleeding with LMWH.¹³ Neither analysis found differences in mortality between UFH and LMWH.

The outcomes of HIT are significant. Among patients who receive treatment for HIT, new thrombosis occurs in 10% to 20%, amputation is necessary in 5% to 15%, and death occurs in 10% to 20%.³⁰ Few studies have evaluated rates of HIT with thromboprophylaxis in medical patients, but a meta-analysis evaluating HIT rates in 15 clinical trials directly comparing LMWH with UFH for thromboprophylaxis, mostly in surgical patients, found that the incidence of HIT was more than 10 times higher with UFH than with LMWH (2.6% vs 0.2%).³¹

Thus, this 76-year-old woman with four risk factors for VTE and no contraindications to anticoagulants should receive prophylaxis with either LMWH or three-times-daily low-dose UFH. LMWH is preferred, given its association with lower rates of DVT in the meta-analysis by Wein et al,¹² its association with lower bleeding risk in the meta-analysis by Mismetti et al,¹³ its lower incidence of HIT, and its once-daily dosing.

■ IS EXTENDED PROPHYLAXIS INDICATED?

Should this patient be offered out-of-hospital extended prophylaxis? If so, for how many days?

In the EXCLAIM trial, which evaluated 28 days of extended prophylaxis following discharge, 1-month rates of VTE, proximal DVT, and symptomatic VTE were 44% lower, 34% lower, and 73% lower, respectively, in patients who received extended prophylaxis with LMWH relative to those who did not.²¹ When the EXCLAIM results were analyzed by patients' primary diagnosis at study entry, extended prophylaxis was associated with a 36% relative reduction in the risk of VTE among patients with a primary diagnosis of heart failure and a 34% relative reduction among patients with acute infectious disease as a primary diagnosis.

The EXCLAIM investigators concluded that the num-

ber needed to treat with extended prophylaxis to prevent one VTE event is much smaller than the number needed to harm in terms of major bleeding (46 vs 224). This, together with the fact that age greater than 75 years was one of the trial's amended entry criteria, supports consideration of 28 days of extended prophylaxis in our patient.

■ OTHER CONSIDERATIONS

What if the patient had renal insufficiency or were on dialysis?

Sanderink et al assessed antifactor Xa levels and anti-Xa clearance in a study of healthy volunteers and patients with mild, moderate, or severe renal impairment given enoxaparin 40 mg once daily for 4 days.³² On day 4, anti-Xa clearance was 39% lower in patients with severe renal impairment (creatinine clearance $\leq$ 30 mL/min) than in healthy controls ($P = .0001$), but anti-Xa exposure was not significantly different between controls and patients with mild or moderate renal impairment. The authors recommended a decrease in enoxaparin dosage to 30 mg/day in patients with creatinine clearance of 30 mL/min or less but no dosage adjustment in those with mild or moderate renal impairment, as reflected in enoxaparin labeling. In contrast, no adjustment in the dosage of dalteparin appears to be necessary in patients with severe renal insufficiency.³³

In the case of dialysis patients, there are no studies to support using LMWH for pharmacologic prophylaxis. Because the risk of HIT is extremely low in patients on dialysis, especially compared with orthopedic surgery patients, expert consensus generally favors using UFH for VTE prophylaxis in patients on dialysis.

What if the patient weighed more than 100 kg?

Data are sparse in the obese medically ill population, but in a series of patients undergoing bariatric surgery, VTE prophylaxis with 40 mg of enoxaparin twice daily was associated with significant reductions in length of hospital stay, operating room time, and rates of postoperative VTE compared with 30 mg of enoxaparin twice daily, without any increase in bleeding complications.³⁴

rate of major bleeding, although the incidence of major bleeding was low. The investigators concluded that the net clinical effect of extended-duration prophylaxis with enoxaparin is favorable, as only 46 patients would need to be treated to prevent one VTE event, whereas 224 patients would need to be treated to result in one major bleeding event.²¹

For this reason, it is reasonable to consider extended prophylaxis for hospitalized medical patients after identifying these patients' risk factors. In keeping with the trial's amended inclusion criteria, patients older than

age 75 and those with cancer or prior VTE should receive special consideration for extended prophylaxis.

■ RECOMMENDED APPROACH TO VTE PREVENTION IN HOSPITALIZED MEDICAL PATIENTS

Given the wide gap between the evidence reviewed above and current practice worldwide,^{8,22,23} we propose the algorithm presented in **Figure 2** for the prevention of VTE in hospitalized medical patients. Our recommended approach is guided by the principles below:

- All hospitalized medical patients should be

screened at the time of admission, and patients at risk for VTE should receive prophylaxis.

- All patients with reduced mobility and one or more other risk factors for VTE are candidates for prophylaxis.
- Patients should be reassessed daily for the development of VTE risk factors during their hospitalization if risk factors are absent on admission.
- If screening or reassessment reveals any VTE risk factors, pharmacologic prophylaxis is the mainstay of therapy. If exclusion criteria for pharmacologic prophylaxis are present, mechanical prophylaxis with graduated compression stockings and intermittent compression devices should be used. For very high-risk medical patients without a contraindication to anticoagulants, combination prophylaxis with both an anticoagulant and mechanical devices is preferred.
- In this patient population, LMWH agents are preferred as pharmacologic prophylaxis over UFH and over fondaparinux (which is not currently approved by the US Food and Drug Administration for this population).
- If UFH is to be used in this patient population, 5,000 U *three times daily* is the preferred dosage.
- Extended pharmacologic prophylaxis should be considered in patients older than age 75 and in patients with a cancer diagnosis or a prior VTE episode.

■ DISCUSSION: ADDITIONAL PERSPECTIVES FROM THE AUTHORS

Dr. Jaffer: Dr. Spyropoulos, are there any guidelines, other than those from the ACCP, that speak to VTE prophylaxis in hospitalized medical patients? If so, what are their take-home messages and how do they differ from the ACCP guidelines?

Dr. Spyropoulos: I was part of the group that developed the International Consensus Statement (ICS) published in *International Angiology* in 2006,¹¹ which is more recent than the latest ACCP guidelines, which were published in 2004. The ICS drew on much of the same data that the ACCP did, but we did an updated review of clinical trials.

For VTE prophylaxis in hospitalized medical patients, the ICS recommendations are more specific with regard to the type, dose, and dosing frequency of anticoagulant agents. First, they specify doses for both LMWH agents in this patient setting: 40 mg once daily for enoxaparin, and 5,000 IU once daily for dalteparin.

The ICS document also states that if UFH is the choice for prophylaxis, a regimen of 5,000 U three times daily should be considered. In the past year alone, two analyses suggest that three-times-daily dos-

ing of UFH in medical patients provides superior efficacy to twice-daily dosing, although perhaps at the expense of more bleeding episodes.^{12,16} It is important to remember that no large placebo-controlled trial supports the efficacy of a UFH regimen of 5,000 U twice daily in this population.

Finally, the ICS document states that fondaparinux 2.5 mg once daily is a viable option for prophylaxis in medical patients, based on the ARTEMIS trial,³ even though this represents an off-label use.

Dr. Jaffer: Real-world use of VTE prophylaxis is far from optimal, especially in medical patients, and this is partly a result of system-of-care issues. I'd like to conclude by asking each of my colleagues to offer your perspectives on how your own institutions have improved their systems of care to promote better use of VTE prophylaxis and what lessons might be shared with others. Dr. McKean, you work at Brigham and Women's Hospital, which recently reported impressive results with an electronic alert system designed to increase clinicians' consideration of VTE risk assessment and use of prophylaxis.²⁴ Please tell us about that study and the alert system.

Dr. McKean: Despite many educational initiatives at Brigham and Women's Hospital, there were still some patients at high risk for VTE who were not receiving appropriate prophylaxis. What Dr. Samuel Goldhaber and his colleagues wanted to determine was whether changing the system of care could result in a reduced incidence of VTE.²⁴ They devised a computer software program linked to the patient database that used eight common risk factors to determine each hospitalized patient's risk profile for VTE. Each risk factor was weighted according to a point scale, with major risk factors (cancer, prior VTE, or hypercoagulability) assigned 3 points, the intermediate risk factor of surgery assigned 2 points, and minor risk factors (advanced age, obesity, immobility, or use of hormone replacement therapy or oral contraceptives) assigned 1 point. For patients with a total risk score of 4 or greater, the computer screen generates a color-coded VTE risk alert that requires the physician to acknowledge the alert and choose one of three options: order prophylaxis as appropriate, review a 60-page document on the computer to learn more about prophylaxis, or do nothing.

The study found that hospitalized patients who were randomized to treatment under the computer alert system were significantly more likely to receive VTE prophylaxis and significantly less likely to develop VTE than were patients randomized to a control group. The alert system reduced the risk of DVT or

PE at 90 days by 41% in patients considered to be at high risk. It was particularly interesting that the incidence of VTE was lower in the intervention group even when physicians chose not to use prophylaxis, which suggests that simply having this alert system in place improved outcomes, perhaps by raising awareness of the risk of VTE.²⁴

Additional studies are needed to better understand physicians' behavior and determine why they seem to have a disproportionate fear of the risk of bleeding relative to the risk of clotting, including fatal PE, because that is really the heart of the matter. When patients are not given prophylaxis, often it is because of fear of bleeding. It is not clear, however, why some of these patients did not receive mechanical devices as an alternative form of prophylaxis, but this seems to be the case worldwide, as shown recently by the multinational ENDORSE study.²² Meanwhile, as we await studies to better understand physician perceptions and behaviors regarding prophylaxis, we need to work hard to change the system of care.

Dr. Deitelzweig: Over the past couple of years, the Ochsner Clinic has grown from a one-hospital teaching organization to a seven-hospital system with a mix of closed and open medical staff. The challenge is how to take a process that worked well in the one center, where appropriate prophylaxis was used about 90% of the time, and transfer it to the other centers in the larger system. We have endorsed several types of performance tools, such as the change-acceleration processes used by General Electric. The aim is to share a vision of heightening awareness. To do that, we have worked to mobilize the key stakeholders, at least half of them, to build algorithms that they all will endorse. It is easier said than done, however, and we have found it essential to involve both physicians and non-physician colleagues from pharmacy and nursing who have political and organizational clout.

Dr. Brotman: At Johns Hopkins, I took a bit more draconian approach to this issue because I thought that hospitalists often knew that they should be using VTE prophylaxis but sometimes weren't, and I am not convinced that clinicians always look at prompts. So we came up with a system that incorporates both billing and documentation simultaneously. We put a hard stop on users' documentation so that they could not sign off on a note or bill for their care until they checked off the kind of VTE prophylaxis they were using. Since hospitalists ultimately care about billing for their work, this system has at least ensured that everybody has considered and documented VTE prophylaxis on a daily basis.

There are other hard stops that can be implemented in computer order-entry systems as well, and we are considering ways to roll them out on a broader scale.

However, all of these systems can have problems because patient situations change from day to day. For instance, VTE prophylaxis is not necessarily indicated in a 38-year-old ambulatory patient who comes in with a sickle cell crisis, but you will need to reconsider if the patient ends up in acute chest syndrome in the intensive care unit. I do not yet have a good way to ensure that this is being done on a daily basis with all patients.

Dr. Amin: At the University of California, Irvine, we implemented an electronic alert system, but we locked users in so that they could not complete their admission orders until they answered questions about VTE prevention. This practice increased our VTE prophylaxis rates tremendously. Because we are a level I trauma center, we allow users to bypass the screens one time, but the next time they log in, even to get a simple lab result, they have to answer the questions about VTE prevention.

With any system you develop, you also have to continue with the education process, because clinicians sometimes get into bad habits or simply forget things.

Dr. Spyropoulos: At Lovelace Medical Center, we didn't have the sophistication of an electronic order-entry system, but we had an experienced clinical pharmacist (the director of inpatient pharmacy) who helped to develop and champion VTE prevention guidelines that have then been used throughout the system in close conjunction with our hospitalists' rounds. This system has been used successfully for the past 7 years.

AUTHOR DISCLOSURES

Dr. Jaffer reported that he has received consulting fees and honoraria for teaching/speaking from Sanofi-Aventis, consulting fees and research grant support from AstraZeneca, and consulting fees from Roche Diagnostics and Boehringer Ingelheim; he also serves on the governing board of the Society for Perioperative Assessment and Quality Improvement (SPAQI) and the board of directors of the Anticoagulation Forum. **Dr. Amin** reported that he has received research funding and honoraria for speaking from Sanofi-Aventis, Eisai, and GlaxoSmithKline. **Dr. Brotman** reported that he has no financial relationships with commercial interests that are relevant to this article. **Drs. Deitelzweig and McKean** each reported that they have received honoraria for teaching/speaking from Sanofi-Aventis. **Dr. Spyropoulos** reported that he has received consulting fees from Sanofi-Aventis, Eisai, and Boehringer Ingelheim.

Each author received an honorarium for participating in the roundtable that formed the basis of this supplement. The honoraria were paid by the Cleveland Clinic Center for Continuing Education from the educational grant from Sanofi-Aventis underwriting this supplement. Sanofi-Aventis had no input on the content of the roundtable or this supplement.

REFERENCES

1. Samama MM, Cohen AT, Darmon JY, et al. A comparison of enoxaparin with placebo for the prevention of venous thrombo-

- embolism in acutely ill medical patients. Prophylaxis in Medical Patients with Enoxaparin Study Group. *N Engl J Med* 1999; 341:793–800.
2. Leizorovicz A, Cohen AT, Turpie AG, et al. Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. *Circulation* 2004; 110:874–879.
3. Cohen AT, Davidson BL, Gallus AS, et al. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. *BMJ* 2006; 332:325–329.
4. Baglin TP, White K, Charles A. Fatal pulmonary embolism in hospitalised medical patients. *J Clin Pathol* 1997; 50:609–610.
5. Piazza G, Seddighzadeh A, Goldhaber SZ. Double trouble for 2,609 hospitalized medical patients who developed deep vein thrombosis: prophylaxis omitted more often and pulmonary embolism more frequent. *Chest* 2007; 132:554–561.
6. Amin A, Stemkowski S, Lin J, Yang G. Thromboprophylaxis rates in US medical centers: success or failure? *J Thromb Haemost* 2007; 5:1610–1616.
7. Geerts WH, Heit JA, Clagett GP, et al. Prevention of venous thromboembolism. *Chest* 2001; 119(1 Suppl):132S–175S.
8. Tapson VF, Decousus H, Pini M, et al. Venous thromboembolism prophylaxis in acutely ill hospitalized medical patients: findings from the International Medical Prevention Registry on Venous Thromboembolism. *Chest* 2007; 132:936–945.
9. Geerts WH, Pineo GF, Heit JA, et al. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004; 126(3 Suppl):338S–400S.
10. Dentali F, Douketis JD, Gianni M, Lim W, Crowther MA. Meta-analysis: anticoagulant prophylaxis to prevent symptomatic venous thromboembolism in hospitalized medical patients. *Ann Intern Med* 2007; 146:278–288.
11. Cardiovascular Disease Educational and Research Trust; Cyprus Cardiovascular Disease Educational and Research Trust; European Venous Forum; International Surgical Thrombosis Forum; International Union of Angiology; Union Internationale de Phlébologie. Prevention and treatment of venous thromboembolism. International Consensus Statement (guidelines according to scientific evidence). *Int Angiol* 2006; 25:101–161.
12. Wein L, Wein S, Haas SJ, Shaw J, Krum H. Pharmacological venous thromboembolism prophylaxis in hospitalized medical patients: a meta-analysis of randomized controlled trials. *Arch Intern Med* 2007; 167:1476–1486.
13. Mismetti P, Laporte-Simitsidis S, Tardy B, et al. Prevention of venous thromboembolism in internal medicine with unfractionated or low-molecular-weight heparins: a meta-analysis of randomised clinical trials. *Thromb Haemost* 2000; 83:14–19.
14. Lechler E, Schramm W, Flosbach CW. The venous thrombotic risk in non-surgical patients: epidemiological data and efficacy/safety profile of a low-molecular-weight heparin (enoxaparin). The Prime Study Group. *Haemostasis* 1996; 26(Suppl 2):49–56.
15. Kleber FX, Witt C, Vogel G, et al; the PRINCE Study Group. Randomized comparison of enoxaparin with unfractionated heparin for the prevention of venous thromboembolism in medical patients with heart failure or severe respiratory disease. *Am Heart J* 2003; 145:614–621.
16. King CS, Holley AB, Jackson JL, Shorr AF, Moores LK. Twice vs three times daily heparin dosing for thromboembolism prophylaxis in the general medical population: a meta-analysis. *Chest* 2007; 131:507–516.
17. Burleigh E, Wang C, Foster D, et al. Thromboprophylaxis in medically ill patients at risk for venous thromboembolism. *Am J Health Syst Pharm* 2006; 63(20 Suppl 6):S23–S29.
18. Leykum L, Pugh J, Diuguid D, Papadopoulos K. Cost utility of substituting enoxaparin for unfractionated heparin for prophylaxis of venous thrombosis in the hospitalized medical patient. *J Hosp Med* 2006; 1:168–176.
19. Creekmore FM, Oderda GM, Pendleton RC, Brixner DI. Incidence and economic implications of heparin-induced thrombocytopenia in medical patients receiving prophylaxis for venous thromboembolism. *Pharmacotherapy* 2006; 26:1438–1445.
20. Spencer FA, Lessard D, Emery C, Reed G, Goldberg RJ. Venous thromboembolism in the outpatient setting. *Arch Intern Med* 2007; 167:1471–1475.
21. Hull RD, Schellong SM, Tapson VF, et al. Extended-duration venous thromboembolism (VTE) prophylaxis in acutely ill medical patients with recent reduced mobility: the EXCLAIM study. Presentation at: International Society on Thrombosis and Haemostasis XXIst Congress; July 6–12, 2007; Geneva, Switzerland.
22. Cohen AT, Tapson VF, Bergmann JF, et al. Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): a multinational cross-sectional study. *Lancet* 2008; 371:387–394.
23. Kahn SR, Panju A, Geerts W, et al; CURVE study investigators. Multicenter evaluation of the use of venous thromboembolism prophylaxis in acutely ill medical patients in Canada. *Thromb Res* 2007; 119:145–155.
24. Kucher N, Koo S, Quiroz R, et al. Electronic alerts to prevent thromboembolism among hospitalized patients. *N Engl J Med* 2005; 352:969–977.
25. Anderson FA Jr, Wheeler HB, Goldberg RJ, et al. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. *Arch Intern Med* 1991; 151:933–938.
26. Howell MD, Geraci JM, Knowlton AA. Congestive heart failure and outpatient risk of venous thromboembolism: a retrospective, case-control study. *J Clin Epidemiol* 2001; 54:810–816.
27. Smeeth L, Cook C, Thomas S, Hall AJ, Hubbard R, Vallance P. Risk of deep vein thrombosis and pulmonary embolism after acute infection in a community setting. *Lancet* 2006; 367:1075–1079.
28. Alikhan R, Cohen AT, Combe S, et al. Prevention of venous thromboembolism in medical patients with enoxaparin: a subgroup analysis of the MEDENOX study. *Blood Coagul Fibrinolysis* 2003; 14:341–346.
29. Anderson FA Jr, Spencer FA. Risk factors for venous thromboembolism. *Circulation* 2003; 107(23 Suppl 1):I9–I16.
30. Greinacher A, Warkentin TE. Recognition, treatment, and prevention of heparin-induced thrombocytopenia: review and update. *Thromb Res* 2006; 118:165–176.
31. Martel N, Lee J, Wells PS. Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: a meta-analysis. *Blood* 2005; 106:2710–2715.
32. Sanderink GJ, Guimart CG, Ozoux ML, Jariwala NU, Shukla UA, Boutouyrie BX. Pharmacokinetics and pharmacodynamics of the prophylactic dose of enoxaparin once daily over 4 days in patients with renal impairment. *Thromb Res* 2002; 105:225–231.
33. Douketis J, Cook D, Zytaruk N, et al. Dalteparin thromboprophylaxis in critically ill patients with severe renal insufficiency: the DIRECT study [abstract]. *J Thromb Haemost* 2007; 5(Suppl 2):P-S-680.
34. Scholten DJ, Hoedema RM, Scholten SE. A comparison of two different prophylactic dose regimens of low molecular weight heparin in bariatric surgery. *Obes Surg* 2002; 12:19–24.

Correspondence: Amir K. Jaffer, MD, Chief, Division of Hospital Medicine, Leonard M. Miller School of Medicine, University of Miami, 1120 NW 14th Street, 933 CRB (C216), Miami, FL 33136; ajaffer@med.miami.edu.