Prevention of Venous Thromboembolism in Hospitalized Medical Patients

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Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), remains a common cause of morbidity and mortality in hospitalized medical patients. Without anticoagulant prophylaxis, hospitalized medical patients develop VTE at a rate of 5% to 15%,[1–3] with the rate depending on the means of detecting the thrombus.[4] Although most DVTs are subclinical and resolve completely when mobility is restored, the morbidity of DVT can be extensive and may include valvular damage (leading to chronic venous insufficiency) and PE.[5–7] Additionally, one quarter of patients with PE die suddenly and two thirds die within the first 30 minutes of the acute event, before diagnosis and treatment can commence.[6,8] For these reasons, prophylaxis is more effective for reducing morbidity and mortality from VTE than treatment of the established event. Unfortunately, thromboprophylaxis is underutilized in hospitalized medical patients, despite strong evidence supporting its use in at-risk medical patients. This article provides an overview of the evidence supporting the effectiveness of pharmacologic prophylaxis for VTE in hospitalized medical patients, highlights the need for more widespread use of prophylactic measures, and reviews the approach to pharmacologic prophylaxis in medical patients.

TAKE HOME POINTS

- Although randomized controlled trials have shown that the incidence of venous thromboembolism (VTE) in hospitalized medical patients can be substantially decreased using safe and effective pharmacologic prophylaxis, up to 60% of at-risk medical patients do not receive prophylaxis.
- The agents that have been proven effective in medical patients are enoxaparin, dalteparin, unfractionated heparin, and fondaparinux.
- All patients admitted to the hospital should undergo VTE risk assessment on admission and be reassessed if their status changes.
- Pharmacologic VTE prophylaxis is recommended in patients admitted with congestive heart failure or severe respiratory disease, most intensive care unit patients, and patients confined to bed who have at least 1 additional risk factor for thromboembolism (eg, cancer, sepsis).
- Pharmacologic VTE prophylaxis does not cause an increase in major bleeding events.

VTE RISK AND PROPHYLAXIS IN MEDICAL PATIENTS

Prophylaxis for VTE is underutilized in acutely-ill hospitalized medical patients.[9,10] A recent prospective study that used a registry of 5451 patients with DVT confirmed by ultrasonography from US hospitals showed that medical patients were 43% more likely to experience PE than their nonmedical counterparts and 47% less likely to receive VTE prophylaxis.[11] Similarly, the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) study showed that of 15,000 international medical patients, only 60% of those eligible for prophylaxis by current guidelines received it (**Table 1**).[10] Finally, the recently published ENDORSE study provided a broad overview of VTE risk and prophylaxis practices throughout the world.[12] Involving 60,000 patients from over 30 countries, the main objectives of ENDORSE were to assess the prevalence of VTE risk in the acute hospital care setting and to determine the proportion of at-risk patients who received the recommended prophylaxis using the American College of Chest Physician (ACCP) evidence-based consensus guidelines.[13] There were 2 categories of hospitalized patients in this study: medical patients aged 40 years and older and surgical patients aged 18 years and older. In this study, 52% of hospitalized patients surveyed were at risk for VTE (64% of surgical patients

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Table 1. Summary of Studies of Venous Thromboembolism Prevention in Hospitalized Medical Patients

Study (Year)	Design	Result/Conclusion
IMPROVE[10] (2007)	Ongoing observational study	Only 60% of medical patients who met criteria for prophylaxis received it
ENDORSE[12] (2008)	Cross-sectional survey	Of 60,000 international at-risk medical inpatients, 60% did not receive VTE prophylaxis
PRIME[19] (1996)	Prospective, randomized trial	Enoxaparin was at least as efficacious as 3-times-daily UFH and was associated with fewer major bleeding events
MEDENOX[1] (1999)	Placebo-controlled trial	Enoxaparin decreased risk for VTE by 63% with no increase in major bleeding
THE-PRINCE[20] (2003)	Prospective, randomized trial	LMWH was at least as efficacious as UFH in heart failure and severe respiratory disease with fewer adverse events
PREVENT[2] (2004)	Placebo-controlled trial	Dalteparin decreased risk for VTE and sudden death by 45% with no increase in major bleeding
ARTEMIS[3] (2006)	Placebo-controlled trial	Fondaparinux decreased risk for VTE by 47% with no increase in major bleeding
PREVAIL[24] (2007)	Prospective, randomized trial	Enoxaparin reduced risk of VTE by 43% compared with twice-daily UFH in patients with acute ischemic stroke with no difference in clinically significant bleeding
EXCLAIM[27] (forthcoming)	Prospective, randomized trial	Extended duration (1 mo) of prophylaxis after discharge was associated with significantly fewer VTE events

LMWH = low-molecular-weight heparin; UFH = unfractionated heparin; VTE = venous thromboembolism.

and 42% of medical patients). Despite the high prevalence of risk, only 50% of hospitalized patients at risk for VTE received a method of prophylaxis recommended by the ACCP, corresponding to 59% of surgical patients and 40% of medical patients. ENDORSE demonstrates that VTE remains a critical safety issue in the hospitalized patient, and this risk was noted in all countries surveyed.

RISK ASSESSMENT

All patients admitted to the hospital should undergo VTE risk assessment on admission and be reassessed if their status changes (eg, when transferred to another unit or following a surgical procedure).[14] A patient's risk for VTE is determined by the presence of factors that predispose to thrombosis. The 2008 ACCP guidelines for prevention of VTE recommend pharmacologic VTE prophylaxis in the following groups of medical patients: those admitted with congestive heart failure or severe respiratory disease, most intensive care unit patients, and those who are confined to bed with 1 or more of the following additional risk factors: active cancer, previous VTE, sepsis, acute neurologic disease, or inflammatory bowel disease.[15] Other notable risk factors for VTE include surgery, trauma, advanced age, paresis, presence of a central venous catheter, estrogen-containing oral contraceptives or hormone replacement therapy, erythropoiesis-stimulating agents, obesity, smoking, nephrotic syndrome, myeloproliferative syndromes, paroxysmal nocturnal hemoglobinuria, varicose veins, inherited or acquired thrombophilia, pregnancy, and the postpartum period.[15]

EVIDENCE FOR THROMBOPROPHYLAXIS

The surgical literature abounds with evidence that VTE prophylaxis decreases the rate of VTE and fatal and nonfatal PE.[16] The first large prospective, placebo-controlled study to show a significant decrease in fatal PE with pharmacologic prophylaxis involved general surgery patients and was published in 1975.[17] Recently, there have been 3 large prospective, double-blind, placebo-controlled trials of pharmacologic VTE prophylaxis in medical patients. Although these trials were not powered to detect differences in mortality, they did demonstrate statistically significant reductions in the incidence of VTE in patients treated with pharmacologic prophylaxis versus placebo.[1–3]

Low-Molecular-Weight Heparin

The Prophylaxis in Medical Patients with Enoxaparin (MEDENOX) study[1] and the Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized Patients Trial (PREVENT)[2] evaluated the efficacy of low-molecular-weight heparins (LMWH) for VTE prophylaxis in hospitalized medical patients. These 2 studies established LMWH as an effective strategy for reducing the rate of VTE in medical patients. MEDENOX compared 2 regimens of the LMWH enoxaparin (20 mg and 40 mg subcutaneously daily) with placebo in at-risk medical patients. A total of 1102 patients were enrolled in the study, and 45% of those enrolled had 2 or more reasons for admission; the most common diagnoses were acute respiratory failure, acute infectious disease, and New York Heart Association (NYHA) class III or IV heart failure. All patients were

older than age 40 years and 97% had at least 1 additional risk factor for VTE (eg, age > 75 yr, cancer, history of VTE, obesity, varicose veins, hormone therapy, chronic heart failure, and chronic respiratory failure). Exclusion criteria included a serum creatinine level greater than 1.7 mg/dL, HIV infection, recent anticoagulation, intubation, abnormal clotting times, and conditions predisposing to hemorrhage. The 40-mg enoxaparin group had a significantly lower rate of VTE than the placebo group (5.5% versus 14.9%; $P = 0.001$), with a 63% relative risk reduction. This reduction in VTE was maintained over the 3-month follow-up period. The group treated with enoxaparin 20 mg daily experienced no reduction in VTE incidence.[1]

PREVENT compared the LMWH dalteparin 5000 U once daily with placebo in 3706 acutely ill medical patients. These patients were all older than age 40 years, and the most common admitting diagnoses were NYHA class III or IV heart failure, acute infectious disease, and acute respiratory failure. The risk factors for VTE and inclusion criteria were similar to those used in MEDENOX. In PREVENT, the incidence of a composite endpoint of VTE and sudden death at day 21 was 2.7% in patients treated with subcutaneous dalteparin 5000 U once daily versus 4.96% in placebo patients, resulting in a 45% risk reduction.

It is important to note that the patient risk profiles in these 2 studies differed somewhat. Patients in MEDENOX were sicker than those in PREVENT, with the former study's placebo group having a higher 90-day mortality rate (13.9% versus 6.01%, respectively). Also, the treatment group in PREVENT was younger, with a mean age of 68.5 years versus 73.1 years for the MEDENOX treatment group. The PREVENT trial, therefore, demonstrated that VTE prophylaxis should be extended to a larger, lower-risk population of medical patients.[2] The risk reduction in PREVENT was lower than in MEDENOX, and it can be reasonably concluded that sicker patients gain a greater benefit from VTE prophylaxis with LMWH.

Fondaparinux

The third trial that evaluated thromboprophylaxis in medical patients, Arixtra for Thromboembolism Prevention in a Medical Indications Study (ARTEMIS),[3] compared fondaparinux (an activated factor Xa inhibitor) with placebo in 849 patients with acute medical illness (age > 60 yr). The mean age of the study patients was 75 years, and in the treatment group the most common diagnoses for admission were acute infectious or inflammatory disease, NYHA class III or IV heart failure, and acute respiratory disease. Risk factors included age greater than 75 years, history of VTE, and cancer, and exclusion criteria were similar to those used in MEDENOX and PREVENT. The treatment group received subcutaneous fondaparinux 2.5 mg once daily. In this study, the incidence of VTE was 5.9% in the treatment group and 10.5% in the placebo group, resulting in a 47% relative risk reduction for VTE.[3] Fondaparinux should be considered for VTE prophylaxis in nonobese medical patients whose creatinine clearance is greater than 30 mg/dL, especially those with a history of heparin-induced thrombocytopenia.[18]

While MEDENOX, PREVENT, and ARTEMIS were not powered to show a significant difference in mortality, trends toward decreased mortality were seen in MEDENOX and ARTEMIS.[1,3] Additionally, VTE is considered to be a good surrogate marker for fatal PE.[15] There were no significant differences in the rates of major bleeding between the treatment and placebo groups in these 3 trials.

Unfractionated Heparin Versus LMWH

Several studies have evaluated classic unfractionated heparin (UFH) versus newer LMWH for thromboprophylaxis in medical patients. Randomized trials[19,20] that compared UFH with LMWH as well as recent meta-analyses[21,22] have shown that LWMH is at least as efficacious as UFH in preventing VTE in hospitalized medical patients with no increase in major bleeding events. The Thromboembolism Prophylaxis in Internal Medicine with Enoxaparin (PRIME) study was a multicenter, randomized, double-blind trial involving high-risk groups of hospitalized medical patients; it showed that enoxaparin 40 mg was as efficacious (with fewer major bleeding events) as subcutaneous UFH 5000 U 3 times daily for VTE prevention.[19] Another multicenter randomized study (THromboEmbolism PRevention IN Cardiac or respiratory disease with Enoxaparin [THE-PRINCE]) showed that LMWH was at least as efficacious as UFH for prevention of VTE in patients with heart failure or severe respiratory disease, with no differences in major bleeding episodes.[20] A meta-analysis of randomized trials of UFH versus LMWH for VTE prophylaxis in medical patients showed a 52% reduction in major hemorrhage with LMWH as compared with UFH.[21] Finally, a 2007 meta-analysis on pharmacologic VTE prophylaxis in hospitalized medical patients showed that LMWH is more effective than UFH in preventing DVT, but there was no difference in risk of bleeding between the 2 agents.[22]

Two recent meta-analyses evaluated the efficacy and bleeding risk of 2 dosing regimens of UFH: 5000 U twice daily versus 5000 U 3 times daily. The meta-analysis by Wein et al[22] showed that the 3-times-daily regimen was

more effective in preventing DVT than twice daily dosing. This finding was supported by another 2007 meta-analysis, which showed that 3-times-daily dosing had better efficacy in preventing clinically relevant VTE events but caused significantly more major bleeding episodes.[23]

Prophylaxis in Acute Stroke Patients

Acute ischemic stroke is a particularly important risk factor for VTE in hospitalized patients, especially when a leg is paralyzed. The Prevention of VTE after Acute Ischemic Stroke with LMWH Enoxaparin (PREVAIL) study[24] evaluated the safety and efficacy of enoxaparin 40 mg once daily compared with UFH (twice daily) for VTE prevention after ischemic stroke. Twice-daily dosing was used for UFH because of concerns about increased intracranial hemorrhage in stroke patients treated with UFH 3 times daily. PREVAIL showed that once-daily enoxaparin conferred a 43% relative risk reduction for VTE as compared with UFH, and there was no difference in a composite endpoint of clinically important bleeding events between the 2 groups. The risk of symptomatic intracranial hemorrhage was low (1%) and was similar between the 2 study groups, notwithstanding the fact that 80% of patients were also treated with antiplatelet agents. The authors concluded that enoxaparin was preferable to UFH because of the convenience of once-daily dosing and a better benefit-to-risk ratio (number needed to treat to prevent 1 VTE = 13; number needed to harm to produce 1 clinically important bleeding event = 173).[24]

APPROACH TO PROPHYLAXIS

Pharmacologic Agents

Pharmacologic VTE prophylaxis can be given effectively with LMWH, UFH, or fondaparinux without a significant increase in the risk of major bleeding (**Table 2**). LMWH should be used cautiously in patients with renal insufficiency and avoided in those with end-stage renal disease. In terms of contraindications, patients were excluded from the large placebo-controlled trials if they had a platelet count less than 100,000 cells/μL, cerebral metastasis, recent hemorrhagic stroke, bacterial endocarditis, active peptic ulcer disease, and other conditions associated with hemorrhage. A meta-analysis from 2005 showed that the risk of heparin-induced thrombocytopenia for patients receiving enoxaparin for prophylaxis was 0.2% as compared with 2.6% for those receiving UFH.[25] Based on the available data, the ACCP concluded that low-dose UFH twice or 3 times daily, enoxaparin 40 mg subcutaneously once daily, dalteparin 5000 U daily, or fondaparinux 2.5 mg daily were efficacious in preventing VTE in hospitalized medical patients.[15] They found no compelling data to recommend twice-daily versus 3-times-daily UFH. The data showed greater efficacy with 3-times-daily dosing but a trend toward less bleeding with twice-daily dosing.[15]

Table 2. Pharmacologic Regimens for Prevention of Venous Thromboembolism in Medical Patients

Agent	Dose
Enoxaparin	40 mg subcutaneously once daily
Dalteparin	5000 U subcutaneously once daily
Unfractionated heparin	5000 U subcutaneously twice or 3 times daily
Fondaparinux	2.5 mg subcutaneously once daily

Nonpharmacologic Measures

No prospective randomized trials have confirmed the efficacy of sequential compression devices for VTE prophylaxis in medical patients. However, the efficacy of such measures has been shown in surgical patients, and they are a reasonable option for medical patients in whom anticoagulants are contraindicated.[15]

Duration of VTE Prophylaxis

The optimal length of time that pharmacologic VTE prophylaxis should be used is unknown. An original observational study by Spencer and colleagues[26] raised important points regarding the duration of VTE prophylaxis. In their study, outpatient VTE was 3 times more common than inpatient VTE, almost half of the outpatients with VTE had been hospitalized in the preceding 3 months, and less than half of the recently hospitalized patients had received VTE prophylaxis during their hospitalization. Half of the patients who developed VTE post-hospitalization had a length of stay of less than 4 days. Although outpatient VTE was 3 times as common as inpatient VTE, 36.8% of cases of outpatient VTE actually originated during a prior hospitalization, and only 42.8% of these patients received prophylaxis. These data suggest that VTE prophylaxis needs to be considered even when the anticipated length of hospital stay is brief and highlight the need for studies involving extended VTE prophylaxis following hospital discharge.[26]

The preliminary results of a study designed to investigate extended VTE prophylaxis in medical patients following hospital discharge (Extended Clinical Prophylaxis in Acutely Ill Medical Patients [EXCLAIM]) were presented in July 2007 at the Congress of the International Society of Thrombosis and Hemostasis. In this trial, more than 5000 hospitalized patients with varying levels of immobility received subcutaneous

enoxaparin 40 mg daily for an average of 10 days. The patients were then randomized to either placebo or continued enoxaparin for an additional 28 days.[27] Preliminary results indicated that a 44% reduction in VTE events can be achieved with 28 additional days of VTE prophylaxis with enoxaparin. There was a small but significant increase in minor bleeding complications. The reduction in risk of VTE extended to 90 days, and there was no difference in all-cause mortality between the study groups. This study, once subjected to peer review and published, could usher in a major change in current practice for prevention of VTE.

INCREASING AWARENESS

In light of the underuse of VTE prophylaxis in medical patients, hospitals should improve education of health care professionals to increase awareness of the problem and implement evidence-based protocols for preventing VTE in medical patients.[8] An approach to improving prophylaxis rates in medical patients was recently evaluated by investigators at the Brigham and Women's hospital.[28] They performed a randomized controlled study of 2506 hospitalized patients to evaluate a strategy of issuing electronic alerts to physicians whose patients were not receiving VTE prophylaxis.[28] The electronic alert group (n = 1255) had a 41% lower risk of DVT or PE at 90 days than the nonintervention group and a higher rate of orders for prophylaxis (33.5% versus 14.5%). Additionally, the computer alert system was effective in patients with a wide spectrum of risk factors, including advanced age, prior VTE, and cancer.

CONCLUSION

VTE is an issue that affects the majority of patients on the medical service. The Agency for Healthcare Research and Quality ranks prevention of VTE as the first priority out of 79 preventive initiatives that can improve patient safety in health care settings.[4] Hospital physicians can play an integral role in the prevention of morbidity and mortality from VTE by assessing risk and considering prophylaxis for each patient they admit. Effective VTE prophylaxis can be achieved with 1 of several pharmacologic regimens with a very low risk of adverse events. Hospitals should implement systems to remind physicians to use thromboprophylaxis, and when anticoagulants are contraindicated, mechanical prophylactic measures should be utilized. **HP**

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