

Prevention of venous thromboembolism in medical patients and outpatients

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Abstract | The majority of fatal cases of pulmonary embolism in hospitalized patients occur in acutely ill, medically treated patients. Current guidelines, based on a large number of prospective, randomized, controlled trials evaluating the safety and efficacy of pharmacologic venous thromboembolism (VTE) prophylaxis in medical patients, now recommend using VTE prophylaxis in this population. Unfortunately, prophylaxis rates in medical patients are unacceptably low, despite efforts to develop strategies for improving implementation of prophylaxis regimens. Studies indicate that a substantial proportion of patients with VTE present after hospital discharge, but no clinical trials evaluating VTE prophylaxis for medical outpatients have yet been published. In this Review, we examine the literature on VTE prophylaxis in hospitalized medical patients, and evaluate the available data for the outpatient setting.

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Learning objectives

Upon completion of this activity, participants should be able to:

- 1 Describe the use of venous thromboembolism (VTE) prophylaxis among medical inpatients.
- 2 List the clinical benefits associated with VTE prophylaxis.
- 3 Compare low-molecular-weight heparin and unfractionated heparin in VTE prophylaxis.
- 4 Describe the current recommendations for extended VTE prophylaxis.

Introduction

Data in the medical literature clearly demonstrate the benefit of prophylaxis for venous thromboembolism (VTE), and current guidelines recommend VTE

Competing interests

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prophylaxis for most hospitalized patients.¹ Despite this evidence, however, VTE prophylaxis is under-prescribed.^{2–5} Widespread failure to diagnose VTE, and to administer prophylaxis when necessary, means that this condition has become the most common cause of unexpected death in hospitalized patients, and one of the primary reasons for medical litigation.⁶

Although VTE has traditionally been considered a surgical condition, the vast majority of hospitalized patients with symptomatic VTE have not undergone recent surgery.^{7–9} Indeed, 70–80% of in-hospital fatal pulmonary embolisms (PEs) occur in nonsurgical patients.^{10,11} Data from the DVT FREE (the Prospective Registry of 5,451 Patients with Ultrasound-Confirmed Deep Vein Thrombosis) study³ have led to a paradigm shift in our knowledge of VTE. At least half of all patients who developed VTE in this study were outpatients, many of whom had been recently hospitalized.^{3,12} The trends in medical practice toward shorter hospital stays, and the availability of outpatient therapies, have made outpatient prophylaxis of acute VTE a necessity.

Since the late 1990s, there has been a dramatic increase in the number of studies—including randomized clinical trials, meta-analyses, large registries, and observational studies—on VTE prophylaxis in acutely ill, medically treated patients.^{13–26} In addition, studies have been designed to evaluate strategies for improving rates of VTE prophylaxis through education and clinical reminders.^{27–30} Placebo-controlled trials have shown that the incidence of objectively-confirmed, subclinical VTE in acutely ill, hospitalized medical patients ranges from 5% to 28% (Table 1), and can be reduced by between a half and two-thirds with appropriate VTE prophylaxis.^{13–17} Although VTE prophylaxis in hospitalized medical and surgical patients is generally recommended, two groups of patients undergoing surgery should be considered

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for extended prophylaxis—postoperative orthopedic patients, and individuals with cancer or a history of VTE, undergoing major surgical procedures.¹ In this Review, we first examine the robust data on VTE prophylaxis for medical inpatients, before discussing VTE risk in the outpatient setting, and the potential for outpatient VTE prophylaxis in nonsurgical patients.

VTE prophylaxis in medical inpatients

Currently, the recommended agents for the prevention of VTE in acutely ill medical patients include low-molecular-weight heparin (LMWH), fondaparinux, and unfractionated heparin (UFH).¹ Here, we examine the evidence for these recommendations in the inpatient setting.

LMWH or fondaparinux versus placebo

The Prophylaxis of VTE in Medical Patients with Enoxaparin (MEDENOX) study¹³ was a phase III, prospective, multicenter, randomized, double-blind, placebo-controlled trial of the LMWH enoxaparin. The investigators enrolled 1,102 patients with an acute illness. Patients were included if they were older than 40 years, recently immobilized, and had been hospitalized because of heart failure or acute respiratory failure (not requiring mechanical ventilation). Patients hospitalized because of an acute infectious disease (without septic shock), acute rheumatic disorder, or active episode of inflammatory bowel disease were also eligible if their illness was accompanied by at least one additional risk factor for VTE. Notable exclusion criteria included pregnancy, stroke or major surgery in the previous 3 months, serum creatinine >1.7 mg/dl (150 μmol/l), HIV infection, uncontrolled hypertension, and conditions conferring risk of hemorrhage or hypersensitivity to heparin. The primary end point was symptomatic or asymptomatic VTE between days 1 and 14, and all patients underwent contrast venography of the legs between days 6 and 14. The study revealed a significant reduction in the incidence of VTE at day 14 in patients who received prophylaxis with enoxaparin 40 mg per day (5.5%), compared with patients who received enoxaparin 20 mg per day and those on placebo (15.0% and 14.9%, respectively, $P < 0.001$ for both comparisons).¹³ The absolute risk reduction for VTE was 9.4% with a relative risk (RR) of 0.37 (97.6% CI 0.22–0.63, $P < 0.001$). Enoxaparin 40 mg per day was also associated with a significant reduction in the incidence of proximal deep-vein thrombosis (DVT; 1.7%) compared with enoxaparin 20 mg per day and placebo (4.9% and 4.5%, respectively, $P = 0.037$ for comparison with placebo).^{6,13} There was also a reduction in risk for VTE events at 110 days in patients who took enoxaparin 40 mg per day. Four patients (1.1%) in the placebo group, one patient (0.3%) in the enoxaparin 20 mg per day group, and six patients (1.7%) who received enoxaparin at 40 mg per day developed major hemorrhage by day 14.¹³ No significant differences in survival estimates at 3 months were observed between the three prophylaxis groups.¹³ This landmark study

Key points

- Patients should be assessed for their risk of venous thromboembolism (VTE) at hospital admission
- Anticoagulant medication should be given to patients at risk of VTE unless contraindications exist, in which case mechanical prophylaxis should be used
- American College of Chest Physicians guidelines recommend the use of low-molecular-weight heparin, low-dose unfractionated heparin, or fondaparinux for VTE prophylaxis in at-risk medical patients
- Data from observational studies indicate that rates of VTE prophylaxis need to be improved
- A large proportion of outpatient cases of VTE occur within 3 months of hospitalization
- Most medical patients do not receive the duration of VTE prophylaxis given in clinical trials, owing to shorter hospital stays

demonstrated the efficacy and safety of VTE prophylaxis with a LMWH in medical inpatients.

Subsequently, two prospective, randomized clinical trials, with similar designs to the MEDENOX study, have demonstrated efficacy and safety for other anticoagulant preparations—dalteparin and fondaparinux (Arixtra®, Glaxo Group Limited, Greenford, UK). These studies were the randomized, placebo-controlled trial of Dalteparin for the Prevention of Venous Thromboembolism in Acutely Ill Medical Patients (PREVENT)¹⁴ and the Arixtra for Thromboembolism Prevention in a Medical Indications Study (ARTEMIS).¹⁵

In PREVENT, the LMWH dalteparin was compared with placebo in 3,706 patients with an acute medical condition and a projected hospitalization of 4 days or longer. Patients were included if they were at least 40 years of age and had one of the following: acute congestive heart failure, acute respiratory failure that did not require mechanical ventilation, infection without septic shock, acute rheumatologic disorders, or inflammatory bowel disease. In addition, except for the patients with congestive heart failure or acute respiratory failure, patients had to have one or more additional risk factor for VTE. The primary end point was symptomatic or asymptomatic VTE. Unlike MEDENOX and ARTEMIS, PREVENT evaluated for DVT by leg ultrasonography rather than venography. Although ultrasonography is known to be less sensitive than contrast venography for detecting DVT, it is more common in clinical practice. The incidence of VTE was 2.77% (42 of 1,518 patients) in the group who received 5,000 IU subcutaneous dalteparin per day, and 4.96% (73 of 1,473 patients) in the placebo group.¹⁴ The absolute reduction in risk of VTE for dalteparin was 2.19%, and the RR was 0.55 (95% CI 0.38–0.80, $P = 0.0015$). The incidence of proximal DVT by day 21 was significantly lower in the dalteparin group than in the placebo group. No significant difference between the two groups was observed for symptomatic VTE (dalteparin 0.93% versus placebo 1.33%), or all-cause mortality at 90 days after commencing treatment. Major bleeding was reported in nine patients (0.49%) in the dalteparin group and in three patients (0.16%) in the placebo group ($P = 0.15$).¹⁴

Table 1 | Placebo-controlled trials of LMWH for VTE prophylaxis in medical patients

Author, year (trial)	Treatment	Number of patients	Days of prophylaxis	Primary outcome	Incidence of VTE in placebo group (%)	Incidence of VTE in prophylaxis group (%)	Relative risk of VTE in prophylaxis group
Samama <i>et al.</i> 1999 (MEDENOX) ¹³	Enoxaparin	866	6–14	VTE days 1–14	14.90	5.50	0.37 ($P < 0.001$)
Fraisse <i>et al.</i> 2000 ¹⁷	Nadroparin	221	2–21	VTE days 1–21	28.20	15.50	0.57 ($P = 0.045$)
Leizorovicz <i>et al.</i> 2004 (PREVENT) ¹⁴	Dalteparin	3,706	14	VTE days 1–21	4.96	2.77	0.55 ($P = 0.0015$)
Cohen <i>et al.</i> 2006 (ARTEMIS) ¹⁵	Fondaparinux	849	6–14	VTE days 1–15	10.50	5.60	0.53 ($P = 0.029$)

Abbreviation: VTE, venous thromboembolism.

In ARTEMIS, the efficacy and safety of fondaparinux—a synthetic selective factor Xa inhibitor—were assessed for the prevention of VTE in older, acutely ill medical inpatients.¹⁵ Patients were included if they were aged 60 years or older, and admitted to the hospital for congestive heart failure, acute respiratory illness in the presence of chronic lung disease, or acute infectious or inflammatory disease and were expected to remain in bed for at least 4 days. The 849 participants were randomly assigned to receive 2.5 mg of fondaparinux or placebo subcutaneously for 6–14 days. The composite end point of incidence of DVT detected by routine bilateral venography, and symptomatic VTE was 10.5% (34 of 323 individuals) in the placebo group and 5.6% (18 of 321 individuals) in the fondaparinux group. The absolute risk reduction was 4.9% and the RR was 0.53 (95% CI 0.31–0.92, $P = 0.029$). Major bleeding occurred in one patient in each group. After 1 month, 14 patients (3.3%) in the fondaparinux arm had died, compared with 25 patients (6.0%) in the placebo group ($P = 0.06$).¹⁵

The results of these three trials demonstrate that enoxaparin, dalteparin, and fondaparinux are all superior to placebo for VTE prophylaxis in medical inpatients. There are a number of notable limitations to these trials, however. First, no definite mortality benefit was seen for the study drug in any of these placebo-controlled studies. Second, each of these trials screened all patients for DVT and used rates of asymptomatic DVT in the end point. The clinical significance of asymptomatic DVT is unclear. One might extrapolate from these data that rates of symptomatic DVT would also be reduced, although much larger trials would be required to show this definitively. Third, the precise inclusion criteria and definition of immobility differed between the three trials, which unfortunately makes detailed comparisons between the studies difficult. The inclusion criteria are, however, similar—generally capturing patients at risk for VTE, such as those with congestive heart failure, severe respiratory disease, and inflammatory states. No trials involving head-to-head comparisons of enoxaparin, dalteparin, and fondaparinux have yet been performed, so for the foreseeable future MEDENOX, PREVENT, and ARTEMIS will be the main clinical trials to inform clinical practice.

Meta-analyses of UFH, LMWH, or fondaparinux

Lloyd and colleagues,¹⁶ performed a meta-analysis of data from MEDENOX, PREVENT, ARTEMIS and a study conducted by Fraisse *et al.*¹⁷ This meta-analysis included a total of 5,516 patients and demonstrated that VTE prophylaxis with anticoagulant medication was associated with a significantly lower risk of any asymptomatic DVT (RR 0.51, $P < 0.00001$), and of asymptomatic proximal DVT (RR 0.45, $P < 0.00001$) than placebo. In the pooled analysis, the incidence of major bleeding in patients who received VTE prophylaxis was, however, significantly higher than those on placebo (RR 2.00, $P = 0.03$). There was no difference in all-cause mortality between the two treatments.

Dentali and associates¹⁹ performed a meta-analysis of nine clinical trials (19,958 patients) to determine the effect of prophylactic anticoagulant medications—including enoxaparin, dalteparin, fondaparinux, heparin and nadoparin—on the incidence of symptomatic VTE and asymptomatic DVT, respectively, in at-risk, hospitalized medical patients. PE occurred in 0.2% of patients who received prophylaxis and 0.49% of those who did not (RR 0.43, 95% CI 0.26–0.71). Fatal PE was assessed in seven trials and occurred in 0.14% of patients who received prophylaxis and in 0.39% of patients who did not (RR 0.38, 95% CI 0.21–0.69). There was a non-significant trend towards fewer cases of symptomatic DVT in the group who received prophylaxis in the four trials that included this end point. There was no difference between prophylaxis and placebo for all-cause mortality (assessed in five trials) or major bleeding (assessed in eight trials).

The randomized clinical trials and meta-analyses discussed here provide strong evidence for the use of anticoagulant VTE prophylaxis for the vast majority of medical inpatients. Use of anticoagulant VTE prophylaxis reduces the risk of both fatal and nonfatal PE and DVT, and is associated with a low risk of bleeding (albeit higher than placebo).

LMWH versus UFH

Various regimens, predominantly with LMWH or UFH, for VTE prophylaxis have been compared against each other in medical patients. Contemporary studies

use a regimen of UFH 5,000 units three-times daily, which is more aggressive than the therapy commonly used in earlier studies (UFH 5,000 units twice daily). The Prevention of Thromboembolism in Medical Patients with Enoxaparin (PRIME) trial²⁰ and the Thromboembolism Prevention in Cardiopulmonary Diseases with Enoxaparin (PRINCE) study²¹ both enrolled high-risk hospitalized patients who were randomly assigned to either 40 mg of enoxaparin or 5,000 units of UFH every 8 h. In the PRIME trial, the incidence of DVT was 0.2% in the enoxaparin group and 1.4% among those who received UFH. These results were not significant in a test for superiority ($P=0.12$), but were highly significant in a test for equivalence ($P<0.001$),²⁰ meaning that the two agents showed a statistically similar benefit. These results are supported by the findings of the PRINCE study, in which the incidence of DVT in patients with severe respiratory disease was not significantly different between those received enoxaparin and those who received UFH (5.9% versus 7.1%, $P=0.19$).²¹ In patients with heart failure, however, the incidence of DVT was 9.7% with enoxaparin and 16.1% with UFH ($P=0.01$). The investigators concluded that 40 mg of enoxaparin was at least as effective as 5,000 units of UFH every 8 h for the prevention of VTE in patients with cardiopulmonary disease.

The PREVAIL study²² of 1,762 patients with acute ischemic stroke who were unable to walk unassisted, revealed that the risk of VTE was reduced by 43% with enoxaparin 40 mg daily when compared with UFH 5,000 units every 12 h (RR 0.57, 95% CI 0.44–0.76, $P=0.0001$). The incidence of bleeding was the same in both treatment groups (8%). Importantly, the composite end point of symptomatic intracranial and major extracranial hemorrhage occurred infrequently (1% of patients in both groups). These studies indicate that once daily enoxaparin is comparable to UFH every 8 h for VTE prophylaxis and has been shown to be superior—at least in patients with stroke—to UFH every 12 h.

Meta-analyses comparing LMWH and UFH

In addition to randomized, placebo-controlled prophylaxis trials, meta-analyses have been conducted for studies comparing LMWH with UFH and for twice daily versus three-times daily UFH regimens. In their meta-analysis of nine studies, which included a total of 12,391 patients (8,357 of whom were enrolled in placebo-controlled trials), Kanaan and colleagues found no significant difference between LMWH (including fondaparinux) and UFH (5,000 units every 12 h) for the prevention of DVT (odds ratio 0.68, 95% CI 0.27–1.70) or in the incidence of major bleeding (odds ratio 0.69, 95% CI 0.29–1.68).²³ In a second meta-analysis of 36 studies, UFH 5,000 units three-times per day was more effective at preventing DVT than the same dose given twice per day (RR 0.27, 95% CI 0.20–0.36 versus RR 0.52, 95% CI 0.28–0.96).²⁴ Mortality was not reduced by the use of UFH or LMWH. The 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) was lower for LMWH than for UFH, but there was no difference between the two agents in the risk of bleeding or thrombocytopenia.

King and colleagues conducted a meta-analysis of 12 studies (total of 7,978 patients) evaluating 5,000 units twice per day versus 5,000 units three-times per day UFH regimens.²⁵ After adjustment for baseline risk, there was no difference in the incidence of VTE between the two treatment regimens. There was, however, a trend toward a decrease in the incidence of PE cases per 1,000 patient days (0.5 versus 1.5, $P=0.09$) and proximal DVT and PE cases per 1,000 patient days (0.9 versus 2.3, $P=0.05$) with the three-times per day strategy. The risk of major bleeding was, however, significantly increased with the three-times daily UFH regimen (0.96 versus 0.35 cases per 1,000 patient days, $P<0.001$). Twice per day UFH dosing, therefore, seems to cause fewer episodes of major bleeding, while a three-times per day regimen offers somewhat better efficacy in preventing clinically relevant VTE events.

When assessing the relevance of these data, however, the limitations of meta-analyses must be considered. These meta-analyses combine trials of different therapies for VTE prophylaxis in an attempt to compare them head-to-head. The individual trials differed in their inclusion and exclusion criteria, in their primary end point, and their definitions of bleeding. Some of the trials were placebo-controlled and some compared LMWH with UFH. This raises concerns about heterogeneity in the populations of patients and studies. In addition, publication bias is always a consideration with meta-analyses, and there is some suggestion that this could be a concern in trials of VTE prophylaxis.¹⁹ Nevertheless, some useful information can be gleaned from these meta-analyses. Both UFH and LMWH are effective and safe in preventing VTE in medical patients. Dosing of UFH every 8 h and LMWH daily is probably superior to dosing of UFH every 12 h. In addition, there could be some advantages to LMWH therapy, including once daily dosing, fewer site hematomas and lower rates of heparin-induced thrombocytopenia.³¹ Furthermore, LMWH has been shown to be cost effective.³²

Risk of VTE in outpatients

Evidence for outpatient occurrence of VTE

Medical patients are often discharged from the hospital while their illness is still active although under control, a situation that has become increasingly commonplace. Medical patients are sent home from the hospital with intravenous antibiotics or other medications and often remain immobile, or with substantially reduced mobility, thus increasing their risk of VTE.

The Sirius study was designed to identify risk factors for VTE in the outpatient setting.²⁶ Case patients (636 individuals presenting with DVT) were matched by age and sex with control participants (636 patients presenting with influenza or rhinopharyngitis). Risk factors for

Box 1 | Risk factors for deep-vein thrombosis**Risk factors in medical outpatients²⁶**Significant ($P < 0.05$)

- History of venous thromboembolism
- Venous insufficiency
- Chronic heart failure
- Obesity (BMI > 30 kg/m²)
- Standing for > 6 h per day
- History of > 3 pregnancies
- Current pregnancy
- Muscular trauma
- Deterioration in general physical condition
- Immobilization
- Long-distance travel
- Infectious disease

Trend toward significance ($P < 0.10$)

- Cancer
- Blood group A
- Inflammatory bowel disease
- Rheumatologic disease
- Use of oral contraceptives

Traditional risk factors³³

Hereditary

- Antithrombin deficiency
- Protein C deficiency
- Protein S deficiency
- Factor V Leiden
- Activated protein C resistance without factor V Leiden
- Prothrombin gene mutation
- Dysfibrinogenemia
- Plasminogen deficiency

Acquired

- Acute medical illness
- Cancer
- Reduced mobility
- Advanced age
- Major surgery
- Trauma
- Spinal cord injury
- Pregnancy/postpartum period
- Polycythemia vera
- Antiphospholipid antibody syndrome
- Oral contraceptives
- Hormonal replacement therapy
- Heparins
- Chemotherapy
- Obesity (BMI > 30 kg/m²)
- Central venous catheters
- Immobilizer/cast
- Nephrotic syndrome

VTE that reached statistical significance, and those with a trend toward significance, are compared with traditional risk factors for VTE in Box 1.^{26,33} An observational study by Spencer and coworkers, published in 2007, was designed to assess the frequency of VTE in outpatients, evaluate VTE risk factors and the use of prophylaxis.¹² VTE was confirmed in 1,897 patients, 1,399 (73.7%) of whom developed the condition as outpatients. Just over a third of these individuals had been hospitalized within the previous 3 months, and most had been hospitalized within the past month. Only 59.7% of patients who developed VTE as outpatients had received some form of VTE prophylaxis and just 42.8% received anticoagulant medication. This study indicates that a substantial proportion of VTE cases occur in the outpatient setting and many of these patients have been recently hospitalized. These findings emphasize the need to expand the evidence-base for extended VTE prophylaxis in certain groups of patients after hospital discharge.

Extended VTE prophylaxis

Clearly, the risk of VTE does not suddenly disappear when a patient is discharged from the hospital. In current guidelines, extended VTE prophylaxis is recommended for several groups of surgical patients. For example, the American College of Chest Physicians (ACCP) recommends that prophylaxis be extended beyond 10 days, and up to 35 days, after surgery in orthopedic patients who have undergone total hip replacement or surgery for hip fracture.¹ This strong, grade 1A recommendation is based on extensive, randomized trial data. The same extended course of treatment is indicated for patients who have undergone total knee replacement, although the recommendation is weaker (grade 2B) based on the available data.¹ Finally, for selected, high-risk, general surgery patients—including those who have undergone major surgery for cancer, or have previously had VTE—there is a grade 2A recommendation for continued VTE prophylaxis with LMWH for up to 28 days after hospital discharge.¹

Extended VTE prophylaxis in medical patients has been studied, but not yet published. The Extended Clinical Prophylaxis in Acutely Ill Medical Patients (EXCLAIM) study¹⁸ was designed to evaluate the efficacy and safety of 38 days of VTE prophylaxis in a cohort of several thousand acutely ill patients. All participants received enoxaparin (40 mg per day) for approximately 10 days, and were then randomly assigned to 28 additional days of enoxaparin or placebo. The results of this trial were presented at the 2007 International Society of Thrombosis and Hemostasis congress³⁴ and are expected to be published by 2010.

Guidelines for VTE prophylaxis

The ACCP guidelines,¹ published in June 2008, recommend that patients hospitalized with an acute medical illness be treated with LMWH, low-dose UFH, or fondaparinux for VTE prophylaxis. Patients at risk of VTE

include those admitted with congestive heart failure, severe respiratory disease, or those confined to bed with one or more additional risk factors, such as active cancer, a history of VTE, sepsis, acute neurologic disease, or inflammatory bowel disease. The ACCP guidelines also advise the use of mechanical VTE prophylaxis with graduated compression stockings or intermittent pneumatic compression in patients with a contraindication to anticoagulant medication, although the supportive data for this recommendation are inadequate. Compliance is crucial to the effectiveness of these mechanical devices. The guidelines also advise against the use of aspirin alone for VTE prophylaxis. There are, however, no recommendations for the prophylaxis of outpatients or the use of extended anticoagulant regimens for discharged medical patients.¹ In addition to these patient-specific guidelines, the ACCP recommends that every general hospital develop a written policy that addresses the prevention of VTE. The guidelines also include a recommendation to implement strategies shown to improve adherence to VTE prophylaxis, including computerized reminders and decision support, preprinted order sets for VTE prophylaxis, and periodic audit and feedback.¹

'Real-world' use of VTE prophylaxis

Despite overwhelming evidence for the benefit of VTE prophylaxis, and recommendations made in published guidelines,¹ the underuse of this preventative therapy is a global problem, which has been highlighted in several studies (Table 2). In DVT FREE,³ 14.5% (395 of 2,726) inpatients were identified as having PE, and only 42.0% of those diagnosed with VTE had received prophylaxis within the preceding 30-day period. In the outpatient setting, the median time to diagnosis of DVT was 3 days after commencement of symptoms, and 80% of patients diagnosed with DVT as outpatients were subsequently hospitalized for treatment of DVT (median duration 5 days).³

In the observational Venous Thromboembolism Prophylaxis in Acutely Ill Hospitalized Medical Patients: Findings from the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) study,⁵ only 61% of all patients who met the 2004 ACCP guideline³⁵ criteria for VTE prophylaxis received such therapy. Furthermore, only 33% of patients enrolled from the US, and 47% of patients enrolled from other countries, received VTE prophylaxis in the form of anticoagulant medication. The authors also showed that among those patients in the IMPROVE study who would have been eligible for inclusion in the MEDENOX and PREVENT trials or in ARTEMIS, only 62–64% received some form of prophylaxis during hospitalization, and only 44–47% received LMWH.⁵ An even lower rate of VTE prophylaxis was reported in the multicenter evaluation of the use of VTE prophylaxis in acutely ill medical patients in Canada (CURVE) study.⁴ Just 23% of patients (391 of 1,702) who had an indication for VTE prophylaxis, on the basis of ACCP guidelines, received some

Table 2 | Observational studies evaluating rates of VTE prophylaxis

Author, year (trial)	Number of patients ^c	Patients receiving any form of VTE prophylaxis (%)
Goldhaber and Tapson 2004 (DVT FREE) ^{3,a}	2,726 (medical patients: 1,362) (surgical patients: 1,364)	42 (individual percentages for medical and surgical patients not available)
Kahn <i>et al.</i> 2007 (CURVE) ^{4,b}	1,894	23
Tapson <i>et al.</i> 2007 (IMPROVE) ^{5,b}	6,824	61
Cohen <i>et al.</i> 2008 (ENDORSE) ²	35,329 (medical patients: 15,487) (surgical patients: 19,842)	53 (medical patients: 45) (surgical patients: 59)

^aAll patients in the DVT FREE study had DVT confirmed by ultrasonography at enrollment. ^bStudies exclusively enrolling medical patients. ^cNumber of hospitalized patients meeting the American College of Chest Physicians criteria for VTE prophylaxis. ¹ Abbreviation: VTE, venous thromboembolism.

type of prophylaxis, and only 16% received appropriate thromboprophylaxis. Moreover, the CURVE investigators found that a diagnosis of cancer reduced the likelihood that the patient would receive VTE prophylaxis.⁴

The Epidemiologic International Day for the Evaluation of Patients at Risk for Venous Thromboembolism in the Acute Hospital Care Setting (ENDORSE) study² was a multinational, cross-sectional assessment of VTE risk and rates of prophylaxis. Of the 68,183 patients enrolled, 35,329 (51.8%) had an indication for VTE prophylaxis on the basis of ACCP guidelines, including 19,842 surgical patients and 15,487 medical patients. Overall, however, 17,732 (50.2%) of these individuals received appropriate VTE prophylaxis, 11,613 of whom were surgical patients and 6,119 of whom were medical patients. LMWH was the most commonly used form of VTE prophylaxis. Mechanical prophylaxis was used in just 13% of the surgical patients and 10% of the medical patients who had a contraindication for anticoagulant medication.² The National Anticoagulation Benchmark and Outcomes Report (NABOR) investigators evaluated the use of anti-thrombotic therapy in patients with various conditions, including 928 who had undergone hip or knee surgery.³⁶ Although the appropriate dose and schedule of VTE prophylaxis was administered to 85.6% of these patients, the mean duration of VTE prophylaxis was only 3–5 days, which falls far short of the ACCP recommendation that prophylaxis be continued for 10–35 days after orthopedic surgery.¹ These studies indicate that between 20% and 65% of medical inpatients receive VTE prophylaxis, but that the actual 'real-world' rates of appropriate VTE prophylaxis are likely to be lower.

Strategies to improve prophylaxis

Several approaches to improving rates of VTE prophylaxis use have been studied. Kucher *et al.* developed a computer program linked to a database of patients, which identified hospitalized patients at risk for DVT and notified physicians with an electronic alert.²⁷ The majority (~80%) of the 2,506 patients were receiving medical, rather than surgical, treatment. The electronic system

was associated with a significant improvement in the use of VTE prophylaxis (33.5% versus 14.5%, $P < 0.001$) and a decrease in clinically diagnosed and objectively confirmed VTE at 90 days (4.9% versus 8.2%, hazard ratio 0.59, $P = 0.001$) when compared with standard care.²⁷ Mosen *et al.* performed a similar study in a 2,077 post-operative surgical patients.²⁸ The rate of VTE prophylaxis increased from 89.9% to 95.0% after the introduction of a computerized reminder system ($P < 0.0001$).

The minimizing errors of omission: Behavioral Reinforcement of Heparin to Avert Venous Emboli (BEHAVE) study was designed to improve the use of anticoagulant prophylaxis in an intensive care unit in Canada, using an extensive educational program.²⁹ The program included educational in-services, verbal reminders, computerized daily nurse recording of VTE prophylaxis, and a weekly graphic record of adherence, which was publicly displayed. There was a significant improvement in the use of anticoagulant VTE prophylaxis for the duration of the study (1 year), which was maintained in the 3-month follow-up phase.²⁹ Tothter *et al.* performed a systematic review of 30 studies assessing various approaches to improving VTE prophylaxis use in hospitalized patients.³⁰ In general, multiple strategies used together were found to be most effective. Incorporating automatic reminders to assess patients for VTE risk, electronic decision support or paper-based reminders, and an audit or feedback were among the most effective methods of improving prophylaxis rates, whereas passive distribution of guidelines was least effective.³⁰

Although there has been a tremendous increase in our knowledge about VTE prophylaxis in hospitalized medical patients, and much attention has been paid to improving VTE prophylaxis rates in this setting, there is a paucity of data evaluating VTE prophylaxis in outpatients. In most of the clinical trials of VTE prophylaxis in medical patients, the average length of hospital stay was 5–7 days, and target prophylaxis duration was 6–14 days. Most medical patients do not spend 1–2 weeks as inpatients³ and, therefore, receive a shorter duration of VTE prophylaxis than patients enrolled in clinical trials. Reducing the length of hospital stay makes good sense from patient-care and economic standpoints, but leads to an increase in the number of debilitated and immobile outpatients who could benefit from extended VTE prophylaxis.

Conclusions

The use of VTE prophylaxis in at-risk, acutely ill medical patients is evidence-based and recommended in current guidelines.¹ Medical patients should be assessed for VTE risk at the time of hospital admission, and anticoagulant medication should be prescribed unless contraindications exist. Although there are currently no clinical trial data for mechanical VTE prophylaxis in medical patients, this strategy should be used in patients who have contraindications to anticoagulants. Despite large, randomized, placebo-controlled clinical trials such as MEDENOX, PREVENT, and ARTEMIS—which demonstrate the clear benefit of VTE prophylaxis and the low risk of bleeding in medical patients—rates of VTE prophylaxis use need to be improved. Data from large registries and observational studies indicate low rates of VTE prophylaxis (20–65%) in medical inpatients, who represent the majority of cases of symptomatic VTE and fatal PE. Several strategies for improving rates of VTE prophylaxis use in clinical practice have been studied, including computerized alerts and decision-support tools, paper or computerized order sets including VTE prophylaxis, and chart audit with provider-specific feedback. ACCP guidelines recommend implementing these strategies in every general hospital.

Work still needs to be done in this area. Although we have some data to help us identify outpatients at risk of VTE, we have no data on whether these individuals should receive different prophylactic regimens to inpatients. The study by Spencer *et al.* revealed that over 70% of their patients with VTE presented as outpatients.¹² Although many of these patients had been recently hospitalized, almost two-thirds had not. Forthcoming data from the EXCLAIM study could determine whether certain at-risk medical patients should receive an extended course of VTE prophylaxis after hospital discharge. Further studies, specifically enrolling at-risk outpatients who have not been hospitalized, are needed to help define the optimum strategy for VTE prophylaxis in this population.

Review criteria

We searched PubMed for English-language papers using combinations of the following search terms “venous thrombosis”, “thromboembolism”, “prophylaxis”, “ambulatory care”, “heparin”, “low molecular weight heparin”, “dalteparin”, “enoxaparin”, and “fondaparinux”. We further searched the reference lists of identified papers for relevant manuscripts.

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