The importance of appropriate prophylaxis for the prevention of venous thromboembolism in at-risk medical patients

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SUMMARY

Background: Venous thromboembolism (VTE), which encompasses both deep-vein thrombosis and pulmonary embolism, is a significant healthcare problem, leading to considerable morbidity, mortality and resource utilisation. Aims: This review discusses the adherence to VTE guideline recommendations and the available clinical evidence on the appropriate type, dose and duration of VTE prophylaxis.

Methods: A literature survey was conducted using Pub Med and EMBASE to identify publications related to appropriate thromboprophylaxis in medically ill patients at risk of VTE. Results: Despite evidence from clinical trials and national guidelines, VTE prophylaxis in medically ill patients remains underutilised. The use of unfractionated heparin three-times-daily, low-molecular-weight heparin once-daily and fondaparinux once-daily has demonstrated effectiveness in clinical trials of medically ill patients. However, controversy exists about the use of unfractionated heparin twice-daily, and fondaparinux has not yet received US Food and Drug Administration approval for VTE prophylaxis in medically ill patients.

Conclusion: It is important for clinicians to have an understanding of the evidence-based literature when selecting an appropriate drug, at the appropriate dose, for the appropriate duration for VTE prophylaxis in medically ill patients. VTE prophylaxis in medically ill patients is cost-effective, and drugs that are expensive may still be cost-effective when considering improved efficacy and/or safety. Recently, the underutilisation of VTE prophylaxis has led to the involvement of government and other regulatory agencies in an attempt to increase appropriate VTE prophylaxis in US hospitals and improve the clinical and economic outcomes in medical patients at risk of VTE.

Introduction

Venous thromboembolism (VTE), a serious disease that encompasses both deep-vein thrombosis (DVT) and pulmonary embolism (PE), continues to be a significant cause of morbidity and mortality in the US (1). In the absence of prophylaxis, the incidence of objectively confirmed, hospital-acquired DVT is approximately 10–40% among medical or general surgical patients and 40–60% following major orthopaedic surgery (1). Moreover, patients with a clinically recognised PE (with or without DVT) or DVT alone have a high rate of 1-year all-cause mortality (26.0% vs. 20.3%, respectively) with a substantial proportion of these deaths occurring in the first 30 days (2).

In addition to the well-recognised high risk of VTE among surgical patients, medical inpatients are also particularly susceptible to the development of VTE. In a population-based case–control study, hospitalisation for medical illness and hospitalisation for surgery were found to account for similar proportions of total VTE cases (24% and 22%, respectively) (3). Furthermore, autopsy studies suggest that more than two-thirds of fatal PE cases occur in non-surgical patients (4,5). In addition, not only are medical inpatients at a high risk of VTE but a given VTE event is more likely to present as PE rather than DVT in medical patients compared with non-medical patients (22.2% vs. 15.5%, respectively; p < 0.001) (6). Common risk factors for VTE in medical patients include advanced age, prolonged immobility, malignancy, heart failure and obesity (7).

Studies in acutely ill medical patients have demonstrated that thromboprophylaxis with unfractionated
heparin (UFH), low-molecular-weight heparin (LMWH) and fondaparinux can reduce the incidence of VTE by approximately 50% without a significant increase in bleeding (1,8–11). These findings have been incorporated into evidence-based guidelines, such as those published by the American College of Chest Physicians (ACCP) and the International Union of Angiology, which provide specific recommendations on appropriate prophylactic regimens to be used in hospitalised medical patients at risk of VTE (1,12). However, large-scale registry studies suggest that current thromboprophylaxis practices are suboptimal and VTE prophylaxis is frequently underused and inappropriately prescribed, especially in at-risk medical patients (6,13–16).

Recently, the Acting Surgeon General issued a ‘Call to Action to Prevent Deep Vein Thrombosis and Pulmonary Embolism’ in the US (17). This call for action emphasises the importance of evidence-based practices in the management of VTE and urges US hospitals to implement a coordinated multifaceted plan to reduce the number of VTE cases. This review will examine guideline-recommended prophylaxis practices and discuss the clinical and economic implications of inappropriate VTE prophylaxis in medical patients.

**Guideline recommendations and adherence in practice**

The evidence-based VTE prevention guidelines published by the ACCP address all relevant patient indications and are widely regarded as the clinical practice standard (1). The current ACCP guidelines recommend that thromboprophylaxis is given to acutely ill medical patients admitted to hospital with heart failure or severe respiratory disease, or those who are confined to bed and have one or more additional risk factors (e.g. active cancer, previous VTE, sepsis, acute neurological disease, inflammatory bowel disease) (1). The anticoagulants recommended for use in medical patients are low-dose UFH, LMWHs and the factor Xa inhibitor fondaparinux (all Grade 1A recommendations) (1). These agents were recommended on the basis of data from several randomised clinical trials, which demonstrated their efficacy and safety profiles in several different at-risk medical patient populations (Table 1) (8–11,18–22).

Despite the widespread availability of evidence-based guidelines, several studies have reported that VTE prophylaxis is suboptimal in everyday practice (Table 2) (6,13–16,23). A recent report from the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE), an ongoing registry of acutely ill medical patients, demonstrated that only 61% of at-risk patients actually received any prophylaxis (14). Furthermore, in a registry study of patients with objectively confirmed DVT, only 25.4% of medical patients received any thromboprophylaxis prior to VTE diagnosis, significantly lower than the prophylaxis rates observed in non-medical patients (53.8%; p < 0.001) (6).

The appropriateness of thromboprophylactic practices has also been investigated (13,15,16). The cross-sectional Epidemiologic International Day for the Evaluation of Patients at Risk for Venous Thromboembolism in the Acute Hospital Care Setting (ENDORSE) study assessed the proportion of at-risk patients from 358 hospitals in 32 countries worldwide who received guideline-recommended prophylaxis (13). In this study, only 48% of medical patients received any prophylaxis and, of note, only 40% received prophylaxis in accordance with the 2004 ACCP guidelines. In a study of 196,104 medical patients discharged from US hospitals, the overall prophylaxis rate was 61.8%. However, only 33.9% of patients received appropriate prophylaxis according to the 2001 ACCP guidelines (16). Furthermore, of the 66.1% of patients not receiving appropriate prophylaxis, 38.4% received no prophylaxis, 4.7% received mechanical prophylaxis only, 6.3% received an inappropriate dose and 16.7% received an inappropriate duration of prophylaxis.

**Appropriate type of prophylaxis**

The ACCP recommendations on thromboprophylaxis in medical patients are based on results from several randomised controlled clinical trials (Table 1) (1,8–11,18–22). These trials compared UFH, LMWHs or fondaparinux with no thromboprophylaxis or placebo. A number of clinical trials have evaluated the ability of UFH 5000 IU administered two- or three-times-daily for VTE prevention in medical patients (8,18–21). Although not all trials of UFH prophylaxis have demonstrated benefit, most of the data support a significant reduction in VTE events without a significant increase in bleeding risk.

The efficacy and safety of a LMWH compared with placebo has been evaluated in two major clinical trials (9,10). In the Prophylaxis in Medical Patients with Enoxaparin (MEDENOX) trial, once-daily enoxaparin 20 mg or enoxaparin 40 mg administered for 6–14 days was compared with placebo in 1102 acutely ill medical patients (9). The incidence of VTE by day 14 was significantly reduced by 63% in the enoxaparin 40 mg group compared with placebo (p < 0.001), with no significant difference in major bleeding (Table 1) (9). The incidence of proximal DVT was also significantly reduced by 65% for
Table 1 Randomised clinical trials on VTE prophylaxis in hospitalised medical patients

| Reference                  | n   | DVT detection       | Regimens                                                                 | VTE, % | Major bleeding, % |
|----------------------------|-----|---------------------|--------------------------------------------------------------------------|--------|-------------------|
|                            |     |                     | Drug vs. Control p                                                       |       |                   |
|                            |     |                     | p                                                                        |       |                   |
|                            |     |                     | p                                                                        |       |                   |
| Gallus et al. (18)         | 78  | ¹²⁵I-fibrinogen scanning | UFH 5000 IU tid vs. no prophylaxis                                       | 2.6   | 0.05              |
|                            |     |                     |                                                                          | 22.5  | 0                 | ns               |
| Belch et al. (8)           | 100 | ¹²⁵I-fibrinogen scanning | UFH 5000 IU tid vs. no prophylaxis                                       | 4     | < 0.01            |
|                            |     |                     |                                                                          | 26    | 0                 | ns               |
| Cade (19)                  | 131 | ¹²⁵I-fibrinogen scanning | UFH 5000 IU bid vs. placebo                                              | 2     | ns                |
|                            |     |                     |                                                                          | 10    | –                 | –                |
| Ibarra-Perez et al. (20)   | 192 | ¹²⁵I-fibrinogen scanning | UFH 5000 IU bid vs. GCS and/or EB vs. aspirin vs. no prophylaxis          | 2.6   | < 0.05            |
|                            |     |                     |                                                                          | 26.1  | –                 | –                |
| Heparin Prophylaxis Group (21) | 11,693 | Autopsy              | UFH 5000 IU bid vs. no prophylaxis                                       | 49    | ns                |
|                            |     |                     |                                                                          | 49    | 7.2               | 3.2              | 0.076            |
| Dahan et al. (22)          | 270 | ¹²³I-fibrinogen scanning | Enoxaparin 60 mg once-daily vs. placebo                                 | 3     | 0.03              |
|                            |     |                     |                                                                          | 9.1   | 0.8               | 1.4              | –                |
| MEDENOX (9)                | 1102| Venography or ultrasonography | Enoxaparin 40 mg qd vs. placebo                                         | 5.5   | 14.9              | < 0.001          |
|                            |     |                     |                                                                          | 14.9  | 1.7               | 1.1              | ns               |
| PREVENT (10)               | 3706| Compression ultrasonography | Dalteparin 5000 IU qd vs. placebo                                       | 2.77  | 4.96              | 0.002            |
|                            |     |                     |                                                                          | 4.96  | 0.49              | 0.16             | ns               |
| ARTEMIS (11)               | 849 | Venography           | Fondaparinux 2.5 mg qd vs. placebo                                       | 5.6   | 10.5              | 0.029            |
|                            |     |                     |                                                                          | 10.5  | 0.2               | 0.2              | ns               |

*Symptomatic and asymptomatic VTE.

ARTEMIS, Arixtra for Thromboembolism Prevention in a Medical Indications Study; bid, twice-daily; DVT, deep-vein thrombosis; EB, elastic bandages; GCS, graduated compression stockings; MEDENOX, Prophylaxis in Medical Patients with Enoxaparin; ns, not significant; PREVENT, Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized Patients Trial; qd, once-daily; tid, three times daily; UFH, unfractionated heparin; VTE, venous thromboembolism.

Table 2 Rates of prophylaxis in investigations of medical patients at-risk of venous thromboembolism

| Reference          | Study setting                  | Patients at risk of venous thromboembolism | Received any prophylaxis, % | Received appropriate prophylaxis, % |
|--------------------|--------------------------------|--------------------------------------------|-----------------------------|-------------------------------------|
| Tapson et al. (14) | IMPROVE registry               | Total: 6824                                | 61                          | ND                                  |
|                    |                                | US: 1773                                   | 61                          | ND                                  |
| Piazza et al. (6)  | DVT-FREE registry              | 2609                                       | 25                          | ND                                  |
| Burleigh et al. (23)| Retrospective analysis of patient discharges from hospitals across the US | 2,367,362 | 30 | ND      |
| Amin et al. (16)   | Retrospective analysis of patient discharges from hospitals across the US | 196,104 | 62 | 34*     |
| Yu et al. (15)     | Retrospective analysis of patient discharges from hospitals across the US | 62,012 | 26 | 15*     |
| Cohen et al. (13)  | ENDORSE multinational observational cross-sectional survey | Total: 15,487 | 48 | 40‡      |
|                    |                                | US: 2720                                   | 64                          | 48‡                                 |

*Based on 2001 ACCP recommendations.
‡Based on 2004 ACCP recommendation.
ACCP, American College of Chest Physicians; DVT, deep-vein thrombosis; ENDORSE, Epidemiologic International Day for the Evaluation of Patients at Risk for Venous Thromboembolism in the Acute Hospital Care Setting; IMPROVE, International Medical Prevention Registry on Venous Thromboembolism; ND, not determined.
patients receiving enoxaparin 40 mg compared with placebo (1.7% vs. 4.9%; \( p = 0.04 \)). The incidence of VTE in the enoxaparin 20 mg group (15%) and the placebo group (14.9%) was similar, supporting that enoxaparin 20 mg once-daily is not an appropriate regimen in medically ill patients. The efficacy and safety of the LMWH dalteparin was assessed in the Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized Patients Trial (PREVENT) (10). Dalteparin 5000 IU once-daily for up to 14 days significantly reduced the incidence of VTE by 45% compared with placebo (\( p = 0.002 \)), without significantly increasing major bleeding (Table 1).

Results from the Arixtra for Thromboembolism Prevention in a Medical Indications Study (ARTEMIS) provided the basis for ACCP recommendations regarding fondaparinux (11). In ARTEMIS, 849 medical patients were randomised to receive either fondaparinux 2.5 mg once-daily for 6–14 days or placebo. Fondaparinux significantly reduced the incidence of VTE by 46.7% compared with placebo (\( p = 0.029 \)), without an increase in major bleeding (Table 1). Unlike UFH, enoxaparin and dalteparin, fondaparinux is not currently US Food and Drug Administration-approved for VTE prophylaxis in medically ill patients. Concerns about the use of fondaparinux include a single placebo-controlled study, no significant reduction in DVT (5.6% fondaparinux vs. 9.1% placebo; \( p = 0.097 \)) and a 4-fold increase in VTE in patients with cancer (\( n = 98 \)) (17% fondaparinux vs. 3.9% placebo; \( p < 0.001 \)) (24).

There have been several head-to-head trials that have directly compared UFH and LMWHs in at-risk medical patients (Table 3) (25–30). Most of these trials have compared enoxaparin 40 mg once-daily to UFH 5000 IU three-times-daily. At present, no studies have evaluated dalteparin or fondaparinux to an active comparator group in medical patients.

The PRIME (Thromboembolism Prophylaxis in Internal Medicine with Enoxaparin) study group found an 85% reduction in the incidence of VTE with the use of LMWH, but superiority was not proven (Table 3) (26). Although major bleeding was not different between the groups, there was significantly less haematoma at the injection site in patients receiving enoxaparin compared with UFH (4.6% vs. 10.8%; \( p < 0.001 \)). The PRINCE (Thromboembolism Prevention in Cardiopulmonary Diseases with Enoxaparin) study group also found no significant difference between the two prophylactic regimens (Table 3) (27). Based on the fact that medically ill patients represent a very heterogeneous patient population, the PRINCE investigators conducted a subgroup analysis based on the different risk of VTE in patients with respiratory disease (6.5%) and in those with heart failure (13%). In the lower-risk respiratory disease patients, the incidence of VTE

| Table 3 | Randomised head-to-head clinical trials on VTE prophylaxis in hospitalised medical patients |
|--------|---------------------------------------------------|
| Reference | \( n \) | DVT detection | Regimens | VTE, % | Major bleeding, % |
| | | | | Enoxaparin | UFH | \( p \) | Enoxaparin | UFH | \( p \) |
| EMSG (25) | 442 | \(^{125}\text{I}-\text{fibrinogen scanning}\) | Enoxaparin 20 mg qd vs. UFH 5000 IU bid | 4.8 | 4.6 | ns | 0.9* | 1.8* | ns |
| PRIME (26) | 885 | Compression ultrasound | Enoxaparin 40 mg qd vs. UFH 5000 IU tid | 0.2 | 1.4 | 0.12 | 0.4 | 1.5 | ns |
| PRINCE (27) | 665 | Venography | Enoxaparin 40 mg qd vs. UFH 5000 IU tid | 8.4 | 10.4 | ns | 0.3 | 0.3 | ns |
| Harenberg et al. (28) | 877 | Venography | Enoxaparin 40 mg qd vs. UFH 5000 IU tid | 15.6† | 22.1† | 0.04 | 1.8* | 3.2* | ns |
| Hillbom et al. (29) | 212 | Venography | Enoxaparin 40 mg qd vs. UFH 5000 IU tid | 19.7 | 34.7 | 0.04 | 13.2‡ | 18.9‡ | ns |
| PREVAIL (30) | 1762 | Venography | Enoxaparin 40 mg qd vs. UFH 5000 IU bid | 10 | 18 | < 0.001 | 1.3 | 0.7 | 0.23 |

*Includes any bleeding.
†Primary outcome includes death and VTE.
‡Represents stroke haemorraghic transformation.
bid, twice-daily; DVT, deep-vein thrombosis; EMSG, Enoxaparin Medical Study Group; PREVAIL, Prevention of Venous Thromboembolism After Acute Ischaemic Stroke; PRIME, Thromboembolism Prophylaxis in Internal Medicine with Enoxaparin; qd, once-daily; ns, not significant; PRINCE, Thromboembolism Prevention in Cardiopulmonary Diseases with Enoxaparin; tid, three times-daily; UFH, unfractionated heparin; VTE, venous thromboembolism.
was similar between enoxaparin (7.1%) and UFH (5.9%). In the higher-risk heart failure patients, enoxaparin resulted in a near 40% relative reduction in VTE compared with UFH three-times-daily (9.7% vs. 16.1%). Although these data are from subgroup analysis, there is a suggestion of benefit with the use of LMWHs in higher-risk medically ill patients. This is supported by data from Harenberg and colleagues who demonstrated a significant reduction in VTE and death in patients receiving a LMWH compared with UFH three-times-daily (Table 3) (28). Similar to what was demonstrated in the PRINCE trial, as a patient’s risk of VTE increased, so did the benefit of LMWH over UFH. In the lower-risk respiratory disease patients, there was an absolute reduction with LMWH of 3.2% compared with UFH (9.4% vs. 12.6%). However, in higher-risk heart failure patients, the absolute reduction was 5.7% (14.7% vs. 20.4%), and the highest-risk ischaemic stroke patients received the greatest absolute reduction of 13.2% with a LMWH (26.5% vs. 39.7%). The evidence to use a LMWH in the high-risk subgroup of medically ill patients with ischaemic stroke is provided by Hillbom and colleagues, and the Prevention of Venous Thromboembolism After Acute Ischaemic Stroke (PREVAIL) Study, in which enoxaparin 40 mg once-daily was superior to UFH 5000 IU three-times-daily and twice-daily, respectively (29,30).

In a recent meta-analysis of 36 studies, the LMWHs were associated with a lower risk of DVT [relative risk (RR) 0.68; 95% confidence interval (CI): 0.52–0.88] and injection site haematoma (RR 0.47; 95% CI: 0.36–0.62) compared with UFH, but no significant difference was observed between the two agents in the risk of bleeding and thrombocytopenia (31). Similar results have been observed in a large US multi-hospital study that used administrative data to compare clinical outcomes among acutely ill medical patients receiving enoxaparin (n = 479) or UFH (n = 2837) in real-world clinical practice (32). The incidence of VTE was 1.7% with enoxaparin, which was significantly lower than the incidence of 6.3% observed with UFH (p < 0.001). The occurrence of major bleeding, death and thrombocytopenia was similar in the two groups.

**Appropriate dose of prophylaxis**

In addition to the type of prophylactic agent used, the selected dose and dosing frequency also have an important impact on patient outcomes and hospital resources. Unfractionated heparin has a relatively short half-life (0.5–3 h) and low bioavailability (29%) and is administered by subcutaneous injection either two- or three-times-daily (33). In contrast, the LMWHs have high bioavailability (81–100%) and longer half-lives (1.7–7 h) and can be administered as a single daily dose, improving convenience (33). As the LMWHs are predominantly cleared by the kidneys, there is the potential for dose-accumulation in patients with renal insufficiency (1). Patients with severe renal insufficiency [creatinine clearance (CrCl) 10–30 ml/min] can receive enoxaparin for thromboprophylaxis, but at a reduced dose of 30 mg once-daily as detailed in the prescribing information. Patients with mild or moderate renal insufficiency do not require dose adjustment with enoxaparin. Fondaparinux has 100% bioavailability and a half-life of 17–20 h, which also permits once-daily administration without the need for dose adjustments (33). However, fondaparinux is also cleared via the kidneys and should be used with caution in patients with moderate renal insufficiency (CrCl 30–50 ml/min) and is contraindicated in patients with severe renal insufficiency (CrCl 10–30 ml/min) (33).

The ACCP guidelines do not recommend a specific dosing frequency for UFH, however, current International Union of Angiology guidelines specify a three-times-daily regimen for medical patients at high risk of VTE (1,12). There are currently only two trials that suggest a possible benefit of UFH twice-daily in medically ill patients (20,34). One trial distributed 192 patients to control or one of four to other treatment groups (Table 1) (20). The group receiving UFH 5000 IU twice-daily experienced significantly fewer DVT events compared with control (1/39 UFH patients vs. 12/46 control patients).

Although these results were significant, the lack of randomisation, blinding and the small number of patients per group presented significant limitations to make strong conclusions about these data. The other trial by Halkin and colleagues evaluated UFH 5000 IU twice-daily compared with no therapy in 1102 patients (34). This trial demonstrated a significant reduction in mortality with the use of UFH (7.8%) compared with no therapy (10.9%; p < 0.05). Although this may be considered an impressive finding, there are significant limitations to these data. This was an uncontrolled, open-labelled trial conducted over 25 years ago. Patients in this trial were randomised by medical record number, which combined with the open-label design, demonstrated to have potentially influenced the number of patients considered eligible for treatment with UFH. Therefore, the trials suggesting a possible benefit of UFH twice-daily in medically ill patients have serious trial design flaws limiting their application in clinical practice.
There is a body of evidence suggesting a lack of benefit of UFH twice-daily in medically ill patients (Table 1). Cade and colleagues failed to demonstrate a significant reduction in DVT in a well-conducted randomised, double-blind, placebo-controlled trial (19). The Heparin Prophylaxis Study Group conducted the largest trial performed in medically ill patients ($n = 11,693$) (21). In this trial, there was no reduction in VTE or mortality (5.3% vs. 5.3%) with the use of UFH twice-daily compared with placebo. The Enoxaparin Medical Study Group (EMSG) demonstrated equal efficacy between UFH twice-daily and enoxaparin 20 mg daily for VTE prophylaxis in medically ill patients (Table 3) (25). These results are consistent with the findings from the MEDENOX trial in which 20 mg of enoxaparin was equal to placebo in preventing VTE (9).

In a recent meta-analysis of 36 studies in hospitalised medical patients, UFH 5000 IU three-times-daily was more effective in preventing DVT than UFH 5000 IU twice-daily when compared with controls (RR 0.27; 95% CI: 0.20–0.36 vs. RR 0.52; 95% CI: 0.28–0.96) (31). Similarly, in a meta-analysis of 12 trials, UFH three-times-daily compared with twice-daily showed a trend towards a decrease in the rate of PE (1.5 vs. 0.5; $p = 0.09$) and proximal DVT plus PE (2.3 vs. 0.9; $p = 0.05$), but an increase in the rate of major bleeding (0.96 vs. 0.35; $p < 0.001$) (35). On the basis of the available evidence, there is a need to clarify the most appropriate dosing frequency for UFH in at-risk medical patients.

**Appropriate duration of prophylaxis**

In most randomised clinical trials of medical patients, the duration of in-hospital prophylaxis is 6–14 days, which is considered the standard duration (9–11). The current average length of hospital stay is 4.8 days (36). As a result, if patients do not receive VTE prophylaxis postdischarge, they may not complete the course of prophylaxis, placing them at greater risk of VTE (16). Efficient prophylaxis implies that the standard duration is provided to patients (1). Clinical trials have demonstrated that extended-duration prophylaxis in these high-risk medical patients is effective in reducing the incidence of 'late' VTE events (9–11).

In the MEDENOX trial, eight additional VTE events, including four fatal PEs, occurred after the study medication was discontinued (9). Similarly, nine additional cases of symptomatic DVT were diagnosed between days 21 and 90 in PREVENT (10). In ARTEMIS, two-thirds of the VTE events and half of the fatal PE events were observed after the initial 6–14 days prophylaxis phase (11). Medical patients often have multiple risk factors for VTE, which are present after discharge and lead to prolonged risk (7). In a registry study of 1897 patients with confirmed VTE, nearly three-quarters of patients (73.7%) developed VTE in the outpatient setting, and approximately 40% of those events occurred in the first 30 days after the discontinuation of VTE prophylaxis (37). Patients hospitalised for non-surgical reasons accounted for 36.8% of all patients with VTE, with 66.9% of them diagnosed as having VTE within 1 month after hospital discharge, 19.9% between 1 and 2 months after hospital discharge, and the remainder (13.2%) between 2 and 3 months (37).

Clinical guidelines from the ACCP and International Union of Angiology advocate extended-duration prophylaxis in specific groups of high-risk surgical patients. However, no specific recommendations on duration of prophylaxis are provided for acutely ill medical patients (1,12). This lack of guidance regarding duration may reflect the scarcity of published data, as presently few clinical trials have been conducted in this area. The Extended Clinical Prophylaxis in Acutely Ill Medical Patients (ExCLAIM) trial included 4114 acutely ill medical patients with recent reduced mobility who received enoxaparin 40 mg once-daily for 10 ± 4 days. Patients were then randomly assigned to enoxaparin 40 mg or placebo for an additional 28 days. The incidence of any VTE was significantly reduced by 44% for patients receiving prolonged enoxaparin compared with placebo (2.8% vs. 4.9%; $p = 0.011$) with a numerically small, but statistically significant increase in major bleeding (0.6% vs. 0.15%; $p = 0.019$). These data are still awaiting publication in a peer-reviewed journal (38).

**Economic aspects of appropriate prophylaxis**

In addition to the clinical challenges, VTE also poses a major economic burden (39–41). In a large retrospective analysis, the total annual healthcare costs of a VTE event ranged from $7594 to $16,644, depending on the type of event and whether it was a primary or secondary diagnosis (40). Moreover, an economic analysis reported that an initial DVT event was associated with an annual hospitalisation cost of $17,512 compared with $680 in matched control patients (39). Furthermore, it is not only the initial costs of the primary DVT event, but patients are often at increased risk of recurrent events that add to the economic implications of the disease (40).

Studies have demonstrated that thromboprophylaxis is cost-effective compared with no prophylaxis
in medical patients, because the initial costs of VTE prophylaxis are offset by the avoidance of future costs associated with the downstream consequences of a VTE event (42–44). A recent study modelled patient outcomes and healthcare costs associated with prophylaxis in medical patients at-risk of VTE over 2 years (44). Total average costs per patient were higher in patients receiving no prophylaxis ($2245) compared with patients who received VTE prophylaxis ($1264 for the enoxaparin group and $1585 for the UFH group) (Figure 1) (44). Cost-effectiveness analysis models have also demonstrated that despite higher drug-acquisition costs, the LMWHs are more cost-effective than UFH (43,44). The LMWHs were also found to be cost-effective compared with UFH in a large study of real-world medical and surgical patients in the US ($3056 for the LMWHs compared with $3476 for UFH, representing a significant cost-saving of $420 in favour of the LMWHs (p < 0.001).

**Future perspectives**

Several healthcare organisations, such as the National Quality Forum, the Joint Commission on Accreditation of Healthcare Organizations, and the Agency for Healthcare Research and Quality, have recognised the need to reduce the large number of preventable VTE events in hospitalised patients. The National Quality Forum in collaboration with the Joint Commission has developed a set of six performance measures to allow the assessment of the quality and appropriateness of VTE prevention practices (46). The introduction of performance measures should increase the accountability of hospital management and clinical teams for implementing VTE prevention strategies and facilitate the process of improving adherence with best-practice guidelines. Consistent with the national drive towards optimising prophylaxis practices, the ACCP guidelines recommend that all hospitals should develop a formal, active strategy that addresses VTE prevention (1). A written, hospital-wide VTE prophylaxis policy is endorsed by the ACCP, and the use of computer decision support systems, preprinted orders and periodic audit and feedback is advocated.

In addition to the strategies outlined in the ACCP guidelines, other approaches have been shown to improve the level and appropriateness of thromboprophylaxis (47,48). Education, for example, has been shown to be a key component of a successful prophylaxis programme. A comprehensive pharmacy-driven educational programme in a 493-bed community teaching hospital, which included presentations and newsletters directed at nurses, pharmacists, and physicians on the improvement of VTE prophylaxis in medically ill patients significantly increased the use of any form of prophylaxis and increased appropriate prophylaxis (47). In addition, a randomised controlled study evaluating the use of a computer-alert program to prevent VTE among hospitalised patients increased the rate of both mechanical prophylaxis (10.0% vs. 1.5%; p < 0.001) and pharmacological prophylaxis (23.6% vs. 13.0%; p < 0.001) compared with the control group (48). The integration of several quality improvement initiatives into everyday practice should help to optimise current prophylaxis prescribing patterns and promote implementation of performance measures.

![Figure 1](image-url)  Total average cost of VTE prophylaxis per medical patient. Reproduced from Deitelzweig et al. 2008 (44).

HIT, heparin-induced thrombocytopenia; Tx, treatment; UFH, unfractionated heparin; VTE, venous thromboembolism
Conclusions

Clinical guidelines are based on up-to-date clinical evidence and consensus-based expert opinion, and they provide an important resource for healthcare professionals regarding optimum VTE prophylaxis practices. However, despite the existence of such guidelines and their widespread dissemination, VTE prophylaxis is often underutilised and prescribed inappropriately in day-to-day clinical practice. Failing to provide appropriate prophylaxis has clinical implications, in terms of the higher rates of preventable VTE-related morbidity and mortality, and also the considerable impact on already overstretched healthcare resources. Several initiatives have been developed to drive improvement, and in so doing, narrow the gap between guideline recommendations and clinical practice. The development of hospital-wide VTE prevention strategies and the implementation of national and local performance measures should increase the use of appropriate VTE prophylaxis and improve the clinical and economic outcomes of medical patients at risk of VTE.

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