Prophylaxis against venous thromboembolism in hospitalized medical patients: an evidence-based and practical approach

James D. Douketis, Imran Moinuddin

Department of Medicine, McMaster University and St. Joseph's Healthcare, Hamilton, ON, Canada

Abstract: To discuss the evidence regarding the efficacy and safety of anticoagulant prophylaxis against deep vein thrombosis (DVT) in hospitalized medical patients; to understand barriers to implementation of prophylaxis and how they can be overcome; and to have a practical approach as to which patients should and should not receive anticoagulant prophylaxis. The frequency of DVT in hospitalized medical patients, in the absence of prophylaxis varies from 10–15%. Autopsy studies have shown that pulmonary embolism (PE) is associated with 5–10% of deaths in hospitalized patients. With appropriate use of anticoagulant prophylaxis, there is a 57% reduction in the risk for symptomatic PE (relative risk [RR] 0.43, 95% CI 0.26–0.71), a 62% reduction in the risk for fatal PE (RR 0.38, 95% CI 0.21–0.69), and a 53% reduction in the risk for symptomatic DVT (RR 0.47, 95% CI 0.22–1.00). Anticoagulant prophylaxis is also associated with a non-significant increased risk for major bleeding (RR 1.32, 95% CI 0.73–2.37). Risk factors for DVT and bleeding in medical patients may help to identify patients in whom anticoagulant prophylaxis is indicated or contraindicated but validated risk stratifications schemes are lacking. Among hospitalized medical patients, randomized trials have established an acceptable therapeutic benefit-to-risk ratio of anticoagulant prophylaxis to reduce the incidence of clinically silent and symptomatic venous thromboembolism, including a reduction in the incidence of fatal PE. Additional research is needed to develop a validated risk stratification model for hospitalized medical patients that can help identify patients who would benefit most from anticoagulant prophylaxis.

Key words: anticoagulant prophylaxis, anticoagulants, medical patients, venous thromboembolism

INTRODUCTION

Venous thromboembolism (VTE), which consists of deep venous thrombosis (DVT) and pulmonary embolism (PE), is a major and often unrecognized cause of morbidity and mortality in hospitalized medical patients, with PE being the cause of mortality in 5–10% of all hospital-associated deaths [1]. Despite consensus that at-risk medical patients should receive VTE prophylaxis, administration of appropriate VTE prophylaxis remains suboptimal, with many at-risk medical patients receiving no or inadequate prophylaxis.

The objectives of this review are: 1) to become familiar with the evidence regarding the efficacy and safety of anticoagulant prophylaxis against VTE in hospitalized medical patients; 2) to understand barriers to widespread implementation of anticoagulant prophylaxis in medical patients and how they can be overcome; and 3) to have a practical approach as to which medical patients should, and which patients should not, receive anticoagulant prophylaxis.

Correspondence to:
Assoc. Professor James D. Douketis, MD, FRCP(C), Department of Medicine, St. Joseph's Hospital, McMaster University, 50 Charlton Ave. East, Hamilton, ON, LBN 4A6, Canada, phone: 001-905-521-6178, fax: 001-905-521-6068, e-mail: jdouket@mcmaster.ca
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Importance of VTE prophylaxis in hospitalized medical patients

Clinical significance of VTE in medical patients

Previous studies have shown that hospitalization for medical illness confers a 6- to 11-fold increased risk for developing VTE [2]. Linked administrative database studies indicate that the absolute risk for development of symptomatic VTE in hospitalized medical patients is 1.7% within 3 months of hospitalization [3]. Prospective studies have shown that in hospitalized medical patients who have at least one major risk factor for VTE, such as cardiac or respiratory disease, the absolute risk for developing DVT as detected by venography is approximately 10–15% if they do not receive prophylaxis [4,5]. Furthermore, studies have shown that 25–30% of non-fatal VTEs occur in patients with prior hospitalization

for medical illness [2,6], while 70–80% cases of fatal PEs occur in medical patients [1].

Uptake of VTE prophylaxis in medical patients

Despite the fact that the hospitalized medical patients are at a considerable risk for developing VTE, only 15–33% of at-risk medical patients receive VTE prophylaxis based on clinical practice audits [7-9] as compared to at-risk surgical patients, 85–95% of whom receive postoperative VTE prophylaxis [10,11].

A recent clinical practice audit was completed in 6 hospitals of Ontario, Canada which considered 1261 patients hospitalized on a general medicine ward for more than 3 days [12]. Of these patients, only 483 (38%) received anticoagulant prophylaxis. To further explore this gap between existing knowledge and clinical practice, a survey of 1601 health care professionals was conducted in Ontario, Canada to assess perceptions about VTE prophylaxis in medical patients, potential barriers to implementation and potential solutions to increased VTE prophylaxis [13]. Almost all respondents recognized the importance of VTE prophylaxis in medical patients but only half of them utilized current VTE prophylaxis strategies.

Reasons for underutilization of VTE prophylaxis in hospitalized medical patients

The reason for the suboptimal utilization of VTE prophylaxis in hospitalized medical patients is likely due to the fact that, unlike surgical patients in whom the need for prophylaxis is driven by the type of surgery they undergo, medical patients are a more heterogeneous group in terms of underlying disease and mobility status and it may not be clear who should (and should not) receive prophylaxis. From a practical perspective, the lack of established criteria as to which patients should (and should not) receive VTE prophylaxis may account, in part, for the low rates of prophylaxis administration in hospitalized medical patients. The aforementioned survey identified potential barriers to optimal use of anticoagulant prophylaxis in hospitalized medical patients [13]. These included perceived concerns about an increased risk for bleeding from anticoagulants, lack of clear indications and contraindications for anticoagulant prophylaxis, and lack of time to consider VTE prophylaxis in every patient.

Potential interventions to optimize prophylaxis in medical patients

The aforementioned survey identified several interventions to optimize VTE prophylaxis in medical patients. Yearly multi-educational meetings, pre-printed order sheets, pharmacist reminders to physicians, computerized reminders to physicians, and periodic audit/feedback to healthcare professionals are some of the interventions that have been considered as feasible and potentially successful for optimization of VTE prophylaxis in hospitalized medical patients.

Evidence that anticoagulant prophylaxis prevents clinically significant VTE

Implementation of anticoagulant prophylaxis in at-risk hospitalized medical patients is problematic, in part, because clinicians do not see the benefits derived from the intervention. Therefore, to convince clinicians to implement anticoagulant prophylaxis, there is a need for strong evidence that the intervention being used is efficacious, safe and easy to implement.

Most studies assessing anticoagulant prophylaxis have relied on asymptomatic DVT, detected by venography or ultrasound, as a measure of efficacy against no prophylaxis [4,14-21]. Individual trials and meta-analyses have consistently shown that anticoagulants reduce the risk for DVT by 39–60% and proximal DVT by 49–69% [4]. However, some authors have questioned the clinical significance of these findings, claiming that asymptomatic DVTs, especially those in distal (or calf) veins, are not clinically important [22,23]. The following rationale may support the clinical importance of asymptomatic DVT in hospitalized medical patients: because such patients are usually recumbent, the typical clinical features of DVT observed in ambulatory patients, such as leg pain and swelling, are unlikely to be present and the initial manifestation of DVT may be life-threatening PE [24].

Irrespective of the significance of asymptomatic DVT, the issue of whether anticoagulant prophylaxis is effective to prevent clinically important VTE may be addressed by considering the findings of a meta-analysis that assessed the efficacy of anticoagulants to prevent symptomatic DVT, symptomatic non-fatal PE, and fatal PE, all of which would be considered clinically important [25]. As shown in Table 1, anticoagulant prophylaxis was associated with a 57% reduction in the risk for any symptomatic PE (relative risk [RR] 0.43, 95% CI 0.26–0.71) [25], a 62% reduction in the risk for fatal PE (RR 0.38, 95% CI 0.21–0.69) [25], and a 53% reduction in symptomatic DVT (RR 0.47, 95% CI 0.22–1.00), though the later finding was not quite statistically significant. These findings should be considered within the context of the absolute risk reduction (ARR) and number needed-to-treat (NNT) with anticoagulant prophylaxis to prevent one symptomatic PE (ARR 0.29%, NNT 345), one fatal PE (ARR 0.25%, NNT 400) or one symptomatic DVT (ARR 0.43%, NNT 232).

Taken together, these findings support the efficacy of anticoagulant prophylaxis to prevent clinically silent (or asymptomatic) DVT and symptomatic DVT and PE. Though the ARRs for symptomatic outcomes are modest, the overall therapeutic benefits may be considerable as there are more than 7 million medical patients hospitalized annually in the U.S. alone [26].

Table 1. Effects of anticoagulant prophylaxis on venous thromboembolism and bleeding outcomes [25]

Outcome	Relative risk (95% CI)	Absolute risk reduction (%)†	Number needed-to-treat†
Deep vein thrombosis			
any (proximal or distal) asymptomatic	0.51 (0.39–0.67)	2.6	36
proximal asymptomatic	0.45 (0.31–0.65)	1.8	55
any (proximal or distal) symptomatic	0.47 (0.22–1.00)	–	–
Pulmonary embolism			
symptomatic (non-fatal + fatal)	0.43 (0.26–0.71)	0.29	345
fatal	0.38 (0.21–0.69)	0.25	400
Major bleeding	1.32 (0.73–2.37)	–	–
All-cause mortality	0.97 (0.79–1.19)	–	–

† Calculated for outcomes in which relative risk was statistically significant

Therapeutic options for VTE prophylaxis in medical patients

Anticoagulant methods of prophylaxis

Table 2 summarizes the different pharmacological agents available for VTE prophylaxis. These consist of unfractionated heparin (UFH), the low-molecular-weight heparins (LMWHs), consisting of enoxaparin or dalteparin, and the synthetic anti-factor Xa inhibitor fondaparinux [27]. All of these drugs have been assessed in large randomized trials involving medical patients. Tinzaparin is another LMWH that can be considered for VTE prophylaxis, but this drug has not been studied widely for VTE prophylaxis in medical patients.

Clinical factors and pharmacokinetics mainly determine the type of anticoagulant to be used for VTE prophylaxis. In patients with renal dysfunction (creatinine clearance <30 ml/min), UFH is considered safer as compared to LMWHs because of their potential for bioaccumulation in such patients due to their dependence on renal clearance [28]. However, according to a recent single-arm clinical trial, dalteparin 5000 IU once a day (OAD) does not demonstrate bioaccumulation (excessive anticoagulant effect) in critically ill patients with severe renal insufficiency [29]. Consequently, this drug may be used as an alternative to UFH in such patients.

In patients with prior heparin-induced thrombocytopenia (HIT), prophylaxis should be given with fondaparinux because it is a synthetic agent having no known cross reactivity with HIT antibodies, or danaparoid, a low-molecular-weight heparinoid used for the treatment of HIT [30,31].

Except for the very obese patients (body mass index ≥35 kg/m^2), the anticoagulant dose for VTE prophylaxis is a fixed daily dose that is not dependent on the body weight. However, in very obese patients, it may be reasonable to administer a higher anticoagulant dose such as enoxaparin 30 mg twice a day (*bis in die* – BID) regimen, which has been proven to be effective for VTE prophylaxis in surgical patients [32], as compared to 40 mg OAD regimen. There is some debate regarding the optimal dose of UFH. Two drug regimens (5000 IU BID and 5000 IU three times a day) have been studied in hospitalized medical patients and have been found to have superior efficacy as compared to no prophylaxis. However, it may be reasonable to use the higher dose regimen in high-risk or very obese patients.

Although a 7–10 day anticoagulation regimen is considered to be effective to prevent VTE in hospitalized medical patients; this issue still remains controversial, particularly in medical patients with chronic illness in whom the at-risk period can extend beyond 7–10 days. A recent randomized trial comparing extended-duration (5 weeks) and short-duration (10 days) VTE prophylaxis with enoxaparin, 40 mg OAD in 4726 patients showed that extended-duration prophylaxis decreased the risk for any VTE by 44% (2.8% vs. 4.9%, p = 0.001) and the risk for symptomatic VTE by 73% (0.3% vs. 1.1%, p = 0.004) [33]. This treatment benefit for VTE outcomes was maintained for 2 months after prophylaxis was stopped (3.0% vs. 5.2%, p = 0.0015). However, prophylaxis conferred a 4-fold increased risk for major bleeding (0.6% vs. 0.15%, p = 0.019).

Mechanical prophylaxis

Mechanical methods of VTE prophylaxis are considered for at-risk medical patients in whom anticoagulants are contraindicated because of active bleeding or if they are at increased risk for bleeding (e.g., recent gastrointestinal or intracranial bleed) [32]. These methods include graduated compression stockings and intermittent pneumatic compression devices (calf-length compressible sleeves or foot pumps).

Although no studies have assessed VTE prophylaxis with mechanical devices in hospitalized medical patients; efficacy is probable based on relevant surgical studies that found that mechanical devices should be used for at-risk medical patients in whom anticoagulants are contraindicated [32]. However, many patients find the compression stockings to be uncomfortable and constrictive, thereby limiting their effictive-

Table 2. Anticoagulant methods for VTE prophylaxis in medical patients

Anticoagulant type	Dosing	Comments
Unfractionated heparin	5000 IU BID	BID dosing considered standard treatment for medical patients
	5000 IU TID	TID dosing may be considered for selected high-risk patient groups or for very obese patients (BMI ≥35 kg/m^2)
		preferred drug in patients with impaired renal function
Enoxaparin	40 mg OAD	not studied in patients with impaired renal function
		increased dose (30 mg BID) has efficacy to prevent VTE after major surgery and may be considered for very obese patients
		only agent studied, at this time, for extended-duration (~5 weeks) prophylaxis
Dalteparin	5000 IU OAD	alternative to unfractionated heparin in patients with impaired renal function
Tinzaparin	75 IU/kg OAD or 4500 IU OAD	this dose has efficacy to prevent VTE after major surgery but not widely studied for VTE prophylaxis in medical patients
Fondaparinux	2.5 mg OAD	not studied in patients with impaired renal function
		longer half-life (17 hours) compared to low-molecular-weight heparins (4–6 hours)
		for patients with prior heparin-induced thrombocytopenia

BMI – body mass index, BID – twice a day (*bis in die*), IU – international units, OAD – once a day, TID – three times a day (*ter in die*), VTE – venous thromboembolism

ness, while the pneumatic compression devices are expensive and may not be widely available.

Identifying medical patients who should and should not receive VTE prophylaxis

Unlike in surgical patients, a risk stratification scheme has not yet been developed for medical patients to separate them into low, moderate or high risk group for VTE, thereby making decisions as to who should (and should not) receive anticoagulant prophylaxis problematic.

Table 3 attempts to provide a list of criteria that would warrant anticoagulant prophylaxis. Medical patients presenting with: 1) ischemic stroke; 2) chronic heart failure; 3) chronic obstructive pulmonary disease; or 4) active cancer (treated within 6 months or palliative) are considered a high-risk group for VTE and should receive anticoagulant prophylaxis. Other criteria for prophylaxis are listed in Table 3. Patient-specific factors that increase the risk for VTE include immobility (in bed >50% of time), recent (within 3 months) surgery or other hospitalization and prior VTE.

At-risk hospitalized medical patients who should not receive anticoagulant prophylaxis include: 1) those with active bleeding, such as from gastrointestinal tract, intracranial bleeding or active bleeding from any other site; and 2) those who are at risk for bleeding, such as patients who had recent (within 4 weeks) bleeding, or have impaired hemostasis (international normalized ratio >1.5; activated partial thromboplastin time >40 sec; or platelet count $<75 \times 10^9$/l). In these at-risk hospitalized medical patients, mechanical methods of prophylaxis should be considered.

Risks of anticoagulant prophylaxis in medical patients

The two major risks of anticoagulant prophylaxis are bleeding and HIT. Bleeding typically occurs at the site of injection; however, it is not uncommon to have bleeding at a remote site such as the gastrointestinal tract with an occult peptic ulcer that is prone to bleeding. The incidence of clinically significant bleeding is between 0.2–5.6% [4,14-21]. The relative risk for having clinically significant bleeding in patients receiving anticoagulant prophylaxis is 32% as compared to patients who do not receive anticoagulant prophylaxis [25]. The risk however did not achieve statistical significance (RR 1.32, 95% CI 0.73–2.37) but this may be because the pooled studies were underpowered to show a difference in risk.

Heparin-induced thrombocytopenia is an infrequent, but a potentially devastating complication of anticoagulants derived from heparin, and is associated with arterial or venous thrombosis. The risk of HIT is substantially less in medical patients as compared to the surgical patients with the inference that the surgical milieu may promote the development of HIT. The absolute risk for developing HIT in surgical patients receiving anticoagulant prophylaxis with UFH is 2.6% [34], as compared to 1.4% (95% CI 0.5–3.2) in medical patients receiving anticoagulant prophylaxis with low-dose UFH [35]. The absolute risk for HIT in surgical patients who receive anticoagulant prohylaxis with LMWH is 0.2% [33].

Table 3. Criteria for use and avoidance of anticoagulant prophylaxis in hospitalized medical patients

Indications for anticoagulant prophylaxis	Comments
Decreased mobility	no standardized definition for decreased mobility VTE prophylaxis reasonable in patients with "complete bed rest"; "bed rest with bathroom privileges"; or confined to bed >50% of time
Previous DVT or PE	major risk factor for hospital VTE
Recent hospitalization for surgery or other illness	major risk factor for hospital VTE
Ischemic stroke	risk for VTE in patients with lower limb paralysis or paresis is 40–60% without prophylaxis
Congestive heart failure	most hospitalized patients with this disease will have NYHA class III or IV congestive heart failure
Chronic obstructive/interstitial lung disease	most hospitalized patients will have severe forms of these diseases
Severe inflammatory disease	e.g., flare-up of inflammatory bowel disease, rheumatoid arthritis or systemic lupus erythematosus
Active cancer	e.g., cancer that has been treated within the past 6 months with surgery, radiotherapy or chemotherapy or is palliative
Severe infectious disease	e.g., pneumonia, pyelonephritis, cellulitis, meningitis, sepsis
Contraindications to anticoagulant prophylaxis	**Comments**
Actively bleeding	e.g., patients admitted due to gastrointestinal or intracranial bleeding
At high risk for bleeding	e.g., subjective assessment that may include patients with recent (within 4 weeks) bleeding that required hospitalization
Impaired hemostasis	e.g., INR >1.5; PTT >40 sec; platelets $<75\times10^9$/l

DVT – deep venous thrombosis, INR – international normalized ratio, PE – pulmonary embolism, PTT – partial thromboplastin time, other – see Table 2

SUMMARY

Venous thromboembolism has been acknowledged as a clinically significant and common medical problem in hospitalized medical patients. Recent clinical trials have established an acceptable therapeutic efficacy of currently available prophylactic anticoagulants.

However, additional research is needed to develop a validated risk stratification model for hospitalized medical patients that can help identify patients who would benefit most from anticoagulant prophylaxis. Furthermore, there is a need to encourage the routine use of VTE prophylaxis in at-risk medical patients through proper implementation of current evidence-based guidelines in hospitals.

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