

Prevention of Venous Thromboembolism in Medical Patients: Recent Advances and Future Directions

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Deep vein thrombosis and pulmonary embolism, together referred to as venous thromboembolism, represent a leading cause of in-hospital morbidity and mortality. PE is responsible for 5%–10% of in-patient deaths, making this the most common form of preventable death in hospitalized patients [1].

A common presentation (up to 10%) of PE is sudden death without preceding symptoms of DVT, thus VTE prevention is an important goal in hospital practice [2]. Furthermore, chronic complications such as pulmonary hypertension and the post-phlebotic syndrome are causes of significant morbidity resulting from acute VTE and have significant health and economic consequences [3,4].

The need for VTE prophylaxis in both surgical and medical patients is well established, with evidence-based guidelines available for both groups of patients [5-7]. However, these recommendations have been implemented far more widely in surgical than in medical departments [8,9]. Reasons for this difference are not fully understood but may be related to clinician perception of VTE risk: surgeons, particularly orthopedists and trauma surgeons, are more aware of the significant VTE risk in their patients than are internists [10].

In this paper we review the published studies on VTE prophylaxis in medical patients, focusing on important recent research. We also present recently published practice guidelines for VTE prevention in medical patients. Finally, we discuss methods to improve compliance with VTE prevention strategies.

PE = pulmonary embolism
 DVT = deep vein thrombosis
 VTE = venous thromboembolism

RANDOMIZED CONTROLLED STUDIES OF VTE PREVENTION IN MEDICAL PATIENTS

MEDENOX [11] was the first randomized multicenter study to explore the efficacy and safety of thromboprophylaxis in patients with acute medical illness at risk for VTE, which had previously been documented only in surgical patients. The study was conducted in 60 centers in 9 countries. The 1102 study patients were randomized into 3 groups to receive: subcutaneous enoxaparin 40 mg daily, subcutaneous enoxaparin 20 mg daily, or placebo – each for 6–14 days. Patients were included if they were over age 40 years and had one of the following conditions: acute respiratory failure (not on ventilator support), congestive heart failure (New York Heart Association III or IV), acute infection, an acute rheumatic disorder, an episode of inflammatory bowel disease, and at least one of the following additional risk factors for VTE: age > 75, previous VTE, hormone therapy, obesity, chronic heart or respiratory failure. Patients with stroke or known thrombophilia were not included. The primary outcome was DVT or PE in the first 14 days, and secondary outcomes were DVT or PE within 110 days. The VTE incidence was 5.5% among patients receiving enoxaparin 40 mg/day while those receiving enoxaparin 20 mg had a 15% incidence of VTE, and patients in the

placebo arm had a 14.9% incidence of VTE. Adverse events (mortality, major hemorrhage and thrombocytopenia) were similar in all three groups. This

study therefore documented the incidence of VTE in medical patients and also established the efficacy of prophylaxis in these patients as well as the appropriate dosage of enoxaparin.

THE-PRINCE study [12] aimed to determine the efficacy and safety of enoxaparin compared to unfractionated heparin for thromboprophylaxis in patients with heart failure or severe respiratory disease. This was a multicenter, randomized, open-label study conducted in 64 medical departments in Germany. Patients were randomized to receive subcutaneous enoxaparin 40 mg daily or subcutaneous UFH 5000 units 3 times daily for 10 ± 2 days. The primary endpoint was VTE up to one day after the end of the treatment period. Altogether, 665 patients were

UFH = unfractionated heparin

enrolled of whom 451 could be evaluated. The incidence of VTE in those patients who had received enoxaparin was 8.4% and in those who had received UFH 10.4%. In the group that received enoxaparin there were fewer deaths, less bleeding and fewer adverse events ($P = 0.044$). This study concluded that enoxaparin is at least as effective as UFH in preventing VTE in acutely ill medical patients, has a better side effect profile and has an advantageous once-daily administration.

The PREVENT study [13] examined the efficacy of the low molecular weight heparin dalteparin in preventing VTE in medical patients. This was a randomized, multicenter, multinational, placebo-controlled study. Of the 3706 patients in 219 centers in 26 countries, 1518 received dalteparin and 1473 received placebo; both groups could be assessed. Inclusion criteria were similar to those of the MEDENOX study. Patients were randomized to receive either subcutaneous dalteparin 5000 units once daily or placebo for 14 days. Patients were evaluated for VTE every day during admission, on the last day of treatment, and on day 21 and day 90. Primary endpoints were all venous thromboembolic events or sudden death within 21 days. Secondary endpoints were all-cause mortality by day 14, 21 and 90; symptomatic DVT on day 21; bleeding, allergic reactions and thrombocytopenia by day 21; or symptomatic VTE by day 90. Dalteparin reduced the occurrence of VTE from 4.96% in the placebo group to 2.77% in the treatment group ($P = 0.0003$) and was not associated with increased major hemorrhage. This study also showed the need for VTE prophylaxis in these high risk medical patients and established the efficacy and safety of dalteparin for this purpose.

The ARTEMIS study [14] examined the efficacy and safety of the pentasaccharide fondaparinux in the prevention of VTE in elderly medical patients. A total of 849 patients were randomized to receive fondaparinux 2.5 mg daily or placebo for 6–10 days. The incidence of VTE was 10.5% in the placebo arm and 5.6% in the fondaparinux arm ($P = 0.029$). Major bleeding was identical in both arms (0.2%). Mortality at day 32 was 3.3% in the fondaparinux group and nearly double that (6%) in the placebo group. While this study has been criticized for its randomization to a placebo group, it demonstrated that a new class of anticoagulants, namely a pentasaccharide, is effective and safe in the prevention of VTE in medical patients.

The PREVAIL study [15] compared the efficacy and safety of enoxaparin to UFH in patients with acute ischemic stroke in whom the prevalence of DVT is 20–50%. Pulmonary embolism is the third most common cause of death in these patients (after stroke itself and infection). The study population comprised 1762 patients in 200 centers with computed tomography-

confirmed acute ischemic stroke who could not walk and were within 48 hours of admission; these patients were randomized to receive subcutaneous UFH 5000 IU twice daily or subcutaneous enoxaparin 40 mg daily, both for a period of 10 days. Primary endpoints were symptomatic or asymptomatic DVT, PE or fatal PE. Safety endpoints were intracranial hemorrhage or major extracranial hemorrhage. Enoxaparin was found to more effectively reduce the incidence of VTE in these patients from 18% to 10% (relative risk reduction of 43%) and was more convenient to administer due to its once-daily dose. Enoxaparin and UFH resulted in the same incidence of intracranial and major extracranial hemorrhage (1%).

The EXCLAIM study [16] was based on the need for VTE prophylaxis in medical patients as shown in the studies detailed above. Acutely ill medical patients are likely to be relatively immobilized after hospital discharge and this study set out to establish the appropriate duration of prophylaxis therapy. It was a multicenter randomized study. All patients were over 40 and were hospitalized for an acute medical illness that had rendered them immobilized for up to 3 days. All eligible patients received 10 ± 4 days of subcutaneous enoxaparin 40 mg daily. Thereafter, patients were randomized to receive either subcutaneous enoxaparin 40 mg daily or placebo for a further 28 ± 4 days. The primary efficacy endpoint was the incidence of DVT (symptomatic and asymptomatic) or PE. Safety endpoints were major hemorrhage and all-cause mortality.

Compared with placebo, extended enoxaparin therapy reduced the relative risk of all VTE events by 44% (from 4.9% to 2.8%), of asymptomatic VTE by 34% (from 3.7% to 2.5%), and relative risk of symptomatic VTE by 73% (from 1.1% to 0.3%). Major bleeding occurred in 12 patients receiving extended-duration enoxaparin compared with 3 patients receiving placebo (0.6% vs. 0.1%, $P = 0.0192$). There was no difference in all-cause mortality at 90 days in the two arms. This study therefore concluded that extended-regimen thromboprophylaxis with enoxaparin is both effective and safe in acutely ill medical patients who are immobilized.

Table 1 summarizes the main features of published randomized studies of VTE prophylaxis in medical patients.

ACCP GUIDELINES FOR VTE PROPHYLAXIS IN MEDICAL PATIENTS

The American College of Chest Physician guidelines published in June 2008 represent the most current practice recommendations for VTE in general and in medical patients

in particular [7]. The ACCP guidelines recommend that acutely ill medical patients who are confined to bed receive thromboprophylaxis if they have at least one risk factor for VTE in addition to their immobility. Risk factors include active cancer, previous VTE, sepsis, acute neurological disease, and inflammatory bowel disease. Chemical prophylaxis using LMWH, UFH or fondaparinux are equally acceptable (grade 1A evidence), and in the event of a contraindication to anticoagulant use, graded compression stockings or intermittent pneumatic compression devices should be used (grade 1A evidence). There is currently no recommendation for routine extended out-of-hospital VTE prophylaxis.

IMPLEMENTATION OF VTE PROPHYLAXIS GUIDELINES

The ENDORSE study [17] was an international, observational cross-sectional survey designed to assess the prevalence of VTE risk in hospitalized patients and to determine the proportion of at-risk patients receiving appropriate prophylaxis. Patients were enrolled from 358 randomly selected hospitals in 32 countries on 6 continents. All patients were either ≥ 40 years if admitted to a medical ward or ≥ 18 years if admitted to a surgical or trauma ward. Patient charts were reviewed and ACCP guidelines were used to determine VTE risk and prophylaxis use. A total of 68,183 patient charts were reviewed: 37,356 (55%) were medical and 30,827 (45%) were surgical patients. In the total study population, 64.4% of the surgical patients were judged as requiring VTE prophylaxis and 58.5% of them received VTE prophylaxis, while 41.5% of medical patients were candidates for VTE prophylaxis but only 39.5% of them received VTE prophylaxis. This study thus demonstrates that, overall, more than 50% of acutely hospitalized patients require VTE prophylaxis and currently only half of these patients receive prophylaxis. Furthermore, VTE prophylaxis is practiced to a greater extent by physicians treating surgical patients than those treating medical patients.

Reasons for this difference in practice are not well established but may be because it is easier to assess surgical than medical patients regarding the need for VTE prophylaxis. The type of surgical procedure that the patient will undergo is one of the dominant factors in VTE risk assessment, whereas in medical patients the need for prophylaxis may be less obvious and more difficult to determine since immobilization is a major risk factor for VTE in medical patients and this may vary over hospital stays. Also, studies determining the need for VTE prophylaxis in surgical patients predate those in medical patients, thus physicians have had longer exposure to VTE prophylaxis recommendations in surgical patients [18].

LMWH = low weight molecular heparin

Table 1. Summary of the recent randomized controlled studies of venous thromboembolism prophylaxis in medical patients

Ref.	Study	Study population	Study arms	Incidence of VTE*
11	MEDENOX	Age > 40 years with acute illness and risk factor for VTE	Enoxaparin 40 mg vs. enoxaparin 20 mg vs. placebo	Enoxaparin 40 mg – 5.5% Enoxaparin 20 mg – 15% Placebo – 14.9%
12	THE-PRINCE	CHF or respiratory disease	Enoxaparin 40 mg vs. UFH 5000 units tid	Enoxaparin 40 mg – 8.4% UFH – 10.4%
13	PREVENT	Age > 40 years with acute illness and risk factor for VTE	Dalteparin 5000 units vs. placebo	Dalteparin – 2.77% Placebo – 4.96%
14	ARTEMIS	Age > 60 years with acute illness and immobilized > 3 days	Fondaparinux 2.5 mg vs. placebo	Fondaparinux – 5.6% Placebo arm – 10.5%
15	PREVAIL	Acute ischemic stroke, non-ambulatory	Enoxaparin 40 mg vs. UFH 5000 units bd	Enoxaparin 40 mg – 10% UFH – 18%
16	EXCLAIM	Age > 40 years with acute illness and immobilized for up to 3 days	Enoxaparin 40 mg vs. placebo (for 28 ± 4 days after initial enoxaparin for all patients)	Enoxaparin 40 mg – 2.8% Placebo – 4.9%

* Results are all statistically significant with a *P* value < 0.05.
CHF = congestive heart failure, UFH = unfractionated heparin

METHODS FOR IMPROVING ADHERENCE TO VTE PROPHYLAXIS GUIDELINES

A number of studies have shown that alerting physicians to patients with VTE risk increases the probability of giving VTE prophylaxis.

Dexter et al. [19] conducted a randomized controlled trial in which a computerized system automatically reminded physicians of hospitalized patients in need of VTE prophylaxis. Patients were randomized to an intervention or control group. Prophylactic heparin was given in 32.2% of patients in the intervention group as compared 18.9% of patients in the control group.

In another study, Kucher and team [20] evaluated the use of a computer alert system to improve VTE prophylaxis in medical and surgical patients. A computer program was devised to identify patients at increased risk for VTE according to eight predetermined risk factors. Each of these was weighted according to a point scale and classified as a major, intermediate or minor risk factor. Patients were then assigned a cumulative score of risk for VTE and were randomized to a control or intervention group. Physicians of patients in the intervention group received a computerized alert recommending the use of VTE prophylaxis. These physicians were required to acknowledge receipt of the alert and to document a decision to omit VTE prophylaxis or choose from options for prophylaxis of VTE including compression stockings, heparin or warfarin. Physicians of patients assigned to the control group were not alerted and were unaware of participation in the study. All patients were then fol-

lowed for 90 days. The primary endpoint was DVT or PE in the patients studied. Orders for VTE prophylaxis in the intervention group were twice those in the control group (33.5% vs. 14.5%) and there was a 41% reduction in the incidence of VTE in the intervention versus control group. There was no difference in bleeding or mortality between the two groups.

A recently published study encouragingly reported on the sustained efficacy of an electronic alert system for preventing VTE in hospitalized patients. A Spanish group [21] screened more than 19,000 patients for eligibility for VTE prophylaxis over three 6 month periods in 2005 (pre-study phase), 2006 and 2007. In 2006, electronic alerts were sent to the physicians of 32.8% of the patients (the percent needing VTE prophylaxis), and in 2007, alerts were sent to 32.2%. Appropriate prophylaxis was ordered by 89.7% (2006) and 88.5% (2007) of physicians treating surgical patients, and 49.2% (2006) and 64.4% (2007) of physicians treating medical patients. This study demonstrates the tremendous educational impact of the alert system on the medical setting and its ability to achieve sustained compliance with prophylaxis guidelines. An accompanying editorial [22] saliently notes that, ultimately, electronic systems should not replace physicians but should complement and guide them in their decision-making processes.

COST-EFFECTIVENESS OF THROMBOPROPHYLAXIS IN MEDICAL PATIENTS

Analyses of the cost-benefit ratio for the use of prophylactic doses of UFH and LMWH have been performed in Europe and the United States. In the U.S., Deitelzweig and co-authors [21] used a Markov model to compare the additional costs accrued by patients receiving either UFH or LMWH for VTE prophylaxis to the costs of treating VTE and anticoagulant-related major hemorrhage in a theoretical cohort of hospitalized medical patients. They concluded that both UFH and LMWH perform favorably compared to no prophylaxis in economic terms.

A similar study was performed in Germany using safety and efficacy parameters from the MEDENOX and THE-PRINCE studies. Once again the use of both UFH and LMWH was found to be cost-effective when considering expenses incurred in the treatment of established VTE [24]. Interestingly, both studies demonstrated a small cost advantage from the use of enoxaparin compared to UFH.

CONCLUSIONS

In this paper we described the strides that have been made over the past decade in defining appropriate VTE prophylaxis for hospitalized medical patients. Recognition of the fact that

recently admitted at-risk medical patients continue to be at risk for VTE for at least a month after discharge introduces the field of VTE prophylaxis into the realm of the primary community physician who will also need to be familiarized with appropriate prophylactic strategies for these patients.

Despite these high quality studies and ensuing practice guidelines, there is evidence that throughout the world VTE prophylaxis, especially in medical patients, is under-utilized leading to excess morbidity and mortality. Novel methods utilizing the power of bioinformatics have been successfully implemented to improve physician performance in this area.

Clearly, more needs to be done and this is reflected by the recent "call to action" issued by the Surgeon General of the USA, who noted: "... the Institute of Medicine has classified the

failure to provide appropriate screening and preventive treatment to hospitalized, at-risk patients as a medical error, and the Agency for Healthcare Research and Quality has ranked the provision of such preventive treatment as one of the most important things that can be done to improve patient safety. Proven effective measures are available to prevent and treat DVT and PE in high risk individuals" [23]. It behooves all physicians caring for patients at risk for VTE to heed this call.

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