REVIEW

Prevention of venous thromboembolism in medically ill patients: a clinical update

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The risk of venous thromboembolism (VTE) in hospitalised medically ill patients is often underestimated, despite the fact that it remains a major cause of preventable morbidity and mortality in this group. It is not well recognised that the risk of VTE in many hospitalised medically ill patients is at least as high as in populations after surgery. This may partly be attributed to the clinically silent nature of VTE in many patients, and the difficulty in predicting which patients might develop symptoms or fatal pulmonary embolism. Two large studies, Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized Patients Trial and prophylaxis in MEDical patients with ENOXaparin, have shown that low-molecular-weight heparins provide effective thromboprophylaxis in medically ill patients, without increasing bleeding risk. Recent guidelines from the American College of Chest Physicians recommend that acutely medically ill patients admitted with congestive heart failure or severe respiratory disease, or those who are confined to bed and have at least one additional risk factor for VTE, should receive thromboprophylaxis.

Venous thromboembolism (VTE) remains a major cause of morbidity and mortality in hospitalised medical patients. The incidence of VTE has been reported to be at least as high in this patient group as in patients undergoing general surgery.[1–3] Available data indicate that the frequency of deep vein thrombosis (DVT) in medically ill patients, in the absence of prophylaxis, varies from 10% to 26%.[4–6] Pulmonary embolism is responsible for up to 10% of deaths that occur in hospital, and 75% of fatal pulmonary emboli are in medical patients.[7]

The conditions that predispose a patient to VTE are well known and include venous stasis, endothelial injury and hypercoagulability.[8 9] However, as it is difficult to predict which patients will develop clinically important VTE, and fatal pulmonary embolism can develop without warning, it has been argued that routine thromboprophylaxis should be given to all patients considered to be at risk of VTE.[3]

For the tailoring of appropriate thromboprophylaxis, the importance of identifying medically ill patients at risk of VTE is increasingly recognised by clinicians,[1 2 10] although evidence from several countries indicates that thromboprophylaxis continues to be underused in these patients.[11–13] However, recent data from two large clinical trials, PREVENT (Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized Patients Trial) and MEDENOX (prophylaxis in MEDical patients with ENOXaparin), have shown the efficacy of low-molecular-weight heparins (LMWHs) for thromboprophylaxis in hospitalised medically ill patients[14 15] and should now prompt a reappraisal of current clinical practice.

RISK OF VTE IN MEDICALLY ILL PATIENTS

Risk factors for VTE have been analysed in several epidemiological studies[3 16–18] and are summarised in the guidelines on antithrombotic and thrombolytic treatment published by The American College of Chest Physicians (ACCP).[19] An increased risk of VTE is generally associated with patient-related characteristics (such as age, obesity and restricted mobility) and disease-related characteristics (including malignancy, congestive heart failure, stroke and recent myocardial infarction).

Many hospitalised medically ill patients have multiple risk factors for VTE, and the risks seem to be cumulative.[3 17 19] Although there is much less evidence for medically ill patients than for patients undergoing surgery,[19] it is well known that patients with thrombophilia or a history of VTE are at increased risk of VTE, as are patients with lower limb paralysis from acute ischaemic stroke.[20] Moreover, evidence is accumulating that patients hospitalised with conditions requiring medical treatment, such as acute cardiovascular or pulmonary disease, cancer or acute infectious disease, are also at increased risk of VTE (table 1).[3 17 22] Age, obesity and immobility are additional, patient-related factors that increase the risk of VTE.[17]

THROMBOPROPHYLAXIS IN CLINICAL PRACTICE

Much of the research on the prevention of VTE conducted in the past two decades has concentrated on populations undergoing surgery, with only limited attention given to medically ill patients.[19] Furthermore, it is generally recognised that routine thromboprophylaxis continues to be less widely used in the medically ill compared

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Abbreviations: ACCP, The American College of Chest Physicians; DVT, deep vein thrombosis; LDUH, low-dose unfractionated heparin; LMWH, low-molecular-weight heparin; MEDENOX, prophylaxis in MEDical patients with ENOXaparin; PREVENT, Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized Patients Trial; VTE, venous thromboembolism

Table 1 Risk factors for venous thromboembolism in hospitalised medically ill patients[19 21]

Acute medical risk factors
Acute medical illnesses, eg acute myocardial infarction, heart failure, respiratory failure, acute infectious disease
Active cancer
Treatment for cancer (hormonal, chemotherapy, radiotherapy)
Inflammatory bowel disease
Nephrotic syndrome
Myeloproliferative disorders
Paroxysmal nocturnal haemoglobinuria
Central venous catheter
Vena caval filter
Immobility
Permanent risk factors
Advanced age
Obesity
Varicose veins
Previous venous thromboembolism
Oestrogen-containing oral contraception or hormone replacement therapy
Paresis
Inherited or acquired thrombophilia

with the population undergoing surgery in hospitals, despite the risk in medically ill patients being at least as high as in patients undergoing surgery.[6 10–12 22–24]

A retrospective study assessed adherence to the published guidelines in 516 patients discharged from two hospitals in Italy, with clinical indications for VTE prophylaxis, and found that only a small proportion of patients received adequate prophylaxis.[11] Clinical indications for VTE prophylaxis, according to consensus guidelines, were identified in 165 (32%) patients. Of these, 42 patients had clinical contraindications to antithrombotic treatment and 11 were receiving long-term anticoagulant treatment, leaving 112 patients eligible for the review. Thromboprophylaxis had been prescribed for only 52 of these 112 (46%) patients. The use of thromboprophylaxis was more common in patients with acute ischaemic stroke or heart failure than in those with malignancy, acute infection or acute respiratory failure.

A retrospective review of all cases of DVT and pulmonary embolism diagnosed over a 1-year period in a large teaching hospital in Montreal, Canada, supports these findings.[12] Among 65 patients with VTE for whom thromboprophylaxis was indicated according to the ACCP guidelines, thromboprophylaxis was considered inadequate in 44 (68%); it was omitted entirely in 21 patients and was given for an inadequate duration in 10 patients. The evidence therefore suggests that adequate thromboprophylaxis is not universally implemented in current clinical practice, despite the recommendations of international guidelines. The ACCP suggests that a lack of awareness of the magnitude of the problem and concerns about bleeding are the most common explanations for underuse of thromboprophylaxis in hospitalised medically ill patients.[19] Further obstacles to the widespread use of thromboprophylaxis in medically ill patients include difficulties in identifying patients at risk of VTE and, until recently, a lack of firm evidence of the safety and efficacy of thromboprophylaxis in medically ill patients.

VTE PREVENTION IN MEDICALLY ILL PATIENTS

Thromboprophylaxis can be achieved by physical or pharmacological means. Physical approaches include the use of intermittent pneumatic compression devices or graduated compression stockings. These approaches have not been studied in heterogeneous medically ill populations and are not generally recommended for routine prophylaxis.[8 19] Intermittent pneumatic compression has several limitations in medical populations: mechanical devices must be worn continuously and this restricts patient mobility, which paradoxically may increase the risk of VTE; also, the devices are uncomfortable to wear, which reduces patient compliance. Although graduated compression stockings may have a role in reducing the risk of DVT in patients undergoing surgery,[25] they are generally reserved for patients with contraindications to anticoagulant-based thromboprophylaxis, or as an adjunct to these agents.[8 19]

For pharmacological prophylaxis, low-dose unfractionated heparin (LDUH) and LMWHs are generally recommended for medically ill patients.[8 9 19 26 27] Unfractionated heparin has been the reference agent in the prevention of VTE for many years,[9 26] but evidence for its efficacy is based largely on data from surgical populations, in addition to open-label studies. Unfractionated heparin also has disadvantages compared with LMWHs: it requires administration by subcutaneous injection twice or three times daily, and has less predictable pharmacokinetics.[28] For these reasons, in surgical thromboprophylaxis, LMWHs have generally replaced LDUH.

In a meta-analysis of nine trials comparing prophylactic LDUH or LMWHs with no active treatment in medically ill populations, no marked difference was detected between the heparins in the incidence of DVT, clinical pulmonary embolism or mortality.[27] Furthermore, LMWHs were associated with a 52% risk reduction in major haemorrhage compared with LDUH ($p = 0.049$). However, in common with most meta-analyses, these findings should be interpreted with caution in view of the differences in doses of heparins used in the individual trials, and the heterogeneity of the patient populations that were studied.

The two largest studies in the meta-analysis evaluated the effect of thromboprophylaxis on mortality. The first, a multicentre, randomised, double-blind, placebo-controlled trial of nadroparin (7500 U/day for a maximum of 21 days) in 2474 hospitalised medically ill patients with restricted mobility, showed no significant differences in all outcome measures, including mortality, between treatment groups.[29] In a larger study of patients admitted to infectious disease wards, in which 11 693 patients aged >55 years received open-label LDUH (5000 U twice daily for a maximum of 21 days) or no treatment, no significant difference in total mortality was observed.[30]

More recently, two large trials have evaluated the efficacy and safety of LMWHs in medically ill patients. The first, MEDENOX, involved the comparison of two doses of enoxaparin with placebo in 1102 acutely medically ill patients.[15] Subsequently, PREVENT investigated the role of thromboprophylaxis with dalteparin in acutely medically ill patients.[14] The results of PREVENT are noteworthy, because it is the largest double-blind, placebo-controlled trial of LMWH prophylaxis to be undertaken in this indication, and the first such trial to use a composite of major DVT and clinical VTE as the primary end points.[31]

PREVENT randomly assigned 3706 medically ill patients to receive either subcutaneous dalteparin 5000 IU/day or placebo for 14 days. The primary end point was clinically relevant VTE at day 21, defined as symptomatic DVT, pulmonary embolism or sudden death, or asymptomatic proximal DVT detected by compression ultrasonography. PREVENT showed a significant 45% reduction in the primary end point in patients randomised to receive dalteparin compared with those receiving placebo, from 4.96% to 2.77% ($p = 0.002$). Proximal DVT occurred in 29 patients receiving dalteparin compared with 60 patients receiving placebo. Importantly, there was no significant difference in bleeding risk between the two treatment groups.

PREVENT builds on the data from the MEDENOX study,[15] which reported a reduction in the incidence of VTE in

866 medically ill patients treated with 40 mg enoxaparin compared with placebo (5.5% *v* 14.9%). These results are mainly based on the incidence of venographically confirmed DVT, including asymptomatic distal DVT. However, the clinical relevance of asymptomatic DVT in the calf veins is uncertain, and proximal DVT is believed to carry a higher risk of pulmonary embolism and mortality than distal DVT.[32–34] A recently published retrospective analysis of the PREVENT data has shown a link between asymptomatic proximal DVT and increased mortality, and highlights the importance of prevention of VTE, as asymptomatic routine surveillance imaging is not performed in asymptomatic patients.[34]

In PREVENT, the marked reduction in VTE, based mainly on the reduction of asymptomatic proximal DVT in patients treated with dalteparin, is a clinically relevant finding. In addition to differences in the assessment of VTE, the patient populations in PREVENT and MEDENOX also differed, with a higher proportion of ''high-risk'' patients in MEDENOX (ie more patients who were elderly or had cancer, infectious disease or previous VTE), and differences in the duration of treatment in each study (table 2). Furthermore, LMWHs are distinct chemical entities, and evidence for benefit cannot be extrapolated from one LMWH to another.[35] Nonetheless, both PREVENT and MEDENOX provide sound clinical evidence to support the routine implementation of thromboprophylaxis with LMWHs in hospitalised medically ill patients at risk of VTE.

In view of the evidence from these two latest studies and the similarity of these findings to those of previous studies, the latest ACCP guidelines recommend that the risk of VTE should be evaluated in all medically ill patients admitted to hospital. Furthermore, the guidelines state that patients with congestive heart failure or severe respiratory disease, or those who are confined to bed and have at least one additional risk factor for VTE, should receive thromboprophylaxis using either LDUH or LMWHs (grade 1A recommendation).[19]

Table 2 Comparison of PREVENT and MEDENOX studies

Study characteristic	PREVENT	MEDENOX
Number of patients	3706	1102
Baseline characteristics (%)		
⩾75 years	33.3	50.3
Coexisting cancer	5.2	14.2
Previous DVT/PE	3.9	9.4
Acute infectious disease	36.9	53.0
Study treatments	Dalteparin 5000 IU/day, or placebo	Enoxaparin, 20 mg/day or 40 mg/day, or placebo
Median duration of treatment (days)	14	7
Detection of DVT	Compression ultrasonography (21 days after randomisation)	Venography (6–14 days after randomisation)
Primary outcome measure	Symptomatic DVT, symptomatic PE and asymptomatic DVT, or sudden death	Venographically detected DVT or documented PE
Incidence of VTE (%)	2.77 in dalteparin group *v* 4.96 for placebo (RR = 0.55; p = 0.002)	5.5 for 40 mg enoxaparin *v* 14.9 for placebo (RR = 0.37; p<0.001)
Major bleeding events (%)	0.49 in dalteparin group *v* 0.16 for placebo (p = 0.15)	0.3 in 20 mg group and 1.7 in 40 mg group *v* 1.1 for placebo (p = NS)

DVT, deep vein thrombosis; MEDENOX, prophylaxis in MEDical patients with ENOXaparin; PE, pulmonary embolism; PREVENT, Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized Patients Trial; VTE, venous thromboembolism.

New data are emerging on the use of fondaparinux, a factor Xa inhibitor, in the prevention of VTE in hosptialised medically ill patients. In a double-blind trial of thromboprophylaxis in elderly patients who were bedridden because of medical illness (Aritrixa (fondaparinux) for Thromboembolism prevention in Medical Indications Study), fondaparinux was shown to markedly reduce the risk of VTE.[36] In the trial, 849 patients aged ⩾60 years, who were admitted to hospital with acute cardiac, respiratory, infectious or inflammatory disease and expected to remain bedridden for at least 4 days, were randomised to receive either fondaparinux (2.5 mg/day, subcutaneously) or placebo for 6–14 days. The incidence of VTE, defined as any combination of venographically confirmed DVT, symptomatic DVT or fatal or non-fatal pulmonary embolism, was significantly reduced among patients receiving fondaparinux (5.6%) compared with placebo (10.5%; p = 0.029), with no increase in the risk of major bleeding. This trial supports the findings of earlier studies and indicates that patients who are hospitalised and immobilised with medical illnesses are at risk of VTE, and that effective thromboprophylaxis should be considered for these patients.

In response to the current underuse of thromboprophylaxis in hospitalised patients, a recent trial has evaluated the use of a computer-alert program to encourage the use of prophylaxis for ''high-risk'' patients.[37] A computer program linked to a hospital patient database was developed to identify patients at risk of DVT. The program was used to randomly assign 1255 eligible patients to an intervention group, where the responsible doctor was alerted to the risk of DVT, or a control group, where no alert was issued. The doctor receiving the alert was required to acknowledge the alert, and either withhold or order appropriate thromboprophylaxis (mechanical or pharmacological). The study showed that, compared with no intervention, the use of the alert system was associated with an increased use of both mechanical prophylaxis (1.5% *v* 10.0%, respectively; p<0.001) and pharmacological prophlyaxis (13.0% *v* 23.6%; p<0.001). Similarly, the rate of VTE (defined as clinically diagnosed, objectively verified DVT or pulmonary embolism at 90 days) was significantly reduced in the intervention group (4.9%) compared with the control group (8.2%), a 41% reduction in the risk of VTE (p = 0.001). Thus, by the use of a simple computer-based system, the uptake of thromboprophylaxis

Further reading

1. Geerts WH, Pineo GF, Heit JA, *et al*. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;**126**(Suppl):338S–400S.
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can be improved, and the risk of VTE substantially reduced among hospitalised patients at risk of thrombosis.

SUMMARY

Thromboprophylaxis remains underused in hospitalised medically ill patients despite increasing evidence that VTE is a major cause of morbidity and mortality in these patients. This is partly because, until recently, there has been a relative lack of clinical trial data on the efficacy and safety of thromboprophylaxis in medically ill patients. The benefits of thromboprophylaxis with LMWHs in medically ill patients have now been confirmed in two recent double-blind, placebo-controlled trials, MEDENOX and PREVENT. PREVENT, which investigated thromboprophylaxis with dalteparin, is notable as the largest trial of thromboprophylaxis in this patient group and for its use of clinically important outcomes.

These findings should lead to the more widespread and routine use of thromboprophylaxis in hospitalised medically ill patients, with LMWHs at doses that have shown efficacy and safety. This recommendation may substantially reduce the number of preventable deaths and complications from VTE in this large, heterogeneous patient population.

SELF ASSESSMENT QUESTIONS (TRUE (T), FALSE (F); ANSWERS AT THE END OF THE REFERENCES)

1. The incidence of venous thromboembolism (VTE) is higher in patients undergoing surgery than in those with medical conditions.
2. Recent evidence has shown the safety and efficacy of thromboprophylaxis in medically ill populations at risk of VTE.
3. The use of compression stockings and intermittent pneumatic compression are effective alternatives to pharmacological thrompoprophylaxis in medically ill patients.
4. The American College of Chest Physicians recommends that patients with congestive heart failure or severe respiratory disease, or those who are confined to bed and have at least one additional risk factor for VTE, should receive thromboprophylaxis using either unfractionated heparin or low-molecular-weight heparin.
5. Despite evidence that VTE is a major cause of morbidity and mortality in hospitalised medically ill patients, thromboprophylaxis is underused in this group.

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ANSWERS

1. F; 2. T; 3. F; 4. T; 5. T.