Risk assessment for venous thromboembolism in acute medical illness

Venous thromboembolism (VTE) is an important cause of mortality and morbidity and its prevention is an everyday concern for clinicians. The major consequences of VTE are sudden death as a result of pulmonary embolism (PE) and the long-term problem of post-thrombotic syndrome. Evidence shows that acute VTE is associated with higher mortality than previously estimated, with up to 30% of patients with acute PE dying within 30 days of diagnosis (Heit, 2002).

VTE is a multicausal disease – a combination of inherent and acquired risk factors act in concert to create a prothrombotic environment. It is now clear that one of the most important acquired risk factors for VTE is acute medical illness. Recent studies and a meta-analysis have sought to quantify the risk of VTE in acute medical illness, and to define the efficacy and safety of thromboprophylaxis in preventing occurrence (Samama et al, 1999; Mismetti et al, 2000; Kleber et al, 2003). These studies show that acute medical illness is associated with a similar thromboembolic risk as general surgery patients, with about 19% of patients shown by objective criteria to have VTE in randomized studies.

Heparin thromboprophylaxis, in particular with low-molecular weight heparin (LMWH), has been shown to result in relative risk reductions of around 60% in patients with defined medical illness (Samama et al, 1999). The challenge now is to transfer this knowledge into clinical practice through programmes of risk assessment and thromboprophylaxis implementation.

DEFINING THE MAGNITUDE OF RISK

Data show that fatal thromboembolism, particularly in hospitalized non-surgical patients, is still a common finding. In a retrospective review of all autopsies from 1991–2000 at King's College Hospital, London, the frequency of fatal PE and the clinical characteristics of those who died were analysed. Of the fatal emboli, 214 of 265 (80.8%) occurred in patients who had not undergone recent surgery. Of these patients, 110 (51.4%) had suffered an acute medical illness in the 6 weeks before death (Alikhan et al, 2002).

A meta-analysis of randomized trials conducted in medically ill patients has helped to define the overall risk of VTE (Mismetti et al, 2000). Seven trials that included a placebo arm were reviewed. In the 15 095 internal medicine patients randomized, the risk of deep vein thrombosis (DVT) was about 19% when no thromboprophylaxis was provided. This risk of DVT is similar to that in general surgery and acute myocardial infarction, but lower than that in acute ischaemic stroke or orthopaedic surgery.

DEFINING THE EFFICACY AND SAFETY OF THROMBOPROPHYLAXIS

The MEDENOX study (Samama et al, 1999) comprised 1102 immobilized, hospitalized medical patients treated with LMWH (enoxaparin) 20 mg or 40 mg daily, or placebo, and determined the risk of VTE in clearly defined groups of acutely ill medical patients. The main finding in MEDENOX was that LMWH (40 mg once daily) significantly reduced the absolute incidence of VTE from 15.5% (placebo) to 5.5% (relative risk 0.37, $P<0.001$) and of proximal DVT (relative risk 0.35, $P=0.04$).

Recently, subgroup analysis of the MEDENOX database has shown that patients with acute respiratory failure had the greatest reduction in the relative risk of VTE when treated with enoxaparin compared with placebo (Alikhan et al, 2003a). Logistic regression analyses of the MEDENOX database have identified independent patient risk factors associated with an increased risk of VTE. The four factors identified were: age > 75 years, a history of malignancy or previous VTE, and acute infectious disease (Alikhan et al, 2003b). A recent meta-analysis has shown that the provision of heparin thromboprophylaxis in patients with acute medical illness is associated with a low risk of major bleeding or thrombocytopenia and that treatment with LMWH (enoxaparin) appears to offer an advantage over unfractionated heparin in terms of reduced rates of minor bleeding (Alikhan and Cohen, 2003).

This accumulating evidence from key clinical trials such as MEDENOX (Samama et al, 1999) and THE-PRINCE (Kleber et al, 2003) has supported the licensing of the LMWH, enoxaparin, for prevention of VTE in acutely ill medical patients and prompted the American College of Chest Physicians (ACCP) and the International Union of Angiology to extend their initial recommendations on heparin thromboprophylaxis. The ACCP guidelines now include acutely ill medical patients with defined risk factors for VTE, specifically immobility, heart failure, severe lung disease and cancer.

DEVELOPING PREVENTION STRATEGIES

Thromboprophylaxis is rarely prescribed in medical patients. Audits confirm that thromboprophylaxis is underused in medical patients at risk of VTE (Mismetti and Laporte, 2002). In a major London teaching hospital, only 14% of medical patients at moderate or high risk of VTE received thromboprophylaxis. An Italian group showed that although teaching hospitals fared better

than non-teaching hospitals, the extent of use of thromboprophylaxis in both types of institutions was still inadequate.

Why do physicians fail to use prophylaxis? There may be some debate about the clinical relevance of data on which the ACCP recommendations are based. The primary efficacy endpoint in the MEDENOX study was objective venographic DVT; although the effectiveness of LMWH prophylaxis in terms of symptomatic VTE has been confirmed in surgical patients, it is yet to be adequately demonstrated in a clinical trial in acutely ill medical patients. Given that the majority of cases of VTE are silent, an objective efficacy endpoint may provide more reliable efficacy data.

There may be questions concerning the most appropriate dose regimen of LMWH, although MEDENOX clearly showed a dose–effect relationship with enoxaparin, with only the higher dose (40 mg) significantly reducing VTE (Samama et al, 1999). Additional analyses have confirmed that only 40 mg once daily was superior to placebo in reducing the number and size of thrombi (Alikhan et al, 2000). Regarding the use of other LMWH, no other heparin is licensed for thromboprophylaxis in acutely ill medical patients.

Probably the most immediate challenge lies in the exact identification of which patients are at risk of VTE. Currently, there is no precise patient risk profile for medical illness that would precipitate a mandatory recommendation for thromboprophylaxis. It is anticipated that the data provided by additional analyses of the MEDENOX database and the identification of independent risk factors for VTE in medical illness will change this and facilitate the formulation of risk assessment models based on clinical evidence.

A risk assessment model was proposed by a German specialist panel (Lutz et al, 2002). Starting with a surgical risk assessment scheme previously used in Germany, the authors attempted to develop 'a clearly understandable decision-making tool for assessing the risk of thromboembolism in internal medicine'. Their approach was to formulate a simple diagram that facilitates assessment of overall risk and, based on the definition of 'basic' risks (patient factors that predispose to VTE) and 'acute' risks (essentially the medical illness), was specifically intended to avoid overestimation of the risk without oversimplifying the complex nature of risk assessment. The authors noted, however, that, given the limited available data and the complexity of the problem of risk assessment, they could offer no clear-cut scoring system.

The initial outline of another model was presented at the International Society for Thrombosis and Haemostasis meeting in July 2003, and is based upon the findings of a global advisory panel (Cohen et al, 2002). This risk assessment model is simpler, and allows for a 'yes/no' decision for prescribing thromboprophylaxis in medical patients based on their underlying illness and predisposing risk factors. This model will provide assistance to clinicians and should improve uptake of thromboprophylaxis. Publication is expected later in 2003.

CONCLUSION

Evidence-based recommendations support the routine implementation of thromboprophylaxis in acutely ill medical patients at risk of VTE. Effective risk assessment and thromboprophylaxis policy implementation are the keys to an effective programme. Although further work is required to define a simple risk assessment model for such patients, the authors believe that clinical practice will change and mirror the process in surgical patients. Medical patients who are acutely ill and at risk of VTE will be identified and receive adequate and effective thromboprophylaxis. HM

KEY POINTS

- Evidence-based international guidelines recommend thromboprophylaxis in acutely ill medical patients with defined risk factors for venous thromboembolism.
- Patients with cardiorespiratory disease, acute respiratory infection and cancer are among those at highest risk of venous thromboembolism.
- Audits indicate substantial underuse of thromboprophylaxis in medical patients.
- The development of a simple risk assessment model will substantially influence the successful implementation of thromboprophylaxis in medical patients.

KK Hampton
Senior Lecturer and Consultant
Division of Genomic Medicine
Royal Hallamshire Hospital
Sheffield S10 2JF
I Walker
Professor and Consultant
Department of Haematology
Glasgow Royal Infirmary
Glasgow G4 0SF

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