Thromboprophylaxis in medical patients

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Recent clinical studies have confirmed that acutely ill medical patients are at substantial risk of venous thromboembolism, which can be reduced by thromboprophylaxis with low molecular weight heparin. These studies have resulted in approval of a low molecular weight heparin (enoxaparin) for the prophylaxis of venous thromboembolism in medical patients bedridden as a result of acute illness.

Venous thromboembolism (VTE) is a major public health problem and its prevention is an everyday concern for both surgeons and physicians. Deep vein thrombosis (DVT) is common in hospital patients and is frequently associated with the complication of pulmonary embolism (PE). In a 5-year retrospective analysis, up to 10% of autopsy-investigated hospital deaths were caused by PE and as many as 75% of these deaths occurred in patients who had not undergone a surgical procedure relating to their last illness (Sandler and Martin, 1989). PE is frequently clinically silent (Meignan et al, 2000) and the first manifestation may be sudden death (Clagett et al, 1998).

Although VTE is common in medical patients, much more is known about its occurrence in surgical patients. It is accepted that patients are at risk of VTE following surgery, in particular after orthopaedic surgery. As a result, thromboprophylaxis has become established in clinical practice as a safe and effective means of reducing VTE in surgical patients (Clagett et al, 1998).

In contrast, the situation for medical patients is much less certain (Goldhaber, 1999). Medical patients are a diverse group and the incidence of VTE varies widely depending on the clinical setting. For patients with acute myocardial infarction (AMI) or stroke, the risk of VTE is defined (Clagett et al, 1998) but for general medical patients the relative risks associated with different conditions have been unknown and consequently the efficacy and safety of thromboprophylaxis had not been established. In addition, patient-related factors that confer increased risk of VTE (*Table 1*) are common and contribute further to the diversity in risk (Anderson et al, 1992; Samama et al, 1993). Unlike in surgical patients, where the surgical event is acute and of limited duration, in medical patients the risk factors often persist for prolonged periods.

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RISK OF VTE IN GENERAL MEDICAL PATIENTS

Although definitive information on the risk of VTE in general medical patients has been lacking, a risk classification for these patients was proposed by the Thromboembolic Risk Factors Consensus Group (THRIFT) based on extrapolation of data from surgical patients and available studies of medical patients (THRIFT, 1992). Risk

TABLE 1.
Risk factors for venous thromboembolism in medical patients

Patient factors	Age
	Obesity
	Varicose veins
	Immobility
	Pregnancy
	Previous venous thromboembolism
	Thrombophilia
	High-dose oestrogen therapy
	Central venous catheter
Patient condition	Surgery
	Malignancy
	Heart failure
	Recent myocardial infarction
	Paralysis of lower limbs
	Infection
	Inflammatory bowel disease
	Nephrotic syndrome

Adapted from THRIFT II (1998)

was categorized as high, medium or low by reviewing the incidence of VTE in various medical conditions in the absence of thromboprophylaxis.

The risk of VTE and risk reductions achieved with thromboprophylaxis are most clearly defined in medical patients with AMI or stroke. Pooled data from clinical studies have shown a reduction in the incidence of VTE in AMI from 24% to 7% using low dose unfractionated heparin (UFH) and from 63% to 23% in acute ischaemic stroke using low dose UFH and to 16% using low molecular weight heparin (LMWH) (Clagett et al, 1998). A number of studies have been carried out in general medical patients but these failed to determine risk accurately in defined patient populations and failed to use consistent and objective measurements of VTE (Belch et al, 1981; Cade, 1982; Ibarra-Pérez et al, 1988; Harenberg et al, 1990, 1996). The incidence of DVT in general medical patients not given thromboprophylaxis is estimated by THRIFT at 10–40% and these patients are classified as being at moderate risk of VTE (THRIFT, 1992). This risk is similar to major trauma patients, or patients with a history of VTE who are undergoing minor surgery.

TYPES OF THROMBOPROPHYLAXIS

A variety of options exist for the provision of thromboprophylaxis in patients at risk of VTE. Pharmacological agents are used extensively and include warfarin, UFH and LMWH. Alternatively, physical methods such as elasticated compression stockings, which reduce the risk of VTE by improving venous blood flow, are also used. The use of warfarin for thromboprophylaxis represents a complex option. Patients must be monitored to ensure they receive the correct dosage and interactions between warfarin and other drugs are common.

Until recently, UFH was the most widely used agent for thromboprophylaxis. However, LMWHs offer specific advantages over UFH and are becoming accepted as the agent of choice for both treatment and thromboprophylaxis of VTE. Differences include better bioavailability, a longer half-life and predictable pharmacokinetics that enable once-daily dosing without the need for anticoagulant monitoring (Hirsh and Levine, 1992). Thus, LMWH can be given once daily, as compared to twice or three times daily for UFH and, if appropriate, can be continued after the patient has been discharged from hospital using LMWH in pre-filled syringes. Overall, LMWHs represent an effective and more convenient option and can be considered to be the treatment of choice.

CLINICAL STUDIES OF VTE IN GENERAL MEDICAL PATIENTS

Almost 100 000 surgical patients have been studied in clinical trials of VTE (Mismetti et al, 2000), compared to just 15 000 medical patients. Establishing the risk in general medical patients has been limited by the quality of the studies undertaken (Clagett et al, 1998). Patient populations tended to be small, different, mostly non-objective methods were used to diagnose VTE and different definitions of outcome were chosen.

Most importantly, patient populations were heterogeneous. Patients confined to bed were selected regardless of the acute illness responsible for their immobilization. Finally, most of the studies did not take into account the presence of additional risk factors for VTE such as age and obesity. As a consequence, there has been a lack of clear information about the risk of VTE and hence the efficacy and safety of thromboprophylaxis in general medical patients was uncertain.

Despite these shortcomings, most of the studies have shown that VTE was a common occurrence in medical patients and that thromboprophylaxis with LMWH or UFH reduced the incidence of VTE (Belch et al, 1981; Cade, 1982; Ibarra-Pérez et al, 1988; Harenberg et al, 1990, 1996). Some of the studies also showed significant or non-significant reductions in mortality (Halkin et al, 1982; Bergmann and Caulin, 1996; Caulin, 1989; Gärdlund, 1996).

NEW VTE STUDIES IN ACUTELY ILL GENERAL MEDICAL PATIENTS

MEDENOX

MEDical patients with ENOXaparin (MEDENOX) was a randomized, placebo-controlled study in a population of acutely ill medical patients representative of those patients found on general medical wards (Samama et al, 1999). The average age of patients was 73 years and most had been admitted to hospital as a result of heart failure, respiratory failure or acute infection (*Table 2*). The aims of the study were to determine the incidence of objectively determined VTE and to test the efficacy of two doses of the LMWH enoxaparin compared with placebo in reducing the incidence of VTE. Results showed that VTE events occurred in 14.9% of placebo group patients but in those patients given 40 mg enoxaparin once daily for 6–14 days a greater than 60% reduction in the rate of VTE events was demonstrated at day 14 (*Figure 1*). The difference was statistically significant and the benefit was maintained at 3 months after therapy. There was a 20% reduction in overall mortality in the patients receiving enoxaparin compared with placebo. Relative risk reductions were similar

TABLE 2.
Disease groups receiving thromboprophylaxis in MEDENOX

Congestive heart failure (NYHA class III or IV)
Acute respiratory failure
Acute infectious disease (+ 1 additional VTE risk factor*)
Acute rheumatic disorder (+ 1 additional VTE risk factor*)
Inflammatory bowel disease (+ 1 additional VTE risk factor*)

NYHA = New York Heart Association. *Additional risk factors predefined as: age >75 years, cancer, previous venous thromboembolism (VTE), obesity, varicose veins, hormone therapy, chronic heart failure, chronic respiratory failure. Adapted from Samama et al (1999)

when proximal DVT rates were examined alone. The adverse event profile of enoxaparin was similar to placebo, with no increase in bleeding complications and no evidence of severe heparin-associated thrombocytopenia. The adverse events are presented in *Table 3*.

Unexpectedly, there were no differences in efficacy between enoxaparin 20 mg and the placebo group in any of the comparisons performed. In a previous study, enoxaparin 20 mg once daily, the licensed dose for use in moderate risk general surgery patients, was found to be equivalent to twice-daily UFH 5000IU in the prevention of DVT (Bergmann and Neuhart, 1996). However, it is likely that this was a population of less severely ill elderly medical patients. One explanation for the failure to demonstrate efficacy with enoxaparin 20 mg is that the medical patients studied in MEDENOX should be considered high risk, rather than moderate risk. Thus high-risk medical patients may require a higher dose of thromboprophylaxis than those at moderate risk, just as high-risk surgery requires a higher dose than moderate-risk surgery.

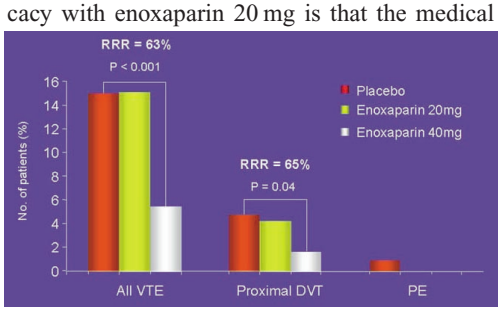

Figure 1. Efficacy results of the MEDENOX study. Adapted from Samama et al (1999). DVT = deep vein thrombosis; PE = pulmonary embolism; RRR = relative risk ratio; VTE = venous thromboembolism.

TABLE 3.
Summary of adverse events in MEDENOX and PRINCE

	MEDENOX (days 1–14)		PRINCE (days 1–13)	
	Placebo	Enoxaparin 40 mg once daily	UFH 5000 IU three times daily	Enoxaparin 40 mg once daily
	n = 362	*n* = 360	*n* = 333	*n* = 332
Deaths (any cause, *n*)	16	12	15	9
Total haemorrhage (*n*)	31	45	12	5
Thrombocytopenia (*n*)	13	8	NP	NP
Total adverse events (*n*)	NP*	NP*	179†	152†

*NP = no figures were provided in the publication, although there were no significant differences between enoxaparin and placebo in the occurrence of other adverse events.
†Significantly fewer adverse events with enoxaparin (*P*=0.044).

PRINCE

THromboEmbolism PRevention IN Cardiopulmonary disease with Enoxaparin (THE-PRINCE), a randomized controlled study (Kleber at al, 1999), was designed to compare the efficacy of LMWH and UFH for the prevention of VTE in patients with severe cardiopulmonary disease. Patients with severe respiratory disease or severe heart failure were randomized to receive 40 mg enoxaparin once a day or 5000 units UFH three times a day for 8–12 days. The incidence of VTE was similar in both groups (enoxaparin 8.4%, UFH 10.4%, *Figure 2*). Bleeding complications were low in both treatment groups, and the use of enoxaparin 40 mg once daily was associated with significantly fewer adverse events compared with UFH (*Table 3*).

PRINCE showed that the incidence of VTE events was higher in the sub-group of patients with severe heart failure than patients with severe respiratory disease. There was a lower incidence of VTE in patients treated with enoxaparin (9.7%) compared to UFH (16.1%), although this was not statistically significant. In the PRINCE study, the proportion of patients with New York Heart Association class IV heart failure was higher than that recorded in MEDENOX.

Of note, the detection of a positive D-dimer/fibrin monomer test was used to trigger venography in this study. These tests were centrally assessed as positive in 84/236 patients of the enoxaparin group and in 86/212 patients of the UFH group. This led to 82 venographies in the enoxaparin group and 84 in the UFH group. As this decision algorithm is not fully validated, the incidence of DVT observed may be underestimated. Only one DVT, in the UFH group, was not diagnosed by venography but by autopsy.

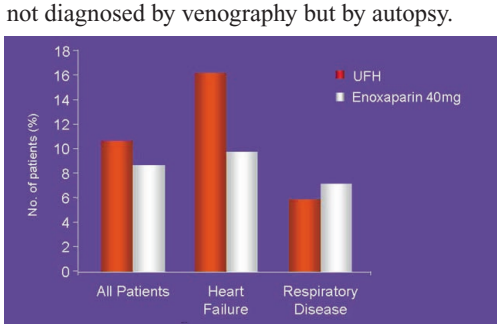

Figure 2. Efficacy results of the PRINCE study. Adapted from Kleber et al (1999). UFH = unfractionated heparin.

In conclusion, the MEDENOX study establishes that patients admitted to general medical wards are at substantial risk of VTE and that thromboprophylaxis with enoxaparin 40 mg given once daily as a subcutaneous injection is effective in significantly reducing the risk of VTE events. PRINCE demonstrates that enoxaparin 40 mg is as effective as UFH in preventing VTE in bedridden patients with severe cardiopulmonary disease.

CLINICAL GUIDELINES

As a result of the previous lack of quality clinical data on VTE in general medical patients, current recommendations for thromboprophylaxis are, of necessity, based on extrapolation of data from large trials looking at surgical patients and the existing small scale studies of medical patients. Reports from the Thromboembolic Risk Factors Consensus Group (THRIFT, 1992; THRIFT II, 1998) highlight the urgent need for clinical trials, such as MEDENOX and PRINCE.

The current guidelines recommend the use of LMWH, UFH and physical prophylaxis methods for various groups of medical patients. One LMWH (enoxaparin) is licensed for the prophylaxis of VTE in medical patients bedridden as a result of acute illness. It is likely that results from the MEDENOX and PRINCE studies will lead to modifications of the guidelines including recommended doses for LMWHs.

CONCLUSIONS

VTE is known to occur frequently in medical patients but information on the level of risk and the efficacy and safety of thromboprophylaxis has not been available because of a lack of reliable clinical data. The recent MEDENOX and PRINCE studies have provided evidence to show that acutely ill medical patients are at substantial risk of VTE and that this can be effectively reduced using thromboprophylaxis with LMWH without significant increases in adverse events. HM

Conflict of interest: none.

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KEY POINTS

- Venous thromboembolism (VTE) is a major cause of death and serious illness in hospital patients.
- The risk of VTE in medical patients was poorly defined and the efficacy and safety of thromboprophylaxis was uncertain.
- Recent clinical studies have provided evidence that acutely ill general medical patients are at substantial risk of VTE.
- Thromboprophylaxis with the low molecular weight heparin enoxaparin effectively reduces the risk of VTE in acutely ill medical patients.
- One low molecular weight heparin, enoxaparin, is licensed to provide thromboprophylaxis in medical patients bedridden as a result of acute illness.