Treating venous thromboembolism: enoxaparin

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This article reviews the developments that have occurred in the treatment of venous thromboembolism during the last decade, with emphasis on the establishment of low molecular weight heparin as a therapeutic agent of proven efficacy and examines the evidence that supports the movement from inpatient to outpatient hospital management of venous thromboembolism.

For many years the standard treatment for acute deep vein thrombosis (DVT) and pulmonary embolism (PE) was an initial 5–10-day course of unfractionated heparin (UFH) in hospital followed by 3–6 months of oral anticoagulants after discharge. Since the beginning of the 1990s, there has been a progressive movement away from UFH towards the use of low molecular weight heparin (LMWH) for the management of venous thromboembolism (VTE) (Hirsh and Bates, 2001). Clinical trials have demonstrated that LMWH is at least as effective and safe as UFH (Gould et al, 1999; Dolovich et al, 2000; Merli et al, 2001) but LMWH offers significant additional advantages which explains its increasing use (*Table 1*).

Treatment of VTE with UFH requires intravenous administration with careful monitoring and adjustment of the dose to ensure optimal anticoagulation. In contrast, VTE is effectively treated with LMWH by subcutaneous injection of a weight-adjusted dose given once daily without the need for laboratory monitoring in the majority of cases (Hirsh and Bates, 2001).

Current strategies for the management of VTE propose a movement away from inpatient treatment towards outpatient hospital treatment with LMWH for patients with acute DVT, and possibly for patients with sub-massive PE. A number of clinical trials have shown that outpatient treatment is feasible and potentially cost-saving and is suitable for most patients (Koopman et al, 1996; Levine et al, 1996; Belcaro et al, 1999; Boccalon et al, 2000). Improved quality of life for patients and significant cost savings are anticipated. The challenge for the future will be to translate the promising results obtained in clinical trials into daily clinical practice.

Enoxaparin (Clexane®, Aventis Pharma, Frankfurt, Germany), supported by strong clinical evidence, is licensed in the UK for the treatment of VTE presenting with DVT, PE or both. Two other LMWHs, dalteparin and tinzaparin, are licensed for the treatment of DVT and PE. This article reviews the clinical evidence describing the efficacy and safety profile of enoxaparin specifically, and LMWH generally, for the initial treatment of acute DVT and PE. It also examines the evidence supporting the outpatient treatment of DVT and PE and the treatment of special patient groups with LMWH. Evidence of the benefit and cost advantages of enoxaparin provided in an outpatient setting is also examined.

HISTORY OF VTE TREATMENT

Heparin has been used to treat VTE since the 1940s but for many years the only evidence that it was effective came from animals studies and uncontrolled clinical experience. Evidence of the efficacy of heparin as an anticoagulant was only obtained at the beginning of the 1960s. In a randomized clinical trial Barritt and Jordan (1960) reported reduced recurrence of VTE and mortality in patients with acute PE treated with intravenous heparin and oral anticoagulants. The study had a major impact on clinical practice

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TABLE 1.
Comparison of treatment with unfractionated heparin (UFH) and low molecular weight heparin (LMWH)

	UFH	LMWH
Administration	Intravenous	Subcutaneous
Dose	Variable	Fixed, weight based
Laboratory monitoring	Yes	Not required

and a 10-day course of heparin in hospital with warfarin after discharge was adopted as the standard treatment for both DVT and PE.

The importance of heparin in anticoagulant therapy was not finally demonstrated until 1992. In a randomized, double-blind trial (Brandjes et al, 1992), patients with proximal vein thrombosis treated with oral anticoagulants only were compared with those given combined oral anticoagulants and heparin. The study demonstrated the importance of heparin when it was terminated early on safety grounds because of an excess of symptomatic thrombotic events in the group receiving oral anticoagulants only. Other studies seeking to optimize treatment showed that early initiation of warfarin therapy allowed the standard 10-day course of heparin to be safely reduced to 5 days, reducing the time spent in hospital (Gallus et al, 1986; Hull et al, 1990).

The 1980s saw the introduction of LMWHs for the treatment of VTE. Clinical studies during the 1980s and 1990s showed them to be at least as effective and safe as UFH for the treatment of DVT and PE (Gould et al, 1999; Dolovich et al, 2000). However, it was also apparent that LMWHs offer significant advantages over UFH. A reduced tendency to bind plasma proteins and cell surfaces gives them more predictable pharmacokinetics, including a longer half-life and improved bioavailability, compared with UFH (Young et al, 1994). These features give LMWH a more predictable and longer lasting anticoagulant effect, allowing subcutaneous administration as a weight-based dose which does not require laboratory monitoring (Handeland et al, 1990; Bratt et al, 1990; Weitz, 1997; Hirsh and Levine, 1992). In contrast, the shorter lived anticoagulant effect of UFH necessitates intravenous administration in hospital and the less predictable anticoagulant effect (associated with binding of acute phase proteins) means that frequent monitoring of activated partial thromboplastin time (aPTT) and adjustment of the dose are required (Schafer, 1996). The ability to administer LMWH subcutaneously offered the possibility to treat VTE on an outpatient basis.

In the late 1990s, clinical studies demonstrated that outpatient treatment was feasible and did not result in increased recurrence of VTE or adverse bleeding complications (Koopman et al, 1996; Levine et al, 1996; Belcaro et al, 1999; Boccalon et al, 2000). However, the studies also highlighted the importance of patient selection and education and adequate patient support programmes (Eikelboom and Baker, 2001). The initial success of outpatient treatment programmes promise a simpler, more cost-effective therapy and represent the current paradigm for the treatment of VTE.

USE OF LMWHS TO TREAT VTE IN HOSPITAL PATIENTS

The development of LMWHs in the 1980s led to a series of clinical trials to determine their efficacy and safety compared to UFH for the treatment of VTE (Bratt et al, 1985, 1990; Holm et al, 1986; Albada et al, 1989; Handeland et al, 1990; Hull et al, 1992; Lopaciuk et al, 1992; Prandoni et al, 1992; Simonneau et al, 1993). The studies varied widely in the quality of the methodologies used with variations in patient selection procedures, treatment protocols and measures of outcome. However, LMWH was found to be at least as effective as UFH with a similar bleeding profile.

These initial studies were followed by the publication of meta-analyses that attempted to clarify the position by selecting studies with more robust methodologies for analysis (*Table 2*). Three meta-analyses were published in the mid 1990s. Two found LMWH to be superior to UFH with significant reductions in recurrence of VTE, major bleeding complications and mortality (Lensing et al, 1995; Siragusa et al, 1996). The third reported significant reductions in mortality and major bleeding and a non-significant trend in favour of LMWH towards a reduction in risk of recurrence of VTE (Leizorovicz, 1996).

These studies were followed by the publication of two further meta-analyses (Gould et al, 1999; Dolovich et al, 2000) which included large clinical trials completed after the publication of the earlier meta-analyses. The conclusions of these studies were more conservative. Both found that LMWH and UFH were at least as effective, with equivalent rates of VTE recurrence and major bleeding. A further important finding was the significant reduction in mortality found in favour of LMWH.

TABLE 2.
Meta-analysis of pulmonary embolism treatment comparing enoxaparin and unfractionated heparin

	Symptomatic initial PE		No symptomatic initial PE	
	UFH incidence (%)	enox *vs* UFH RR (95% CI)	UFH incidence (%)	enox *vs* UFH RR (95% CI)
PE	4.5	0.44 (0.10–1.90)	1.1	0.68 (0.23–2.02)
DVT	5.2	0.91 (0.30–2.81)	4.2	0.86 (0.52–1.43)
VTE	8.4	0.78 (0.32–1.91)	4.6	0.90 (0.55–1.45)
Major bleed	5.5	0.67 (0.22–2.07)	2.1	1.02 (0.49–2.12)
Death	7.9	0.50 (0.18–1.35)	4.2	0.84 (0.51–1.39)

CI = confidence interval; DVT = deep vein thrombosis; enox = enoxaparin; PE = pulmonary embolism; RR = relative risk; UFH = unfractionated heparin; VTE = venous thromboembolism; incidence weighed by the size of the trials. From Mismetti at al (2001)

Other studies addressed the question of treatment regimens for LMWH. The efficacy of enoxaparin as treatment for VTE was recently confirmed in a global study (Merli et al, 2001). The study showed that once- or twice-daily weight-adjusted doses of enoxaparin are as effective as UFH with a similar bleeding profile in the treatment of recurrent, symptomatic VTE, including obese patients. These results were seen in patients with DVT, and in patients with PE.

The international study enrolled 900 patients with symptomatic lower extremity DVT and included 287 patients with confirmed PE. Patients received dose-adjusted intravenous UFH or subcutaneous enoxaparin given at one of two fixed dosages, either 1.0 mg/kg every 12 hours or 1.5 mg/kg every 24 hours. Long term oral anticoagulant therapy (warfarin sodium) was started in all patients within 72 hours of randomization and continued for 3 months. The study confirmed that enoxaparin once-daily was as efficacious as UFH. Symptomatic recurrent VTE occurred in 12 of 290 UFH patients (4.1%), 13 of 298 enoxaparin once-daily patients (4.4%) and 9 of 312 enoxaparin twice-daily patients (2.9%). There were no significant or clinically relevant differences between groups in the incidence of haemorrhage during the initial treatment period.

A recent meta-analysis examining the efficacy and safety of enoxaparin compared to UFH in the treatment of patients with DVT and/or PE found enoxaparin to be at least as effective with a similar bleeding profile to UFH (Mismetti et al, 2001). The investigators identified all randomized clinical trials comparing enoxaparin with UFH in patients with symptomatic DVT and/or PE. A stipulation of the meta-analysis was that individual patient data were available for study inclusion. The incidence of DVT, clinical PE, VTE, death at 3 months and major bleeding by day 10 were compared both in patients presenting symptomatic initial PE and in patients without symptomatic initial PE. Three studies comparing enoxaparin with UFH were included, with a total of 1801 patients. Among the patients, 275 had presented with an initial symptomatic PE and 1526 had experienced DVT. The rates of all the efficacy and safety outcomes were higher in patients with initial symptomatic PE than in those without initial symptomatic PE. Enoxaparin appeared to be at least as effective and safe as UFH in both patient groups (*Table 2*).

USE OF LMWHS TO TREAT HOSPITAL OUTPATIENTS

The results of the randomized clinical trials comparing LMWH with UFH for the treatment of DVT have led to an acceptance that the two therapies are broadly equivalent in terms of efficacy and adverse events. However, the simpler dosing and administration associated with the use of LMWH offers distinct advantages, including the possibility of treating patients with acute DVT as hospital outpatients. This is clearly an attractive proposition, potentially delivering improved quality of life for patients during treatment and considerable savings in health-care costs. The possibility of out of hospital treatment is further enhanced by the availability of LMWH in the form of pre-filled syringes. Features of these syringes are outlined in *Table 3*.

A series of randomized clinical trials have been carried out to determine the feasibility and safety of outpatient treatment with LMWH (Koopman et al, 1996; Levine et al, 1996;

TABLE 3.
Posology and administration of low molecular weight heparin for the treatment of venous thromboembolism

	Enoxaparin		Tinzaparin		Dalteparin	
Recommended dose	1.5 mg/kg once daily		175 IU/kg once daily		200 IU/kg once daily or 100 IU/kg twice daily	
Administration	Subcutaneous		Subcutaneous		Subcutaneous	
Duration of treatment	Minimum 5 days with oral anticoagulation		Minimum 6 days with oral anticoagulation		Minimum 5 days with oral anticoagulation	
Syringe type (graduated)	100 mg/ml syringes:	20 mg/0.2 ml	25 000 IU/ml syringes:	0.40 ml for 46–56 kg	20 000 IU/ml syringes:	0.5 ml
		40 mg/0.4 ml		0.50 ml for 57–68 kg		0.7 ml
		60 mg/0.6 ml		0.60 ml for 69–82 kg		0.9 ml
		80 mg/0.8 ml		0.72 ml for >83 kg		
		100 mg/1.0 ml				
	150 mg/ml syringes:	120 mg/0.8 ml				
		150 mg/1.0 ml				

Belcaro et al, 1999; Boccalon et al, 2000). The results show that rates of recurrence of VTE and major bleeding are not adversely affected when patients are treated out of hospital.

Compared with in-hospital treatment with dose-adjusted UFH, enoxaparin administered primarily at home was as effective for the treatment of acute proximal DVT (Levine et al, 1996). In a multicentre, parallel group study to assess the treatment of acute proximal DVT in the community, patients were randomized to enoxaparin 1 mg/kg every 12 hours subcutaneously or UFH intravenous bolus (5000 IU) followed by continuous infusion. Warfarin was initiated on the second day of treatment. The incidence of recurrent thromboembolism was similar in the two treatment groups (5.3% *vs* 6.7% respectively), as was the incidence of major bleeding (5 cases with enoxaparin *vs* 3 cases with UFH). Remarkably, 120 of the 247 patients who received enoxaparin treatment were never admitted to hospital, demonstrating the feasibility of outpatient management for this patient group.

Recently, a prospective multicentre, open-label, randomized controlled clinical trial (Chong et al, 2001) investigated once-daily enoxaparin home treatment regimen compared with continuous UFH infusion given in hospital. The primary efficacy endpoints were recurrent symptomatic and confirmed DVT and PE. Patients received either enoxaparin 1.5 mg/kg once daily out of hospital or UFH given as continuous infusion in hospital, with the dose adjusted to an aPTT of 1.5–2.5 times the control value. Warfarin, dose-adjusted to give an international normalized ratio of 2–3, was continued for 3 months. The clinical follow-up period was 6 months.

In total, 298 patients with symptomatic proximal and distal DVT were randomized to receive enoxaparin (n=150) or UFH (n=148). Symptomatic recurrence of VTE occurred in 2.0% (3 of 150) patients treated with enoxaparin compared with 8.1% (12 of 148) patients treated in hospital with UFH. Seven of the UFH patients had recurrent DVT and 5 patients had PE. No patients in the enoxaparin arm experienced a major bleed, compared with 2.0% of patients receiving UFH. Considering all bleeding events, 10.0% of enoxaparin patients compared with 13.5% of the UFH patients had some form of bleed.

Some uncertainty remains, however, regarding the selection of patients for home treatment. In some trials, as many as 50% of patients presenting with proximal vein thrombosis were rejected as ineligible for home treatment (Eikelboom and Baker, 2001). A variety of exclusion criteria were cited including history of recurrent VTE, increased risk of bleeding, concomitant symptomatic PE, coexisting conditions requiring hospitalization or concerns about the feasibility of administering heparin at home. This has led to questions about the feasibility of translating the results of clinical trials into everyday clinical practice and may explain the reluctance of some centres to embrace home treatment.

The randomized clinical trials of home treatment have been followed by a series of cohort studies evaluating outpatient treatment programmes for DVT. At least eight, including two from the UK, have been published and there is now a growing body of evidence which suggests that as many as 80% of patients presenting with acute DVT can be safely and effectively treated as outpatients (Lindmarker and Holmstrom, 1996; Dedden et al, 1997; Grau et al, 1998; Harrison et al, 1998; O'Shaughnessy et al, 1998, 2000; Ting et al, 1998; Wells et al, 1998; Eikelboom and Baker, 2001). Experience from trials suggests that success in clinical practice will be dependent on a number of factors. These include the accessibility of multidisciplinary clinical services with expertise in the diagnosis and management of VTE and proper education of patients. Education should include the nature of VTE, treatment with anticoagulants and their potential complications. Although home treatment programmes offer advantages for patients and health-care providers, careful monitoring of individual centres will be required to ensure their success, and treatment through an outpatient anticoagulation clinic may the ideal care provision vehicle for outpatient management.

USE OF LMWHS TO TREAT PE

In most of the clinical trials that established the efficacy and safety of LMWH for the treatment of acute DVT, patients with associated symptomatic PE were excluded because they were considered to have more serious thromboembolic disease or formed only a small proportion of the study population (Lensing et al, 1995; Leizorovicz, 1996; Siragusa et al, 1996). It is generally accepted that DVT and PE are different expressions of the same disease process and the development of objective criteria for determining a high probability of PE, based on techniques such as ventilation–perfusion lung scanning and pulmonary angiography, has shown that at least 50% of patients with objectively determined DVT also have asymptomatic PE (Hull et al, 1983; Huisman et al, 1989). Since many patients treated with LMWH for DVT would have also had asymptomatic PE, clinical trials were set up

to evaluate the efficacy and safety of LMWH compared to UFH for the treatment of PE.

Two initial randomized clinical trials were published simultaneously in the same journal in 1997. In one study (Simonneau et al, 1997), patients presenting with symptomatic PE were randomized to receive UFH or LMWH. Statistically equivalent rates of VTE recurrence, major bleeding and death occurred in each treatment group, the authors concluding that LMWH was as effective and had a similar bleeding profile as UFH for the treatment of acute PE. However, it should be noted that in this study with tinzaparin, only 42% of patients screened for trial entry presenting with symptomatic PE were included. Thus, a minority of cases of PE were deemed suitable for treatment with tinzaparin. The second study examined unselected patients presenting with acute, symptomatic DVT with or without accompanying PE (Anonymous, 1997). Equivalent rates of VTE recurrence, major bleeding and death were reported for patient groups treated with UFH or LMWH. The authors concluded that LMWH is equally as effective and safe as UFH for the treatment of VTE regardless of whether the patient has accompanying PE.

These initial studies were followed and confirmed by two further studies, published within the last year. Patients with objectively determined PE and underlying DVT were randomized to receive UFH or LMWH (Hull et al, 2000). In a second study described previously, patients with objectively determined DVT, with or without accompanying PE, received UFH or enoxaparin given once or twice daily (Merli et al, 2001). Both studies reported equivalent rates of recurrent VTE, bleeding and mortality for the UFH and LMWH treatment groups.

Following on from the success of outpatient treatment programmes for DVT, the possibility of treating PE in an outpatient setting was investigated in a cohort study (Kovacs et al, 2000). Patients with objectively determined PE were randomized to inpatient or outpatient treatment with LMWH. The results showed similar outcomes in terms of recurrence of VTE, bleeding and mortality suggesting that outpatient treatment of PE with LMWH may be a feasible and safe option. However, it should be noted that these remain provisional studies and PE treatment in the outpatient setting is not routine and not widely used.

The clinical trials published to date are in close agreement, reporting similar rates for recurrence of VTE, bleeding and mortality. They provide good evidence that treatment of PE with LMWH is at least as effective and safe as UFH. However, the total number of patients involved in trials remains low and further studies are required to confirm the observations of the trials carried out to date.

LMWH TREATMENT IN SPECIAL PATIENT GROUPS

Clinical studies have demonstrated that outpatient management of acute DVT using LMWH is feasible and safe for many patients (Koopman et al, 1996; Levine et al, 1996; Belcaro et al, 1999; Boccalon et al, 2000). There remain, however, groups of patients who have been judged unsuitable for outpatient treatment because of enhanced risk of VTE or bleeding complications (Dunn and Coller, 1999). These patients fall into a number of categories.

1. Pulmonary embolism: Current evidence indicates that patients with massive PE with haemodynamic instability should be treated in hospital and with monitored and adjusted UFH rather than LMWH. Such patients with massive PE may require other interventions that can include thrombolytic therapy and pulmonary embolectomy
2. History of thromboembolism: Patients who suffer from recurrent episodes of VTE and are judged to be at high risk of recurrence may be more safely treated as hospital inpatients
3. Haemorrhagic risk: Patients with active bleeding, active intestinal ulcerative disease or familial bleeding disorders are unsuitable

TABLE 4.
Selected studies comparing the efficacy and safety of inpatient and outpatient treatment for VTE

Study	Inpatient treatment	Outpatient treatment	No. patients		VTE recurrence (%)			Major bleeding (%)		
			UFH	LMWH	UFH	LMWH	*P*	UFH	LMWH	*P*
Koopman et al (1996)	UFH	LMWH	198	202	8.6	6.9	NS	2.0	0.5	NS
Levine et al (1996)	UFH	LMWH	253	247	6.7	5.3	NS	1.2	2.0	NS
Belcaro et al (1999)	UFH	LMWH	98	196	6.2	6.6	NS	0.0	0.0	NS

LMWH = low molecular weight heparin; UFH = unfractionated heparin; VTE = venous thromboembolism.

for outpatient treatment because of the increased risk of bleeding complications

4. Patients with active malignant disease: Patients with cancer are more resistant to heparin therapy and may be better served in-hospital.

Several other groups of patients are considered unsuitable for outpatient treatment, mostly for logistical reasons. These include patients requiring parenteral analgesia, those requiring hospitalization for more than 5 days because of concurrent medical conditions and patients with uncertain compliance to treatment and follow-up.

Other patients with a variety of medical conditions are excluded from LMWH treatment or must be closely monitored during treatment because of limited information on safety and efficacy (Dunn and Coller, 1999). These include pregnant women, children, patients with severe liver disease, obese patients and patients with renal insufficiency. The latter two groups are now considered in more detail:

Renal insufficiency

LMWH is eliminated primarily via renal excretion. As a result, elimination is delayed and peak anti-factor Xa levels are higher in patients with marked renal insufficiency. At present, there are limited data to determine the safety or otherwise of LMWH in patients with renal impairment. Patients should therefore be treated cautiously with monitoring of anti-factor Xa levels.

A recent study has examined the pharmacokinetics and pharmacodynamics of enoxaparin in patients with renal impairment (Sanderink et al, 2001a). The study was conducted in age-, weight- and sex-matched volunteers who had normal, mild or severely impaired renal function. The study showed that anti-Xa clearance decreases linearly with renal function, with a log-transformed anti-Xa area-under-curve (0–24 hours) in severely impaired patients that was 65% higher than in normal individuals. The relationship between anti-Xa levels and therapeutic effect in these patients is not well characterized. The authors concluded that dose reduction should be considered in those severely impaired renal function patients receiving enoxaparin.

Obesity

As a result of weight-based dosage, obese individuals receive higher doses of LMWH. However, it is not clear if weight-adjusted doses result in optimal anticoagulation in obese patients. Similar uncertainty applies to patients who are under weight.

Merli et al (2001), as described previously, examined the efficacy of enoxaparin at once- and twice-daily weight-adjusted doses and included a subgroup analysis of obese individuals. The study showed that there was no statistically significant difference in outcome between the once- and twice-daily dose of enoxaparin in obese patients, and the study included patients up to 155 kg in weight.

A recent study has examined the pharmacokinetics and pharmacodynamics of enoxaparin in obese patients (Sanderink et al, 2001b). The study was conducted in age-, sex- and height-matched obese and non-obese volunteers. The study detailed the body weight of the patients included, and patients up to 144 kg were enrolled in the trial. The findings showed that weight-adjusted doses of enoxaparin led to only marginally higher anti-Xa levels and half-life in obese patients. The higher anti-Xa levels occurred mainly during the elimination phase and did not significantly influence the maximum activity of the drug. The authors concluded that no dose adjustment appears necessary in obese patients, including those up to 144 kg, receiving enoxaparin. In patients above these weights the use of LMWHs is not well characterized.

CLINICAL GUIDELINES AND LMWH USE

The American College of Chest Physicians (ACCP) and the European Society of Cardiology (ESC) have provided detailed task force and consensus conference recommendations respectively for the management of VTE (Anonymous, 2000; Hyers et al, 2001). The ACCP guidelines were formulated in 2000 and provide an extensive review of clinical evidence followed by graded therapeutic recommendations. The clinical review notes that subcutaneous LMWH will largely replace UFH in the initial treatment of VTE. The clinical guidelines 'recommend that patients with DVT or PE should be treated acutely with LMWH, unfractionated intravenous heparin, or adjusted-dose subcutaneous heparin (all Grade A1)'.

The guidelines on diagnosis and management of PE, issued by the ESC in 2000, specifically refer to the diagnosis and management of acute PE. This document extensively reviews the clinical evidence and concludes that LWMH may be used in patients with symptomatic non-massive PE.

COST ANALYSIS OF LMWH COMPARED WITH UFH

Clinical studies have shown that LMWH has the advantage of simpler dosing and administration when compared with UFH (Gould et al, 1999;

Dolovich et al, 2000). The relative costs and cost issues of prescribing LWMH and UFH have been investigated to a limited extent, and a number of studies have begun to clarify this issue.

A comparison of the costs associated with the inpatient treatment of acute DVT was carried out as a sub-study of a safety and efficacy trial comparing enoxaparin with UFH (de Lissovoy et al, 2000). The study, carried out from a third party payer perspective in the USA, found that the average total cost across the three treatment arms was statistically equivalent. Although acquisition costs for enoxaparin were higher than UFH, these were offset by lower readmission rates and a shorter duration of VTE-related readmissions. However, the authors suggested that their findings might underestimate the economic benefits of enoxaparin given the introduction of outpatient treatment.

Another study, from the perspective of the NHS, analysed costs associated with enoxaparin treatment of VTE, administered to hospital inpatients and to outpatients either at home or attending anticoagulation clinics (unpublished data, SJ Anderson et al, 2001). The study found that outpatient treatment with enoxaparin was associated with the lowest costs, with similar savings achieved in the anticoagulation clinic and home setting. The study concluded that a strong argument exists for transferring patients with acute DVT from a secondary to a primary care setting.

A number of other studies reported similar findings with cost savings as high as 60% associated with the use of LMWH in outpatient programmes (Lindmarker and Holmstrom, 1996; Boccalon et al, 2000; Bossuyt and Prins, 2000; Tillman et al, 2000). Although more studies are required, current evidence indicates the potential for cost savings with the use of LMWH in the outpatient settings.

CONCLUSIONS

Clinical studies show enoxaparin to be at least as effective with a similar bleeding profile to UFH for the initial treatment of acute DVT and submassive PE. Simple dosing and administration without monitoring has led to increasing use of LMWH in preference to UFH for hospitalized patients and has facilitated the development of outpatient treatment programmes. Clinical studies demonstrate that most patients with acute DVT can be treated safely and effectively in the outpatient setting. Recent cost analysis demonstrates that enoxaparin treatment in the outpatient anticoagulant clinic has the potential to reduce costs substantially. HM

Conflict of interest: none.

Anonymous (1991) A randomised trial of subcutaneous low molecular weight heparin (CY 216) compared with intravenous unfractionated heparin in the treatment of deep vein thrombosis. A collaborative European multicentre study. *Thromb Haemost* **65:** 251–6

Anonymous (1997) Low-molecular-weight heparin in the treatment of patients with venous thromboembolism. The Columbus Investigators. *N Engl J Med* **337:** 657–62

Anonymous (2000) Guidelines on diagnosis and management of acute pulmonary embolism. Task Force on Pulmonary Embolism, European Society of Cardiology. *Eur Heart J* **21:** 1301–36

Albada J, Nieuwenhuis HK, Sixma JJ (1989) Treatment of acute venous thromboembolism with low molecular weight heparin (Fragmin). Results of a double-blind randomized study. *Circulation* **80:** 935–40

Barritt DW, Jordan SC (1960) Anticoagulant drugs in the treatment of pulmonary embolism: a controlled trial. *Lancet* **i:** 1309–12

Belcaro G, Nicolaides AN, Cesarone MR et al (1999) Comparison of low-molecular-weight heparin, administered primarily at home, with unfractionated heparin, administered in hospital, and subcutaneous heparin, administered at home for deep-vein thrombosis. *Angiology* **50:** 781–7

Boccalon H, Elias A, Chale JJ, Cadene A, Gabriel S (2000) Clinical outcome and cost of hospital vs home treatment of proximal deep vein thrombosis with a low-molecular-weight heparin: the Vascular Midi-Pyrenees study. *Arch Intern Med* **160:** 1769-1773

Bossuyt PM, Prins MH (2000) Does low-molecular-weight heparin reduce the costs of venous thromboembolism treatment? *Haemostasis* **30** Suppl 2: 136–40

Brandjes DP, Heijboer H, Buller HR, de Rijk M, Jagt H, ten Cate JW (1992) Acenocoumarol and heparin compared with acenocoumarol alone in the initial treatment of proximal-vein thrombosis. *N Engl J Med* **327**: 148–9

Bratt G, Tornebohm E, Granqvist S, Aberg W, Lockner D (1985) A comparison between low molecular weight heparin (KABI 2165) and standard heparin in the intravenous treatment of deep venous thrombosis. *Thromb Haemost* **54:** 813–17

Bratt G, Aberg W, Johansson M, Tornebohm E, Granqvist S, Lockner D (1990) Two daily subcutaneous injections of fragmin as compared with intravenous standard heparin in the treatment of deep venous thrombosis (DVT). *Thromb Haemost* **64:** 506–10

Chong BH, for the Enoxaparin Study Group (2001) A randomized prospective multi-centre study of the treatment of deep vein thrombosis comparing once daily enoxaparin

KEY POINTS

- Enoxaparin, given as a once-daily weight-adjusted dose, is at least as effective with a similar bleeding profile as unfractionated heparin for the initial treatment of patients with acute deep vein thrombosis (DVT) and submassive pulmonary embolism (PE).
- Simpler dosing and administration of low molecular weight heparin (LMWH) has led to their increasing use in preference to unfractionated heparin and has facilitated the development of outpatient treatment programmes.
- Clinical studies show outpatient treatment of acute DVT is effective and safe and is suitable for most patients. Outpatient treatment for patients with submassive PE may also be possible.
- Some groups of patients (massive PE, history of venous thromboembolism, increased bleeding risk) are unsuitable for outpatient treatment.
- Some patients (renal insufficiency, severe liver disease, obesity, pregnancy, children) should not be treated with LMWH or should be treated with caution because there is incomplete information on safety and efficacy.
- Initial studies indicate substantial cost saving associated with outpatient treatment of acute DVT.
- Enoxaparin treatment in an anticoagulation clinic is cost saving compared with inhospital unfractionated heparin.

given mainly at home with unfractionated heparin given in hospital. *Thromb Haemost* **86:** 1664 (abstract)
de Lissovoy G, Yusen RD, Spiro TE, Krupski WC, Champion AH, Sorensen SV (2000) Cost for inpatient care of venous thrombosis: a trial of enoxaparin *vs* standard heparin. *Arch Intern Med* **160:** 3160–5
Dedden P, Chang B, Nagel D (1997) Pharmacy-managed program for home treatment of deep vein thrombosis with enoxaparin. *Am J Health Syst Pharm* **54:** 1968–72
Dolovich LR, Ginsberg JS, Douketis JD, Holbrook AM, Cheah G (2000) A meta-analysis comparing low-molecular-weight heparins with unfractionated heparin in the treatment of venous thromboembolism: examining some unanswered questions regarding location of treatment, product type, and dosing frequency. *Arch Intern Med* **160:** 181–8
Dunn AS, Coller B (1999) Outpatient treatment of deep vein thrombosis: translating clinical trials into practice. *Am J Med* **106:** 660–9
Eikelboom J, Baker R (2001) Routine home treatment of deep vein thrombosis. *Br Med J* **322:** 1192–3
Gallus A, Jackaman J, Tillett J, Mills W, Wycherley A (1986) Safety and efficacy of warfarin started early after submassive venous thrombosis or pulmonary embolism. *Lancet* **ii:** 1293–6
Gould MK, Dembitzer AD, Doyle RL, Hastie TJ, Garber AM (1999) Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis. A meta-analysis of randomized, controlled trials. *Ann Intern Med* **130:** 800–9
Grau E, Real E, Pastor E, Viciano V, Aguilo J (1998) Home treatment of deep vein thrombosis: a two-years experience of a single institution. *Haematologica* **83**: 438–41
Handeland GF, Abildgaard U, Holm HA, Arnesen KE (1990) Dose adjusted heparin treatment of deep venous thrombosis: a comparison of unfractionated and low molecular weight heparin. *Eur J Clin Pharmacol* **39:** 107–12
Harrison L, McGinnis J, Crowther M, Ginsberg J, Hirsh J (1998) Assessment of outpatient treatment of deep-vein thrombosis with low-molecular-weight heparin. *Arch Intern Med* **158:** 2001–3
Hirsh J, Bates SM (2001) Clinical trials that have influenced the treatment of venous thromboembolism: a historical perspective. *Ann Intern Med* **134:** 409–17
Hirsh J, Levine MN (1992) Low molecular weight heparin. *Blood* **79:** 1–17
Holm HA, Ly B, Handeland GF et al (1986) Subcutaneous heparin treatment of deep venous thrombosis: a comparison of unfractionated and low molecular weight heparin. *Haemostasis* **16** Suppl 2: 30–7
Huisman MV, Buller HR, ten Cate JW et al (1989) Unexpected high prevalence of silent pulmonary embolism in patients with deep venous thrombosis. *Chest* **95**: 498–502
Hull RD, Hirsh J, Carter CJ et al (1983) Pulmonary angiography, ventilation lung scanning, and venography for clinically suspected pulmonary embolism with abnormal perfusion lung scan. *Ann Intern Med* **98:** 891–9
Hull RD, Raskob GE, Rosenbloom D et al (1990) Heparin for 5 days as compared with 10 days in the initial treatment of proximal venous thrombosis. *N Engl J Med* **322:** 1260–4
Hull RD, Raskob GE, Pineo GF et al (1992) Subcutaneous low-molecular-weight heparin compared with continuous intravenous heparin in the treatment of proximal-vein thrombosis. *N Engl J Med* **326:** 975–82
Hull RD, Raskob GE, Brant RF et al (2000) Low-molecular-weight heparin *vs* heparin in the treatment of patients with pulmonary embolism. American-Canadian Thrombosis Study Group. *Arch Intern Med* **160:** 229–36
Hyers TM, Agnelli G, Hull R et al (2001) Antithrombotic therapy for venous thromboembolic disease. *Chest* **119**: 176S–193S
Koopman MM, Prandoni P, Piovella F et al (1996) Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with subcutaneous low-molecular-weight heparin administered at home. The Tasman Study Group. *N Engl J Med* **334:** 682–7
Kovacs MJ, Anderson D, Morrow B, Gray L, Touchie D, Wells PS (2000) Outpatient treatment of pulmonary embolism with dalteparin. *Thromb Haemost* **83:** 209–11
Leizorovicz A (1996) Comparison of the efficacy and safety of low molecular weight heparins and unfractionated heparin in the initial treatment of deep venous thrombosis. An updated meta-analysis. *Drugs* **52** Suppl 7: 30–7
Lensing AW, Prins MH, Davidson BL, Hirsh J (1995) Treatment of deep venous thrombosis with low-molecular-weight heparins. A meta-analysis. *Arch Intern Med* **155:** 601–7
Levine M, Gent M, Hirsh J et al (1996) A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis. *N Engl J Med* **334:** 677–81
Lindmarker P, Holmstrom M (1996) Use of low molecular weight heparin (dalteparin), once daily, for the treatment of deep vein thrombosis. A feasibility and health economic study in an outpatient setting. Swedish Venous Thrombosis Dalteparin Trial Group. *J Intern Med* **240:** 395–401
Lopaciuk S, Meissner AJ, Filipecki S et al (1992) Subcutaneous low molecular weight heparin versus subcutaneous unfractionated heparin in the treatment of deep vein thrombosis: a Polish multicenter trial. *Thromb Haemost* **68:** 14–18
Merli G, Spiro TE, Olsson CG et al (2001) Subcutaneous enoxaparin once or twice daily compared with intravenous unfractionated heparin for treatment of venous thromboembolic disease. *Ann Intern Med* **134:** 191–202
Mismetti P, Quenet S, Laporte S, Bregeault M-F, Decousus H (2001) Treatment of deep-vein thrombosis and/or pulmonary embolism by enoxaparin versus unfractionated heparin: a meta analysis on individual data from clinical trials. *Thromb Haemost* **86:** 2334 (abstract)
O'Shaughnessy DF, Tovey C, Miller AL et al (1998) Outpatient management of deep vein thrombosis. *J Accid Emerg Med* **15:** 292–3
O'Shaughnessy D, Miles J, Wimperis J (2000) UK patients with deep-vein thrombosis can be safely treated as outpatients. *QJM* **93:** 663–7
Prandoni P, Lensing AW, Buller HR et al (1992) Comparison of subcutaneous low-molecular-weight heparin with intravenous standard heparin in proximal deep-vein thrombosis. *Lancet* **339:** 441–5
Sanderink G-J, Guimart C, Jariwala N et al (2001a) Enoxaparin pharmacokinetics and pharmacodynamics in renal impairment. *J Am Coll Cardiol* **37**(Suppl A) 229A, abstract 1076-169
Sanderink G-J, Le Liboux A, Jariwala N et al (2001b) Enoxaparin pharmacokinetics and pharmacodynamics in obese subjects. *J Am Coll Cardiol* **37**(Suppl A) 229A, abstract 1076-172
Schafer AI (1996) Low-molecular-weight heparin--an opportunity for home treatment of venous thrombosis. *N Engl J Med* **334:** 724–5
Simonneau G, Charbonnier B, Decousus H et al (1993) Subcutaneous low-molecular-weight heparin compared with continuous intravenous unfractionated heparin in the treatment of proximal deep vein thrombosis. *Arch Intern Med* **153:** 1541–6
Simonneau G, Sors H, Charbonnier B et al (1997) A comparison of low-molecular-weight heparin with unfractionated heparin for acute pulmonary embolism. The THESEE Study Group. Tinzaparine ou Heparine Standard: Evaluations dans l'Embolie Pulmonaire. *N Engl J Med* **337:** 663–9
Siragusa S, Cosmi B, Piovella F, Hirsh J, Ginsberg JS (1996) Low-molecular-weight heparins and unfractionated heparin in the treatment of patients with acute venous thromboembolism: results of a meta-analysis. *Am J Med* **100:** 269–77
Tillman DJ, Charland SL, Witt DM (2000) Effectiveness and economic impact associated with a program for outpatient management of acute deep vein thrombosis in a group model health maintenance organization. *Arch Intern Med* **160:** 2926–32
Ting SB, Ziegenbein RW, Gan TE et al (1998) Dalteparin for deep venous thrombosis: a hospital-in-the-home program. *Med J Aust* **168:** 272–6
Weitz JI (1997) Low-molecular-weight heparins. *N Engl J Med* **337:** 688–98
Wells PS, Kovacs MJ, Bormanis J et al (1998) Expanding eligibility for outpatient treatment of deep venous thrombosis and pulmonary embolism with low-molecular-weight heparin: a comparison of patient self-injection with home-care injection. *Arch Intern Med* **158**: 1809–12
Young E, Wells P, Holloway S, Weitz J, Hirsh J (1994) Ex-vivo and in-vitro evidence that low molecular weight heparins exhibit less binding to plasma proteins than unfractionated heparin. *Thromb Haemost* **71:** 300–4