Management of venous and cardiovascular thrombosis: enoxaparin

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Enoxaparin has strong clinical evidence that supports its license in a broad spectrum of therapeutic indications, including thromboprophylaxis in surgical patients, medical patients bedridden because of acute illness, the once-daily treatment of venous thromboembolism and the treatment of unstable angina and non-Q wave myocardial infarction.

As low molecular weight heparins (LMWHs) continue to replace unfractionated heparin (UFH) in the management of venous thromboembolism (VTE) and cardiovascular thrombosis, this article reviews the clinical evidence for use of enoxaparin (Clexane®, Aventis Pharma, Frankfurt, Germany). Clinical trials have shown that enoxaparin provides effective and convenient thromboprophylaxis in surgical patients. Recently, enoxaparin was licensed for prophylaxis in medical patients bedridden because of acute illness. Unmonitored once-daily subcutaneous enoxaparin injections provide effective treatment for VTE with the potential for treatment in the outpatient setting.

International clinical studies have also demonstrated the superiority of unmonitored subcutaneous injections of enoxaparin to UFH in the treatment of acute coronary syndromes (ACS) without ST segment elevation (i.e. patients with unstable angina (UA) or non-Q wave myocardial infarction (NQMI)). Administered concurrently with aspirin, enoxaparin has become the standard of care in the treatment of such coronary syndromes. Enoxaparin has strong clinical evidence that supports a broad spectrum of clinical indications. This may influence hospital formularies considering rationalization of LMWH provision.

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VENOUS THROMBOEMBOLISM AND CARDIOVASCULAR THROMBOSIS

VTE, which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common medical disorder that results in considerable morbidity and mortality (Clagett et al, 1998). The annual incidence of VTE in the western world is estimated at 1 per 1000 (Anderson et al, 1991), and the occurrence of VTE heralds a fatal outcome in a substantial proportion of cases.

Autopsy studies have revealed that PE remains a major cause of death in surgical patients and as many as one in 10 hospital deaths are caused by fatal PE (Sandler and Martin, 1989; Lindblad et al, 1991; Fennerty, 1998). It is now apparent that, in addition to the traditional 'at-risk' surgery patient, acutely ill medical patients (Samama et al, 1999), patients with congenital thrombophilia (Poort et al, 1996) and pregnant women (Greer, 1999) are at substantial risk of VTE. It is also apparent that patients who experience a VTE are exposed to the long-term morbidity associated with post-thrombotic syndrome — an unpleasant and financially costly outcome that includes skin discoloration, oedema and, most significantly, ulceration (Franzeck et al, 1996).

ACS describe a spectrum of diseases, ranging from UA to myocardial infarction (MI), that are associated with high morbidity and mortality. In the UK, approximately 300 000 MIs and 1.4 million cases of angina occur annually, representing a significant health and economic burden for the NHS (Peterson et al, 1999). On average, ACS patients receive hospital treatment for 7 days. One patient in 10 progresses to MI or death within 6 months of diagnosis and up to 14% will die within 1 year; half of these deaths occur within the first 4 weeks after an acute coronary event.

PREVENTION OF VTE

Extensive clinical trials have reported the efficacy and safety of enoxaparin as thromboprophylaxis in surgical patients at both moderate and high risk of VTE, including the provision of extended thromboprophylaxis for those patients at the highest risk. In addition, new evidence provided by the MEDENOX and PRINCE trials has helped to demonstrate that acutely ill general medical patients are at substantial risk of VTE

and that thromboprophylaxis with LMWH is effective. These studies have recently resulted in licensing of enoxaparin as the first LMWH for prophylaxis of VTE in medical patients (Kleber et al, 1999; Samama et al, 1999).

Enoxaparin thromboprophylaxis in surgical patients

General surgery: Numerous studies have investigated the use of enoxaparin as thromboprophylaxis in general surgery. This article will not discuss all the trials, but will consider four representative studies (*Table 1*).

The GENOX studies were three consecutive, randomized open studies to determine the optimal dosage of enoxaparin in major abdominal surgery (Samama et al, 1988). Three subcutaneous doses — 20 mg, 40 mg and 60 mg once daily — were compared with UFH 5000IU given subcutaneously three times daily. All three enoxaparin doses resulted in a non-significant reduction in the incidence of DVT compared with UFH. Only one case of PE was found during the study, in the group of patients receiving UFH, and there was no significant difference in the bleeding complications between the treatments. Enoxaparin 20 mg was suggested as the optimal dosage to provide effective prevention of postoperative thrombosis in this population. A European double-blind, multicentre, randomized study in patients undergoing major surgery (33% with malignancy) found that enoxaparin 20 mg once daily was as effective and safe as UFH 5000IU three times daily (Nurmohamed et al, 1995). There was no significant difference in bleeding complications, but enoxaparin was associated with a lower incidence of thrombocytopenia.

In an international double-blind, multicentre, randomized study of patients undergoing elective surgery for abdominal or pelvic malignancy, enoxaparin 40 mg once daily was as effective and safe as UFH 5000IU three times daily (ENOXACAN Study Group, 1997). There was no significant difference between the two study groups in the incidence of DVT although the majority of DVTs detected in this study were distal. There was no significant difference in bleeding complications between the enoxaparin and UFH treatments. More recently, a double-blind, multicentre, randomized study examined enoxaparin thromboprophylaxis in patients undergoing cranial or spinal surgery (Agnelli et al, 1998). Enoxaparin 40 mg once daily combined with compression stockings was significantly more effective than compression stockings alone in the prevention of VTE (17% *vs* 33%). The most feared complication — intracranial bleeding — was uncommon and of similar frequency in both groups. The authors concluded that compression stockings and enoxaparin 40 mg once daily begun within 24 hours after surgery should be the thromboprophylaxis of choice for the majority of patients undergoing elective neurosurgery.

Orthopaedic surgery: Numerous studies have investigated enoxaparin for prophylaxis during orthopaedic surgery. This paper will review two representative studies, one comparing enoxaparin with UFH and the other comparing enoxaparin with tinzaparin (*Table 2*).

Planés et al (1988) conducted a multicentre, randomized, double blind study that revealed enoxaparin 40 mg once daily was significantly more effective than UFH 5000IU given three times daily in the prevention of postoperative DVT. Enoxaparin reduced the total DVT rate from 25% to 12.5% (P=0.03) compared with UFH. Similarly the rate of proximal DVT was reduced from 18.5% to 7.5% when patients received enoxaparin (P=0.01). Enoxaparin is the only LMWH proven superior to UFH in orthopaedic surgery patients, who are defined as at high risk of VTE according to THRiFT risk classification (Second Thromboembolic Risk Factors (THRiFT II) Consensus Group, 1998).

Planés also conducted a direct comparison between enoxaparin and tinzaparin in the preven-

TABLE 1.
Selected clinical studies with enoxaparin in general surgery

Study	Heparin type	Dose	DVT	Haemorrhage
Samama et al (1988)	Enoxaparin	20 mg od	7.6%	NS
	UFH	5000IU tds	3.8%	NS
Nurmohamed et al (1995)	Enoxaparin	20 mg od	7.5%	NS
	UFH	5000IU tds	5.2%	NS
ENOXACAN (1997)	Enoxaparin	40 mg od	14.4%	NS
	UFH	5000IU tds	17.6%	NS
Agnelli et al (1998)	Enoxaparin	40 mg od	17%	NS
	Placebo	–	33%	NS

DVT = deep vein thrombosis; NS= not significant; od = once daily; tds = three times daily; UFH = unfractionated heparin

TABLE 2.
Selected clinical studies with enoxaparin in orthopaedic surgery

Study	Heparin type	Dose	DVT	Haemorrhage
Planés et al (1988)	Enoxaparin	40 mg od	12.5%	NS
	UFH	5000IU tds	25.0%	NS
Planés et al (1999)	Enoxaparin	40 mg od	20.1%	NS
	Tinzaparin	4500IU od	21.7%	NS

DVT = deep vein thrombosis; NS= not significant; od = once daily; tds = three times daily; UFH = unfractionated heparin

tion of DVT in hip replacement patients (Planés et al, 1999). Enoxaparin was chosen as the comparator because it was regarded as the reference LMWH for thromboprophylaxis in orthopaedic surgery. The incidence of DVT was described as equivalent for both groups (the total DVT rate was 20.1% when patients received enoxaparin compared with 21.7% in the tinzaparin treated patients), although the statistical methods employed in this study and the conclusions drawn have been questioned (Cohen, 2000).

Orthopaedic surgery patients fall within the highest risk category for VTE. Data from the National Confidential Enquiry into Peri-Operative Deaths revealed that PE constitutes a significant cause of death, despite many of these patients receiving thromboprophylaxis (Campling et al, 1996). Six randomized clinical trials have examined whether extended thromboprophylaxis, up to 35 days post-surgery, is beneficial in reducing the incidence of VTE in this at-risk patient group (reviewed by Pineo and Hull in 1999).

Two randomized studies have compared post-discharge enoxaparin with placebo in hip arthroplasty patients, following in hospital prophylaxis with enoxaparin for all enrolled patients. In the study led by Planés, randomization took place at hospital discharge and only included patients with no venographically detectable DVT (Planés et al, 1996). After 3 weeks of treatment, de-novo DVT occurred in 19.3% of patients receiving placebo, compared with 7.1% in the enoxaparin group, a significantly lower percentage (P=0.018). In a similar study (Bergqvist et al, 1996), patients received subcutaneous enoxaparin 40 mg once daily (n=131), or placebo (n=131) for a total treatment period of 4 weeks after discharge. Prolonged enoxaparin thromboprophylaxis significantly reduced the incidence of proximal DVT (7% *vs* 24% with placebo, P<0.001), and was associated with a reduction in symptomatic thromboembolic complications (9% placebo *vs* 2% enoxaparin). These studies show that extending the duration of thromboprophylaxis beyond the normal hospitalized period significantly reduces the incidence of VTE.

Enoxaparin thromboprophylaxis in medical patients

VTE is a common finding at autopsy in medical patients who die in hospital. Autopsy series of deceased hospital inpatients have shown that only a minority of patients who die from PE had recently undergone surgery (Sandler and Martin, 1989; Lindblad et al, 1991). Some medical conditions, such as ischaemic stroke and heart failure, and some patient characteristics, such as age and obesity, have been clearly identified as risk factors for VTE (Clagett et al, 1998). Despite this, and in contrast to surgical patients, the incidence of VTE in internal medical patients was only recently estimated by meta-analysis (Mismetti et al, 2000).

The MEDENOX trial (Samama et al, 1999) enrolled immobilized patients over 40 years old hospitalized with heart failure (New York Heart Association (NYHA) class III or IV) or acute respiratory failure and patients with a predefined thromboembolic risk factor in association with acute infection, inflammatory bowel disease, or rheumatic disorder. MEDENOX demonstrated that acutely ill medical patients are at substantial risk of VTE, since 14.9% of patients who received placebo experienced a VTE event. Treatment with enoxaparin at a dose of 40 mg once daily significantly reduced the incidence of VTE compared with placebo (5.5% *vs* 14.9%, P<0.001) without any significant increase in adverse events. This benefit was also evident in the incidence of proximal DVT (4.9% *vs* 1.7%, P=0.019) and was maintained at 3 months follow-up.

PRINCE assessed a similar patient population to MEDENOX, but limited recruitment to those patients presenting with heart failure (NYHA III or IV) or acute respiratory failure (Kleber et al, 1999). PRINCE confirmed that general medical patients are at risk of VTE and revealed that enoxaparin (40 mg once daily) is as effective and safe as UFH (5000IU three times daily) in the provision of thromboprophylaxis. In PRINCE, heart failure patients were shown to be at higher risk of VTE than the respiratory patient group. Both MEDENOX and PRINCE demonstrated the efficacy of enoxaparin in reducing VTE incidence in severe heart failure patients. Based on the results of these clinical trials, enoxaparin recently became the only LMWH to be licensed for prophylaxis of VTE in medical patients bedridden because of acute illness.

Enoxaparin for haemodialysis

Enoxaparin is approved for the prevention of thrombus formation in the extracorporeal circulation during haemodialysis. The pharmacokinetics of enoxaparin and UFH have been compared in patients with chronic renal failure (Follea et al, 1986). The anticoagulation activity of a single dose of each drug measured as anti-factor-Xa activity was compared. Anti-Xa activity was no longer detectable 150 minutes after injection with UFH, but was still present up to 6 hours after a weight-adjusted dose (0.5 mg/kg) of enoxaparin.

Recently, a direct comparison of enoxaparin with standard UFH for haemodialysis anticoagulation was described, which demonstrated that

enoxaparin can make a difference as an effective and convenient alternative to UFH (Saltissi et al, 1999). In a randomized study comparing the safety, clinical efficacy and cost effectiveness of enoxaparin with UFH, 36 chronic patients received enoxaparin (1 mg/kg body weight) or heparin for 12 weeks (36 dialyses) before crossing over to the alternate therapy for a further 12 weeks. Dialysis with enoxaparin significantly reduced the frequency of minor fibrin/clot formation in the dialyser and lines compared with UFH ($P<0.001$), and although accompanied by increased frequency of minor haemorrhage between dialyses ($P<0.001$), dose reduction eliminated these excess minor haemorrhages without increasing clotting frequencies. The authors concluded that a single-dose protocol of enoxaparin is an effective and very convenient alternative to UFH.

TREATMENT OF VTE

The biology and pathogenesis of DVT and PE are similar, and it is widely accepted that they form a spectrum of one disease — VTE — and approaches to treatment are essentially the same (Bates and Hirsh, 1999). There is a strong association between DVT and PE (Plate et al, 1985; Stein, 2000). About 70% of patients with a confirmed clinically symptomatic PE have an asymptomatic DVT. A recent study revealed that up to 50% of patients with proximal DVT had a 'silent PE' (detected by lung scans) with no clinical signs (Meignan et al, 2000).

The main treatment is anticoagulant therapy. Thrombolytic agents may be used, and surgical intervention, including the placement of vena caval filters or pulmonary embolectomy, is occasionally indicated. The traditional approach to the treatment of VTE is UFH administered for 5–7 days while oral anticoagulant therapy is established, followed by long-term oral anticoagulation with warfarin (for at least 3 months depending on patient risk) (Hyers et al, 1998). UFH is a proven, effective anticoagulant but requires hospitalization for intravenous infusion, in association with careful activated partial thromboplastin time (aPTT) monitoring and dose adjustment to ensure optimal treatment. Despite monitoring, under clinical trial conditions as few as 23% of patients treated for acute MI were optimally anticoagulated with UFH within 6–12 hours, climbing to only 40% within 96 hours (Antman, 1996).

Clinical trials have confirmed the theoretical advantages of LMWH therapy. When delivered as unmonitored once-daily subcutaneous injections, enoxaparin, tinzaparin and dalteparin have each demonstrated efficacy and safety at least equivalent to monitored intravenous UFH for the treatment of VTE (Hull et al, 1992; Lindmarker et al, 1994; Simonneau et al, 1997; Enoxaparin Clinical Trial Group, 1997). A meta-analysis has suggested that patients experience fewer bleeding events when receiving unmonitored LMWH compared with monitored UFH (Hirsh et al, 1995). In addition, several studies have shown the potential for outpatient treatment with enoxaparin (Levine et al, 1996) and dalteparin (Kovacs, 2000), an option that may benefit both the patient and health-care providers.

Although unmonitored LWMH therapy is efficacious, as safe as UFH and widely employed in clinical trials, certain patient populations are excluded from clinical studies and there is considerable debate among haematologists whether these patients require more careful clinical assessment and monitoring. These patients include renal failure, patients on intensive care units and pregnant women. Monitoring, if required, is performed using an anti-Xa assay, which is not routinely available in all laboratories.

A review of VTE treatment studies

Deep vein thrombosis: A landmark study published by Hull et al (1992) provided the first evidence of the efficacy and safety of a LMWH for the treatment of VTE, in this case proximal DVT. In a double-blind, randomized study, 432 patients received either tinzaparin (175 IU/kg once daily for 5–6 days) or intravenous UFH (dose-adjusted for 5–6 days) and all patients received concomitant warfarin therapy begun on day 2. Six of 213 patients who received LMWH (2.8%) and 15 of 219 patients who received intravenous UFH (6.9%) had new episodes of VTE ($P=0.07$). Major bleeding associated with initial therapy occurred in 1 patient receiving LMWH (0.5%) and in 11 patients receiving intravenous UFH (5.0%), a reduction in risk of 91% ($P=0.006$).

The Enoxaparin Clinical Trial Group described a key prospective randomized trial for the treatment of patients with lower extremity DVT with or without PE that indicated the similar efficacy and safety of either once- or twice-daily doses of enoxaparin (Enoxaparin Clinical Trial Group, 1997). Patients received subcutaneous enoxaparin once or twice daily (1.5 mg/kg and 1.0 mg/kg respectively) or intravenous UFH (dose-adjusted, based on aPTT) for at least 5 days, with warfarin started within 72 hours of randomization. This regimen demonstrated equivalent efficacy between the UFH and enoxaparin treatments and showed that enoxaparin was equally effective when administered as a once- or twice-daily dose. Furthermore, no significant

differences were observed in the safety profiles of the three treatment regimens. It is notable that a substantial proportion of patients (32%) successfully treated in this study had documented concomitant PE at presentation. In 1998, enoxaparin was approved for the treatment of DVT with or without PE as a once-daily regimen.

Pulmonary embolism: More recently, the concept that DVT and PE are distinct clinical presentations of the same pathophysiological process has resulted in clinical trials of LMWH in the treatment of PE. Hull revisited his data from 1992 with the goal of establishing the efficacy of LMWH in the treatment of patients with PE (Hull et al, 2000). Almost half of the study population (200 of 419 patients, 47.7%) had high probability lung scan findings at randomization. This finding and the randomized trial design allowed Hull to compare LMWH with UFH treatment in patients with documented PE and proximal DVT, and to determine whether LMWH administered as a once-daily subcutaneous injection without anticoagulant monitoring was effective and safe. None of the LMWH patients experienced new VTE, compared with 6.8% of patients receiving UFH, a significant difference (P=0.01). Hull concluded that these findings extend the use of LMWH without anticoagulant monitoring to patients with submassive PE.

In an earlier study, the Tinzaparine ou Heparine Standard: Evaluation dans l'Embolic Pulmonaire (THESEE) study group compared tinzaparin with UFH in the treatment of symptomatic PE. The trial recruited patients with symptomatic PE (documented by lung scan or angiography) or an inconclusive lung scan with a DVT (confirmed by venography or ultrasonography). In comparison with intravenous dose-adjusted UFH, tinzaparin (175 IU/kg once daily) was as safe and effective for treatment of symptomatic PE in terms of death, recurrent thromboembolism or major bleeding (Simonneau et al, 1997).

Outpatient treatment with enoxaparin: Compared with in-hospital treatment with dose-adjusted UFH, enoxaparin administered primarily at home is as safe and effective for the treatment of acute proximal DVT (Levine et al, 1996). This multicentre, parallel group study enrolled 500 patients and was the first 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 (5000IU) 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 that received enoxaparin treatment were never admitted to hospital, demonstrating the feasibility of outpatient management for this patient group. Further evidence has demonstrated that the more convenient once-daily dose regimen has similar efficacy to twice-daily enoxaparin injections (Enoxaparin Clinical Trial Group, 1997).

The convenience of subcutaneous administration of enoxaparin without monitoring opens the possibility of outpatient, or primary care group (PCG), provision of VTE treatment. Treatment outside the hospital setting is effective, improves the patient's quality of life and has the potential for substantial savings for the NHS. The cost benefits have been examined. Easier administration and fewer adverse events alone result in cost savings (Valette et al, 1995), and a recent study, which included the cost of hospitalization, revealed substantial savings when enoxaparin is provided out of hospital (*Table 3*) (Anderson et al, 1999).

The movement of VTE treatment into PCGs would have an immediate beneficial effect on patient quality of life and reduce the overall costs of management. However, the financial management of outpatient implementation in the current trust environment is complex. Most PCGs have fixed, block contracts with hospital trusts. The allocation of funds within hospitals that covers nurses' and doctors' salaries, bed use and associated hospital laboratory costs is also fixed. This rigidity within the system means the required switching of funds to individual PCG budgets is not easily achieved. However, as the modernization of the NHS proceeds at a pace, it seems likely that the VTE treatment paradigm will shift to the outpatient setting.

TABLE 3.
Economic implications of enoxaparin treatment in the outpatient setting

		Enoxaparin		
	UFH	Community	Anticoagulation clinic	Hospital
Drug costs	£4.93	£55.15	£55.15	£55.15
Administration costs	£60.78	£40.45	£40.45	£40.45
Outpatient/inpatient	£1055.00	£135.00	£300.00	£1055.00
Total	£1120.71	£230.60	£395.60	£1150.60

Adapted from Anderson et al (1999). UFH = unfractionated heparin

VTE in the pregnant woman

Pregnancy represents a special VTE management situation. The risk of VTE in pregnancy is substantially higher (up to six times greater) than in non-pregnant women and remains a

major cause of death among women during pregnancy and the puerperium (THRiFT Consensus Group, 1992).

PE is the single most common cause of maternal death in developed countries and occurs in one in eight patients with untreated DVT (THRiFT Consensus Group, 1992; Greer, 1999). The overall risk of DVT in pregnancy (0.06–0.12%) (Macklon and Greer, 1996) is higher in women with a previous history of VTE, possibly reaching a recurrence rate of 15% (Ginsberg and Hirsh, 1998). The form of delivery is an important risk factor for VTE. Emergency caesarean section has a high risk, and maternal age and weight are also important predictive factors (Macklon and Greer, 1996).

Antithrombotic therapy in pregnancy is employed as thromboprophylaxis and treatment of VTE and also has a role in the management of recurrent pregnancy loss (Ginsberg and Hirsh, 1998). Despite the recognized importance of VTE in pregnant women, much remains to be defined about the efficacy of thromboprophylaxis and there is limited quality evidence from randomized clinical trials (Gates, 2000). None of the LMWHs are licensed for use in pregnant women, although they are widely used in treatment and prophylaxis at the doctor's discretion. Neither UFH nor LMWH cross the placenta or are secreted in breast milk.

A recent study described a large retrospective survey conducted in France to examine the safety of enoxaparin in 624 patients (Borel-Derlon et al, 1999). The authors concluded:

> **'The adverse event profile did not show any unexpected data compared to the same type of pregnancies not treated with anticoagulant. In this large series of patients, the rate of serious adverse events assessed as reasonably related to the study drug was very low. Foeto-maternal safety of enoxaparin is well documented in this study.'**

Recent pilot trials of enoxaparin initiated by the Perinatal Trials Service (www.npeu.ox.ac.uk) may lead to large randomized studies and provide definitive data on the benefits of thromboprophylaxis.

THE TREATMENT OF UA/NQMI

ACS are caused by disruption of intracoronary atherosclerotic plaques, a process that triggers thrombogenesis. The central role of coronary artery thrombosis in the pathogenesis of ACS is supported by extensive scientific and clinical evidence. Clot formation at the lesion compromises intra-arterial blood flow, causing unstable angina, MI and in extreme cases cardiac death. In the treatment of ACS patients without ST segment elevation (i.e. patients with UA or NQMI), initial anti-ischaemic therapy includes aspirin, β-blockers, nitrates and effective anticoagulation.

Although UFH has been the anticoagulant of choice for UA/NQMI patients, two LMWHs, enoxaparin and dalteparin, are now licensed in the UK for the treatment of these patients, each with a different body of clinical evidence to support the indication. Uniquely, enoxaparin has been proven superior to UFH in the treatment of UA/NQMI (Cohen et al, 1997; Antman et al, 1999) (*Table 4*). This established efficacy superiority has led the Wessex Development and Evaluation Committee (DEC) to conclude that the clinical evidence strongly supports short-term treatment using enoxaparin, the highest recommendation given to an intervention. In contrast, Wessex DEC determined that there was no randomized controlled trial to compare dalteparin with UFH and raised concern over the excess of deaths in the acute phase of FRIC (Fragmin in Unstable Coronary Artery Disease). The committee therefore considered short term treatment with dalteparin as 'not proven' (Nicholson et al, 2000). This report can be found at www.hta.nhsweb.nhs.uk/rapidhta

TABLE 4.
Overview of trials in acute coronary syndromes that compare enoxaparin or dalteparin with active treatment

				Endpoint components*						
	Trial	Dose	Time to treat	D	MI	RA	UR	Timepoint	RRR	*P*
Enoxaparin	ESSENCE	1 mg/kg twice daily for 2–8 days	Within 24h	✓	✓	✓		day 30	15% reduction, 23.3% *vs* 19.3%	0.02
	TIMI 11B	Initial 30mg bolus, then 1 mg/kg twice daily until discharge or day 8; then 40 mg < 65 kg or 60 mg ≥ 65 kg continued through day 43	Within 24h	✓	✓		✓	day 14	14.9% reduction, 16.7% *vs* 14.2%	0.03
Dalteparin	FRIC	120IU/kg twice daily for 6 days	Within 72h	✓	✓	✓		day 6	18% increase, 7.6% *vs* 9.3%	0.33

*D = death; MI = myocardial infarction; RA = recurrent angina; RRR= relative risk reduction; UR = urgent revascularization

Enoxaparin in UA/NQMI treatment

Two large randomized clinical trials have demonstrated the safety and efficacy of enoxaparin for UA/NQMI patients. After heterogeneity tests demonstrated similarity, the ESSENCE and TIMI 11b trial databases were pooled and meta-analysed (TESSMA; Antman et al, 1999).

ESSENCE was the first trial to demonstrate the efficacy and safety of enoxaparin (1 mg/kg, subcutaneously twice daily) for the treatment of UA/NQMI. Patients who received enoxaparin within 24 hours of chest pain were significantly less likely to experience the triple composite endpoint of death, MI and recurrent angina compared with patients who received UFH (day 30 19.8% *vs* 23.3%, *P*=0.02) (Cohen et al, 1997). The clinical benefit of enoxaparin was evident at 48 hours, maintained at each pre-defined time point through to 1 year (Goodman et al, 1998), and is seen in all patient subgroups (Cohen et al, 1998).

TIMI 11b confirmed the benefit of acute phase treatment with enoxaparin (Antman et al, 1999), and introduced a viable rapid treatment nomology: patients randomized to enoxaparin received an initial intravenous bolus of 30 mg followed by 1 mg/kg (subcutaneously, twice daily). Patients randomized to receive enoxaparin were significantly less likely to experience the composite endpoint of death, MI or urgent revascularization than those patients who received dose-adjusted UFH (day 43 19.7% *vs* 17.3%, *P*=0.048) (Antman et al, 1999). The benefit of enoxaparin treatment was evident in the early hours of treatment and significant at the first prospectively defined timepoint (48 hours).

TESSMA demonstrated that within 48 hours, enoxaparin treatment is associated with a 23% reduction in death and serious cardiac ischaemic events compared with UFH (*P*=0.02) (Antman et al, 1999). The double endpoint of death and MI was also significantly reduced from day 2 to day 43 with enoxaparin treatment (day 43 relative risk reduction 18%, *P*=0.02) (Antman et al, 1999).

These studies demonstrate that enoxaparin simplifies patient care and improves patient outcome, but the cost consequences of any new treatment must be carefully assessed. It appears that the enoxaparin benefits are also accompanied by cost savings when compared with UFH (Mark, 1998; Fox and Bosanquet, 1998). Earlier this year, the Wessex DEC published a cost utility analysis comparing the use of enoxaparin with UFH in the treatment of UA/NQMI from the NHS perspective. Using a base case over 1 year, treatment of 100 patients with enoxaparin may result in a net cost saving of £49 150 and quality-adjusted life-years (QALY) gain of 1.8 based on difference between coronary artery bypass graft rates. Alternatively, considering the highest death rate, £31 400 could be saved per 100 patients with a gain of 3.5 QALY (Nicholson et al, 2000).

As Wessex DEC reported, the improvements in the treatment of UA/NQMI patients have prompted clinical investigation into the potential advantages of enoxaparin for other aspects of ACS. New data and ongoing trials suggest that the proven benefits of enoxaparin in UA/NQMI may extend to patients undergoing angioplasty and patients with ST elevation MI.

Dalteparin in UA/NQMI treatment

Dalteparin treatment of UA/NQMI patients has been investigated in three international clinical trials (FRIC, FRISC and FRISC II; Fragmin during Instability in Coronary Artery Disease); however, only FRIC compared dalteparin with active treatment (standard UFH), while FRISC and FRISC II compared dalteparin with placebo. FRIC did not demonstrate any clinical benefit of short-term treatment with dalteparin over UFH at day 6, or over placebo from days 6–45 (Klein et al, 1997). Furthermore, FRIC revealed a borderline significant increase in death when patients received dalteparin. FRISC demonstrated a significant reduction in death, MI and urgent revascularization when patients received dalteparin compared with placebo (2.2% *vs* 5.7%; *P*<0.001), although there was no significant difference between the two groups after 5 months (FRISC study group, 1996).

FRISC II had a complicated trial design, including an initial stabilization period when all patients received dalteparin for up to 7 days. Following this, a clinical benefit of extended

KEY POINTS

- Venous thromboembolism (VTE) and acute coronary syndromes cause considerable morbidity and mortality in the UK. Low molecular weight heparins (LMWH) are a convenient alternative to traditional unfractionated heparins (UFH) for the treatment of venous and arterial thrombogenic disease.
- When patients are at moderate or high risk of thromboembolic complications enoxaparin is at least as effective and safe as UFH in the prevention of total and proximal deep vein thrombosis. Extending enoxaparin thromboprophylaxis beyond hospitalization significantly reduces VTE.
- Medical patients are at substantial risk of VTE. Enoxaparin is the only LMWH licensed for the prevention of VTE in medical patients bedridden as a result of acute illness.
- For the treatment of VTE, enoxaparin, tinzaparin and dalteparin have each shown efficacy and safety at least equivalent to UFH. Compared with in-hospital treatment, outpatient treatment with enoxaparin is viable and cost effective.
- Enoxaparin is the only LMWH proven superior to UFH in the treatment of unstable angina/non-Q wave myocardial infarction.
- Enoxaparin is licensed in an extensive and broad range of indications that is not exceeded by other LMWHs.

dalteparin treatment compared with placebo was evident at 30 days and 3 months. However, at 6 months, there was no significant efficacy difference between dalteparin and placebo (FRISC II Investigators, 1999).

ENOXAPARIN AND HOSPITAL FORMULARY DRUG RATIONALIZATION

Traditionally, drug efficacy was the major factor in determining whether a drug should be included in the hospital formulary. However, the market-driven changes in the provision of medical care have profoundly influenced drug prescription and delivery in the UK over the last decade. There is continuing pressure to reduce waiting lists, patient hospitalization, the period of stay and to minimize the drug budget. At the same time, the effect of clinical governance means that hospital trusts must be seen to follow 'best practice' guidelines, thus providing the patient with optimal and up-to-date care. However, new treatments and treatment guidelines often increase expenditure and complicate hospital procedures, increasing junior medical and nursing hours.

The unique ability of enoxaparin to provide all thrombosis management needs has advantages. Central to this argument are the issues of administration and the potential for crossover prescribing errors. Use of enoxaparin has been proven to reduce the cost of patient care in both UA/NQMI and DVT (Fox and Bosanquet, 1998; Anderson et al, 1999), and use of a single LMWH will minimize pharmacy management time while offering doctors and nurses confidence and consistency in drug presentation and dosing.

Enoxaparin is licensed in an extensive and broad range of indications that is not exceeded by other LMWHs (*Table 5*). The exclusive provision of enoxaparin within a hospital formulary facilitates the implementation of a single NHS trust-wide protocol for anticoagulation, including peri- and postoperative management, drug reversal, and anticoagulation monitoring when required. HM

Conflict of interest: Mr RH Offord sat on the prelaunch advisory panel for Revasc.

Agnelli G, Piovella F, Buoncristiani P et al (1998) Enoxaparin plus compression stockings compared with compression stockings alone in the prevention of venous thromboembolism after elective neurosurgery. *N Engl J Med* **339:** 80–5

Anderson DJ, Burrel AD, Jackson DL (1999) Economic implications associated with DVT treatment in the community. *Blood* **94(Suppl 1):** 422b

Anderson FA Jr, Wheeler HB, Goldberg RJ et al (1991) A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. *Arch Intern Med* **151**: 933–8

Antman EM (1996) Hirudin in acute myocardial infarction. Thrombolysis and Thrombin Inhibition in Myocardial Infarction (TIMI) 9B trial. *Circulation* **94**: 911–21

Antman EM, Cohen M, Radley D, McCabe C, Rush J, Premmereur J, Braunwald E (1999) Assessment of the treatment effect of enoxaparin for unstable angina/non-Q-wave myocardial infarction. TIMI 11B-ESSENCE meta-analysis. *Circulation* **100:** 1602–8

Antman EM, McCabe CH, Gurfinkel EP et al (1999) Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction. Results of the thrombolysis in myocardial infarction (TIMI) 11B trial. *Circulation* **100:** 1593–601

Bates SM, Hirsh J (1999) Treatment of venous thromboembolism. *Thromb Haemost* **82:** 870–7

Bergqvist D, Benoni G, Bjorgell O et al (1996) Low-molecular-weight heparin (enoxaparin) as prophylaxis against venous thromboembolism after total hip replacement. *N Engl J Med* **335**: 696–700

Borel-Derlon A, Borg JY, Boudignat O et al (1999) Assessment of a LMWH (enoxaparin) safety during pregnancy: a retrospective study of 624-pregnancies. Abstract. *Thromb Haemost* **82(2)**: 1550

Campling EA, Devlin HB, Hoile RW, Lynn JN (1996) *The Report of the National Confidential Enquiry into Perioperative Deaths 1989–1990.* HMSO, London

Clagett GP, Anderson FA Jr, Geerts W et al (1998) Prevention of venous thromboembolism. *Chest* **114:** 531S–560S

Cohen AT (2000) Prevention of deep vein thrombosis after hip replacement. *Thromb Haemost* **83**: 171

Cohen M, Demers C, Gurfinkel EP et al (1997) A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group. *N Engl J Med* **337:** 447–52

Cohen M, Demers C, Gurfinkel EP et al (1998) Low-molecular-weight heparins in non-ST-segment elevation ischemia: the ESSENCE trial. Efficacy and Safety of Subcutaneous Enoxaparin versus intravenous unfractionated heparin, in non-Q-wave Coronary Events. *Am J Cardiol* **82**: 19L–24L

TABLE 5.
Licensed indications of low molecular weight heparins in the UK

			Low molecular weight heparin				
Indication			Enoxaparin	Dalteparin	Tinzaparin	Certoparin	Reviparin
Thromboprophylaxis	Haemodialysis		✓	✓	✓	✗	✗
	Medical patients		✓	✗	✗	✗	✗
	Surgical patients	Low/moderate risk	✓	✓	✓	✓	✓
		High risk	✓	✓	✓	✓	✓
Treatment	DVT	with PE	✓	✓	✓	✗	✗
		without PE	✓	✓	✓	✗	✗
	PE alone		✗	✓	✓	✗	✗
	UA/NQMI*		✓	✓	✗	✗	✗

*Enoxaparin is strongly supported by the Wessex DEC for short-term treatment of unstable coronary artery disease. DVT = deep vein thrombosis; PE = pulmonary embolism; NQMI = non-Q-wave myocardial infarction; UA = unstable angina

ENOXACAN Study Group (1997) Efficacy and safety of enoxaparin versus unfractionated heparin for prevention of deep vein thrombosis in elective cancer surgery: a double-blind randomised multicentre trial with venographic assessment. *Br J Surg* **84**: 1099–103

Enoxaparin Clinical Trial Group (1997) A comparison of subcutaneous enoxaparin given once or twice daily and intravenous unfractionated heparin in the treatment of venous thromboembolic disease. *Thromb Haemost* **80**: 1527

Fennerty T (1998) Pulmonary Embolism - Hospitals should develop their own strategies for diagnosis and management. *Br Med J* **317:** 91–2

Follea G, Laville M, Pozet N (1986) Pharmacokinetic studies of standard heparin and low molecular weight heparin in patients with chronic renal failure. *Haemostasis* **16**: 147–51

Fox KA, Bosanquet N (1998) Assessing the UK cost implications of the use of low molecular weight heparin in unstable coronary artery disease. *Br J Cardiol* **5:** 92–105

Franzeck UK, Schalch I, Jager KA (1996) Prospective 12-year follow-up study of clinical and hemodynamic sequelae after deep vein thrombosis in low-risk patients (Zurich study). *Circulation* **93:** 74–94

FRISC II Investigators (1999) Long-term low-molecular-mass heparin in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. FRagmin and Fast Revascularisation during InStability in Coronary artery disease. *Lancet* **354**: 701–7

FRISC study group (1996) Low-molecular-weight heparin during instability in coronary artery disease. *Lancet* **347**: 561–8

Gates S (2000) Thromboembolic disease in pregnancy. *Curr Opin Obstet Gynecol* **12**: 117–22

Ginsberg JS, Hirsh J (1998) Use of antithrombotic agents during pregnancy. *Chest* **114:** 524S–530S

Goodman S, Bigonzi F, Radley D, le Louer V, Gosset F, Cohen M (1998) One Year follow-up of the ESSENCE trial. *Eur Heart J* **19(Suppl):** 50

Greer IA (1999) Thrombosis in pregnancy: maternal and fetal issues. *Lancet* **353**: 1258–65

Hirsh J, Siragusa S, Cosmi B, Ginsberg JS (1995) Low molecular weight heparins (LMWH) in the treatment of patients with acute venous thromboembolism. *Thromb Haemost* **74:** 360–3

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, Weg JD, Morris TA, Samama M, Tapson VF (1998) Antithrombotic therapy for venous thromboembolic disease. *Chest* **114:** 561–78

Kleber FX, Witt C, Flosbach CW, Koppenhagen K, and the PRINCE Study Group (1999) Comparison of the low molecular weight heparin enoxaparin with unfractionated heparin in the prevention of venous thromboembolic events in medical patients with severe cardiopulmonary disease. *Thromb Haemost* **82 (suppl):** 492

Klein W, Buchwald A, Hillis SE et al (1997) Comparison of low-molecular-weight heparin with unfractionated heparin acutely and with placebo for 6 weeks in the management of unstable coronary artery disease. Fragmin in unstable coronary artery disease study (FRIC). *Circulation* **96:** 61–8

Kovacs J (2000) Outpatient treatment of pulmonary embolism with dalteparin. *Thromb Haemost* **83**: 209–11

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

Lindblad B, Eriksson A, Bergqvist D (1991) Autopsy-verified pulmonary embolism in a surgical department: analysis of the period from 1951 to 1988. *Br J Surg* **78**: 849–52

Lindmarker P, Holmstrom M, Granqvist S, Johnsson H, Lockner D (1994) Comparison of once-daily subcutaneous Fragmin with continuous intravenous unfractionated heparin in the treatment of deep vein thrombosis. *Thromb Haemost* **72:** 186–90

Macklon NS, Greer IA (1996) Venous thromboembolic disease in obstetrics and gynaecology: the Scottish experience. *Scott Med J* **41**: 83–6

Mark D (1998) When innovative therapies make economic sense: economic analysis of enoxaparin versus unfractionated heparin in the ESSENCE trial--an overview. Efficacy and Safety of Subcutaneous in non-Q Wave Coronary Events. *Can J Cardiol* **14** Suppl E: 24E–27E

Meignan M, Rosso J, Gauthier H et al (2000) Systematic lung scans reveal a high frequency of silent pulmonary embolism in patients with proximal deep venous thrombosis. *Arch Intern Med* **160**: 159–64

Mismetti P, Laporte-Simitsidis S, Tardy B, Cucherat M, Buchmuller A, Juillard-Delsart D, Decousus H (2000) Prevention of venous thromboembolism in internal medicine with unfractionated or low-molecular-weight heparins: a meta-analysis of randomised clinical trials. *Thromb Haemost* **83:** 14–19

Nicholson T, Milne R, Stein K (2000) *Dalteparin and enoxaparin for unstable angina and non-Q-wave myocardial infarction: update.* Development and Evaluation Committee Report No. 108. Wessex Institute for Health Research and Development, Southampton

Nurmohamed MT, Verhaeghe R, Haas S et al (1995) A comparative trial of a low molecular weight heparin (enoxaparin) versus standard heparin for the prophylaxis of postoperative deep vein thrombosis in general surgery. *Am J Surg* **169**: 567–71

Peterson S, Mockford C, Rayner M (1999) *Coronary Heart Disease Statistics.* 1999 edition. British Heart Foundation, London

Pineo GF, Hull RD (1999) Prophylaxis of venous thromboembolism following orthopedic surgery: mechanical and pharmacological approaches and the need for extended prophylaxis. *Thromb Haemost* **82:** 918–24

Planés A, Vochelle N, Mazas F et al (1988) Prevention of postoperative venous thrombosis: a randomized trial comparing unfractionated heparin with low molecular weight heparin in patients undergoing total hip replacement. *Thromb Haemost* **60:** 407–10

Planés A, Vochelle N, Darmon JY, Fagola M, Bellaud M, Huet Y (1996) Risk of deep-venous thrombosis after hospital discharge in patients having undergone total hip replacement: double-blind randomised comparison of enoxaparin versus placebo. *Lancet* **348:** 224–8

Planés A, Samama MM, Lensing AW, Buller HR, Barre J, Vochelle N, Beau B (1999) Prevention of deep vein thrombosis after hip replacement--comparison between two low-molecular heparins, tinzaparin and enoxaparin. *Thromb Haemost* **81:** 22–5

Plate G, Ohlin P, Eklof B (1985) Pulmonary embolism in acute iliofemoral venous thrombosis. *Br J Surg* **72:** 912–15

Poort SR, Rosendaal FR, Reitsma PH, Bertina RM (1996) A common genetic variation in the 3'-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. *Blood* **88**: 3698–703

Saltissi D, Morgan C, Westhuyzen J, Healy H (1999) Comparison of low-molecular-weight heparin (enoxaparin sodium) and standard unfractionated heparin for haemodialysis anticoagulation. *Nephrol Dial Transplant* **14**: 2698–703

Samama M, Bernard P, Bonnardot JP, Combe-Tamzali S, Lanson Y, Tissot E (1988) Low molecular weight heparin compared with unfractionated heparin in prevention of postoperative thrombosis. *Br J Surg* **75:** 128–31

Samama MM, Cohen AT, Darmon JY et al (1999) A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. Prophylaxis in Medical Patients with Enoxaparin Study Group. *N Engl J Med* **341:** 793–800

Sandler DA, Martin JF (1989) Autopsy proven pulmonary embolism in hospital patients: are we detecting enough deep vein thrombosis? *J R Soc Med* **82:** 203–5

Second Thromboembolic Risk Factors (THRiFT II) Consensus Group (1998) Risk of and prevention for venous thromboembolism in hospital patients. *Phlebology* **13:** 87–97

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

Stein PD (2000) Silent pulmonary embolism. *Arch Intern Med* **160**: 145–6

THRiFT Consensus Group (1992) Risk of and prophylaxis for venous thromboembolism in hospital patients. *Br Med J* **305:** 567–74

Valette F, Hoffmeyer U, Lloyd A (1995) Economic evaluation of the use of tinzaparin in the treatment of deep vein thrombosis. *Br J Med Econ* **8:** 111–23