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Enoxaparin

A Review of its Use as Thromboprophylaxis in Acutely Ill, Nonsurgical Patients

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Data Selection

Sources: Medical literature published in any language since 1980 on enoxaparin sodium, identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Adis International). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: MEDLINE and EMBASE search terms were 'enoxaparin' and ('acutely ill' or 'bedridden' or 'immobilised' or 'nonsurgical' or 'medical'). AdisBase search terms were 'enoxaparin' and ('acutely ill' or 'bedridden' or 'immobilised' or 'nonsurgical' or 'medical'). Searches were last updated 27 March 2005.

Selection: Studies in bedridden, nonsurgical patients with acute illness who received enoxaparin 40mg once daily. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Enoxaparin, venous thromboembolism, prophylaxis, thromboprophylaxis, acutely ill, immobilised, bedridden, nonsurgical or medical patients, pharmacodynamics, pharmacokinetics, therapeutic use.

Contents

Summary

Abstract

Enoxaparin (Clexane®, Lovenox®) is a low molecular weight heparin (LMWH) that has been widely used in the prevention of venous thromboembolism (VTE) in surgical patients. More recently, with the recognition of the high incidence of VTE in acutely ill medical (nonsurgical) patients, enoxaparin has been evaluated for thromboprophylaxis in this patient population.

Subcutaneous enoxaparin 40mg once daily has shown efficacy in the short-term thromboprophylaxis of VTE in nonsurgical patients with severely restricted mobility due to acute illness in well controlled clinical trials. The drug is at least similar in efficacy to unfractionated heparin (UFH) and its pharmacological profile allows once-daily administration, in contrast to the twice- or three-times-daily administration required with UFH. The tolerability profile of enoxaparin is also similar to that of UFH, except that the incidences of local haematomas and increased liver enzymes are lower with enoxaparin. The optimal duration of prophylaxis in nonsurgical patients is currently being evaluated and the results of extended prophylaxis with enoxaparin evaluated in the EXCLAIM (EXtended CLinical prophylaxis in Acutely Ill Medical patients) trial are awaited with interest. Currently, short-term enoxaparin appears to provide a cost-effective treatment alternative to UFH for VTE prophylaxis in nonsurgical patients.

Pharmacological Properties

Enoxaparin is an LMWH and produces its anticoagulant effect by activating antithrombin which, in turn, down-regulates the coagulation cascade. Compared with UFH, enoxaparin has a higher ratio of anti-factor Xa to IIa activity, reduced interaction with platelets, less propensity for nonspecific binding to tissues and proteins, and a more predictable pharmacodynamic effect.

Subcutaneous enoxaparin has high bioavailability, linear pharmacokinetics and a longer half-life than that of UFH, which facilitates once-daily administration.

Therapeutic Efficacy

Subcutaneous enoxaparin 40mg was significantly more effective than placebo in preventing VTE in acutely ill, nonsurgical patients in the randomised, double-blind MEDENOX (prophylaxis in MEDical patients with ENOXaparin) trial, during both treatment (1–14 days) and follow-up (1–110 days).

The incidence of VTE in acutely ill, immobilised nonsurgical patients receiving subcutaneous enoxaparin 40mg once daily was at least similar to that in recipients of UFH 5000IU three times daily in two well designed trials with a treatment duration up to 12 days.

Tolerability

Haemorrhagic complications were mostly minor, with major bleeding events reported in <2% of patients who received subcutaneous enoxaparin 40mg once daily for up to 14 days. Rates of bleeding and thrombocytopenia were similar for enoxaparin and placebo. Injection site haematoma with enoxaparin occurred more frequently than with placebo.

The tolerability of enoxaparin (including bleeding rates) was similar to that of UFH, except for lower incidences of injection-site haematomas and elevated liver enzymes.

Pharmacoeconomic Considerations

In nonsurgical patients with acute illness, subcutaneous enoxaparin 40mg was cost effective compared with no prophylaxis in several modelling studies based on the MEDENOX trial. Enoxaparin 40mg once daily may also be more cost effective than UFH 5000IU three times daily in the prophylaxis of VTE in this patient group.

1. Introduction

Venous thromboembolism (VTE), which by definition includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a major cause of morbidity and mortality in hospitalised patients. VTE is often asymptomatic or presents with nonspecific symptoms, and its first manifestation may be fatal PE.[1] In the US, more than 200 000 cases of VTE (DVT or PE) occur each year,[2] with >50% of patients dying within 1 year following a PE.[3]

Given the magnitude of the problem and the fact that no universally accepted method for routine screening for VTE exists, identification of at-risk patients and an optimal method of prophylaxis is essential.[1,4] The American College of Chest Physicians (ACCP) guidelines recommend that every hospital should develop a formal strategy to address the prevention of VTE complications.[1] However, until recently, prophylaxis of VTE has been largely overlooked, especially in heterogeneous populations who are not well studied, such as hospitalised medical (nonsurgical) patients with acute illness.[1,4]

Enoxaparin (enoxaparin sodium; Clexane®, Lovenox®)[1] is a low molecular weight heparin (LMWH) that has been widely used in the prevention of VTE in surgical patients.[5] Enoxaparin is also indicated, in combination with aspirin, for the prophylaxis of ischaemic complications of unstable angina and non-Q-wave myocardial infarction.[5] When administered in conjunction with warfarin, enoxaparin is used in the inpatient treatment of acute DVT with or without PE and the outpatient treatment of acute DVT without PE.[5] These indications have been previously reviewed in *Drugs*.[6,7] This article focuses on the use of enoxaparin in the prevention of VTE in hospitalised, acutely ill, nonsurgical patients with restricted mobility and includes additional data to those included in the previous review on this indication.[8]

2. Overview of Pharmacology

Enoxaparin, an LMWH, consists of polysaccharide chains (average molecular weight 4–5 kDa) and is produced through depolymerisation of unfractionated heparin (UFH). The pharmacodynamic and pharmacokinetic properties of enoxaparin have been reviewed in detail previously.[6,7] This section provides an overview of its major pharmacological properties.

2.1 Pharmacodynamics

Like UFH, the primary anticoagulant effect of enoxaparin is mediated via a conformational interaction with antithrombin which, in turn, inactivates procoagulatory serine proteases such as factors IIa (thrombin), IXa and Xa.[9] This results in the inhibition of the coagulation cascade and, consequently, prevention of the formation of a clot.[9]

Both enoxaparin and UFH cause the release of tissue factor pathway inhibitor (TFPI),[10] which inhibits the coagulation cascade.[11] More recent studies have shown that enoxaparin also inhibits the generation of activated factor VII[12,13] and activation of prothrombin.[13] All of these activities of enoxaparin could contribute to its anticoagulant effect.

Significant anti-factor Xa activity is seen in plasma for about 12 hours after subcutaneous administration of enoxaparin 40mg once daily.[5] Enoxaparin has a higher ratio of anti-factor Xa to IIa activity (14 : 1) than UFH (1 : 1), based on the area under anti-factor activity versus time curves.[5]

1 The use of trade names is for product identification purposes only and does not imply endorsement.

There is evidence that this ratio is inversely related to the tendency to cause bleeding.[11] Furthermore, the inhibitory effect of enoxaparin on platelet aggregation is much less pronounced compared with UFH.[14] Enoxaparin retains most of its antithrombotic activity in the face of inhibition by platelet factor 4 released by activated platelets, whereas UFH is almost completely inactivated.[15] This reduced interaction with platelets may be responsible for a lower incidence of heparin-induced thrombocytopenia with enoxaparin.

Single doses of enoxaparin and UFH result in similar increases in free TFPI concentrations.[10] However, continuous multiple-dose administration of UFH, but not enoxaparin, causes partial depletion of total TFPI activity.[16] Furthermore, the binding affinity of UFH to endothelial cells is much higher than that of enoxaparin.[17] UFH also binds nonspecifically to a variety of plasma proteins, whereas enoxaparin shows less propensity for nonspecific binding.[18] The above differences are likely to be responsible for the clinical differences between the two agents, with UFH showing greater variability in pharmacodynamic effects than enoxaparin.[9]

2.2 Pharmacokinetics

The pharmacokinetics of enoxaparin are based on measurement of anti-factor Xa activity.[6,7,9] Table I summarises various pharmacokinetic parameters of single-dose subcutaneous enoxaparin in healthy volunteers.

Following subcutaneous administration, enoxaparin demonstrates high bioavailability (≈100%), producing peak plasma anti-factor Xa and IIa activities within 3–5 hours.[5] The pharmacokinetics of subcutaneous enoxaparin are linear in the dose range 20–80mg.[19] Steady state is reached within two days after repeated subcutaneous administration of enoxaparin 40mg once daily.[5] Single-dose pharmacokinetics of enoxaparin are a good indicator of the steady-state enoxaparin activity levels.[5]

Table I. Mean pharmacokinetic parameters of single doses of subcutaneous enoxaparin 40mg in healthy volunteers[6]

C_{max}	2.8–3.8 mg/L
t_{max}	2.9–3.0 hours
AUC_{36}	32 mg • h/L
V_d	5.2–8.5L
CL	0.8–1.3 L/h
$t_{1/2\beta}$	4.3–4.6 hours

AUC_{36} = area under the plasma concentration-time curve from zero to 36 hours; **CL** = total body clearance; **C_{max}** = maximum plasma concentration; **$t_{1/2\beta}$** = elimination half-life; **t_{max}** = time to C_{max}; **V_d** = volume of distribution.

Desulfation and/or depolymerisation of enoxaparin in the liver results in the formation of lower molecular weight species with substantial loss of activity.[5] Enoxaparin is eliminated renally in a dose-independent, nonsaturable manner; the half-life is longer than that of UFH, facilitating a more sustained anticoagulant effect.[9] The elimination half-life of enoxaparin is about 4.5 hours after a single subcutaneous dose and 7 hours at steady state; however, a significant level of anti-factor Xa activity continues in plasma for about 12 hours after the administration of subcutaneous enoxaparin 40mg once daily.[5]

In a retrospective study (available as an abstract),[20] the median values for absorption constant, elimination constant and volume of distribution of subcutaneous enoxaparin (dosage not stated) in 37 acutely ill hospitalised patients were 0.22/hour, 0.20/hour and 4.5L, respectively.

After repeated subcutaneous enoxaparin 40mg once-daily doses, anti-factor Xa clearance decreases with decline in renal function,[5,21,22] necessitating a reduction in enoxaparin dosage in patients with severe renal impairment (creatinine clearance <30 mL/min)[5] [see section 6]. End-stage renal disease in patients receiving long-term haemodialysis had little effect on enoxaparin pharmacokinetics.[23]

The pharmacokinetics of enoxaparin in obese and non-obese volunteers are generally similar.[24] However, with non-weight adjusted subcutaneous enoxaparin single 40mg dose, the anti-factor Xa exposure was 52% and 27% higher in low-weight women (<45kg) and men (<57kg) compared with that in normal-weight volunteers.[5]

3. Therapeutic Efficacy

Early well designed 10-day trials indicated superior antithrombotic efficacy for subcutaneous enox-

Table II. Inclusion criteria in clinical trials of subcutaneous enoxaparin 40mg once daily for thromboprophylaxis in hospitalised nonsurgical patients

Study	Age (years)	Acute illness/risk factor	Immobilisation
Samama et al.[27] (MEDENOX)	>40	CHF, acute respiratory failure, infection without septic shock, rheumatic disorders, arthritis/episode of rheumatoid arthritis in the legs or IBD episode plus ≥1 additional risk factor for VTE (e.g. age >75 years, cancer, obesity)	Hospitalised for ≥6 days and immobilised for ≤3 days
Hillbom et al.[29]	18–90	Acute ischaemic stroke with CT-confirmed ischaemic brain infarction	Paralysis for ≥24 hours necessitating bedrest
Lechler et al.[28] (THE PRIME)	≥18	≥1 risk factor for VTE such as HF, age >60 years, malignancy, obesity or previous VTE event	Immobilised for >½ of the day-time during the study period
Kleber et al.[30] (THE-PRINCE)	≥18	Severe respiratory disease or HF	Bedridden for ≥⅔ of each day

(C)HF = (congestive) heart failure (New York Heart Association class III or IV); **CT** = computed tomography; **IBD** = inflammatory bowel disease; **MEDENOX** = prophylaxis in MEDical patients with ENOXaparin; **THE PRIME** = THromboEmbolism PRophylaxis in Internal Medicine with Enoxaparin; **THE-PRINCE** = THromboEmbolism-PRevention IN Cardiac or respiratory disease with Enoxaparin; **VTE** = venous thromboembolism.

aparin 60mg once daily versus placebo in unselected nonsurgical elderly inpatients[25] and equivalent efficacy for subcutaneous enoxaparin 20mg once daily and UFH 5000IU twice daily in nonsurgical elderly inpatients.[26] The approved dosage of subcutaneous enoxaparin in the prevention of VTE in acutely ill nonsurgical patients at increased risk of developing thromboembolic complications is 40mg once daily (section 6). The comparative efficacy of subcutaneous enoxaparin 40 mg/day versus placebo[27] or UFH[28-30] in this patient group has been evaluated in three fully published, randomised, double-blind, multicentre trials[27-29] and a less well controlled trial.[30]

Where reported, patients were ≥18 years of age (>40 years in one trial[27]), confined to bed with immobilising conditions and had (in two trials[27,28]) at least one additional risk factor for VTE (table II).

Exclusion criteria varied among these trials and included stroke[27]/haemorrhagic stroke,[28-30] coagulation disorders,[27-30] known thrombophilia,[27] thrombocytopenia,[28] uncontrolled hypertension,[27,29,30] HIV infection,[27,30] active peptic ulcer,[27,29,30] endocarditis[27-29] and hepatic or renal impairment.[28-30]

The primary efficacy assessment was the incidence of VTE, defined as DVT, PE or both, during treatment.[27-30] During the trials, the diagnosis for DVT was confirmed by venography or ultrasonography, and by scan, angiography, tomography or autopsy for PE.

3.1 Versus Placebo

Once-daily enoxaparin 40 mg/day was significantly more effective than placebo in preventing VTE in acutely ill medical patients after 14 days of treatment in the MEDENOX (prophylaxis in MEDical patients with ENOXaparin) trial.[27] The incidence of any VTE event was significantly lower in enoxaparin 40 mg/day than in placebo recipients (table III), with a relative risk ratio (RR) of 0.37 (95% CI 0.22, 0.63; $p < 0.001$). There was no between-group difference in this outcome in patients treated with enoxaparin 20 mg/day (n = 287; incidence of any VTE 15%) and placebo recipients (RR 1.02; 95% CI 0.7, 1.51).[27]

The 3-month (day 1 to 110) follow-up assessments showed that the benefit seen during the 14-day treatment period was maintained at a significant level.[27] The incidence of all VTE events in the enoxaparin 40 mg/day group was significantly lower than in the placebo group (7% vs 17.1%) [RR = 0.41; 95% CI 0.25, 0.68; $p < 0.001$].[27]

3.2 Versus Unfractionated Heparin

Prophylactic treatment with enoxaparin 40mg once daily for up to 12 days was at least as effective as UFH 5000IU three times daily in reducing the

Table III. Thromboprophylactic efficacy of subcutaneous enoxaparin (ENO) in acutely ill nonsurgical patients. Summary of randomised multicentre trials of ENO 40mg once daily versus placebo (PL) or unfractionated heparin (UFH) 5000IU three times daily

Study	Daily treatment regimen (n)	Duration (days)	Incidence of VTE during treatment[a] (%)			
			any event	DVT	PE	DVT and PE
Double-blind trial vs PL						
Samama et al.[27] (MEDENOX)	ENO (291)	14	5.5**	5.5**	0	0
	PL (288)		14.9	13.9	0.7	0.3
Double-blind trials vs UFH						
Hillbom et al.[29]	ENO (76)	10 ± 2	19.7*	18.4	1.3	0
	UFH (72)		34.7	30.6	1.4	2.8
Lechler et al.[28] (THE PRIME)	ENO (442)	7	0.2	0.2	0	0
	UFH (443)		1.4	0.5	0.5	0.5
Nonblind trial vs UFH						
Kleber et al.[b][30] (THE-PRINCE)	ENO (239)	10 ± 2	8.4	7.9	0.4	0
	UFH (212)		10.4	9.9	0	0.5

a During treatment and within 24h of the last administration in two trials.[29,30]

b Assessor-blinded.

DVT = deep vein thrombosis; **MEDENOX** = prophylaxis in MEDical patients with ENOXaparin; **n** = number of patients evaluated; **PE** = pulmonary embolism; **THE PRIME** = THromboEmbolism PRophylaxis in Internal Medicine with Enoxaparin; **THE-PRINCE** = THromboEmbolism-PRevention IN Cardiac or respiratory disease with Enoxaparin; **VTE** = venous thromboembolism; * $p < 0.05$, ** $p < 0.001$ vs comparator.

occurrence of VTE in acutely ill nonsurgical patients in two well designed trials (table III).[28,29] No statistically significant differences between treatments were seen in the large THE PRIME (THromboEmbolism PRophylaxis in Internal Medicine with Enoxaparin) trial in immobilised patients with additional thromboembolic risk factors.[28] Although a significant difference in favour of enoxaparin was seen in a trial in immobilised patients with acute ischaemic stroke,[29] this study was terminated early, before enrolment of the number of patients required for reliable statistical analysis.

The results of the large, nonblind THE-PRINCE (THromboEmbolism-PRevention IN Cardiac or respiratory disease with Enoxaparin) trial corroborated these results, showing at least similar efficacy for enoxaparin and UFH (table III). The treatment difference observed was not considered clinically relevant as it was within the predefined 1-sided equivalence value of −4%.[30] The rate of outcome events (VTE and death combined) was reported to be significantly ($p = 0.04$) lower in enoxaparin (15.6%; $n = 327$) than in UFH (22.1%; $n = 303$) group in another analysis of this trial that additionally included patients with acute ischaemic stroke (available as an abstract).[31]

4. Tolerability

This section reviews tolerability data from clinical trials of subcutaneous enoxaparin 40mg once daily in the prevention of VTE events in acutely ill nonsurgical patients (see section 3).

As expected with drugs interfering with haemostasis, haemorrhagic complications were the most important, and generally the most common, adverse events reported during enoxaparin therapy.[27-31] However, these were mostly minor. Major bleeding was reported in 0.3–1.7% of patients who received enoxaparin 40mg once daily for up to 14 days (figure 1).

There was no significant difference between enoxaparin and placebo in the incidence of any bleeding or major bleeding events during treatment (figure 1) or at 3-month follow-up in the MEDENOX trial.[27] However, enoxaparin administration caused a significantly higher incidence of local reaction at the injection site (haematoma >5cm in diameter) than placebo (1.4% vs 0%; $p = 0.03$).[27]

The incidence of thrombocytopenia (≥30% decrease in platelet count or <100 000 platelets/mm^3) was similar in the placebo and enoxaparin groups during treatment and follow-up; no case of severe

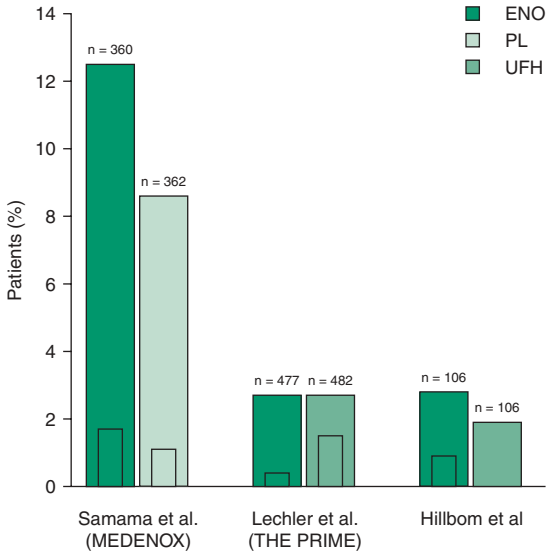

Fig. 1. Haemorrhagic events with the use of enoxaparin (ENO) in nonsurgical patients with increased risk of venous thromboembolism. Percentage of patients with any or major (inner bars) bleeding events reported during treatment with subcutaneously administered ENO 40mg once daily, placebo (PL) or unfractionated heparin (UFH) 5000IU three times daily for 7 (Lechler et al.[28]), 10 ± 2 (Hillbom et al.[29]) or 14 (Samama et al.[27]) days in randomised, double-blind clinical trials (see section 3 for trial details). **MEDENOX** = prophylaxis in MEDical patients with ENOXaparin; **THE PRIME** = THromboEmbolism PRophylaxis in Internal Medicine with Enoxaparin.

thrombocytopenia (<50 000 platelets/mm^3) was reported in the enoxaparin group.[27]

A Kaplan-Meier analysis indicated that the risk of all-cause mortality was numerically lower in the enoxaparin group than in the placebo group, but the difference was not significant (RR = 0.83; 95% CI 0.56, 1.21).[27]

In the two double-blind trials comparing subcutaneous enoxaparin and UFH,[28,29] the proportion of patients with any or major bleeding events was similar (figure 1). However, the incidence of injection-site haematomas (10.8% vs 4.6%; $p < 0.001$) and elevated liver enzymes (data not reported) were significantly higher in the UFH group than in enoxaparin recipients in one trial,[28] and appeared higher in the other (no statistical analysis reported).[29] A randomised, nonblind trial also reported a significant difference ($p < 0.03$) in the incidence of these two adverse events in favour of enoxaparin.[30] In this trial, the incidence of all possibly or probably treatment-related adverse events with enoxaparin was significantly lower than with UFH (2.1% vs 9.0%; $p = 0.00013$).[30]

5. Pharmacoeconomic Considerations

Several pharmacoeconomic analyses have been conducted in various countries to assess the cost effectiveness of thromboprophylaxis with subcutaneous enoxaparin 40mg once daily versus no prophylaxis in nonsurgical patients (table IV).[32-41] Some of the analyses are available as abstracts[36,38,39,41] and/or as a poster[41] only. With the exception of the US study that used a Monte Carlo simulation coupled with regression analysis,[32] all studies used a decision-tree method of analysis.[33-41]

The MEDENOX trial (section 3.1) was the main source of clinical variables and the time horizon was generally the 6- to 14-day treatment period of the trial,[32,34,35,40,41] and the 3-month follow-up period,[33,37] with a few studies extrapolating the data to a long-term or lifetime setting.[37-39] Only direct costs were considered. These included costs associated with efficacy and tolerability outcomes (table IV) and drug costs. Sensitivity analyses, where performed,[32-35,37,40] showed results to be generally robust to changes in key parameters. The year of costing was not reported in some studies.[36,38,39,41]

In all studies, enoxaparin was clearly beneficial and was found to be cost effective or even cost saving compared with placebo (table IV). The additional costs associated with enoxaparin prophylaxis were likely to be counterbalanced by cost savings resulting from avoided future treatment of VTE events.[32] In a Canadian community hospital (inpatient : outpatient ratio 1 : 1), but not in a tertiary setting (ratio 1 : 9), prophylaxis with enoxaparin was cost saving over no prophylaxis, as it reduced both the VTE events and the costs.[33] In several studies, the cost per VTE avoided with enoxaparin decreased with extended periods of follow-up from 3 months to lifetime.[37-39]

Enoxaparin dominated UFH (three times daily) in a German analysis based on data from the THE-PRINCE trial (see section 3), resulting in sav-

Table IV. Pharmacoeconomic studies of enoxaparin (ENO) 40mg once daily for thromboprophylaxis in nonsurgical patients with acute illness. Analyses incorporated results[a] from clinical trials (mainly MEDENOX) and other literature[b] and considered direct costs[c]

Study	Country (year of costing) [perspective]	Timing of analysis	Incremental cost-effectiveness ratio of ENO vs NPP (placebo) per			Conclusions
			VTE event avoided	life-year gained	life saved	
de Lissovoy and Subedi[32]	US (1998) [third party]	Treatment[d]	$US1249–3088[e]			ENO CE; costs probably recouped via avoided treatment
Lamy et al.[33]	Canada (2000) [third party]	3mo FU	$Can87/ −$Can174[f]			ENO CE in tertiary and CS in community hospital settings
Lloyd et al.[34]	UK (2000) [NHS]	Treatment[d]	£796			ENO CE
Lloyd et al.[36][g]	UK (NR) [NR]	NR	£892	£262		ENO CE
Nuijten et al.[37]	Spain (2001) [society]	3mo FU	€432		€1527	ENO CE; positive short- and
		1y FU	€332[h]		€1212[h]	long-term economic benefit.
		5y FU	€296[h]		€1174[h]	Assuming higher risk of
		10y FU	€271[h]		€1283[h]	recurrence of VTE/mortality,
		Lifetime FU	€270[h]	€71[h]		ENO dominant over NPP
Nuijten et al.[38][g]	Brazil (NR) [NHS]	1y FU	$US870[h]		$US3073[h]	ENO CE; positive short- and
		Lifetime FU	$US813[h]/ $US117[i]	$US213[h]/ $US33[i]		long-term economic benefit
Nuijten et al.[39][g]	Italy (NR) [NHS]	1y FU	€2324[h]		€8284[h]	ENO CE; positive short- and
		Lifetime FU	€2243[h]	€605[h]		long-term economic benefit
Offord et al.[35]	UK (2000) [NHS]	Treatment[d]	£796	£185		ENO CE
Pechevis et al.[40]	France (1998) [society]	Treatment[d]	€35 875[j]	€1350/ €2701[i,k]	€8102[j]	ENO CE
Schädlich et al.[41][g]	Germany (NR) [hospital]	Treatment[d]	€1106			ENO CE

a Outcomes considered were VTE,[32-41] bleeding events,[34-36,41] life expectancy[36-40] and death.[36-40]

b Based on the MEDENOX[32-41] and THE-PRINCE[41] trials, meta-analyses involving low molecular weight heparins[34-36,41] and other published literature.[35-39]

c Based on expert opinion,[33,37-40] healthcare databases,[32-35] hospital survey,[32,35,40,41] literature[34,35] and mean national healthcare costs.[32-41]

d MEDENOX trial duration (6–14 days).

e Depending on dispensing and administration costs.

f Tertiary (inpatient : outpatient 1 : 9)/community (1 : 1) hospital settings.

g Available as an abstract[36,38,39,41] and/or poster.[41]

h Cost when assuming no higher risk for recurrence of VTE/mortality for asymptomatic patients.

i Cost when assuming higher risk for recurrence of VTE/mortality for asymptomatic patients.

j Median cost when long-term post-phlebitis syndrome cost excluded; when included, there was a net saving.

k At life expectancy 6/3 years.

CE = cost effective; **CS** = cost saving; **FU** = follow-up; **MEDENOX** = prophylaxis in MEDical patients with ENOXaparin; **NHS** = national healthcare system; **NR** = not reported; **NPP** = no prophylaxis; **THE-PRINCE** = THromboEmbolism-PRevention IN Cardiac or respiratory disease with Enoxaparin; **VTE** = venous thromboembolism.

ings of €55 825 per 1000 patients, with 7.7 fewer major bleeding events.[41] Other studies, using data from trials of enoxaparin and/or other LMWHs, also suggested that marginal cost savings could be made by using enoxaparin versus twice-[34,35] or three-times[36] daily UFH.

6. Dosage and Administration

Subcutaneous enoxaparin is recommended at a dose of 40mg once daily for the prevention of thromboembolic complications due to severely restricted mobility in medical (nonsurgical) patients during acute illness.[5,42] While the usual duration of administration is 6–11 days, the injection can be administered for up to 14 days.[5,42]

Patients with mild (creatinine clearance 50–80 mL/min) or moderate (30–50 mL/min) renal impairment generally do not require a reduction in dosage.[5,42] However, these patients should be observed carefully for signs and symptoms of bleeding. In patients with severe renal impairment (<30 mL/min), the recommended dosage of subcutaneous enoxaparin is 20mg (in the UK)[42] or 30mg (the US)[5] once daily.

For comprehensive dosage and administration guidelines, the local manufacturer's prescribing information should be consulted.

7. Place of Enoxaparin as Thromboprophylaxis in Acutely Ill, Nonsurgical Patients

VTE (DVT or PE) has long been regarded as a complication associated mainly with major surgical procedures. However, more recent data have demonstrated that the risk of VTE in nonsurgical patients is comparable to that in surgical patients at moderate risk for VTE.[1] Nonsurgical institutionalisation was found to be an independent risk factor in 35% of all cases of definite VTE in a large population-based study,[43] and it was estimated that 10–26% of patients admitted to a general medical ward will develop a DVT in the absence of prophylaxis.[44] The incidence was reported to be even higher (26–36%) in autopsy-based studies of hospitalised internal medicine and infectious disease patients.[45] In one study, 75% of patients dying from PE in general hospitals were immobilised patients with medical illness.[46]

Prevention of VTE has not been as well studied in hospitalised medical patients as in surgical patients.[1] It is often difficult to determine the appropriate population and timing of prophylaxis because of the heterogeneity of the population, acute illnesses and comorbidities.[47] Both the ACCP[1] and the International Union of Angiology (IUA)[4] have recognised several factors, alone or in combination with each other, as increasing the risk of VTE; these include immobilisation, cardiac insufficiency, acute respiratory failure, severe infection, malignant disease, previous thromboembolism, increasing age and obesity. This has been further corroborated by the findings of a *post hoc* analysis of the MEDENOX trial.[48]

VTE risk factors in hospitalised patients appear cumulative,[1] with the risk increasing in proportion to the number of predisposing factors.[49] Recognition of risk factors in individual patients forms the basis for interventions for VTE prophylaxis in medical patients.[49] It has been recommended that all medical patients admitted to hospital should undergo risk assessment, and preventive therapy should be considered for those at risk.[4,50,51]

Recent guidelines[1,4] recommend that medical patients with risk factors for VTE should receive thromboprophylaxis with either low-dose subcutaneous UFH or a subcutaneous LMWH, such as enoxaparin or dalteparin. Although mechanical methods of prophylaxis (e.g. graduated elastic compression) are likely to be effective as prophylactic treatment in medical patients, there are currently no reported trials of their efficacy, and thus no recommendations for their use, in these patients.[4]

It should be noted that the ACCP[1] or the IUA[4] have not provided specific guidance for choosing between UFH and LMWH. When selecting UFH or LMWH, physicians must consider the limitations in the use of UFH. UFH has poor bioavailability and should be administered two or three times daily because of its short half-life.[9] The unpredictable pharmacodynamic effects of UFH also necessitate monitoring of the degree of anticoagulation.[9] In contrast, enoxaparin has high bioavailability and a longer half-life (section 2.2), facilitating once-daily administration, and its anticoagulant effect does not require monitoring.[9]

Enoxaparin was the first LMWH approved for thromboprophylaxis in medical patients. In the

MEDENOX trial, once-daily enoxaparin 40mg was significantly more effective than placebo in reducing the incidence of VTE in medical patients considered to be at moderate risk (section 3.1).[27] In addition, data from randomised clinical trials have shown that enoxaparin is at least as effective as UFH in the prevention of VTE in nonsurgical patients (section 3.2).[28,29]

As outlined in section 4, there was no significant difference in the incidence of bleeding events between enoxaparin and placebo in the MEDENOX trial. Their pharmacoydnamic and pharmacokinetic profiles indicate that the risk of bleeding and thrombocytopenia would be higher with UFH than with LMWHs.[9] Meta-analyses of clinical trials have also suggested that the LMWHs, and specifically enoxaparin,[52] may be associated with significantly lower rates of bleeding events (major and/or minor) in medical patients. However, clinical trials comparing enoxaparin and UFH directly found a similar proportion of patients with any or major bleeding events (section 4).

The incidence of injection-site haematomas and elevated liver enzymes was higher with UFH than with enoxaparin in the double-blind trials (section 4). In addition, in a randomised nonblind trial,[30,31] UFH treatment was associated with a higher incidence of all possibly or probably treatment-related adverse events than enoxaparin. However, the claim of a better tolerability of enoxaparin over UFH remains to be confirmed.

One potential limitation of the LMWHs in comparison with UFH is their substantially higher costs.[53] Pharmacoeconomic data from around the world, mainly based on the MEDENOX trial, have suggested that enoxaparin 40mg is cost effective compared with no prophylaxis in medical patients (section 5). In addition, the incremental cost associated with enoxaparin prophylaxis may be offset by the cost savings resulting from the future VTE events avoided. Enoxaparin 40mg once daily may also be more cost effective than UFH 5000IU three times daily (section 5). Nevertheless, pharmacoeconomic data with enoxaparin are weak and any definite conclusions regarding the economic advantages of thromboprophylaxis with enoxaparin in nonsurgical patients require further corroboration in more robust studies.

Finally, as acknowledged by the MEDENOX investigators,[27] the duration of prophylaxis with enoxaparin may have been too short for some of the hospitalised patients and an extension of prophylactic treatment should be considered based on assessment of each individual patient. A randomised, double-blind, placebo-controlled trial is currently underway to evaluate the efficacy and safety of extended prophylaxis with enoxaparin in immobilised nonsurgical patients.[54] The EXCLAIM (EXtended CLinical prophylaxis in Acutely Ill Medical patients) will enrol approximately 6000 patients who will initially receive enoxaparin 40mg once daily for 10 days, followed by randomisation to placebo or continued enoxaparin therapy for an additional 28 days.[54] The results of this trial are likely to provide further insight into, and more robust information on, the incidence of VTE and mortality in medical patients as well as the potential benefits of prolonged prophylaxis with enoxaparin in this patient population.

In conclusion, the short-term thromboprophylactic efficacy of subcutaneous enoxaparin 40mg has been clearly demonstrated in nonsurgical patients with acute illness. The drug is at least similar in efficacy to UFH and its pharmacological profile allows once-daily administration, in contrast to the twice- or three-times daily administration required with UFH. The tolerability profile of enoxaparin is also similar to that of UFH, with the exception of the incidences of local haematomas and increased liver enzymes that were lower with enoxaparin. The optimal duration of prophylaxis in nonsurgical patients is currently being evaluated and the results of extended prophylaxis with enoxaparin evaluated in the EXCLAIM trial are awaited with interest. Currently, short-term enoxaparin appears to provide a cost-effective treatment alternative to UFH for VTE prophylaxis in nonsurgical patients.

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