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Review

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Prophylaxis of postoperative thromboembolism with low molecular weight heparins

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To evaluate the thromboprophylactic use of low molecular weight heparins (LMWHs), publications from 27 orthopaedic trials and 35 studies of patients undergoing general or gynaecological surgery were scrutinized and subjected to a partial meta-analysis. In orthopaedic surgery, LMWHs were superior to placebo or dextran and at least as efficient as unfractionated heparin in the prevention of deep vein thrombosis (DVT). Compared with unfractionated heparin, one of the LMWH preparations significantly reduced the total incidence of DVT. The rate of non-fatal pulmonary embolism was 0·49 per cent in patients receiving LMWH and 1·22 per cent in controls. Seven orthopaedic patients (0·15 per cent) died from pulmonary embolism, none of whom received LMWH. In general surgery, the LMWHs were at least as efficient as unfractionated heparin, with a trend towards a lower risk of pulmonary embolism with the former. Compared with unfractionated heparin, LMWHs did not reduce the postoperative mortality rate, nor did they cause haemorrhage. LMWHs provide safe and efficient prophylaxis by administration once daily.

The use of conventional low-dose unfractionated heparin is a well established method in the prevention of postoperative thromboembolic complications. The administration of low doses of heparin has reduced the incidence of postoperative deep vein thrombosis (DVT) and even fatal pulmonary embolism[1,2]. However, some types of surgery, especially orthopaedic, still carry an unacceptably high risk of DVT, reported by some to be about 30 per cent despite the use of unfractionated heparin in combination with dihydroergotamine (DHE)[3]. Furthermore, the administration of unfractionated heparin is associated with certain side-effects such as an increased bleeding tendency (albeit seldom of clinical significance), allergic manifestations, alteration of platelet function and changes in levels of lipoprotein lipase and liver lipase[4].

Unfractionated heparin is a heterogeneous mixture of molecules of different molecular weights, ranging from 3 to 40 kDa, and with varying amounts of specific biological activity depending on molecular structure and size. Low molecular weight heparins (LMWHs) are derived from unfractionated heparin by either enzymatic cracking or filtration; LMWHs are believed to possess lesser effects on overall clotting as reflected in activated partial thromboplastin and thrombin clotting time assays[5].

Experimental studies have led to the theory that antifactor Xa activity correlates with antithrombotic efficacy, whereas antifactor IIa activity relates to the influence on bleeding. LMWHs have less ability to inactivate thrombin relative to their capacity to inhibit factor Xa, as the inactivation of thrombin by heparins is dependent on the size of the heparin molecule. The specific antifactor Xa:antifactor IIa activity ratio for LMWHs is thus higher than for unfractionated heparin. Therefore, in equipotent antithrombotic doses, LMWHs should cause less bleeding than unfractionated heparin; this has been verified only in animal models[6,7]. Compared with unfractionated heparin, LMWHs exhibit a different pharmacokinetic profile with a longer half-life and higher bioavailability. Also, the suppression of platelet aggregation by LMWHs[8] and their affinity for several plasma proteins are less pronounced[9].

During the past 7 years, several clinical studies using LMWHs for thromboprophylaxis in surgical patients have been published. Controlled trials have been carried out with the following LMWH products: Fluxum (Alfa LMWH; Alfa Farmaceutici, Bologna, Italy), Clexane (Enoxaparin; Rhône–Poulenc Rorer, Gennevilliers, France), Fragmin (Dalteparin; Kabi Pharmacia, Stockholm, Sweden), Fraxiparin (CY 216; Sanofi, Paris, France), Logiparin (Tinzaparin; Novo Nordisk, Bagsværd, Denmark) and Sandoparin (Sandoz LMWH; Sandoz, Nuremberg, Germany). Although there are differences between the LMWHs used[10], the type of operations and the methods of screening for DVT, the present aim is to obtain an overall impression of the clinical value of LMWHs in thromboprophylaxis by analysing the available data.

Methods

To diminish the risk of publication bias[11], this analysis tried to include all published reports, including abstracts from conferences, of randomized controlled trials using LMWHs for thromboprophylaxis in orthopaedic, general or gynaecological surgery. Trials in which the recently developed heparinoids or dermatan sulphates were evaluated were not included. The survey of the literature included a computer-aided *MEDLINE* search from 1980 to 1991, a search of the reference lists of relevant papers by two of the authors (L.N.J., P.W.-J.) independently, and a contemporary computer-aided search of *Current Contents* (field: *Clinical Practice and Life Sciences*) until the end of 1991. The following keywords were used: low molecular weight heparin, heparin, deep venous thrombosis, thromboembolism, pulmonary embolism, surgery and orthopaedic surgery. When data were missing from published reports, the authors responsible for correspondence were contacted. If no answer was received, a reminder was sent after 1 month. If the data were still not forthcoming, the study was excluded

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Table 1 *Definition of high-quality studies (all criteria must be met)*

DVT diagnosis
Orthopaedic surgery
1. Venography
2. ^{125}I-radiolabelled fibrinogen uptake test with or without impedance plethysmography, or plasmin scintimetry if positive results are verified with venography for all the tests
General or gynaecological surgery
1. Venography
2. ^{125}I-radiolabelled fibrinogen uptake test
Follow-up
⩾7 days for regular DVT screening and ⩾30 days for verification of symptomatic DVT, symptomatic pulmonary embolism or death
Completion of trial
1. No or limited selection of patients
2. <15% of patients drop out after inclusion
Bleeding and transfusion
Complete data on amount and type of bleeding, and transfusion requirements

DVT, deep vein thrombosis

from the respective statistical calculations, but still reported. Also excluded from the analysis were dose-finding studies without a control group given another prophylactic treatment for comparison.

The efficacy endpoints assessed were the objectively verified incidences of DVT and pulmonary embolism. Only controlled trials using objective paraclinical diagnostic methods, such as venography, ^{125}I-radiolabelled fibrinogen uptake test, plethysmography, ^{99}Tc-radiolabelled plasmin scintimetry and thermography for the detection of DVT, and pulmonary scintigraphy, pulmonary angiography and autopsy for the verification of pulmonary embolism, were included; the authors are aware that not all of these tests are adequate for diagnosis. The incidence of DVT was based on results of venography in all the studies that applied this method to a majority of patients for the verification of DVT (after initial detection by screening with another objective diagnostic method). In a substantial proportion of studies, separation of results into proximal and distal DVT was not presented; for this reason the total incidence of DVT has been considered. Whenever the relevant data were provided, the incidences of DVT, pulmonary embolism and death were derived from the complete period of follow-up, not just that of thromboprophylaxis or hospital stay. The incidence of DVT was based on patients completing the trial protocol. Whenever possible, data describing the incidences of postoperative pulmonary embolism, postoperative mortality, bleeding complications and transfusion requirements were derived from all patients randomized in the respective trials (i.e. analysis on an intention to treat basis). This was done to avoid the bias that occurs in certain trials from excluding patients because of severe bleeding episodes or death before completion of the trial.

Side-effects such as bleeding complications and requirement for transfusion were not uniformly recorded in the different trials. The studies were scrutinized for significant differences in the total amount of bleeding and transfusions given, irrespective of the time after operation. Bleeding complications included intracranial and gastrointestinal episodes, wound haematoma and significantly raised total blood loss (perioperative and postoperative, including volume in drains). Injection haematomas were not considered in the analysis. A distinction was made between statistically significant differences and tendencies between treatment groups. Whenever there was a significant indication of (1) a higher incidence of life-threatening bleeding episodes, (2) wound haematoma requiring evacuation or (3) discontinuation of prophylaxis because of bleeding, differences between the groups were considered clinically relevant. Transfusion was expressed as the total sum (calculated as the number of units of erythrocyte-containing blood products transfused) given during the period of prophylaxis.

In some analyses relating to diagnostic methods, duration of follow-up and drop-out rate (*Table 1*), a separation was made into two classes of scientific quality (high and low). When different studies had uniform selection of patients and dose regimen, some results were evaluated by combining the data in 2 × 2 tables (Mantel–Haentszel–Peto[2,12,13] method); this allows comparison across studies to obtain an overview of the efficacy and safety of LMWHs compared with different control treatments. Only results from trials with uniformity in the selection of patients and dose regimen were analysed in this way. For each study, the number of observed events (O) (DVT or pulmonary embolism) in patients treated with LMWH was compared with the number expected (E) if the treatment had an effect that was identical with that in the control group. With reference to the variance (Var) of each trial, the differences ($O-E$) were summed and a χ^2 test applied to evaluate whether the number of observed events differed significantly from the number expected if the treatments did not differ. Two-tailed analyses were used, irrespective of the fact that one-tailed statistics had been employed in some publications. Typical odds ratios derived from $\exp[\Sigma (O-E)/\Sigma \mathrm{Var}(O-E)]$, with the 95 per cent confidence interval derived from $\exp[\Sigma (O-E)/\Sigma \mathrm{Var}(O-E)] \pm 1{\cdot}96/\Sigma \mathrm{Var}(O-E)^{1/2}$, are presented[2].

Tests for heterogeneity have not been performed, since these lack statistical power and a certain degree of heterogeneity is always present[2,14]. Instead, heterogeneity has been evaluated from the graphical presentation of the odds ratios for each trial. The overall typical odds ratios are presented in this form only when derived from studies of similar design using identical pharmaceutical products.

In the evaluation of the prophylactic effect on DVT, each drug was tested separately against each main group of controls: placebo, dextran and unfractionated heparin. Three patient populations were assessed, undergoing: elective major orthopaedic operations, hip fracture surgery, and general surgery including abdominal, thoracic, vascular, urological and gynaecological procedures. Studies in which the dose of the respective LMWH tested differed considerably from the recommendations of the manufacturer were excluded from the analysis. No regard was made to supplementary prophylactic treatment (e.g. compression stockings or DHE) if it was used in both the LMWH-treated and control groups. Two sets of analyses were carried out: the first included all studies irrespective of quality and the second evaluated only high-quality investigations. The same methods were applied when the effects on the incidence of pulmonary embolism and death were examined.

Results

Orthopaedic surgery

Reports of 27 investigations were found. In most trials, patients undergoing elective hip arthroplasty or hip fracture surgery were studied. Without prophylaxis these patients are considered to carry a risk of DVT of approximately 50 per cent, and a risk of pulmonary embolism and fatal pulmonary embolism of 1–2 per cent and 2–10 per cent respectively[15].

Controls receiving placebo. Compared with placebo, three LMWHs have in separate trials proved to be significantly superior with respect to prophylaxis of DVT in patients undergoing elective hip arthroplasty[3,16], knee arthroplasty or tibial osteotomy[17], or repair of femoral neck fracture[18] (*Table 2*). Although not all the trials show significant differences, the individual odds ratios all point towards a thromboprophylactic effect of the LMWH that is better than that of placebo, irrespective of the quality rating (*Figure 1*). In two studies[3,19] the LMWH was supplemented with DHE; graded compression stockings were used in both treatment groups in one trial[20]. In all studies reporting the incidence of proximal DVT, a reduction was found in the active treatment group[3,16,17,20]; this was statistically significant in three[3,16,17].

Table 2 *Low molecular weight heparin* versus *plac*

Reference	Follow-up (days)	Surg		LMWH (anti-Xa un		nce of DVT		Bleeding complicat	ransfusion quirements	pulmo ols	nce of embolism‡	
							LMWH				LMWH	
Lecler		Knee arthroplasty			i venogra							
		Elective hip arthroplasty			plus IPG ography							
Jorgensen		Fractured hip repair			graphy							
Torholm		Elective hip arthroplasty										of 54
		Elective hip arthroplasty	bo plu opressi ckings	giparin 50/kg lus compressio tockings								
		Elective hip arthroplas		idoparin 4800 lus DHE × 1	Plasmin scintigraph venography							
		Fractured		idoparin 4800 lus DHE × 1								
Total												
		Elective hip or knee arthropla				9 of 349 (48·4%)	87 of 348 (25·0%					397 (0·5%)
		Fractured hip repair				41 of 88 (47%)	19 of 79 (24%)			3 of 1 3 fatal,		

Knee arthroplasty includes tibial osteotomy. LMWH, low molecular weight heparin; DHE, supplementary treatment with dihydroergotamine 0·5 mg; FUT, ^{125}I-radiolabelled fibrinogen uptake test; FUT/venography, screening with FUT, if positive venography is performed; plasmin scintigraphy/venography, screening with plasmin scintigraphy, if positive venography is performed; IPG, impedance plethysmography; DVT, deep vein thrombosis; 0, no statistically significant difference; +, significantly higher rate of bleeding complications or total transfusion (erythrocytes or whole blood) requirements in the LMWH-treated group. * $P < 0·05$ (control *versus* LMWH, χ^2 test); †first dose given after surgery; ‡first dose (2500 units) 2 h before surgery, second dose (2500 units) 12 h after operation; if nothing is specified, the first dose is given 1–2 h before operation. §Follow-up of mortality 30 days; ¶only symptomatic cases objectively verified

Table 3 *Low molecular we t heparin* versus *pace rge*

Reference	Follow-up		LMWH (anti-Xa unit	Diagnostic	f DVT	ansfusio quiremer	Incidence of pulmonary embolism:	Mortalit
					LMWH		LMWH	
DESG[23]		Elective hip arthroplasty	Clexane 3200 × 1†	Venograph	7 of 108*			
riksson *et al.*		Elective hip arthroplasty	Fragmin 2500 × 2	Venography				
		Elective hip arthroplasty	Logiparin 35/kg × 1	venography				
Mätszch *et al.*		Elective hip arthroplasty	Logiparin 50/kg × 1	FUT/venography				
Total								

LMWH, low molecular weight heparin; DVT, deep vein thrombosis; FUT/venography, screening with ^{125}I-radiolabelled fibrinogen uptake test, if positiv enography is performed; 0, no statistically signific differe −, significantly lower rat eeding complications or total transfusion (erythrocytes or whole blood) requirements in the LMWH-treated group. * $P < 0·05$ (control *versus* LMWH, χ^2 test); †first dose given 12 h bef surgery; if nothing is specified, the first dose is given h befo peration; ‡only symptomat s objectively verified

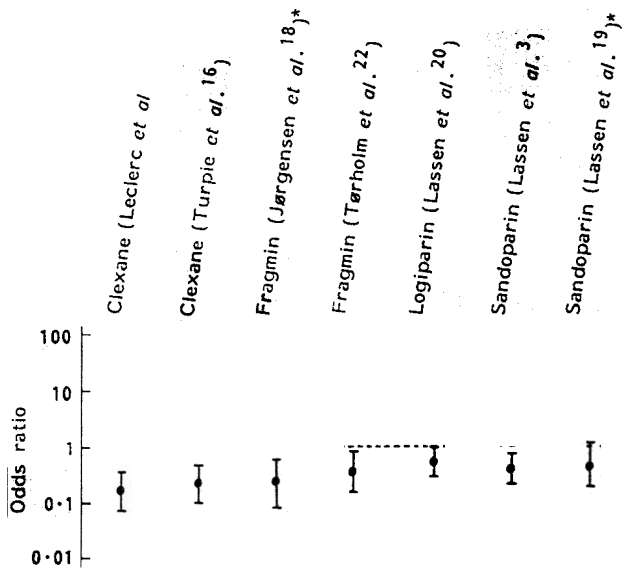

Figure 1 *Prophylactic effect of low molecular weight heparins (with or without dihydroergotamine)* versus *placebo with respect to deep vein thrombosis in orthopaedic surgery. Bars are 95 per cent confidence intervals. * Hip fracture surgery*

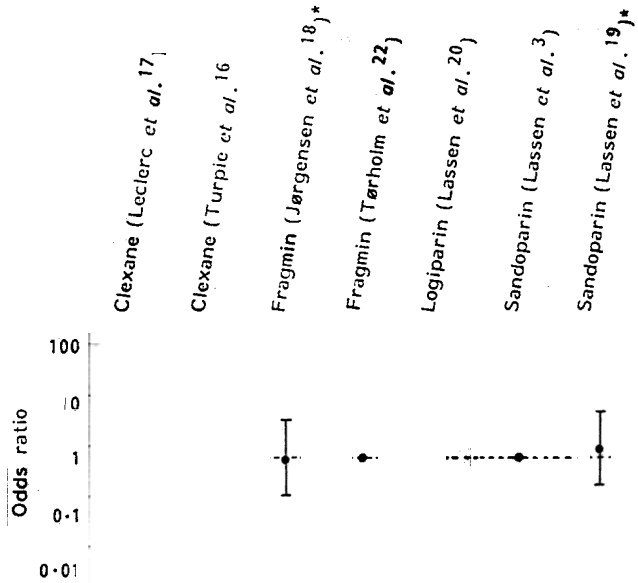

Figure 2 *Prophylactic effect of low molecular weight heparins (with or without dihydroergotamine)* versus *placebo with respect to mortality rate in orthopaedic surgery. Bars are 95 per cent confidence intervals. * Hip fracture surgery*

It is worth noting that in two trials the prophylactic treatment was initiated after surgery[16,17]. To the authors' knowledge these studies, including that of Levine and colleagues[21], are the only reports on postponing the start of LMWH prophylaxis until after surgery.

With respect to the incidence of pulmonary embolism, no overall tendency was detected between the groups when patients undergoing elective surgery were analysed[3,16,17,20,22]; however, the three cases of fatal pulmonary embolism were confined to the placebo-treated group in the two hip fracture studies[18,19] (*Table 2*).

When mortality was evaluated, great heterogeneity between the trials was obvious and no overall tendency shown (*Figure 2*). For this reason, meta-analysis was omitted.

In only one study was there a significantly higher operative blood loss in patients receiving LMWH compared with that in the placebo-treated group[3] (*Table 2*). Two other trials reported a non-significantly higher incidence of bleeding complications in the LMWH-treated group, which did not lead to discontinuation of prophylaxis for any patient[18,20]. Similarly, transfusion requirements were slightly higher in the group receiving active treatment in these studies.

Controls receiving dextran. Three LMWHs have been compared with dextran in patients undergoing hip arthroplasty[23–26] (*Table 3*). The administration of Clexane, Fragmin and Logiparin caused a reduction in the incidence of DVT, which was statistically significant for Clexane and Fragmin (*Figure 3*). In one investigation[25] only a limited reduction was found (odds ratio 0·71), which may be related to use of an insufficient dose of Logiparin (35 rather than the recommended 50 antifactor Xa units/kg daily). The incidence of proximal DVT was not significantly lowered in any trial.

There were only a few pulmonary embolisms and deaths, and no indication of a reduced incidence of either in LMWH-treated patients. In two of the studies[23,24] the amount of bleeding was found to be significantly higher in patients given dextran.

Controls receiving unfractionated heparin with or without dihydroergotamine. The antithrombotic efficacy of LMWHs compared with unfractionated heparin has been evaluated in 18 trials (*Table 4*), mostly on patients undergoing elective hip arthroplasty. Overall, LMWHs exhibited an effect on the incidence of DVT at least as great as that of unfractionated heparin. Indeed, in 11 of 14 hip arthroplasty trials the odds ratio was $< 1{\cdot}0$, favouring the use of LMWHs (*Figure 4*). When a meta-analysis of the results from the two high-quality studies comparing Clexane with unfractionated heparin 15 000 units per day was performed, a significant reduction in the DVT rate was found in patients treated with Clexane (odds ratio 0·67 (95 per cent confidence interval (c.i.) 0·47–0·96)). Treatment of the control group in the Fragmin studies was not homogeneous, making stratification necessary. The typical odds ratio (95 per cent c.i.) for the trials of Fragmin against unfractionated heparin 5000 units subcutaneously three times daily was 0·54 (0·27–1·11)[31,32] and 0·65 (0·27–1·57) (both P not significant) for studies with controls receiving unfractionated heparin 5000 units plus DHE 0·5 mg subcutaneously twice daily[33,34]. Thus, there is evidence that Fragmin is at least as efficient as these conventional prophylactic regimens.

Compared with unfractionated heparin–DHE, Fragmin appears to be at least as antithrombotic[33,34] (*Table 4*). The

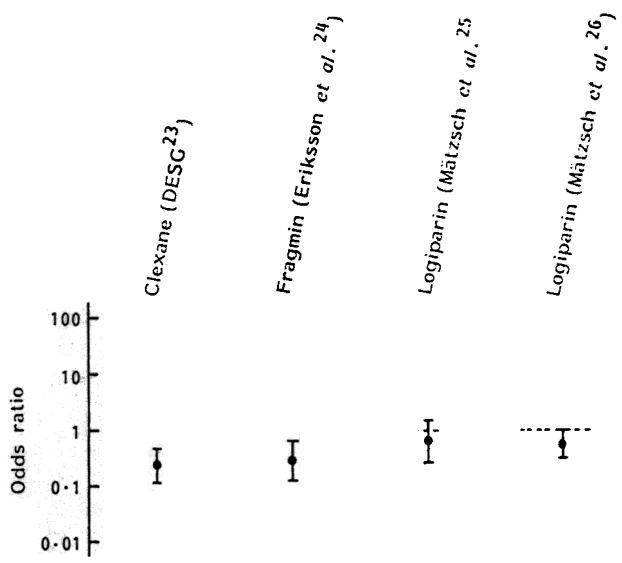

Figure 3 *Effect of low molecular weight heparins* versus *dextran on the incidence of deep vein thrombosis in elective hip arthroplasty. Bars are 95 per cent confidence intervals*

Table 4 *Low molecular weight heparin* versus *low-dose unfractionated heparin in orthopaedic surgery*

Reference	Follow-up (days)	Surgery	Control group (units unfractionated heparin)	LMWH (anti-Xa units)	Diagnostic method	Incidence of DVT		Bleeding complications	Transfusion requirements	Incidence of pulmonary embolism‡‡		Mortality	
						Controls	LMWH			Controls	LMWH	Controls	LMWH
Levine *et al.*[21]	10	Elective hip arthroplasty	7500 × 2	Clexane 2400 × 2†	FUT plus IPG plus venography	61 of 263	50 of 258	0(−)	0	2 of 332	0 of 333	0 of 332	0 of 333
Planes *et al.*[38]		Elective hip arthroplasty		Clexane 3200 × 1 ‖	Venography	27 of 108	15 of 120*				0 of 124	0 of 113	0 of 124
Chiapuzzo *et al.*[27]		Various orthopaedic procedures	5000 × 3	Fluxum 2500 × 2	Doppler		of 70			0 of 70	0 of 70		?
Pini *et al.*[28]	14	Fractured hip repair	5000 × 3	Fluxum 2500 × 2	FUT plus IPG/venography	7 of 24	5 of 25			1 of 24	0 of 25	2 of 24	0 of 25
Barre *et al.*[29]	60	Elective hip arthroplasty	Adjusted dose	Fragmin 2500 × 2§	Venography	4 of 40	7 of 40			0 of 40	0 of 40	0 of 40	1 of 40
Binsack *et al.*[31]		Elective hip arthroplasty	5000 × 3	Fragmin 5000 × 1§	FUT/venography	2 of 41	0 of 34						
Breyer *et al.*[33]	42	Various orthopaedic procedures	5000 plus DHE × 2	Fragmin 5000 × 1§	FUT	6 of 60	3 of 60			0 of 60	0 of 60	0 of 60	0 of 60
Dechavanne *et al.*[30]	10	Elective hip arthroplasty	Adjusted dose	Fragmin 5000 × 1§	FUT plus venography	4 of 38	3 of 39			0 of 40	0 of 41	0 of 40	0 of 41
				Fragmin 2500 × 2§			2 of 38				0 of 41		0 of 41
Eriksson *et al.*[32]	42	Elective hip arthroplasty	5000 × 3	Fragmin 5000 × 1 #	Venography	25 of 59	19 of 63	(clinical)	(clinical)	2 of 69	1 of 67	of 69	0 of 67
Haas *et al.*[34]		Elective hip arthroplasty	5000 plus DHE × 2	Fragmin 5000 × 1§	FUT	7 of 48	6 of 50		+ (clinical)	0 of 55	0 of 55		
Monreal *et al.*[41]		Fractured hip repair	5000 × 3	Fragmin 5000 × 1‡	Clinical/venography	Excluded from analysis				Excluded from analysis (screening for embolism)		3 of 44	2 of 46
GHAT Group[39]	42	Elective hip arthroplasty	5000 × 3 plus compression stockings	Fraxiparin 3300 × 1 # plus compression stockings	Venography		15 of 136**			6 of 168 (2 fatal)	2 of 167	3 of 168	0 of 167
Leyvraz *et al.*[40]	30	Elective hip arthroplasty	Adjusted dose	Fraxiparin 33 50/kg × 1†¶	Venography	28 of 175	22 of 174	0(−)		6 of 204 (1 fatal)	1 of 205	2 of 204	1 of 205
Freick and Haas[36]		Elective hip arthroplasty	5000 plus DHE × 2	Sandoparin 4800 plus DHE × 1	Venography plus Doppler	12 of 48	5 of 52	0(−)		1 of 55	0 of 55	0 of 55	0 of 55
Haas *et al.*[35]		Elective hip arthroplasty	5000 plus DHE × 2	Sandoparin 4800 plus DHE × 1	FUT		15 of 73	0(+)		1 of 80	0 of 80	0 of 80	0 of 80
Korninger *et al.*[37]		Fractured hip repair	5000 × 3 plus acenocoumarol	Sandoparin 4800 × 2	FUT/venography	7 of 33	3 of 35	0		of 33 (fatal)	0 of 35	1 of 33	0 of 35
Lassen *et al.*[3]		Elective hip arthroplasty	5000 plus DHE × 2	Sandoparin 4800 plus DHE × 1	Plasmin scintigraphy/ venography	34 of 112	35 of 107			0 of 122	0 of 118	0 of 122	0 of 118
Lassen *et al.*[19]		Fractured hip repair	5000 plus DHE × 2	Sandoparin 4800 plus DHE × 1	Plasmin scintigraphy/ venography	23 of 54	14 of 53	0		0 of 71	1 of 68	2 of 71	4 of 68
Total		Elective hip arthroplasty plus various orthopaedic procedures				275 of 1272 (21·62%)	222 of 1314 (16·89%)			19 of 1408 (1·35%; 3 fatal)	4 of 1456 (0·27%)	6 of 1283 (0·47%)	2 of 1331 (0·15%)
		Fractured hip repair				37 of 111 (33·3%)	22 of 113 (19·5%)			2 of 128 (1·6%; 1 fatal)	1 of 128 (0·8%)	8 of 172 (4·7%)	6 of 174 (3·5%)

Various orthopaedic procedures excludes hip fracture repair. LMWH, low molecular weight heparin; DHE, supplementary treatment with dihydroergotamine 0·5 mg; DVT, deep vein thrombosis; FUT/venography, screening with ^{125}I-radiolabelled fibrinogen uptake test, if positive venography is performed; IPG, impedance plethysmography; 0, no statistically significant difference in bleeding or transfusion requirements; −, significantly lower rate of bleeding complications or total transfusion (erythrocytes or whole blood) requirements in the LMWH-treated group; +, significantly higher rate of bleeding complications or total transfusion (erythrocytes or whole blood) requirements in the LMWH-treated group. * $P < 0·05$ (control *versus* LMWH, χ^2 test); †first dose given 12 h after surgery; ‡first dose (2500 units) given 2 h before surgery; §first dose (2500 units) given 2 h before surgery, second dose (2500 units) 12 h after operation; #first dose given 12 h before surgery, second dose 12 h after operation; ¶ 42 units per kg per day until day 3, 62 units per kg per day for days 4–10; if nothing is specified, the first dose is given 1–2 h before operation; **, excluding thrombosis confined solely to the muscle veins; ††follow-up of mortality 30 days; ‡‡only symptomatic cases objectively verified

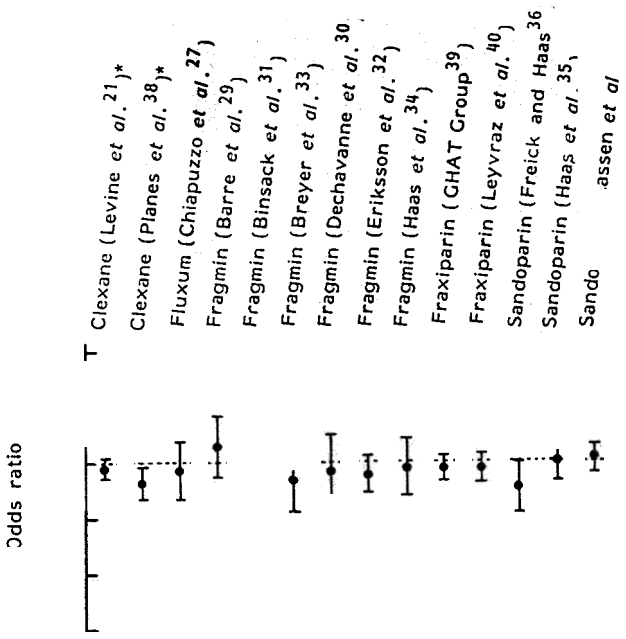

Figure 4 *E low molecular weight heparins (with or without dihydroergot versus unfractionated heparin (with or without nine) on the incidence of deep vein thrombosis in elective hip a y. Bars are 95 per cent confidence intervals. * Typical odds per cent confidence interval 0·47–0·96) (P < 0·05)*

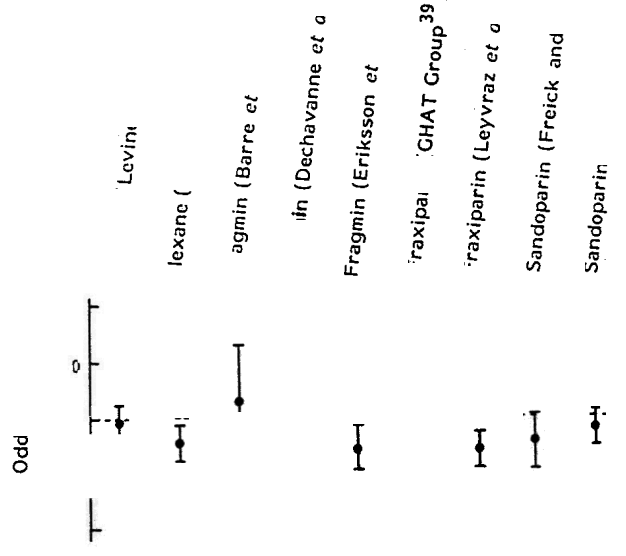

Figure 5 *Effect of low molecular weight heparins (with or without dihydroergotamine) versus unfractionated heparin (with or without dihydroergotamine) on the incidence of proximal deep vein thrombosis in elective hip arthroplasty. Bars are 95 per cent confidence intervals. Typical odds ratio (95 per cent confidence interval): *0·57 (0·34–0·97) (P < 0·05); †0·51 (0·28–0·94) (P < 0·05)*

efficacy of a combination of Sandoparin and DHE compared with unfractionated heparin–DHE has been investigated in four trials[3,19,35,36] (*Table 4*). A meta-analysis performed on the three studies of patients undergoing elective hip arthroplasty showed no significant difference in antithrombotic effect between the two regimens (odds ratio 0·89 (95 per cent c.i. 0·58–1·36)). Similar results were found in patients undergoing hip fracture surgery[19]. Prophylaxis of postoperative DVT using Sandoparin 4800 units combined with DHE 0·5 mg subcutaneously once daily appears at least as effective as that with unfractionated heparin 5000 units plus DHE 0·5 mg subcutaneously twice daily. In one study of patients with hip fracture the thromboprophylactic action of Sandoparin was tested against that of unfractionated heparin followed by the administration of a vitamin K antagonist; no significant difference was found between the groups[37].

In eight of the nine trials reporting on the incidence of proximal DVT the odds ratio was <1·0, again in favour of LMWHs (*Figure 5*). The typical odds ratio (95 per cent c.i.) for the Clexane studies[21,38] was 0·57 (0·34–0·97) ($P < 0·05$) and for the two Sandoparin studies[3,36] 0·51 (0·28–0·94) ($P < 0·05$).

Except for the reports of Eriksson *et al.*[32] and Monreal and colleagues[41], no regular screening for pulmonary embolism was performed in any trial. From 13 elective hip trials comparing LMWHs and unfractionated heparin, the incidence of pulmonary embolism could be obtained (*Table 4*). The results favour the LMWHs, as seven studies showed a higher incidence in the control group (odds ratio <1) and none a higher incidence of pulmonary embolism in LMWH-treated patients (odds ratio >1) (*Figure 6*). In all the orthopaedic trials reviewed, reporting the results from 4615 patients, fatal pulmonary embolism was reported in seven cases (0·15 per cent)[18,19,37,39,40], four of whom underwent femoral neck repair. No patient with fatal pulmonary embolism was treated with LMWH prophylaxis. Eleven cases of pulmonary embolism (0·49 per cent) were reported in 2230 patients receiving LMWH compared with 23 (1·22 per cent) of 1884 controls receiving either unfractionated heparin, unfractionated heparin–DHE, dextran or unfractionated heparin–vitamin K antagonists. The number of deaths was too small to permit comparison between groups.

With respect to the rate of bleeding complications, no overall reproducible difference was found between groups. This was also the case when the data were analysed for each compound. In one investigation comparing Fragmin with unfractionated heparin, significantly less bleeding was observed in patients receiving the LMWH[32]. The dose regimen was unique, as prophylaxis was started 12 h before surgery instead of 2 h.

No obvious pattern was detected when transfusion require-

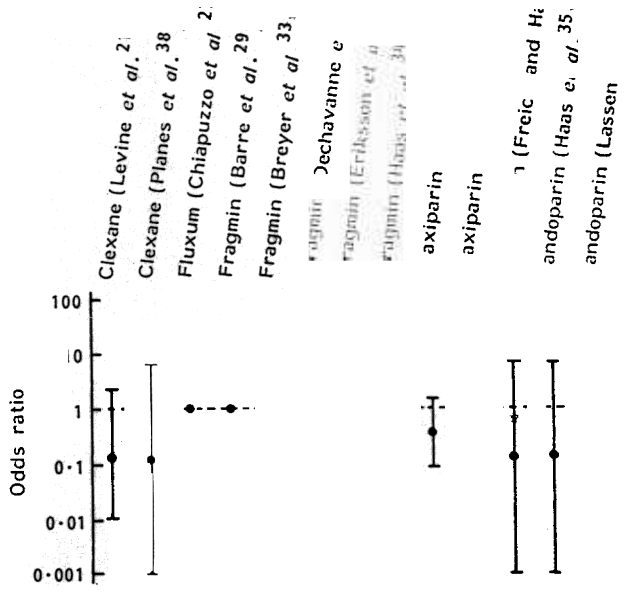

Figure 6 *Effect of low molecular weight heparins (with or without dihydroergotamine) versus unfractionated heparin (with or without dihydroergotamine) on the incidence of pulmonary embolism in elective hip arthroplasty. Bars are 95 per cent confidence intervals. * At least 30 days' follow-up*

Table *molecular weig*

ference	Follo (days		LMWH anti-Xa	DVT MW		MWH		M MWH	
Valle *et al.*[43]		acebo	luxum 2500 ×						
Ockelford *et al.*[4]	42	acebo	ragmin 2500 ×	of 88	f 95			2 of 97	1 of 102
Pezzuoli *et al.*[44]		acebo	raxiparin 2500			4 fatal c	of 2247	8 of 225	8 of 2247
				2·3%	4 of 14 (2·8%)		2 of 147 (1·4%) (4 fatal c 2·17%)	20 of 2348 (0·85%)	9 of 2349 (0·38%)
							(0·0%) (2 fatal of 2399 0·08%)		

LMWH, low molecular weight heparin; DVT, deep vein thrombosis; FUT, ^{125}I-radiolabelled fibrinogen uptake test; 0, no statistically significant difference in bleeding or transfusion requirements; −, significantly lower rate of bleeding complications or total transfusion (erythrocytes or whole blood) requirements in the LMWH-treated group; +, significantly higher rate of bleeding complications or total transfusion (erythrocytes or whole blood) requirements in the LMWH-treated group. *On day of operation 7500 units given 2 h before surgery and 7500 units 12 h after first injection; if nothing is specified, the first dose is given 1–2 h before operation. †Fatal pulmonary embolism assessed; ‡only symptomatic cases. Patients not fully completing the trial included; incidence for the whole follow-up

ments in each treatment group were analysed (*Table 4*). Clinically relevant differences were observed in only two trials. Eriksson and co-workers[32] reported that Fragmin- and unfractionated heparin-treated patients required a mean of 2·3 and 3·3 red cell units respectively, whereas Haas and colleagues[34] found the opposite effect. The regimens tested were, however, not identical.

General and gynaecological surgery

Controls receiving placebo. Of the three studies available, regular screening for DVT with an acceptable method was carried out only by Ockelford and co-workers[42] (*Table 5*). Prophylactic treatment with Fragmin 2500 units subcutaneously once daily reduced the rate of DVT diagnosed by the fibrinogen uptake test from 17·0 per cent (95 per cent c.i. 10·7–25·0 per cent) to 4·2 per cent (95 per cent c.i. 1·4–9·5 per cent) ($P < 0·01$). There was no difference in the bleeding tendency. Fatal pulmonary embolism was assessed as the endpoint in a large-scale assessor-blind study randomizing 4498 patients to treatment with placebo or Fraxiparin 2500 units once daily[44]. Four patients in the placebo-treated group and two receiving LMWH died from pulmonary embolism. The total mortality rate was reduced from 0·80 to 0·36 per cent.

Controls receiving unfractionated heparin with or without dihydroergotamine. The prophylactic use of low-dose unfractionated heparin has been intensively studied. With this treatment the incidence of DVT, pulmonary embolism and fatal pulmonary embolism is approximately 10, 0·5 and 0·2 per cent respectively[45]. Most trials in which the prophylactic effect of LMWHs was investigated were conducted using unfractionated heparin for controls. From 32 studies, 38 comparisons between LMWHs and unfractionated heparin have been published, with supplementary DHE administered to both treatment groups in six investigations[46–51] and exclusively to the unfractionated heparin-treated group in one[52] (*Table 6*). In all studies, the incidence of DVT was the endpoint. The diagnostic method most often used was the fibrinogen uptake test, sometimes with verification by venography. A significant reduction in the incidence of DVT by administration of a LMWH was obtained in three studies. The treatment regimens were Fragmin 5000 units subcutaneously once daily, Fraxiparin 2500 units subcutaneously once daily and Sandoparin 8000 units plus DHE 0·5 mg subcutaneously once daily[47,56,57] and the respective odds ratios (95 per cent c.i.) 0·53 (0·31–0·90), 0·26 (0·10–0·69) and 0·31 (0·12–0·82).

The odds ratios for all the trials were $<1·0$ in 15, 1·0 in nine and $>1·0$ in six; these generally favour the use of LMWHs (*Figure 7*). If only the high-quality studies are included, the corresponding numbers of trials with these odds ratios are four, three and three, with some of the largest studies[56,58–60] belonging to the group favouring LMWHs. Many of the Fragmin studies were not homogeneous and so do not allow proper meta-analysis. This is so even after stratification with respect to dose regimens in the LMWH-treated and control groups of patients. Three studies compared unfractionated heparin 5000 units subcutaneously three times daily with Sandoparin 4800 units subcutaneously once daily[60–62], for which a typical odds ratio of 0·73 (95 per cent c.i. 0·44–1·23) was found, a non-significant reduction in the DVT rate in Sandoparin-treated patients.

The total incidence of symptomatic pulmonary embolism reported for patients receiving LMWH and unfractionated heparin was 0·16 per cent (fatal embolism 0·02 per cent) and 0·60 per cent (fatal embolism 0·13 per cent) respectively (*Table 6*). In none of the studies was regular screening for pulmonary embolism performed. Data on the incidence of pulmonary embolism could be obtained in 27 of the 32 published studies, often only by direct communication with the authors. As the number of observations of pulmonary embolism in each trial was small, the confidence intervals for each odds

Table 6 *Low molecular weight heparin* versus *low-dose unfractionated heparin in general and gynaecological surgery*

Reference	Follow-up (days)	Surgery	Control group (units unfractionated heparin)	LMWH (anti-Xa units)	Diagnostic method	Incidence of DVT		Bleeding complications	Transfusion requirements	Incidence of pulmonary embolism**		Mortality	
						Controls	LMWH			Controls	LMWH	Controls	LMWH
Samama *et al.*[72]		General	5000 × 3	Clexane 1600 × 1	FUT	12 of 158	6 of 159	0(−)	0(+)	0 of 167	0 of 167	0 of 167	1 of 167
			5000 × 3	Clexane 3200 × 1	FUT	3 of 110	3 of 106¶	0	0(−)	0 of 123	0 of 124¶	0 of 123	1 of 124¶
			5000 × 3	Clexane 4800 × 1	FUT	5 of 133	4 of 137¶	0	0	1 of 147	0 of 157¶	0 of 147	2 of 157¶
Catania and Salanitri[53]	?	General	5000 × 2	Fluxum 2500 × 1	Doppler	6 of 85	1 of 88	0(−)	0(−)	0 of 85	0 of 88	3 of 85	2 of 88
Corrado *et al.*[71]	?	Urological	5000 × 2	Fluxum 5000 × 1	FUT	3 of 29	3 of 29	0	?	0 of 29	0 of 29		
Speziale *et al.*[68]	?	Vascular	5000 × 2	Fluxum 5000 × 1	FUT/Doppler	4 of 46	3 of 46	0	?	?	?		
Verardi *et al.*[70]	8	General	5000 × 2	Fluxum 5000 × 1	FUT/Doppler	3 of 44	1 of 44	0(−)	?	?	?	?	
Verardi *et al.*[69]	7	General	5000 × 2	Fluxum 2500 × 1	FUT/Doppler or plethysmography	7 of 134	9 of 250	0(−)	0(−)	0 of 134	1 of 250	?	
			5000 × 3	Fluxum 5000 × 1		12 of 168	1 of 58	0(−)	0(−)	3 of 168	0 of 58	?	
Bergqvist *et al.*[63]	30	General	5000 × 2	Fragmin 5000 × 1	FUT	10 of 192	13 of 190	+ (clinical)	0(+)	1 of 217	0 of 215	5 of 217	5 of 215
Bergqvist *et al.*[56]	30	General	5000 × 2	Fragmin 5000 × 1†	FUT	37 of 405	21 of 421*		0	5 of 497 (1 fatal)	0 of 505	10 of 497	10 of 505
Borstad *et al.*[65]		Gynaecological	5000 × 2	Fragmin 5000 × 1	Plethysmography/ venography	0 of 110	0 of 105	+ (clinical)	+ (clinical)	0 of 110	0 of 105	0 of 110	0 of 105
Briel *et al.*[52]		Gynaecological	5000 plus DHE × 2	Fragmin 5000 × 1‡	Thermography/ venography	of 98	of 95	0(		0 of 98	0 of 95	0 of 98	0 of 95
Caen[59]	30	General/ gynaecological	5000 × 2	Fragmin 2500 ×	FUT	7 of 190	6 of 195			of 190	0 of 195	3 of 190	4 of 195
Creperio *et al.*[54]	?	General	5000 × 2	Fragmin 2500 × 1	FUT	5 of 20	5 of 20	0		?	?		
Fricker *et al.*[64]	30	Gynaecological	5000 × 3	Fragmin 5000 × 1‡	FUT/venography	1 of 40	1 of 40			5 of 40 (1 fatal)	0 of 40	of 40	2 of 40
Hartl *et al.*[77]	30	General	5000 × 2	Fragmin 2500 ×	FUT/venography	5 of 115	5 of 112			1 of 124 (fatal)	1 of 126 (fatal)	of 124	6 of 126
Koller *et al.*[66]	30	General	5000 × 2	Fragmin 7500 × 1	FUT/venography	0 of 20	0 of 23¶	+ (clinical)	+ (clinical)	0 of 20	0 of 23¶	of 20	0 of 23¶
			5000 × 2	Fragmin 2500 × 1		1 of 68	2 of 70	0	0(−)	1 of 75	0 of 75	of 75	0 of 75
Onarheim *et al.*[55]	30	General	5000 × 2	Fragmin 5000 × 1	FUT/venography	0 of 27	1 of 25		0	0 of 27	0 of 25	of 27	0 of 25
Barbui *et al.*[74]		General	5000 × 2	Fraxiparin 2500 × 1	FUT/venography	2 of 33	2 of 27			2 of 173	0 of 171		

Dahan *et al.*[73]		Thoracic (malignant)	5000 × 2/adjusted dose	raxiparin 2500 × 1§	FUT/venography	) of 41	0 of 46	0(		of 40	of 40		
EFSG[58]		General	5000 × 3 plus compression stockings	raxiparin 2500 × 1 # plus compression stockings	FUT	42 of 936	7 of 960	0		4 of 936 (1 fatal)	1 of 960	12 of 936	10 of 960
Kakkar and Murray[57]		General	5000 × 2	raxiparin 2500 × 1		14 of 174	3 of 172*		0(+)	1 of 199 (fatal)	0 of 196	6 of 199	5 of 196
Leizorovicz *et al.*[75]		General		Logiparin 3500 × 1 Logiparin 2500 × 1	FUT/venography	7 of 429	7 of 430 16 of 431¶	0 0(−)	0 0	2 of 429	1 of 430 4 of 431¶	9 of 429	10 of 430 10 of 431¶
Adolf *et al.*[60]		General	5000 × 3	Sandoparin 4800 × 1	FUT	22 of 195	21 of 195	0(−)	0(+)	0 of 202	0 of 202	1 of 202	1 of 202
Baumgartner *et al.*[49]		General	2500 plus DHE × 2	Sandoparin 4800 plus DHE × 1	FUT/venography	7 of 89	6 of 87	0	?	1 of 102 (fatal)	1 of 99	2 of 102	1 of 99
Heilmann *et al.*[61]	28	Gynaecological	5000 × 3	Sandoparin 4800 × 1	Plethysmography/ venography	6 of 150	2 of 150	0(−)		0 of 150	0 of 150	0 of 150	0 of 150
Hoffmann *et al.*[76]	10	General	5000 × 2	Sandoparin 4800 plus DHE × 1	Clinical	0 of 237¶	0 of 245¶	0(−)		0 of 237	0 of 245	0 of 237	0 of 245
Kakkar *et al.*[46]		General	5000 plus DHE × 2	Sandoparin 4800 plus DHE × 1	FUT/venography	10 of 91	8 of 88		0(+)	0 of 91	2 of 88		
Koppenhagen *et al.*[62]		General	5000 × 3	Sandoparin 4800 × 1	FUT/venography	7 of 53	4 of 51	0(+)					
Sasahara *et al.*[48]		General	5000 plus DHE × 2	Sandoparin 4800 plus DHE × 1	FUT/venography	13 of 126	14 of 134	0		2 of 132 (1 fatal)	0 of 137	5 of 132	2 of 137
Schmitz-Huebner *et al.*[67]	30	General	5000 × 2 plus compression stockings	Sandoparin 4000 × 2 plus compression stockings Sandoparin 5600 × 2 plus compression stockings		0 of 39	3 of 40 0 of 41¶	+ (clinical)	0 0(+)	0 of 42	0 of 41 0 of 43¶	0 of 42	0 of 41 2 of 43¶
Steiner *et al.*[50]		Gynaecological	5000 plus DHE × 2/ acenocoumarol	Sandoparin 4800 plus DHE × 1	Clinical/Doppler	of 99¶				0 of 99		0 of 99	0 of 92
Voigt *et al.*[51]		General	5000 plus DHE × 2	Sandoparin 4800 plus DHE × 1	Clinical/venography	1 of 97¶	1 of 103¶			of 103	0 of 107	6 of 103	4 of 107
Welzel *et al.*[47]		General	5000 plus DHE × 2	Sandoparin 8000 plus DHE × 1	FUT	14 of 103	4 of 98*						
Total						266 of 4651 (5·72%)	180 of 4425 (4·07%)			31 of 5186 (0·60%; 7 fatal)	8 of 4931 (0·16%; 1 fatal)	68 of 4551 (1·49%)	63 of 4295 (1·47%)

LMWH, low molecular weight heparin; DHE, supplementary treatment with dihydroergotamine 0·5 mg; DVT, deep vein thrombosis; FUT/venography, screening with ^{125}I-radiolabelled fibrinogen uptake test, if positive venography is performed; 0, no statistically significant difference in bleeding or transfusion requirements; −, significantly lower rate of bleeding complications or total transfusion (erythrocytes or whole blood) requirements in the LMWH-treated group; +, significantly higher rate of bleeding complications or total transfusion (erythrocytes or whole blood) requirements in the LMWH-treated group. *$P < 0·05$ (control *versus* LMWH, χ^2 test); †first dose (5000 units) given 12 h before surgery; ‡first dose (2500 units) given 2 h before surgery, second dose (2500 units) 12 h after first injection; §first dose given 12 h before surgery, on days 3–7 10 000 units once daily; # on day of operation 7500 units given 2 h before surgery and 7500 units 8 h after operation; if nothing is specified, the first dose is given 1–2 h before operation. Acenocoumarol was started on day 2 after operation. ¶Excluded from analysis, dose not as recommended by manufacturer or only symptomatic DVT assessed; **only symptomatic cases objectively verified

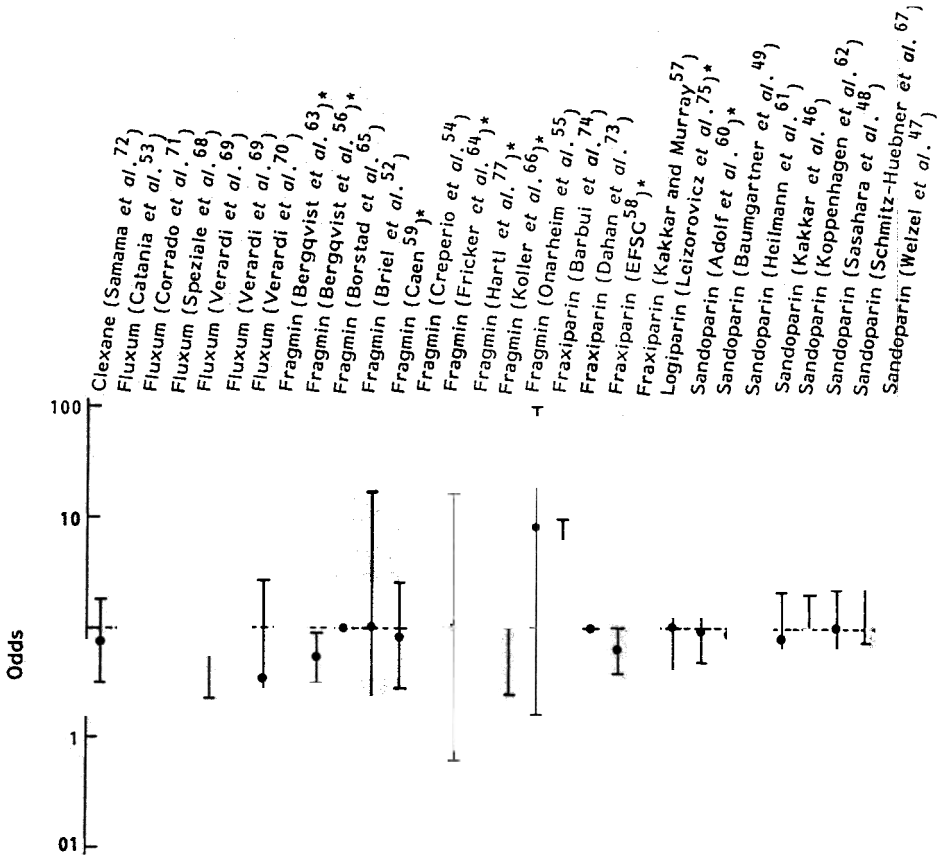

Figure 7 *Effect of low molecular weight heparins (with or without dihydroergotamine)* versus *unfractionated heparin (with or without ergotamine) on the incidence of deep vein thrombosis in general and gynaecological surgery. Bars are 95 per cent confidence intervals. * High-quali*

ratio appear wide, especially if few patients were allocated in the respective trial (*Figure 8*). In 13 studies the odds ratio was $<1{\cdot}0$ (in favour of LMWH), whereas a ratio $>1{\cdot}0$ was observed in only three. In ten investigations no case of pulmonary embolism occurred, leading to an apparent odds ratio of 1·0. If one includes only the high-quality studies, a higher homogeneity appears with no odds ratio $>1{\cdot}0$. There were no cases of pulmonary embolism reported in the three Sandoparin trials. Prophylaxis with Fragmin, Fraxiparin or Logiparin led to a reduced risk of pulmonary embolism although without a clear statistical significance in each single investigation. Meta-analysis of the three high-quality studies[56,63,64], in which the LMWH-treated patients received the high-risk patient dose of Fragmin 5000 units daily, showed a typical odds ratio of 0·13 (95 per cent c.i. 0·04–0·42) ($P < 0{\cdot}01$), suggesting an overall reductive effect on the incidence of postoperative pulmonary embolism of Fragmin compared with that of unfractionated heparin.

There were even fewer cases of postoperative fatal pulmonary embolism; in 21 of 28 trials there were no fatal pulmonary embolisms, leading to an apparent odds ratio of 1·0 in each (*Figure 9*). Again, no trial showed a significant difference between treatment groups. However, there is a weak visual impression of an overall superior prophylactic efficacy of LMWHs over unfractionated heparin. Meta-analysis of the three Fragmin studies mentioned above showed a lower incidence of fatal pulmonary embolism in the Fragmin-treated group that was not statistically significant (typical odds ratio 0·13 (95 per cent c.i. 0·01–2·15)).

With respect to total postoperative mortality, no clear overall difference was found between treatment groups, either for all studies available or for those of high quality (*Figure 10*).

A significantly increased amount of bleeding in LMWH-treated patients was observed in five studies[56,63,65–67] and considered clinically relevant in four (*Table 6*). Different dose regimens related to the prophylactic use of Fragmin have been intensively studied in patients undergoing general surgery. Bergqvist *et al.*[63] found that Fragmin 5000 units daily initiated 2 h before surgery was significantly more haemorrhagic (excessive peroperative bleeding, wound haematomas and number of reoperations for bleeding) than conventional heparin 5000 units twice daily. Similar findings were made by Borstad *et al.*[65] using a similar dose regimen in gynaecological patients. If the time of the first 5000-unit Fragmin dose was advanced to 12 h before surgery, the regimen was still more likely to cause bleeding than the use of unfractionated heparin, but the bleeding episodes were only minor and efficacy was maintained[56]. Another safe and efficient approach[57,64] has been to reduce the dose of Fragmin given 2 h before surgery to 2500 units, repeated after 12 h. Koller *et al.*[66] and Schmitz-Huebner and colleagues[67] used higher LMWH doses than now recommended in some of their studies (Fragmin 7500 units daily, Sandoparin 5600 units twice daily) and experienced a significantly higher number of clinically relevant bleeding complications, leading to interruption of the study of Koller *et al.* Prophylaxis with Fluxum 5000 units once daily[68–71], Clexane 1600 units (20 mg) once daily[72], Fraxiparin 2500 units once daily[57,58,73,74], Logiparin 3500 units once daily[75] or Sandoparin 4800 units (with or without DHE) once daily has proved to be efficient without causing significantly more bleeding than standard low-dose heparin[46,48–51,60–62,76]. It appears, however, that there is no basis for the claim that the prophylactic use of LMWHs as a group causes fewer bleeding complications than that of unfractionated heparin (*Table 6*).

Higher transfusion requirements in Fragmin-treated patients than in those receiving unfractionated heparin were found in two studies[65,66] (*Table 6*) in which Fragmin 5000–7500 units was given 2 h before surgery. Lowering the preoperative dose to 2500 units, but withholding a 5000-unit daily dose in the days after operation, led to the elimination of this tendency[52,64].

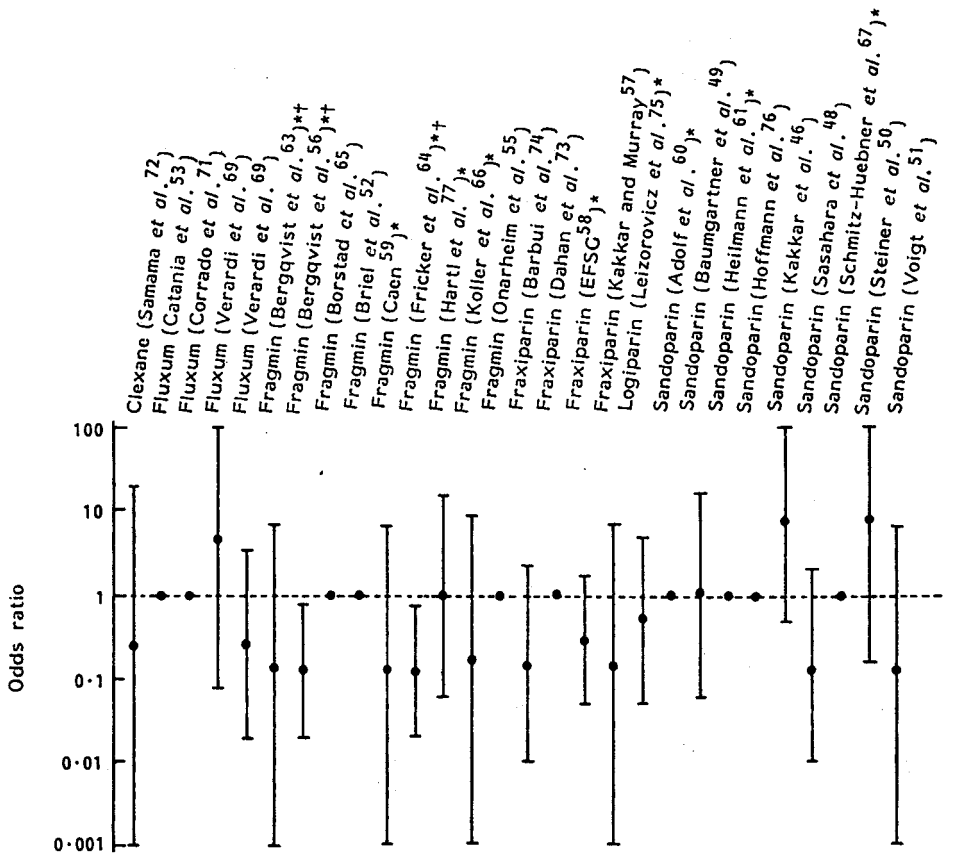

Figure 8 *Effect of low molecular weight heparins (with or without dihydroergotamine) versus unfractionated heparin (with or without dihydroergotamine) on the incidence of pulmonary embolism in general and gynaecological surgery. Bars are 95 per cent confidence intervals. * High-quality studies; † typical odds ratio 0·13 (95 per cent confidence interval 0·04–0·42) (P < 0·05)*

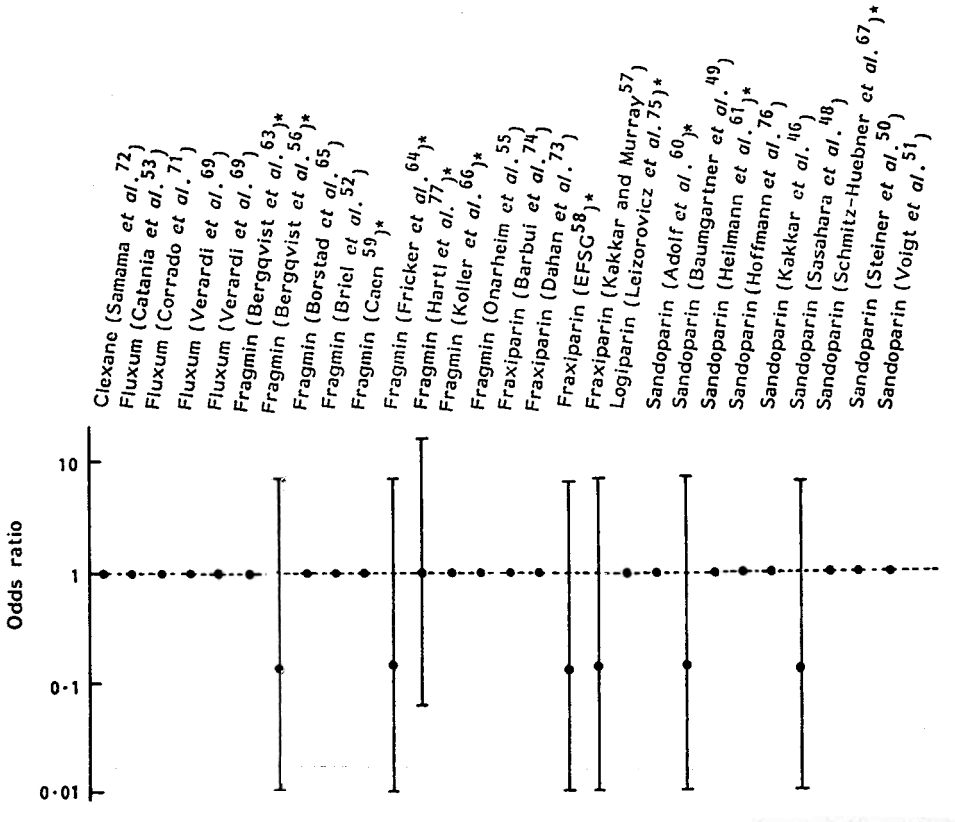

Figure 9 *Effect of low molecular weight heparins (with or without dihydroergotamine) versus unfractionated heparin (with or without dihydroergotamine) on the incidence of fatal pulmonary embolism in general and gynaecological surgery. Bars are 95 per cent confidence intervals. * High-quality studies*

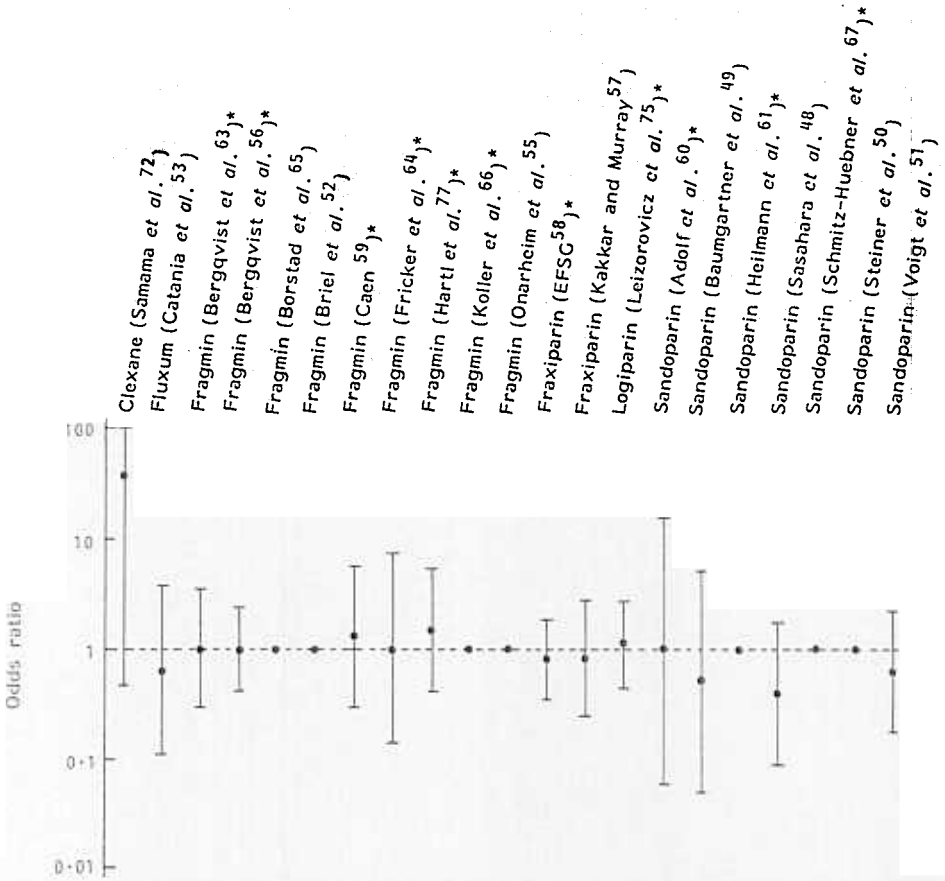

Figure 10 *Effect of low molecular weight heparins (with or without dihydroergotamine) versus unfractionated heparin (with or without dihydroergotamine) on overall mortality rate in general and gynaecological surgery. Bars are 95 per cent confidence intervals. * High-quality studies*

No increase in transfusion requirements of Fragmin-treated patients was observed in any study using this LMWH at 2500 units daily[59,66,77] or in the second trial of Bergqvist *et al.*[56], in which the preoperative 5000-unit Fragmin dose was administered 12 h before surgery. No clear difference in transfusion requirements between the treatment groups was observed in the large studies with Clexane[72], Fraxiparin[58] and Logiparin[75]. The Sandoparin trials are difficult to evaluate because of inconsistent treatment regimens in both unfractionated heparin- and LMWH-treated groups. Most of the studies on Fluxum lack information on transfusion. If the studies are considered as a whole, disregarding the type and dose regimens, there is no indication of a transfusion-saving effect associated with LMWHs.

Discussion

During the past two decades the need to prevent postoperative thromboembolic complications has gained wide acceptance, the final goal being to eradicate the 'silent killer' – fatal pulmonary embolism – which, despite the use of prophylaxis, is still a major concern. Postoperative DVT causes considerable morbidity, with the potential risk of later chronic venous insufficiency. There is no doubt that the use of proper prophylaxis reduces both the postoperative morbidity and mortality rate from thromboembolism. A simple prerequisite is that prophylactic treatment should not be forgotten. Many regimens are not applied in daily practice because of fear of bleeding complications and the burden of such extra therapy to the patient. The development of the LMWHs offers some promising aspects; the drugs are effective on a once-daily basis and do not require paraclinical monitoring. When used in equivalent antithrombotic doses, LMWHs theoretically should, based on animal experiments, cause less bleeding than conventional unfractionated heparin as they cause less inhibition of thrombin[6,7].

In this analysis the main type of surgery and treatment of the control group have been stratified. Instead of performing meta-analysis of inhomogeneous data, which should be avoided[14], graphical presentation of the risk reduction in each trial has been preferred. As the LMWHs show different pharmacodynamic profiles[10], a regular meta-analysis of a set of trials was carried out only when the same type of LMWH in comparable doses was tested against a uniform control group. Only in such a setting do we regard meta-analysis to be statistically valid, contrary to the recent reviews of Nurmohamed *et al.*[78] and Leizorovicz and co-workers[79] in which meta-analyses were performed without differentiation between drugs. The methodology used in the above two reviews differs from that in the present in several other aspects: the definition of high-quality studies[78] was different, some orthopaedic trials[21,36,37,39,40] were not assessed in both reviews, the follow-up period was often restricted to 7–14 days after surgery, results were pooled irrespective of the LMWH dose given[79], heterogeneous groups of bleeding complications (sometimes including postoperative transfusion requirements) were summed, and asymptomatic (screened by the use of scintigraphy in some of the studies) and symptomatic cases of pulmonary embolism were pooled. In addition, not all patients with reported pulmonary embolism had the diagnosis objectively verified, and embolism rate and mortality rate for elective hip surgery and hip fracture repair were assessed in the same analysis. The conclusions from different overviews of the same subject may differ substantially; compared with the two above reviews, the results of the present analysis for calculation of the incidence of pulmonary embolism were more in favour of LMWHs than unfractionated heparin in both orthopaedic and general surgery. A higher incidence of embolism (especially in patients undergoing orthopaedic surgery and receiving LMWH) was found by both Nurmohamed *et al.*[78] and Leizorovicz and associates[79]. We feel that it is justifiable to consider only those cases of symptomatic

pulmonary embolism that have been verified by objective measures; this leads to a much lower incidence and provides a more reliable comparison between unfractionated heparin and LMWHs.

In a review by Bergqvist[80], data were compiled without application of meta-analysis methodology, excluding the possibility of a statistical comparison between treatment groups. It was concluded in that paper that LMWHs are at least as effective as unfractionated heparin. In the present review, it is not known whether publication bias from not publishing negative results is present. Having included all abstracts from conferences, it can only be hoped that such bias is minimized.

Duration of diagnostic follow-up is a keystone of study quality; this is especially true for postoperative fatal pulmonary embolism, since most deaths occur >7 days after surgery[81]. Indeed, Bergqvist and Fredin[82] found that patients who suffered fatal pulmonary embolism after hip fracture repair died at a median of 31 days after operation. Recently, Huber and co-workers[83] reported the incidence of postoperative pulmonary embolism to be increased by 30 per cent if all cases occurring within 30 days of hospital discharge were also included. The results of a substantial proportion of the published studies are erroneously based on a short-term follow-up when thrombo-embolic complications, injection haematoma and bruising are described; only limited, if any, attention is given to the incidence of late pulmonary embolism. This information must be collected directly from the authors but is not always possible to obtain.

Some LMWHs are more efficient than placebo and dextran in the prevention of DVT in both elective and acute hip surgery. It is also clear that LMWHs are at least as efficient as unfractionated heparin in elective orthopaedic operations. Meta-analysis has shown that Clexane significantly reduces the incidence of DVT compared with unfractionated heparin[21,38]. The combination of DHE and unfractionated heparin, two drugs with synergistic action, has been used widely, especially in hip surgery. Although the prophylactic use of this pharmaceutical combination has been reported to be safe[84], DHE has been withdrawn in many countries as a consequence of reported severe arteriospastic side-effects[85]. On the basis of several trials of the prophylactic use of DHE, these side-effects must be considered extremely rare[3,35,46–51], and the use of LMWH with DHE may still appear attractive as a potential alternative, as the daily dose of DHE may be halved. On the other hand, it seems that LMWH without DHE is as effective as unfractionated heparin in combination with DHE[33,34,86].

This paper has reviewed 27 trials in which LMWHs were administered to 2230 patients undergoing orthopaedic surgery. The reported bleeding complications and transfusion requirements give an overall impression that LMWHs are safe in comparison with placebo, dextran or unfractionated heparin with or without DHE. It must be stressed that there is no evidence of fewer bleeding complications in LMWH-treated patients than in those given unfractionated heparin with or without DHE, unlike reports from experimental studies.

Which LMWH has the highest efficacy:side-effect ratio when applied to orthopaedic patients is unknown. Comparisons between compounds will probably never be performed because of the large number of patients needed for such a study. Efficacy and safety must be documented for each LMWH in different surgical situations. It has been claimed for Clexane that there is a close relationship between the antifactor Xa level and the clinical outcome. The optimal antifactor Xa concentration is narrow because levels <0·1 units/ml are related to the development of DVT and those >0·2 units/ml to bleeding complications[87]. Whether LMWHs are more efficient than other regimens in preventing pulmonary embolism in orthopaedic surgery cannot be assessed with current knowledge, although the present review points towards a reductive effect compared with unfractionated heparin with or without DHE. The easy once-daily administration of LMWHs, possibly leading to a higher compliance rate, combined with a probable gain in efficacy against DVT, argues for the use of LMWHs for prophylaxis in orthopaedic surgery. Whether a synergistic prophylactic effect is obtained from the supplementary use of mechanical devices (graded compression stockings or intermittent pneumatic compression) has yet to be shown.

In general surgery the results again show a tendency towards an overall better antithrombotic prophylactic effect using LMWHs compared with unfractionated heparin. So far, LMWHs have not been tested in acute general surgery. It is natural to believe that LMWHs are at least as effective as unfractionated heparin, which is of proven effect, especially when combined with compression stockings[88]. The combination of graded stockings and LMWHs was used in only two studies[58,67]; further evaluation of this combination is lacking. By analogy with the synergistic effect of the combined use of unfractionated heparin and mechanical devices in patients undergoing elective surgery[89], better prophylaxis might be expected by combining LMWHs with compression stockings, but this has so far not been documented.

In some older studies, significantly more bleeding was observed in LMWH-treated patients[63,65–67], but these problems have been solved by altering the dose regimens[56,66,67]. As in the orthopaedic trials, there is no overall indication that LMWHs are associated with fewer bleeding complications than unfractionated heparin, but serious bleeding complications are unusual when recommended doses are employed.

When the high-quality studies in general surgery were analysed, it was found that Fragmin reduced the incidence of symptomatic pulmonary embolism compared with unfractionated heparin. That this could not be shown statistically for the other compounds is probably related to the limited number of investigations rather than to a real difference between the efficacy of different compounds. The incidence of fatal pulmonary embolism was not significantly reduced by any LMWH. To prove a reduction in the number of fatal pulmonary embolisms with LMWHs in general surgery compared with unfractionated heparin, a study of over 50 000 patients is needed. To prove a reduction in total perioperative mortality rate, even larger numbers are required. This does not seem feasible, and it must still be remembered that the clinical interpretation of such a study would require a thorough analysis of cost–effectiveness, facing the fact that LMWHs are still more expensive than unfractionated preparations. The biggest apparent advantage of LMWHs in general surgery is their efficacy by once-daily administration.

It has recently been stated that prophylaxis of DVT with LMWH will benefit orthopaedic but not general surgical patients[78,90]. The present review is partly supportive of this; the percentage reduction in the risk of DVT appears comparable in the two groups of patients, but the incidence of such thrombosis is higher in orthopaedic surgery, leading to a greater absolute number of cases of DVT prevented. Thus, use of a LMWH may be more cost effective in orthopaedic surgery despite the higher price of the drug. If future large-scale trials confirm the tendency in the present literature of a reduced incidence of pulmonary embolism through the use of LMWHs in general surgery, the statement above may have to be modified.

The doses in LMWH prophylactic regimens have been widely examined. The present recommendations for orthopaedic surgery are: 3200 units once daily or 2400 units twice daily (Clexane), 5000 units once daily or 2500 units twice daily (Fragmin), 30–50 units/kg once daily (Fraxiparin) and 50 units/kg once daily (Logiparin). For general surgery, the recommended doses are: 1600 units once daily (Clexane), 2500–5000 units once daily (low- and high-risk patients, Framin), 2500 units (equivalent to 7500 Institute Choay Units) once daily (Fraxiparin) and 3500 units once daily (Logiparin). Even though the optimal plasma concentration of antifactor Xa is 0·1–0·2 units/ml, the differences between the drug doses recommended are considerable and may reflect the pharmacological inhomogeneity of the preparations and the variation in present clinical documentation. Much concern has been expressed on the antifactor Xa:antifactor IIa ratio of LMWHs

with regard to the bleeding risk and antithrombotic efficacy. Whether this ratio is clinically relevant today is a matter of debate. It has been shown that the plasma antifactor Xa level does not correlate with the incidence of thromboembolism[32] or with that of excessive bleeding in patients undergoing hip surgery[91]. Clinical results have shown that the early findings in animal models of a reduced bleeding tendency with LMWHs, compared with unfractionated heparin in equiantithrombotic doses, should not be extrapolated to humans.

Despite the considerable accumulation of literature on LMWHs, some problems must still be solved. The optimal time for beginning and especially for stopping prophylaxis has to be established. Too few data on the efficacy of combinations with mechanical methods of prophylaxis are available. Although it seems safe to combine lumbar extradural or spinal anaesthesia with a LMWH, a review of reported cases of intraspinal bleeding complications in this situation is particularly needed.

Conclusions

The use of LMWHs for prophylaxis against postoperative thromboembolic complications has not been fully evaluated. In orthopaedic surgery, LMWHs are at least as efficient as other regimens in the prevention of DVT and pulmonary embolism. In general surgery, there may be a better prophylactic efficacy against DVT and pulmonary embolism compared with unfractionated heparin. However, no difference between LMWHs and unfractionated heparin with respect to the number of fatal cases could be detected. With the recommended doses, the routine use of the drugs is safe with respect to bleeding complications and transfusion requirements. A major advantage of LMWHs is that they are efficient when administered once daily; this benefits nursing routines.

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