Meta-analysis of low molecular weight heparin in the prevention of venous thromboembolism in general surgery

P. Mismetti, S. Laporte, J.-Y. Darmon*, A. Buchmüller and H. Decousus

Thrombosis Research Group, Clinical Pharmacology Unit, University Hospital, Saint-Etienne and *Medibridge Clinical Research, Velizy, France
Correspondence to: Dr S. Laporte, Clinical Pharmacological Unit, Hôpital Bellevue, Pavillon 5, F-42055 Saint-Etienne, France
(e-mail: laportes@univ-st-etienne.fr)

Background: Low molecular weight heparins (LMWHs) have become routine thromboprophylaxis in general surgery. However, their actual clinical effect, its magnitude relative to that of unfractionated heparin (UFH), and the optimal dose are still debated.

Methods: A meta-analysis was performed of all available randomized trials in general surgery comparing LMWH with placebo or no treatment, or with UFH.

Results: Comparison *versus* placebo or no treatment confirmed that the significant reduction in asymptomatic deep vein thrombosis (DVT) obtained with LMWH (n = 513; relative risk (RR) 0·28 (95 per cent confidence interval 0·14–0·54)) was associated with a significant reduction in clinical pulmonary embolism (n = 5456; RR 0·25 (0·08–0·79)) and clinical venous thromboembolism (VTE) (n = 4890; RR 0·29 (0·11–0·73)), and a trend towards a reduction in overall mortality rate. Comparison *versus* UFH showed a trend in favour of LMWH, with a significant reduction in clinical VTE (P = 0·049), a trend also found for cancer surgery. LMWH at doses below 3400 anti-Xa units seemed to be as effective as, and safer than, UFH, while higher doses yielded slightly superior efficacy but increased haemorrhagic risk, including that of major haemorrhage.

Conclusion: Asymptomatic DVT may be regarded as a reliable surrogate endpoint for clinical outcome in studies investigating thromboprophylaxis in general surgery. LMWH seems to be as effective and safe as UFH. Determination of the optimal dose regimen of LMWH for this indication requires further investigation.

Paper accepted 1 March 2001 British Journal of Surgery 2001, **88,** 913–930

Introduction

Low molecular weight heparins (LMWHs) have become the reference treatment for venous thromboembolism (VTE) prophylaxis in patients undergoing general surgery, mainly on the basis of their ability to reduce the incidence of deep vein thrombosis (DVT) detected systematically using an objective test at the end of the treatment period[1,2]. However, the clinical relevance of a reduction in asymptomatic DVT has been questioned, as it has never been demonstrated in a single clinical study that this is associated with a reduction in the incidence of clinically important VTE[3]. If it is assumed that the reason for this is a lack of statistical power owing to inadequate sample size, meta-analysis may be an appropriate tool to recognize the clinical efficacy of LMWHs in general surgery, as well as their effects on other clinical endpoints such as major haemorrhage or overall mortality rate. Only two rather dated meta-analyses of LMWH *versus* placebo or no treatment have addressed this issue. They showed that a reduction in the risk of asymptomatic DVT was associated with a reduction in the risk of pulmonary embolism (PE) or death[4,5]; this has also been found for other prophylactic indications for both LMWH and unfractionated heparin (UFH)[4–8]. It is now worthwhile to update these two meta-analyses with more recent studies.

The effect of LMWH relative to that of UFH varies between the available meta-analyses, which included different numbers of studies[4,5,9–12]. This may be explained by the different criteria used to select studies, and different exhaustivity in terms of the number of studies included compared with the total number potentially eligible at the time the meta-analysis was performed. Exhaustivity has been postulated to be a critical factor for the validity and interpretation of meta-analyses[13]. Furthermore, the number of published studies conducted in patients undergoing

surgery for cancer should now allow the evaluation of LMWH in this subgroup of patients who are considered to be at high risk of both VTE and haemorrhage[1,2]. The optimal dose of LMWH to be used for thromboprophylaxis in general surgery remains controversial; both low and high doses have been proposed by various manufacturers. According to some authors, a daily subcutaneous dose of more than 3400 anti-Xa units yields no additional benefit in terms of efficacy while leading to an increased haemorrhagic risk[1,10,11].

In the light of the above, a meta-analysis was carried out with three specific objectives in mind. (1) To verify the clinical effect of LMWH from data obtained from all available randomized clinical trials comparing a LMWH with placebo or no treatment, or with UFH, in patients undergoing general surgery. (2) To evaluate this effect in patients undergoing surgery for cancer. (3) To assess the efficacy and safety of low and high prophylactic doses of LMWH in this setting.

Methods

Literature search

An exhaustive literature search, both manual and computer assisted (Medline® and Current Contents®) was performed, encompassing randomized studies comparing a prophylactic regimen of LMWH with any other prophylactic treatment in patients undergoing general surgery, defined as abdominothoracic (excluding vascular), urological and gynaecological surgery, as well as surgery for malignant disease. There was no restriction on the language of the article. The following keywords were used: general surgery, abdominal surgery, cancer surgery, heparin, low molecular weight heparin, postoperative complications, prophylaxis, controlled trial, randomized trial, venous thromboembolism, deep vein thrombosis, pulmonary embolism and mortality. Abstracts of meetings were searched and reference lists in reviews, studies and previous meta-analyses were checked. Particular attention was paid to duplicate reports; when studies were published as an abstract and an original article, only the latter was considered. When more than one article was available from a single study, an attempt was made to extract the information required from all relevant publications. All citations have been included in the list of references.

Study selection

From these articles, open-label, single- or double-blind randomized studies evaluating a LMWH were selected. Only studies with a control group, either untreated or treated with a placebo, or with low-dose UFH, were considered. Studies that included dihydroergotamine or elastic stockings were eligible. Included studies were required to evaluate the efficacy and/or safety of a LMWH using at least one of the following criteria: DVT detected by a systematic objective test, PE, major haemorrhage or death.

Studies were excluded if they were not randomized or clearly stated as such, conducted according to a 'play-the-winner design', or conducted in patients undergoing orthopaedic surgery, non-cancer thoracic surgery, extracorporeal circulation surgery or non-cancer laparoscopic surgery. Dose-ranging studies without a control group given placebo or no treatment, or UFH, for comparison were excluded, as were studies involving heparinoids.

Collection of data

Predefined data from individual trials were initially extracted independently by three of the authors (P.M., S.L., J.-Y.D.). A concordance meeting was organized and, in cases of discrepancy regarding either study selection or data extraction, agreement was reached. The following study characteristics were recorded: name of the first author or study acronym, year(s) of publication, number of patients randomized, indication for surgery (general, abdominal, gynaecological or cancer surgery), percentage of patients undergoing surgery for cancer and, if there was a stratification of patients with cancer, the type, duration and dose regimens of treatments, and whether they were administered before or after operation, in an open-label, single- or double-blind fashion, the type of anaesthesia (general or regional), the method used to detect DVT and at which time point, and the duration of follow-up.

Endpoints

The primary endpoint was the incidence of DVT detected systematically by ultrasonography, fibrinogen uptake test, impedance plethysmography, thermography or venography at the end of the treatment period or earlier in cases of clinical suspicion. Positive results of impedance plethysmography or thermography had to be confirmed by venography.

Secondary endpoints were the incidence of symptomatic PE (both non-fatal and fatal), symptomatic VTE (DVT and/or PE), death, major haemorrhage, wound haematoma and other haemorrhage (excluding haematoma at the injection site) and the percentage of patients requiring postoperative transfusion (if available, otherwise the

percentage of patients requiring transfusion irrespective of time it was used). The definitions of major haemorrhage used in the original articles were heterogeneous. Whenever available, the author's definition was used. Otherwise, haemorrhage leading to death, blood transfusion, reoperation or permanent discontinuation of the treatment under assessment was considered as a major haemorrhage. The incidences of symptomatic VTE and death were derived from the complete period of follow-up, not just that of thromboprophylaxis or hospital stay. Haemorrhagic endpoints were recorded at the end of the treatment period.

Statistical analysis

The results from each trial were summarized on an intention-to-treat basis in two-by-two tables for each endpoint. The denominator used for estimating the incidence of DVT was the number of patients who had undergone a systematic detection test at the end of the treatment period (available patients). For all other endpoints, the denominator was the number of randomized patients in each treatment group.

Two meta-analyses were performed, the first using data from trials comparing LMWH with no treatment or placebo, and the second using data from trials comparing LMWH with UFH. The meta-analyses were performed using a variety of methods: logarithm of the relative risk (RR), logarithm of the odds ratio, Mantel Haenszel, Cochran and Peto[13]. Since the results obtained were similar, only those from the logarithm of the RR method are presented. A RR of 1 indicates no difference between the treatments, less than 1 that LMWH is better, and more than 1 that the control treatment (either no treatment or placebo, or UFH) is better. Association and heterogeneity tests were performed for each meta-analysis. $P \leqslant 0{\cdot}05$ from an association test and a $P \leqslant 0{\cdot}10$ from a heterogeneity test were considered as statistically significant. In the absence of a clear explanation for heterogeneity, a random-effect model for the RR was planned. Meta-analyses were performed using the software EasyMA® (University Claude Bernaud, Lyon, France)[14,15]. Results from these meta-analyses are presented graphically including RRs with 95 per cent confidence intervals (c.i.).

Two sensitivity analyses were performed, the first dealing with studies in which LMWH was given in combination with dihydroergotamine and the second according to the UFH dose regimen (5000 units twice daily *versus* 5000 units three times daily). Subgroup analyses were performed for studies that were well identified double-blind trials, for cancer surgery (studies with over 90 per cent of patients undergoing cancer surgery or data from studies with a cancer surgery stratum), for non-cancer surgery, and for LMWH dose regimens of 3400 anti-Xa units or less and more than 3400 anti-Xa units.

Results

A total of 82 studies, from 1984 to 1999, evaluating the thromboprophylactic effect of LMWH in general surgery was identified. Of these, 21 were excluded for the following reasons: absence or uncertainty of randomization in six studies[16–21], play-the-winner design in two studies[22,23], comparison of LMWHs in seven studies[24–30], use of a heparinoid in two studies[31,32], and incomplete[33,34] or unpublished results (Samama 1990 and Koppenhagen 1990) in four studies. Fifty-nine studies were therefore selected, eight comparing a LMWH with placebo or no treatment[35–43] and 51 comparing a LMWH with UFH[44–103].

Low molecular weight heparin *versus* placebo or no treatment

Description of studies

The eight studies contained 5520 patients; six were double blind[35–40,42] and two were open[41,43] (*Table 1*). The LMWHs used were nadroparin (three studies, 4751 patients), enoxaparin (two studies, 392 patients), dalteparin (one study, 197 patients), parnaparin (one study, 100 patients) and tinzaparin (one study, 80 patients). Two studies, both open, were conducted in cancer surgery[41,43]. DVT was detected systematically at the end of the treatment period in five studies (513 patients); clinical efficacy and safety endpoints were available for 4890–5456 patients (*Table 2*).

Results

In the placebo or no treatment group, the adjusted incidences of events(S.D.) were 14·5(2·2) per cent for systematically detected DVT, 0·5(0·1) per cent for clinical PE, 0·9(0·2) per cent for clinical VTE and 0·9(0·2) per cent for death. A statistically significant 72 per cent reduction in the risk of DVT was observed in the LMWH group (RR 0·28 (95 per cent c.i. 0·14–0·54); $P < 0{\cdot}001$). This reduction was associated with similar significant reductions in the risk of clinical endpoints, 75 per cent for clinical PE (RR 0·25 (0·08–0·79); $P = 0{\cdot}018$) and 71 per cent for clinical VTE (RR 0·29 (0·11–0·73); $P = 0{\cdot}009$), and with a non-significant 46 per cent reduction in overall mortality rate (RR 0·54 (0·27–1·10); $P = 0{\cdot}09$) (*Fig. 1*).

Haemorrhage was more frequent in LMWH-treated than in placebo-treated patients, with an increase of 103 per cent for major haemorrhage, 106 per cent for total haemorrhage, 88 per cent for wound haematoma and 53

Table 1 Low molecular weight heparin *versus* placebo or no treatment: description of studies

Reference	Year	Type of surgery	Cancer surgery (%)	LMWH and dose (anti-Xa units)	Control group	Study design	Time of first administration	Type of anaesthesia	Treatment duration (days)	Diagnosis of DVT*	Follow-up duration	Patients randomized
Le Gagneux *et al.*[35]	1987	Prostatectomy	n.a.	Enoxaparin 6000	Placebo	Blind	Preop. 12 h	n.a.	n.a.	FUT + veno.	n.a.	89
Valle *et al.*[36]	1988	Abdominal and breast	n.a.	Parnaparin 3200	Placebo	Blind	Preop. 2 h	General	7	US + veno.	n.a.	100
Ockelford *et al.*[37]	1989	Abdominal	43	Dalteparin 2500	Placebo	Blind	Preop. 1–2 h	General	5–9	FUT	6 weeks	197
Pezzuoli *et al.*[38,39] (STEP)	1989–1990	General	33	Nadroparin 2850	Placebo	Blind	Preop. 2 h	n.a.	> 7	Not evaluated	3 weeks	4498
Balas *et al.*[40]	1992	General	n.a.	Nadroparin 2850	Placebo	Blind	Preop. 12 h	General	5–8	Veno. but n.a.	n.a.	189†
Marassi *et al.*[41]	1993	Abdominal	100	Nadroparin 2850	No treatment	Open	Preop. 2 h	n.a.	7	FUT + veno.	7 days	64
Bergqvist *et al.*[42]	1996	Abdominal	n.a.	Tinzaparin 3500	Placebo	Blind	Postop.	n.a.	> 5	FUT + veno.	1 month	80
Ho *et al.*[43]	1999	Colorectal	94	Enoxaparin 4000	No treatment	Open	Preop. 12 h	n.a.	> 4	Not evaluated	9 months	303†

*At end of the treatment. †No. of patients for whom the group distribution was available. LMWH, low molecular weight heparin; DVT, deep vein thrombosis; n.a., data not available; preop., before operation; postop., after operation; FUT, fibrinogen uptake test; veno, DVT confirmed by venography; US, ultrasonography; STEP, studio embolia polmonare

Table 2 Low molecular weight heparin *versus* placebo or no treatment: incidence of all evaluation criteria in each treatment group

		Patients randomized		Asymptomatic DVT*		Clinical PE		Clinical thrombo-embolism		Death		Major haemorrhage		Total haemorrhage		Wound haematoma		Transfusion	
Reference	Year	LMWH	C	LMWH	C	LMWH	C	LMWH	C	LMWH	C	LMWH	C	LMWH	C	LMWH	C	LMWH	C
Le Gagneux *et al.*[35]	1987	44	45	0/44	0/45	0	0	0	0	n.a.	n.a.	0	0	n.a.	n.a.	n.a.	n.a.	8	6
Valle *et al.*[36]	1988	50	50	0/50	3/50	0	0	n.a.	n.a.	n.a.	n.a.	0	0	0	1	0	1	5	5
Ockelford *et al.*[37]	1989	102	95	4/95	14/88	0	2	n.a.	n.a.	0	2	4	4	10	4	2	0	n.a.	n.a.
Pezzuoli *et al.*[38,39] (STEP)	1989–1990	2247	2251	n.a.	n.a.	(2)	(8)	5	17	8	18	67	30	439	210	265	141	221	134
Balas *et al.*[40]	1992	94	95	n.a.	n.a.	0	1	n.a.	n.a.	n.a.	n.a.	0	2	4	7	n.a.	n.a.	n.a.	n.a.
Marassi *et al.*[41]	1993	31	33	2/30	11/31	n.a.	n.a.	n.a.	n.a.		0	n.a.	n.a.	0	1	0	1	14	13
Bergqvist *et al.*[42]	1996	39	41	3/39	9/41	0	1	n.a.	n.a.	0	2	1	0	2	0	0	0	n.a.	n.a.
Ho *et al.*[43]	1999	134	169	n.a.	n.a.	0	3	0	5	3	2	3	1	9	3	2	0	25	22
Total no. of studies†		8		5		7		3		5		7		7		6		5	
Total no. of patients†		5520		513		5456		4890		5142		5456		5431		5242		5054	

Values in parentheses are cases of fatal pulmonary embolism (PE). *Denominator is number of patients who had a systematic detection test for asymptomatic deep vein thrombosis (DVT) at the end of the treatment period. †Combined total numbers for low molecular weight heparin (LMWH) and control (C; placebo or no treatment) groups. n.a., Data not available; STEP, studio embolia polmonare

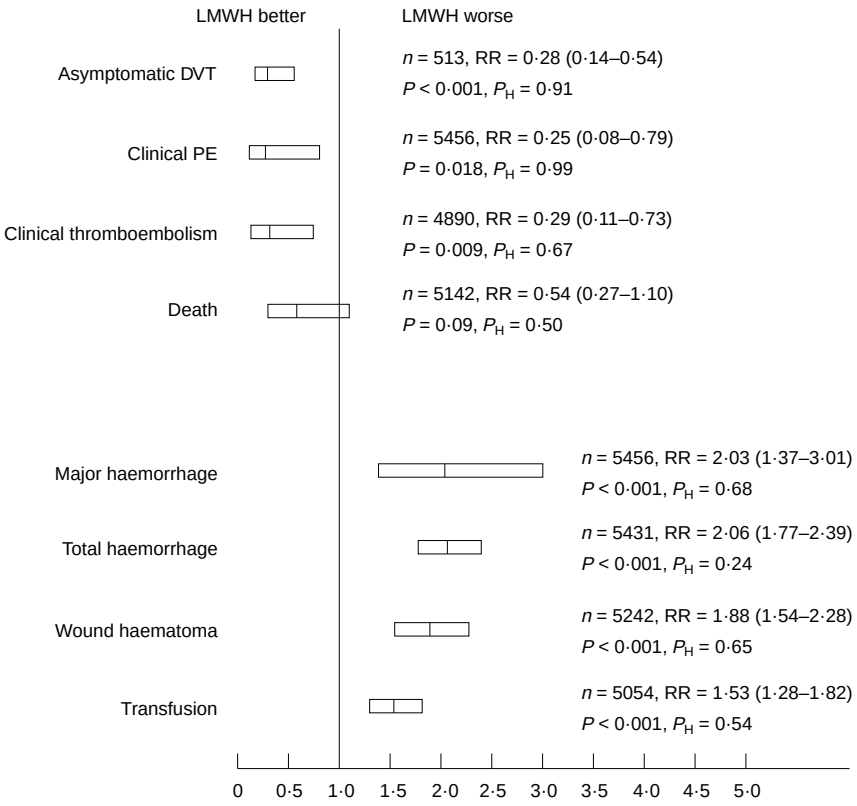

Fig. 1 Meta-analysis (logarithm of relative risk (RR) method) of efficacy and safety criteria comparing low molecular weight heparin (LMWH) with placebo or no treatment. The RR for each criterion is shown as a vertical line within a box, which represents the 95 per cent confidence interval. A RR of less than 1 indicates that LMWH is more effective than placebo or no treatment. If the value of 1 is included in the box, the result is not significant ($P > 0{\cdot}05$). P_H indicates the result of the heterogeneity test. DVT, deep vein thrombosis; PE, pulmonary embolism

per cent for the number of patients requiring postoperative transfusion ($P < 0{\cdot}001$ for all criteria) (*Fig. 1*). For instance, the incidence of major haemorrhage was 2·8(0·3) per cent and that of wound haematoma 10·3(0·6) per cent in the LMWH group. Owing to the small number of studies, subgroup analyses were not performed.

Low molecular weight heparin *versus* unfractionated heparin

Description of studies

The 51 studies involved contained 48 624 patients (*Table 3*). The principal LMWHs were certoparin (15 studies, 27 707 patients, including one study with 23 078 patients), dalteparin (13 studies, 6803 patients), enoxaparin (eight studies, 6017 patients), nadroparin (five studies, 3220 patients), and parnaparin (four studies, 492 patients). Only one study each was identified for other LMWHs. LMWH was administered before operation in 50 of the 51 studies. UFH was given at the dose of 5000 units three times daily in 20 studies, 5000 units twice daily in 30 studies and 2500 units twice daily in one study. Eight studies, including the cancer stratum of the European Fraxiparin Study, involved the treatment of cancer[48,53–55,73,91,100–102]. Thirty-three studies were double blind. DVT was detected systematically at the end of the treatment period in 41 studies (17 995 patients), and the clinical efficacy and safety endpoints were available for 13 776 to 46 646 patients (*Table 4*).

Results

In the UFH group the adjusted incidences of events were 5·0(0·2) per cent for systematically detected DVT, 0·4(0·0) per cent for clinical PE, 1·3(0·1) per cent for clinical VTE and 1·7(0·1) per cent for death. A non-significant 10 per cent reduction in the risk of DVT was observed in the LMWH group (RR 0·90 (0·79–1·02); $P = 0{\cdot}10$) as well as a non-significant 12 per cent reduction in the risk of clinical PE

Table 3 Low molecular weight heparin *versus* unfractionated heparin: description of studies

Reference	Year	Type of surgery	Cancer surgery (%)	LMWH and dose (anti-Xa units)	UFH (units)	Study design	Time of first administration	Type of anaesthesia	Treatment duration (days)	Diagnosis of DVT*	Follow-up duration	Patients randomized
Schmitz-Huebner *et al.*[44]	1984	Abdominal	n.a.	Certoparin (dose 1 and dose 2) b.i.d.	10 000	Blind	Preop. 2 h	General	7	FUT	1 month	126
Törngren *et al.*[45]	1984	General	n.a.	SSHA 50 mg and 37·5 mg	10 000	Blind	Preop. 2 h	General	7	FUT	Discharge	471
Kakkar and Murray[46]	1985	General	31	Nadroparin 2850	10 000	Blind	Preop. 2 h	n.a.	7	FUT	10 days	400
Bergqvist *et al.*[47]	1986	Abdominal	45	Dalteparin 5000	10 000	Blind	Preop. 2 h	General or regional	5–7	FUT	1 month	432†
Onarheim *et al.*[48]	1986	Abdominal	100	Dalteparin 5000	10 000	Blind	Preop. 2 h	General	6	FUT + veno.	1 month	52
Sasahara *et al.*[49]	1986	Abdominal	n.a.	Certoparin 3000 + DHE	10 000 + DHE	Blind	Preop. 2 h	n.a.	7	FUT + veno.	7 days	269
Voigt *et al.*[50]	1986	Abdominal	41	Certoparin 3000 + DHE	10 000 + DHE	Blind	Preop. 2 h	General	> 7	Not evaluated	10 days	200†
Koller *et al.*[51,52]	1986	Abdominal	n.a.	Dalteparin 7500	10 000	Blind	Preop. 1 h	n.a.	> 5	FUT + veno.	30 days	43†
Koller *et al.*[51,52]	1986	Abdominal	n.a.	Dalteparin 2500	10 000	Blind	Preop. 1 h	n.a.	> 5	FUT + veno.	30 days	150
EFS[53,54]	1988	Abdominal	37‡	Nadroparin 2850	15 000	Open	Preop. 2 h	General	7	FUT + veno.	1 month	1 909
Fricker *et al.*[55]	1988	Abdominopelvic	100	Dalteparin 5000	15 000	Open	Preop. 2 h	n.a.	10	FUT + veno.	1–2 months	80
Bergqvist *et al.*[56,57]	1988–1990	Abdominal	63	Dalteparin 5000	10 000	Blind	Preop. 12 h	General or regional	5–8	FUT + veno.	1 month	1 002†
Caen[58]	1988	Abdominal	29	Dalteparin 2500	10 000	Blind	Preop. 2 h	General	7	FUT	1 month	385†
Borstad *et al.*[59]	1988	Gynaecological	n.a.	Dalteparin 5000	10 000	Blind	Preop. 1 h	n.a.	7	IPG + veno.	n.a.	215
Samama *et al.*[60–64]	1988–1994	General	n.a.	Enoxaparin 2000	15 000	Open	Preop. 2 h	General	7	FUT + veno.	7 days	335
Samama *et al.*[60–64]	1988–1994	General	n.a.	Enoxaparin 4000	15 000	Open	Preop. 2 h	General	7	FUT + veno.	7 days	250
Samama *et al.*[60–64]	1988–1994	General	n.a.	Enoxaparin 6000	15 000	Open	Preop. 2 h	General	7	FUT + veno.	7 days	307
Welzel *et al.*[65]	1988	Abdominal	n.a.	Certoparin 2500 + DHE	10 000 + DHE	Open	Preop. 2 h	n.a.	7	FUT	7 days	201†
Briel *et al.*[66]	1988	Gynaecological	n.a.	Dalteparin 5000	10 000 + DHE	n.a.	Preop.	n.a.	8	Thermography + veno.	n.a.	193†
Catania and Salanitri[67]	1988	Abdominal	46	Parnaparin 3200	15 000	Open	Preop. 2 h	General	7	n.a.	n.a.	173
Salcuni *et al.*[68]	1988	Abdominal	52	Parnaparin 3200	15 000	Open	Preop. 2 h	General	7	n.a.	n.a.	141
Kakkar *et al.*[69]	1989	Abdominal	48	Certoparin 3000 + DHE	10 000 + DHE	Blind	Preop. 2 h	n.a.	7–10	FUT + veno.	n.a.	179†
Adolf *et al.*[70]	1989	Abdominal	n.a.	Certoparin 3000	15 000	Blind	Preop. 2 h	n.a.	7–10	FUT + veno.	1 month	410
Heilmann *et al.*[71]	1989	Gynaecological	n.a.	Certoparin 3000	15 000	Blind	Preop. 2 h	General	7	IPG + veno.	10 days	300
Baumgartner *et al.*[72]	1989	Abdominal	16	Certoparin 3000 + DHE	5 000 + DHE	Blind	Preop. 2 h	n.a.	6–10	FUT + veno.	10 days	201
Dahan *et al.*[73]	1989	Thoracic	100	Nadroparin 2850	15 000	Open	Preop. 12 h	n.a.	7	FUT + veno.	n.a.	87†
Verardi *et al.*[74]	1989	Abdominal/ urological	n.a.	Parnaparin 6400	10 000	n.a.	Preop. 2 h	n.a.	7	FUT	n.a.	88
Creperio *et al.*[75]	1990	General	35	Dalteparin 2500	10 000	Blind	Preop. 2 h	General	5	FUT + veno.	n.a.	40
Hartl *et al.*[76]	1990	Abdominal	n.a.	Dalteparin 2500	10 000	Blind	Preop. 2 h	n.a.	7	FUT + veno.	> 7 days	250
Hoffmann and Largiader[77]	1990	Abdominal	n.a.	Certoparin 3000 + DHE	10 000	n.a.	Preop. 2 h	n.a.	n.a.	n.a.	n.a.	916

Table 3 Continued

Reference	Year	Type of surgery	Cancer surgery (%)	LMWH and dose (anti-Xa units)	UFH (units)	Study design	Time of first administration	Type of anaesthesia	Treatment duration (days)	Diagnosis of DVT*	Follow-up duration	Patients randomized
Koppenhagen *et al.*[78]	1990	Abdominal	38	Certoparin 3000	15 000	Blind	Preop. 2 h	General	8	FUT + veno.	7–10 days	104
Barbui *et al.*[79]	1990	General	n.a.	Nadroparin 2850	10 000	Open	n.a.	n.a.	7	FUT + veno.	n.a.	344
Leizorovicz *et al.*[80]	1991	Abdomino-thoracic and gynaecological	n.a.	Tinzaparin 2500 and 3500	10 000	Blind	Preop. 2 h	n.a.	7–10	FUT + veno.	1 month	1 290
Schielke *et al.*[81]	1991	Abdominal	n.a.	Certoparin 3000 + DHE	10 000 + DHE	Open	Preop. 2 h	n.a.	7–10	n.a.	7–10 days	98
Kaaja *et al.*[82]	1992	Gynaecological	18	Enoxaparin 2000	10 000	Blind	Preop. 2 h	General	3	n.a.	1 month	68
Koppenhagen *et al.*[83]	1992	Abdominal	57	Certoparin 3000	15 000	Blind	Preop. 2 h	General	7–10	FUT + veno	3 weeks	673
Borstad *et al.*[84]	1992	Gynaecological	n.a.	Dalteparin 2500	10 000	Blind	Preop. 1 h	n.a.	7	n.a.	n.a.	152
Hoffmann and Largiader[85]	1992	Abdomino-thoracic	n.a.	Certoparin 3000	10 000	Blind	Preop. 2 h	n.a.	> 7	n.a.	n.a.	594
Garcea *et al.*[86]	1992	Abdominal	48	Parnaparin 3200	15 000	Open	Preop. 2 h	n.a.	7	FUT	n.a.	90
Kakkar *et al.*[87–89]	1993–1997	General and gynaecological	41	Reviparin 1750	10 000	Blind	Preop. 2 h	n.a.	> 5	FUT + veno.	n.a.	1 351
Kakkar *et al.*[90]	1993	Abdominal	38	Dalteparin 2500	10 000	Blind	Preop. 1–4 h	General	5–10	n.a.	4–8 weeks	3 809†
Godwin *et al.*[91]	1993	Abdomino-pelvic	100	Ardeparin 90 and 50 units/kg b.i.d	10 000	Blind	Preop. 2 h	General or regional	n.a.	IPG, US + veno	n.a.	904
Gazzaniga *et al.*[92] (ISG)	1993	General and vascular	n.a.	Enoxaparin 2000	10 000	Open	Preop. 2 h	General	7–10	(D or US or IPG) ± veno.	6 weeks	1 122
Limmer *et al.*[93]	1994	General	n.a.	Antixarin 2500	15 000	Open	Preop. 2 h	General	8	FUT + veno.	8 days	203†
Eurin[94]	1994	Abdomino-pelvic	n.a.	Nadroparin 2850	15 000	Open	Postop. 2 h	Regional	7	(D + IPG or US) + veno.	7 days	480
Nurmohamed *et al.*[95]	1995	General	36	Enoxaparin 2000	15 000	Blind	Preop. 2 h	General	10	FUT + veno.	10 days	1 471
McLeod *et al.*[96–98] (Canadian)	1995–1997	Colorectal	n.a.	Enoxaparin 4000	15 000	Blind	Preop. 2 h	General	5–9	Veno.	5–9 days	1 349
Gonzalez *et al.*[99]	1996	Abdominal	n.a.	Bemiparin 2500	10 000	Blind	Preop. 2 h	General	7	(D or IPG) + veno	n.a.	166†
ENOXACAN[100]	1997	Abdomino-pelvic	100	Enoxaparin 4000	15 000	Blind	Preop. 2 h	General	8–12	Veno.	3 months	1 115
Heilmann *et al.*[101,102]	1997 1998	Gynaecological and breast	100	Certoparin 3000	15 000	Blind	Preop. 2 h	General	7	IPG + veno.	10 days	358
Haas *et al.*[103]	1999	General (84%)	26	Certoparin 3000	15 000	Blind	n.a.	n.a.	> 5	n.a.	14 days	23 078

*At end of the treatment. †No. of patients for whom the group distribution was available. ‡stratum of patients with cancer; LMWH, low molecular weight heparin; UFH, unfractionated heparin; DVT, deep vein thrombosis; EFS, European Fraxiparin Study; ISG, Italian Study Group; b.i.d., twice daily; DHE, dihydroergotamine; n.a., data not available; preop., before operation; postop., after operation; FUT, fibrinogen uptake test; veno, DVT confirmed by venography; IPG, plethysmography; US, ultrasonography; D, Doppler; SSHA, semi-synthetic heparin analogue

Table 4 Low molecular weight heparin *versus* unfractionated heparin: incidence of all evaluation criteria in each treatment group

		Patients randomized		Asymptomatic DVT*		Clinical PE		Clinical thrombo-embolism		Death		Major haemorrhage		Total haemorrhage		Wound haematoma		Transfusion	
Reference	Year	LMWH	UFH	LMWH	UFH	LMWH	UFH	LMWH	UFH	LMWH	UFH	LMWH	UFH	LMWH	UFH	LMWH	UFH	LMWH	UFH
Schmitz-Huebner *et al.*[44]	1984	84	42	3/81	0/39	0	0	0	0	n.a.	n.a.	2	0	n.a.	n.a.	17	8	n.a.	n.a.
Törngren *et al.*[45]	1984	309	162	37/279	21/148	2	1	n.a.	n.a.	12	7	n.a.	n.a.	n.a.	n.a.	48	19	29	16
Kakkar and Murray[46]	1985	200	200	5/196	14/199	0	1	0	2	5	6	n.a.	n.a.	n.a.	n.a.	11	14	65	57
Bergqvist *et al.*[47]	1986	215	217	13/215	9/217	0	1	n.a.	n.a.	n.a.	n.a.	10	3	25	10	13	7	75	55
Onarheim *et al.*[48]	1986	25	27	1/25	0/27	0	0	n.a.	n.a.	0	0	1	1	1	2	0	1	n.a.	n.a.
Sasahara *et al.*[49]	1986	137	132	14/134	13/126	0	2	n.a.	n.a.	2	5	n.a.	n.a.	n.a.	n.a.	4	3	19	31
Voigt *et al.*[50]	1986	103	97	1/103	1/97	0	1	0	2	4	6	3	1	6	11	3	10	55	57
Koller *et al.*[51,52]	1986	23	20	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	0	0	6	2	11	2	7	2	5	1
Koller *et al.*[51,52]	1986	75	75	2/70	1/68	0	1	n.a.	n.a.	0	0	1	0	11	11	3	2	4	5
EFS[53,54]	1988	968	941	27/960	42/936	1	5	3	11	11	12	n.a.	n.a.	179	176	83	86	150	144
Fricker *et al.*[55]	1988	40	40	0/40	0/40	0	4	1	5	n.a.	n.a.	2	1	8	13	n.a.	n.a.	n.a.	n.a.
Bergqvist *et al.*[56,57]	1988–1990	505	497	28/505	41/497	0	5	n.a.	n.a.	10	10	n.a.	n.a.	30	15	25	10	223	215
Caen[58]	1988	195	190	6/195	7/190	0	1	n.a.	n.a.	2	3	0	1	4	4	4	3	11	8
Borstad *et al.*[59]	1988	105	110	0/105	0/110	0	0	0	0	n.a.	n.a.	1	1	61	55	26	15	n.a.	n.a.
Samama *et al.*[60–64]	1988–1994	168	167	6/159	12/158	0	0	1	0	1	0	1	1	4	8	1	4	74	61
Samama *et al.*[60–64]	1988–1994	127	123	3/106	3/110	0	0	0	2	1	0	1	0	12	17	10	15	54	54
Samama *et al.*[60–64]	1988–1994	160	147	4/137	5/133	0	1	1	2	2	0	1	1	19	19	15	16	81	71
Welzel *et al.*[65]	1988	98	103	4/98	14/103	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	6	4	n.a.	n.a.
Briel *et al.*[66]	1988	95	98	1/95	1/98	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	3	2	n.a.	n.a.
Catania and Salanitri[67]	1988	88	85	n.a.	n.a.	0	0	1	6	2	3	0	0	5	8	5	8	8	11
Salcuni *et al.*[68]	1988	73	68	n.a.	n.a.	1	2	5	11	n.a.	n.a.	6	5	11	14	5	8	25	32
Kakkar *et al.*[69]	1989	88	91	8/88	10/91	2	0	n.a.	n.a.	n.a.	n.a.	2	0	6	3	2	1	n.a.	n.a.
Adolf *et al.*[70]	1989	205	205	9/202	6/202	3	1	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	14	19	63	48
Heilmann *et al.*[71]	1989	150	150	2/150	6/150	0	0	n.a.	n.a.	n.a.	n.a.	2	3	n.a.	n.a.	19	27	n.a.	n.a.
Baumgartner *et al.*[72]	1989	99	102	6/87	7/89	1	1	n.a.	n.a.	1	2	0	0	n.a.	n.a.	1	0	n.a.	n.a.
Dahan *et al.*[73]	1989	46	41	0/46	0/41	0	0	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	0	4	n.a.	n.a.
Verardi *et al.*[74]	1989	44	44	1/44	3/44	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	1	2	n.a.	n.a.
Creperio *et al.*[75]	1990	20	20	5/20	3/20	0	0	0	0	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Hartl *et al.*[76]	1990	126	124	5/112	5/115	1	1	n.a.	n.a.	6	4	2	3	4	4	1	1	2	9
Hoffmann and Largiader[77]	1990	464	452	n.a.	n.a.	1	0	n.a.	n.a.	n.a.	n.a.	12	12	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Koppenhagen *et al.*[78]	1990	51	53	4/51	7/53	n.a.	n.a.	2	0	0	0	0	0	0	0	0	0	20	16
Barbui *et al.*[79]	1990	171	173	2/27	2/33	0	2	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	10	9	n.a.	n.a.
Leizorovicz *et al.*[80]	1991	861	429	23/861	7/429	5	2	n.a.	n.a.	20	9	22	14	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Schielke *et al.*[81]	1991	47	51	n.a.	n.a.	0	0	0	0	1	2	1	0	n.a.	n.a.	n.a.	n.a.	12	8
Kaaja *et al.*[82]	1992	37	31	n.a.	n.a.	0	0	0	0	n.a.	n.a.	0	6	11	20	11	14	n.a.	n.a.
Koppenhagen *et al.*[83]	1992	336	337	24/323	26/330	0	3	n.a.	n.a.	2	3	n.a.	n.a.	3	1	2	0	7	13
Borstad *et al.*[84]	1992	77	75	n.a.	n.a.	1	0	1	0	2	0	14	9	26	24	5	11	n.a.	n.a.
Hoffmann and Largiader[85]	1992	298	296	n.a.	n.a.	1	1	n.a.	n.a.	n.a.	n.a.	10	7	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Garcea *et al.*[86]	1992	45	45	0/45	1/40	0	0	n.a.	n.a.	n.a.	n.a.	0	5	0	7	0	1	n.a.	n.a.
Kakkar *et al.*[87–89]	1993–1997	672	679	30/648	28/663	1	3	n.a.	n.a.	3	5	4	13	55	80	29	52	79	87
Kakkar *et al.*[90]	1993	1 894	1 915	n.a.	n.a.	22	19	34	32	73	56	69	91	186	243	27	52	n.a.	n.a.
Godwin *et al.*[91]	1993	595	309	0/595	3/309	1	1	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	56	21	n.a.	n.a.	n.a.	n.a

Table 4 Continued

Reference	Year	Patients randomized		Asymptomatic DVT*		Clinical PE		Clinical thrombo-embolism		Death		Major haemorrhage		Total haemorrhage		Wound haematoma		Transfusion	
		LMWH	UFH	LMWH	UFH	LMWH	UFH	LMWH	UFH	LMWH	UFH	LMWH	UFH	LMWH	UFH	LMWH	UFH	LMWH	UFH
Gazzaniga *et al.*[92] (ISG)	1993	561	561	2/561	5/561	3	4	4	5	3	9	1	2	29	34	n.a.	n.a.	n.a.	n.a.
Limmer *et al.*[93]	1994	103	100	3/103	3/100	0	0	0	0	0	0	0	0	n.a.	n.a.	7	5	n.a.	n.a.
Eurin[94]	1994	241	239	1/240	0/239		0	1	0	n.a.	n.a.	1	0	40	37	n.a.	n.a.	7	7
Nurmohamed *et al.*[95]	1995	737	734	42/718	25/709	1	1	1	3	4	6	11	18	111	135	n.a.	n.a.	71	81
McLeod *et al.*[96–98] (Canadian)	1995–1997	674	675	44/468	44/468	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	28	21	70	44	n.a.	n.a.	n.a.	n.a.
Gonzalez *et al.*[99]	1996	84	82	0/84	0/82	0	0	0	0	0	0	0	5	5	20	5	15	n.a.	n.a.
ENOXACAN[100]	1997	555	560	45/312	58/319	0	2	4	6	26	34	23	16	104	96	n.a.	n.a.	284	242
Heilmann *et al.*[101,102]	1997–1998	179	179	10/160	10/164	7	4	n.a.	n.a.	5	3	27	47	39	75	18	29	21	29
Haas *et al.*[103]	1999	11 542	11 536	n.a.	n.a.	(17)	(19)	n.a.	n.a.	166	149	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Total no. of studies†		51		41		45		23		30		36		32		38		25	
Total no. of patients†		48 624		17 995		46 646		13 776		41 387		18 555		19 315		16 087		12 777	

Values in parentheses are cases of fatal pulmonary embolism (PE). *Denominator is number of patients who had a systematic detection test for asymptomatic deep vein thrombosis (DVT) at the end of the treatment period. †Combined total numbers for low molecular weight heparin (LMWH) and unfractionated heparin (UFH) groups. EFS, European Fraxiparin Study; ISG, Italian Study Group; n.a., Data not available

Table 5 Meta-analysis (logarithm of relative risk method) of efficacy and safety criteria comparing low molecular weight heparin* with unfractionated heparin

	Relative risk	*P*	No. of studies	No. of patients
Asymptomatic DVT				
Nadroparin	0·61 (0·41–0·92)	0·02	5	2917
Certoparin	0·86 (0·65–1·14)	0·29	11	2921
Dalteparin	0·90 (0·65–1·26)	0·55	10	2764
Enoxaparin	0·96 (0·77–1·19)	0·70	7	4919
Parnaparin	0·33 (0·05–2·08)	0·24	2	173
Clinical thromboembolism				
Parnaparin	0·37 (0·15–0·88)	0·02	2	314
Nadroparin	0·32 (0·10–0·99)	0·05	3	2789
Enoxaparin	0·65 (0·31–1·36)	0·25	7	4668
Dalteparin	1·00 (0·63–1·58)	0·99	5	4296
Certoparin	0·87 (0·08–9·03)	0·91	4	1340
Major haemorrhage				
Certoparin	0·78 (0·56–1·08)	0·13	10	3076
Dalteparin	0·94 (0·72–1·22)	0·64	10	5568
Enoxaparin	1·09 (0·77–1·54)	0·63	8	6017
Parnaparin	0·89 (0·31–2·54)	0·82	3	404
Wound haematoma				
Certoparin	0·76 (0·58–0·99)	0·048	11	3021
Parnaparin	0·58 (0·29–1·16)	0·12	4	492
Nadroparin	0·92 (0·71–1·19)	0·54	4	2740
Enoxaparin	0·90 (0·49–1·65)	0·72	4	960
Dalteparin	1·24 (0·76–2·04)	0·39	11	6683

Values in parentheses are 95 per cent confidence intervals. *For each criteria, only low molecular weight heparin with two or more clinical trials are presented. DVT, deep vein thrombosis

Table 6 Incidence of all evaluation criteria in the unfractionated heparin group according to type of surgery

	Cancer surgery (%)	Non-cancer surgery (%)
DVT detected systematically at the end of the treatment period	6·0(0·6)	4·8(0·2)
Clinical PE	0·8(0·0)	0·4(0·0)
Clinical thromboembolism	1·8(0·5)	1·2(0·1)
Death	4·8(0·8)	1·5(0·1)
Major haemorrhage	8·1(1·0)	2·7(0·2)
Total haemorrhage	16·0(1·0)	12·0(0·4)
Wound haematoma	13·8(2·2)	5·9(0·3)
Transfusion	36·7(1·8)	19·3(0·5)

Values are adjusted incidences(S.D.). DVT, deep vein thrombosis; PE, pulmonary embolism

(RR 0·88 (0·64–1·20); $P = 0·41$). However, the risk of clinical VTE was significantly reduced by LMWH (RR 0·71 (0·51–0·99); $P = 0·049$) (*Fig. 2*). No reduction in death rate was observed (RR 1·04 (0·89–1·20)).

The incidences of major haemorrhage and wound haematoma in the UFH group were 3·2(0·2) and 6·1(0·3)

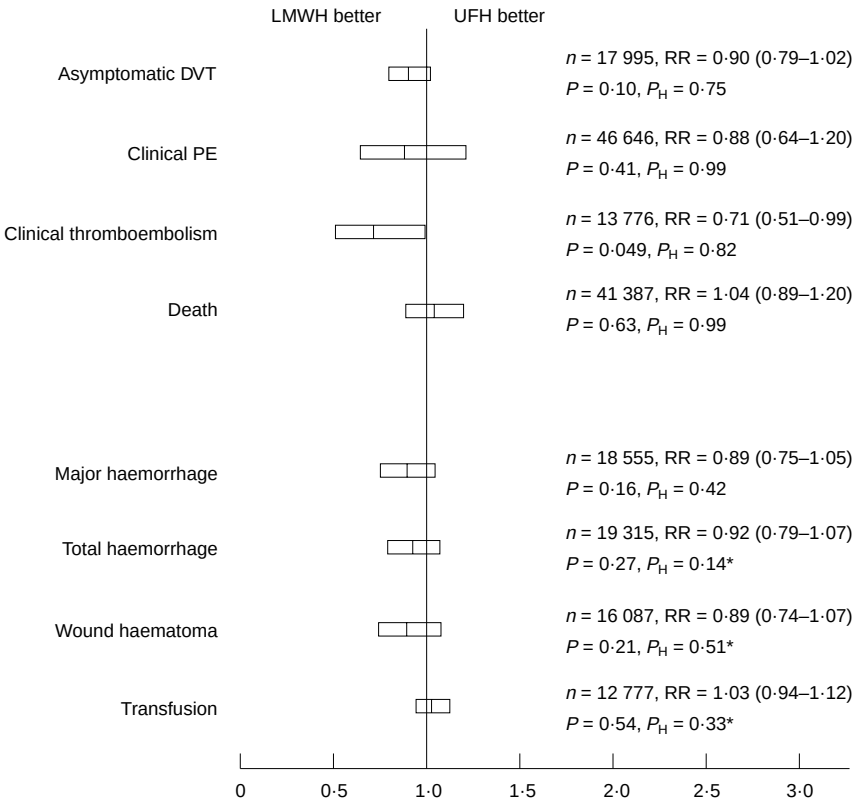

Fig. 2 Meta-analysis (logarithm of relative risk (RR) method) of efficacy and safety criteria comparing low molecular weight heparin (LMWH) with unfractionated heparin (UFH). The RR for each criterion is shown as a vertical line within a box, which represents the 95 per cent confidence interval. A RR of less than 1 indicates that LMWH is more effective than UFH. If the value of 1 is included in the box, the result is not significant ($P > 0{\cdot}05$). P_H indicates the result of the heterogeneity test. *A random model for the RR method had to be used because the heterogeneity test was positive, without any clear explanation for this heterogeneity between studies. DVT, deep vein thrombosis; PE, pulmonary embolism

per cent respectively. There was a reduction in the risk of major haemorrhage, total haemorrhage and wound haematoma in the LMWH group, but this trend did not reach statistical significance (*Fig. 2*).

Table 5 presents the results of this meta-analysis according to the different LMWHs involved. Only criteria for which the overall meta-analysis showed statistical significance or a trend towards statistical significance are displayed.

Sensitivity analyses

The meta-analysis results were not modified when dihydroergotamine treatment was taken into account and did not vary with UFH dose regimen (5000 units twice or three times daily) (data not shown).

Low molecular weight heparin *versus* unfractionated heparin in double-blind studies

When only the well identified double-blind studies were considered, the trends observed in favour of LMWH in the meta-analysis of all studies disappeared, not only for efficacy but also for safety criteria (*Fig. 3*).

Low molecular weight heparin *versus* unfractionated heparin in cancer surgery

The incidences of efficacy and safety criteria were higher in patients undergoing cancer surgery than in other patients (*Table 6*). However, the efficacy and safety of LMWH relative to UFH were similar in patients with cancer to those in patients without malignant disease (*Fig. 4*).

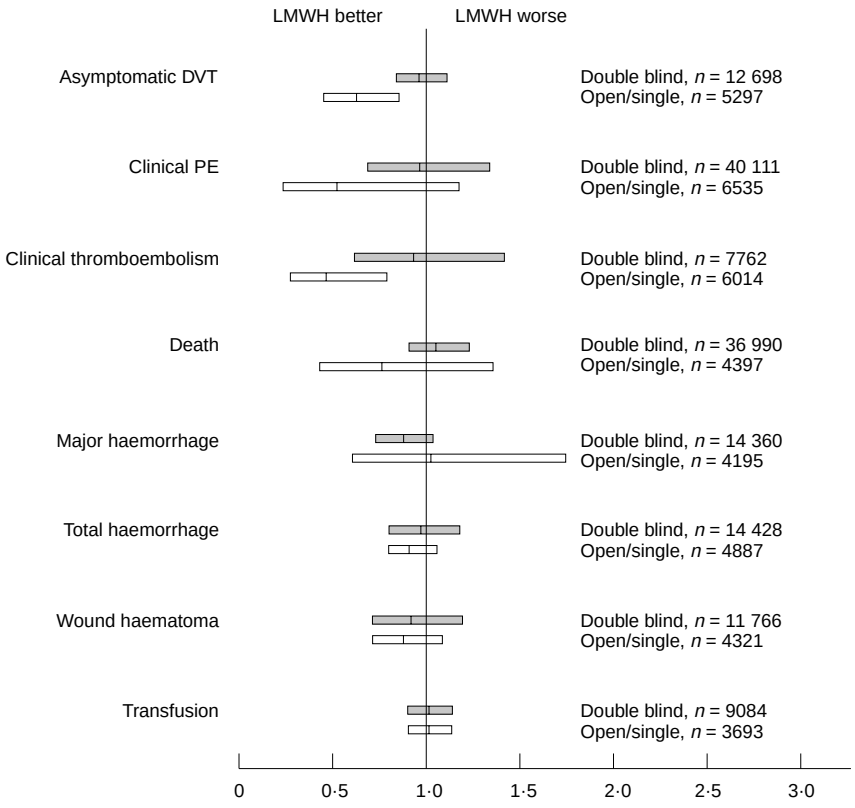

Fig. 3 Meta-analysis (logarithm of relative risk (RR) method) of efficacy and safety criteria comparing low molecular weight heparin (LMWH) with unfractionated heparin (UFH) according to study design. If not specified, the study was considered as open. The RR for each criterion is shown as a vertical line within a box, which represents the 95 per cent confidence interval. A RR of less than 1 indicates that LMWH is more effective than UFH. If the value of 1 is included in the box, the result is not significant ($P > 0{\cdot}05$). DVT, deep vein thrombosis; PE, pulmonary embolism

Low and high prophylactic dose regimens of low molecular weight heparin *versus* unfractionated heparin

Compared with UFH, low-dose LMWH (3400 anti-Xa units or less) did not significantly reduce the risk of VTE irrespective of the criteria used (systematically detected DVT at the end of the treatment period, clinical PE or clinical VTE) (*Fig. 5*). However, while achieving similar efficacy as UFH, low-dose LMWH was associated with a significant reduction in haemorrhagic risk, in particular that of major haemorrhage (RR 0·76 (0·63–0·92); $P = 0{\cdot}005$) (*Fig. 5*).

Conversely, high-dose LMWH (more than 3400 anti-Xa units) appeared to be more effective than UFH, particularly with regard to clinical PE which was significantly reduced in the LMWH group (RR 0·18 (0·04–0·89); $P = 0{\cdot}035$). This better efficacy was counterbalanced by a significant increase in the risk of haemorrhage, in particular that of major haemorrhage (RR 1·53 (1·07–2·19); $P = 0{\cdot}02$) (*Fig. 5*). Although the number of studies was small, similar findings were obtained in patients undergoing cancer surgery (data not shown).

Discussion

In the absence of prophylactic treatment, the incidence of DVT when checked systematically on the tenth day after surgery was found to be approximately 15 per cent, with a risk of PE close to 0·5 per cent. This incidence is lower than that generally accepted in various consensus statements[1,2,104]. Patients undergoing general surgery therefore present an inherent risk of DVT similar to that of internal medicine patients[6] and patients with acute myocardial infarction[105], but less than that of those having orthopaedic surgery[1,2,4,5] or experiencing stroke[8].

This meta-analysis shows that treatment with LMWH at prophylactic doses provides a 72 per cent reduction in the

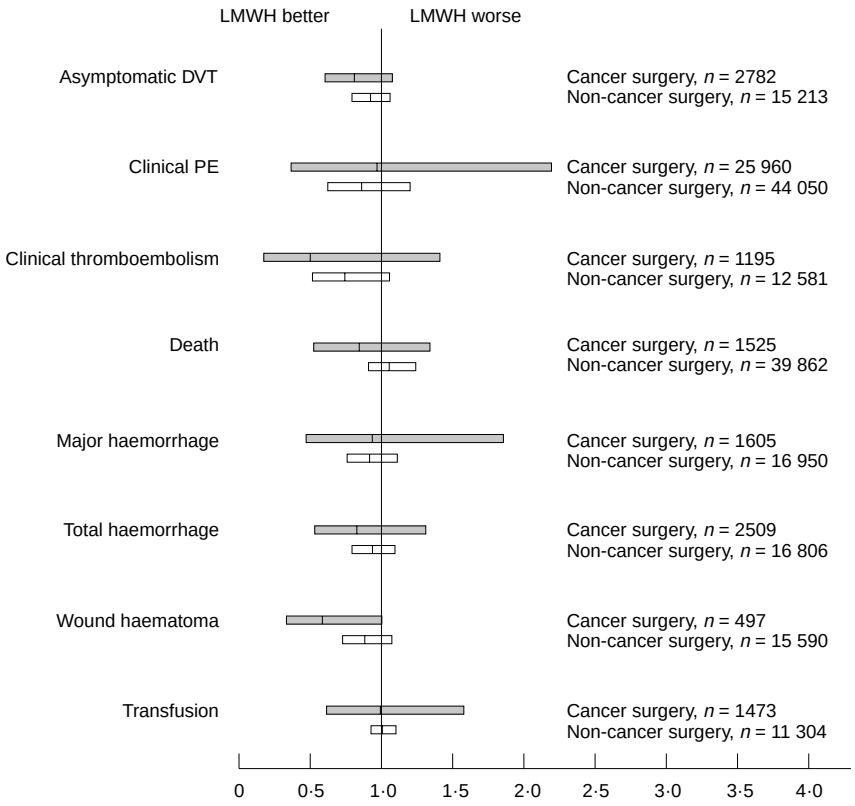

Fig. 4 Meta-analysis (logarithm of relative risk (RR) method) of efficacy and safety criteria comparing low molecular weight heparin (LMWH) with unfractionated heparin (UFH) according to type of surgery. If not specified, the study was considered as non-cancer surgery. The RR for each criterion is shown as a vertical line within a box, which represents the 95 per cent confidence interval. A RR of less than 1 indicates that LMWH is more effective than UFH. If the value of 1 is included in the box, the result is not significant ($P > 0{\cdot}05$). DVT, deep vein thrombosis; PE, pulmonary embolism

risk of DVT checked systematically at the end of treatment, compared with placebo or no treatment. This result is consistent with those reported in the meta-analyses conducted for other indications. Indeed, whether in internal medicine[6], orthopaedic surgery[4,5], stroke[8] or myocardial infarction[105], a constant reduction of 60–70 per cent of the risk of DVT is achieved by UFH or LMWH relative to placebo or no treatment, despite the different intrinsic risks of DVT in these situations in the absence of prophylaxis.

This 72 per cent reduction is associated with similar reductions of 75 per cent in clinical PE and 71 per cent in clinical VTE. This meta-analysis therefore appears to validate the evaluation criterion of 'asymptomatic DVT' as a surrogate endpoint for clinically important postoperative VTE. Despite an increase in major haemorrhage, the observed prophylactic effect of LMWH on VTE also seems to be associated with a non-significant reduction of 46 per cent in overall mortality rate (RR 0·54). The failure of the difference in this criterion to reach statistical significance seems to be a problem of statistical power; only 5142 patients were evaluated on this criterion. To show a significant reduction of 50 per cent in overall mortality, a total of 8000 patients per group would have been necessary (with $\alpha = 5$ per cent and $\beta = 10$ per cent).

With regard to the evaluation of haemorrhagic events, the criterion of wound haematoma could be proposed as a surrogate endpoint for major haemorrhage. Indeed, wound haematomas occur more frequently than major haemorrhages (10·3 *versus* 2·8 per cent) and the increase in frequency of both events under heparin treatment is comparable; RR of 1·88 for wound haematoma and of 2·03 for major haemorrhage.

As the reference treatment for VTE prophylaxis in general surgery in the 1980s was UFH[7], it was of interest to evaluate the effect of LMWH relative to UFH. This meta-analysis indicates that LMWH is at least as effective and safe

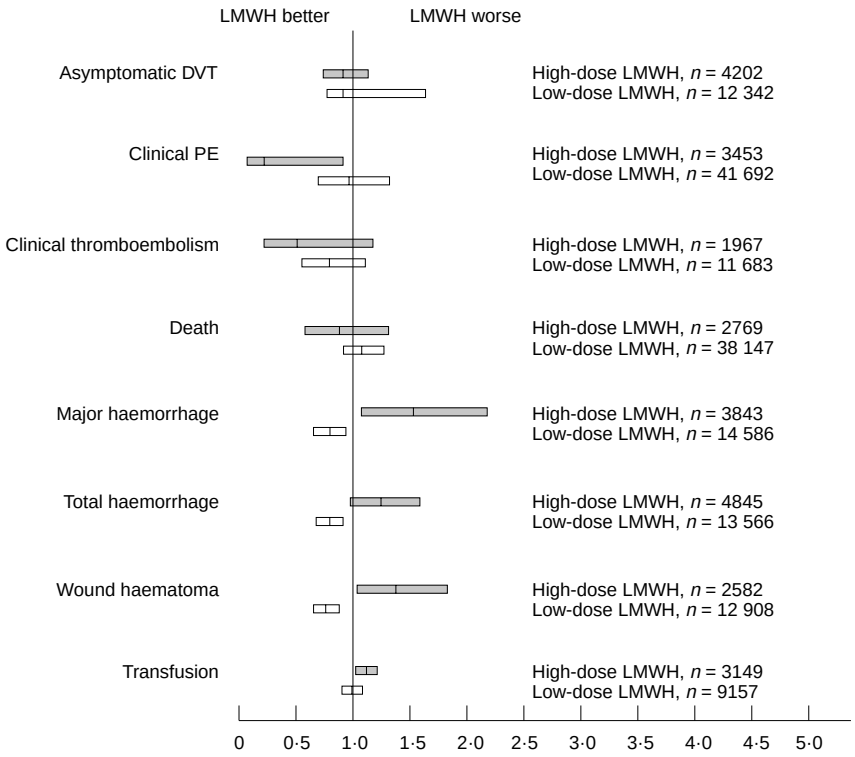

Fig. 5 Meta-analysis (logarithm of relative risk (RR) method) of efficacy and safety criteria comparing low molecular weight heparin (LMWH) with unfractionated heparin (UFH) according to LMWH dose regimen (low dose, 3400 anti-Xa units or less; high dose, more than 3400 anti-Xa units). If the dosage in anti-Xa units was not available, the study was considered as missing. The RR for each criterion is shown as a vertical line within a box, which represents the 95 per cent confidence interval. A RR of less than 1 indicates that LMWH is more effective than UFH. If the value of 1 is included in the box, the result is not significant ($P > 0{\cdot}05$). DVT, deep vein thrombosis; PE, pulmonary embolism

as UFH, in terms of VTE reduction and haemorrhagic events (RR 1 or less for all criteria). These results are not modified by the level of risk associated with the type of surgery, i.e. cancer surgery *versus* non-cancer surgery. The observed trend in favour of LMWH should be viewed with caution since, when only double-blind studies are taken into account, the results show a close similarity of LMWH and UFH with regard to both thromboembolic and haemorrhagic events. These results are in agreement with those published by Koch *et al.*[11] in 1997, with respect to asymptomatic DVT and wound haematoma; they update this previous meta-analysis with eight additional double-blind studies and more than 25 000 additional patients. In addition, similar findings were observed for clinical endpoints. However, even if LMWH is merely as effective as UFH in the prophylaxis of VTE, the former is now the reference treatment for reasons of ease of use.

LMWHs differ to some extent in their pharmacokinetic and anticoagulant profiles, and results obtained with one LMWH may not be simply extrapolated to another since treatment regimens differ somewhat between drugs[106,107]. The present results support this, as nadroparin and parnaparin showed better efficacy than UFH when considering asymptomatic DVT and clinical thromboembolism, whereas there were fewer wound haematomas with certoparin than with UFH (*Table 5*). However, these results should be interpreted cautiously in the absence of any direct comparison between LMWHs.

For general surgery, which involves only moderate thrombotic risk in comparison to orthopaedic surgery, the use of low prophylactic doses of LMWH (3400 anti-Xa units or less) seems to be as effective and safer than UFH. In contrast, high doses of LMWH (more than 3400 anti-Xa units) appear to be more effective, but less safe than UFH. This threshold of 3400 anti-Xa units has already been suggested[1,10,11] and permits a distinction between the low-dose and high-dose prophylactic regimens proposed by the pharmaceutical firms manufacturing the various LMWHs currently available. Three studies provide a direct comparison between low and high doses of LMWH[25,27,29].

However, only the study reported by Bergqvist *et al.*[29] had sufficient statistical power (2097 patients) to show that the high-dose LMWH reduces the incidence of asymptomatic DVT by 50 per cent compared with low-dose LMWH, but at the cost of a fourfold greater risk of major haemorrhage. In view of the paucity of data providing any direct comparison of different doses, it remains difficult to say which dosage regimen of LMWH, high or low, yields the better risk : benefit ratio in general surgery and, in particular, in cancer surgery.

In conclusion, asymptomatic DVT may be regarded as a reliable surrogate endpoint for clinical outcomes in studies investigating thromboprophylaxis in general surgery. LMWH is at least as effective and as safe as UFH. Determination of the optimal dose regimen of LMWH in general surgery requires further investigation.

Acknowledgements

The authors thank Dr M. Cucherat for providing the software EasyMA®[15]. This meta-analysis was funded by a grant from Sanofi–Synthelabo.

References

1 Geerts WH, Heit JA, Clagett GP, Pineo GF, Colwell CW, Anderson FA Jr *et al.* Prevention of venous thromboembolism. *Chest* 2001; **119**(Suppl)**:** 132–75S.
2 Bergquist D, Bonnar J, Clarke-Pearson D, Collins R, Comerota AJ, Eklof B *et al.* Prevention of venous thromboembolism. International Consensus Statement. *Int Angiol* 1997; **16:** 3–38.
3 Prentice CRM. Are symptomatic endpoints acceptable in venous thromboprophylactic studies? *Haemostasis* 1998; **28**(Suppl 3)**:** 109–12.
4 Leizorovicz A, Haugh MC, Chapuis FR, Samama MM, Boissel JP. Low molecular weight heparin in prevention of perioperative thrombosis. *BMJ* 1992; **305:** 913–20.
5 Jorgensen LN, Wille-Jorgensen P, Hauch O. Prophylaxis of postoperative thromboembolism with low molecular weight heparins. *Br J Surg* 1993; **80:** 689–704.
6 Mismetti P, Laporte-Simitsidis S, Tardy B, Cucherat M, Buchmüller A, Juillard-Delsart D *et al.* Prevention of venous thromboembolism in internal medicine with unfractionated or low-molecular-weight heparins: a meta-analysis of randomised clinical trials. *Thromb Haemost* 2000; **83:** 14–19.
7 Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *N Engl J Med* 1988; **318:** 1162–73.
8 Counsell C, Sandercock P. The efficacy and safety of anticoagulant therapy in patients with acute presumed ischaemic stroke: a systematic review of the randomized trials comparing anticoagulants with control. In: Warlow C, Van Gijn J, Sandercock P, eds. *The Cochrane Database Library. Cochrane Collaboration; Issue 1.* Oxford: Update Software, 1997.
9 Nurmohamed MT, Rosendaal FR, Büller HR, Dekker E, Hommes DW, Vandenbroucke JP *et al.* Low-molecular-weight heparin *versus* standard heparin in general and orthopaedic surgery: a meta-analysis. *Lancet* 1992; **340:** 152–6.
10 Kakkar VV. Efficacy and safety of Clivarin® and other LMWHs in general surgery: a meta-analysis. *Blood Coagul Fibrinolysis* 1993; **4**(Suppl 1)**:** S23–7.
11 Koch A, Bouges S, Ziegler S, Dinkel H, Daures JP, Victor N. Low molecular weight heparin and unfractionated heparin in thrombosis prophylaxis after major surgical intervention: update of previous meta-analyses. *Br J Surg* 1997; **84:** 750–9.
12 Palmer AJ, Schramm W, Kirchhof B, Bergemann R. Low molecular weight heparin and unfractionated heparin for prevention of thrombo-embolism in general surgery: a meta-analysis of randomised clinical trials. *Haemostasis* 1997; **27:** 65–74.
13 Cucherat M. *Méta-analyse des Essais Thérapeutiques. Collection Evaluation et Statistique.* Paris: Masson, 1997.
14 Cucherat M, Boissel JP, Leizorovicz A, Haugh MC. EasyMA: a program for the meta-analysis of clinical trials. *Comp Meth Programs Biomed* 1997; **53:** 187–90.
15 Cucherat M. EasyMA software, version 2000. http://www.spc.univ-lyon1.fr/~mcu/easyma.
16 Kakkar VV, Kakkar S, Sanderson RM, Peers CE. Efficacy and safety of two regimens of low molecular weight heparin fragment (Fragmin) in preventing postoperative venous thrombolism. *Haemostasis* 1986; **16**(Suppl 2)**:** 19–24.
17 Verardi S, Casciani CU, Nicora E, Forzano F, Origone A, Valle I *et al.* A multicenter study on LMW-heparin effectiveness in preventing post surgical thrombosis. *Int Angiol* 1988; **7**(Suppl 3)**:** 19–24.
18 Hauch O, Jorgensen LN, Kolle TR, Nerstrom H, Schebye O, Wille-Jorgensen P *et al.* Low molecular weight heparin (Logiparin) as thromboprophylaxis in elective abdominal surgery. A dose finding study. *Acta Chir Scand Suppl* 1988; **543:** 90–5.
19 Corrado F, Fini M, Severini G, Benati A, Monetti N, Levorato M *et al.* Low molecular weight heparin (Fluxum®) prevention of post-operative thrombosis in urological surgery. A controlled study. *Clin Trials Journal* 1989; **26:** 138–48.
20 Benvenuti C, Angelici A, Fabbri F, Poli O, Meloni V, Lupi M *et al.* Prophylaxis of thromboembolism with low molecular weight heparin after surgical treatment. Preliminary notes. *Policlino Sez Chir* 1993; **100:** 13–18.
21 Gioè FP, Arcara M, Scaffidi Abbate F, Mercadante T. Low molecular weight heparin (parnaparin) *versus* calcium heparin in the prevention of thromboembolic disease in general surgery. *Minerva Chir* 1994; **49:** 581–4.
22 Bjerkeset O, Larsen S, Reiertsen O. Evaluation of enoxaparin given before and after operation to prevent venous

thromboembolism during digestive surgery: play-the-winner designed study. *World J Surg* 1997; **21:** 584–9.
23 Reiertsen O, Larsen S, Storkson R, Trondsen E, Lovig T, Andersen OK *et al.* Safety of enoxaparin and dextran-70 in the prevention of venous thromboembolism in digestive surgery. A play-the-winner-designed study. *Scand J Gastroenterol* 1993; **28:** 1015–20.
24 Haas S, Zielke E. Prophylaxis of deep venous thrombosis with 2500 anti-Xa-E units of low molecular weight heparin Kabi in abdominal surgery. *Med Welt* 1987; **38:** 1658–61.
25 Becchi G, Bonomo GM, Scattarella M, Catania G, Salanitri T, Palazzini E. Dose–effect relationship in the prevention of post-surgical thromboembolism by a low molecular weight heparin. A multicenter study. *Acta Therapeutica* 1993; **19:** 163–79.
26 Bounameaux H, Huber O, Khabiri E, Schneider PA, Didier D, Rohner A. Unexpectedly high rate of phlebographic deep venous thrombosis following elective general abdominal surgery among patients given prophylaxis with low-molecular-weight heparin. *Arch Surg* 1993; **128:** 326–8.
27 Bergqvist D, Burmark US, Flordal PA, Frisell J, Hallbook T, Hedberg M *et al.* Low molecular weight heparin started before surgery as prophylaxis against deep vein thrombosis: 2500 *versus* 5000 XaI units in 2070 patients. *Br J Surg* 1995; **82:** 496–501.
28 Tsimoyiannis EC, Floras G, Antoniou N, Papanikolaou N, Siakas P, Tassis A. Low-molecular-weight heparins and Daflon for prevention of postoperative thromboembolism. *World J Surg* 1996; **20:** 968–72.
29 Azorin JF, Regnard JF, Dahan M, Pansart M, les investigateurs du Groupe Thorax. Efficacy and safety of Fraxiparine® in the prevention of thromboembolic complications in oncologic thoracic surgery. *Ann Cardiol Angeiol (Paris)* 1997; **46:** 341–7.
30 Lausen I, Jensen R, Jorgensen LN, Rasmussen MS, Lyng KM, Andersen M *et al.* Incidence and prevention of deep venous thrombosis occurring late after general surgery: randomised controlled study of prolonged thromboprophylaxis. *Eur J Surg* 1998; **164:** 657–63.
31 Blum A, Desruennes E, Elias A, Lagrange G, Loriferne JF. DVT prophylaxis in surgery for digestive tract cancer comparing the LMW heparinoid ORG 10172 (Lomoparan) with calcium heparin. *Thromb Haemost* 1989; **62:** 126 (Abstract).
32 Gallus A, Cade J, Ockelford P, Hepburn S, Maas M, Magnani H *et al.* Orgaran (Org 10172) or heparin for preventing venous thrombosis after elective surgery for malignant disease? A double-blind, randomised, multicentre comparison. ANZ–Organon Investigators' Group. *Thromb Haemost* 1993; **70:** 562–7.
33 Heijboer H, Borm JJJ, ten Cate JW. A double blind placebo controlled study on the efficacy of low molecular weight heparin (LMWH) (K 2165) to prevent deep vein thrombosis in elective abdominal surgery. *Thromb Haemost* 1989; **62:** 527 (Abstract).
34 Weinand HA, Gehrke T, Krieg H, Brünner H. Prevention of thrombosis in surgery: low molecular weight heparin/standard heparin. *Langenbecks Arch Chir* 1990; **Suppl II:** 1175–7.
35 Le Gagneux F, Steg A, Le Guillou M. Subcutaneous enoxaparine (Lovenox®) *versus* placebo for preventing deep vein thrombosis (DVT) after transurethral prostatectomy (TUP). *Thromb Haemost* 1987; **58:** 116 (Abstract).
36 Valle I, Sola G, Origone A. Controlled clinical study of the efficacy of a new low molecular weight heparin administered subcutaneously to prevent post-operative deep venous thrombosis. *Curr Med Res Opin* 1988; **11:** 80–6.
37 Ockelford PA, Patterson J, Johns AS. A double-blind randomized placebo controlled trial of thromboprophylaxis in major elective general surgery using once daily injections of a low molecular weight heparin fragment (Fragmin). *Thromb Haemost* 1989; **62:** 1046–9.
38 Pezzuoli G, Neri Serneri GG, Settembrini P, Coggi G, Olivari N, Buzzetti G *et al.*, the STEP-Study Group. Prophylaxis of fatal pulmonary embolism in general surgery using low-molecular weight heparin CY 216: a multicentre, double-blind, randomized, controlled, clinical trial *versus* placebo (STEP). *Int Surg* 1989; **74:** 205–10.
39 Pezzuoli G, Neri Serneri GG, Settembrini PG, Coggi G, Olivari N, Negri G *et al.*, STEP Study Group. Effectiveness and safety of the low-molecular-weight heparin CY 216 in the prevention of fatal pulmonary embolism and thromboembolic death in general surgery. A multicentre, double-blind, randomized, controlled clinical trial *versus* placebo (STEP). *Haemostasis* 1990; **20**(Suppl 1): 193–204.
40 Balas PE *et al.* Efficacy and safety of nadroparin (Fraxiparine®) *versus* placebo in the prophylactic treatment of deep vein thrombosis in patients with high thrombo-embolic risk undergoing general surgery. *Thromb Res* 1992; **65**(Suppl 1)**:** S113 (Abstract).
41 Marassi A, Balzano G, Mari G, D'Angelo SV, Della Valle P, Di Carlo V *et al.* Prevention of postoperative deep vein thrombosis in cancer patients. A randomized trial with low molecular weight heparin (CY 216). *Int Surg* 1993; **78:** 166–70.
42 Bergqvist D, Flordal PA, Friberg B, Frisell J, Hedberg M, Ljungstrom KG *et al.* Thromboprophylaxis with a low molecular weight heparin (tinzaparin) in emergency abdominal surgery. A double-blind multicenter trial. *Vasa* 1996; **25:** 156–60.
43 Ho YH, Seow-Choen F, Leong A, Eu KW, Nyam D, Teoh MK. Randomized, controlled trial of low molecular weight heparin *vs.* no deep vein thrombosis prophylaxis for major colon and rectal surgery in Asian patients. *Dis Colon Rectum* 1999; **42:** 196–203.
44 Schmitz-Huebner U, Buente H, Freise G, Reers B, Rueschemeyer C, Scherer R *et al.* Clinical efficacy of low molecular weight heparin in postoperative thrombosis prophylaxis. *Klin Wochenschr* 1984; **62:** 349–53.
45 Törngren S, Kettunen K, Lahtinen J, Koppenhagen K, Brücke P, Hartl P *et al.* A randomized study of a semisynthetic

heparin analogue and heparin in prophylaxis of deep vein thrombosis. *Br J Surg* 1984; **71:** 817–20.
46 Kakkar VV, Murray WJG. Efficacy and safety of low-molecular-weight heparin (CY216) in preventing postoperative venous thrombo-embolism: a co-operative study. *Br J Surg* 1985; **72:** 786–91.
47 Bergqvist D, Burmark US, Frisell J, Hallbök T, Lindblad B, Risberg B *et al.* Low molecular weight heparin once daily compared with conventional low-dose heparin twice daily. A prospective double-blind multicentre trial on prevention of postoperative thrombosis. *Br J Surg* 1986; **73:** 204–8.
48 Onarheim H, Lund T, Heimdal A, Arnesjo B. A low molecular weight heparin (KABI 2165) for prophylaxis of postoperative deep venous thrombosis. *Acta Chir Scand* 1986; **152:** 593–6.
49 Sasahara AA, Koppenhagen K, Haring R, Welzel D, Wolf H. Low molecular weight heparin plus dihydroergotamine for prophylaxis of postoperative deep vein thrombosis. *Br J Surg* 1986; **73:** 697–700.
50 Voigt J, Hamelmann H, Hedderich J, Seifert J, Buchhammer T, Kohler A. Effectiveness and side effects of low-molecular weight heparin–dihydroergotamine in preventing thromboembolism in abdominal surgery. *Zentralbl Chir* 1986; **111:** 1269–305.
51 Koller M, Schoch U, Buchmann P, Largiader F, von Felten A, Frick PG. Thrombosis prophylaxis in visceral surgery with the low molecular weight heparin fragment Kabi 2165 (7500 and 2500 anti–Xa IU/day). *Haemostasis* 1986; **16**(Suppl 2)**:** 69–70.
52 Koller M, Schoch U, Buchmann P, Largiarder F, von Felten A, Frick PG. Low molecular weight heparin (Kabi 2165) as thromboprophylaxis in elective visceral surgery. A randomized, double-blind study *versus* unfractionated heparin. *Thromb Haemost* 1986; **56:** 243–6.
53 The European Fraxiparin Study (EFS) Group. Comparison of a low molecular weight heparin and unfractionated heparin for the prevention of deep vein thrombosis in patients undergoing abdominal surgery. *Br J Surg* 1988; **75:** 1058–63.
54 Biegholdt M, for the European Fraxiparin Study Group. Descriptive analysis of the European Fraxiparin Study. *Semin Thromb Hemost* 1989; **15:** 409–13.
55 Fricker JP, Vergnes Y, Schach R, Heitz A, Eber M, Grunebaum L *et al.* Low dose heparin *versus* low molecular weight heparin (Kabi 2165, Fragmin) in the prophylaxis of thromboembolic complications of abdominal oncological surgery. *Eur J Clin Invest* 1988; **18:** 561–7.
56 Bergqvist D, Matzsch T, Burmark US, Frisell J, Guilbaud O, Hallbook T *et al.* Low molecular weight heparin given the evening before surgery compared with conventional low-dose heparin in prevention of thrombosis. *Br J Surg* 1988; **75:** 888–91.
57 Bergqvist D, Burmark US, Frisell J, Guilbaud O, Hallbook T, Horn A *et al.* Thromboprophylactic effect of low molecular weight heparin started in the evening before elective general abdominal surgery: a comparison with low-dose heparin. *Semin Thromb Hemost* 1990; **16**(Suppl)**:** 19–24.
58 Caen JP. A randomized double-blind study between a low molecular weight heparin Kabi 2165 and standard heparin in the prevention of deep vein thrombosis in general surgery. A French multicenter trial. *Thromb Haemost* 1988; **59:** 216–20.
59 Borstad E, Urdal K, Handeland G, Abilgaard U. Comparison of low molecular weight heparin *vs.* unfractionated heparin in gynecological surgery. *Acta Obstet Gynecol Scand* 1988; **67:** 99–103.
60 Samama M, Bernard P, Bonnardot JP, Combe-Tamzali S, Lanson Y, Tissot E. Low molecular weight heparin compared with unfractionated heparin in prevention of postoperative thrombosis. *Br J Surg* 1988; **75:** 128–31.
61 Samama M, Combe-Tamzali S. Prevention of thromboembolic disease in general surgery with enoxaparin. *Br J Clin Pract* 1989; **43**(Suppl: 65)**:** 9–17.
62 Samama M, Combe S. Prevention of thromboembolic disease in general surgery with enoxaparin (Clexane). *Acta Chir Scand Suppl* 1990; **556:** 91–5.
63 Combe S, Samama MM. Prevention of thromboembolic disease in general surgery with Clexane® (enoxaparin). *Semin Thromb Hemost* 1991; **17**(Suppl 3)**:** 291–5.
64 Samama MM. Prevention of postoperative thromboembolism in general surgery with enoxaparin. *Eur J Surg Suppl* 1994; **571:** 31–3.
65 Welzel D, Wolf H, Koppenhagen K. Antithrombotic defense during the postoperative period. Clinical documentation of low molecular weight heparin. *Arzneimittelforschung* 1988; **38:** 120–3.
66 Briel RC, Doller P, Hermann P. Prevention of thromboembolism in hysterectomies with low molecular weight heparin. *Geburtshilfe Frauenheilkd* 1988; **48:** 160–4.
67 Catania G, Salanitri G. Prevention of postoperative deep vein thrombosis by two different heparin types. *Int J Clin Pharmacol Ther Toxicol* 1988; **26:** 304–9.
68 Salcuni PF, Azzarone M, Palazzini E. A new low molecular weight heparin for deep vein thrombosis prevention: effectiveness in postoperative patients. *Curr Ther Res* 1988; **43:** 824–31.
69 Kakkar VV, Stringer MD, Hedges AR, Parker CJ, Welzel D, Ward VP *et al.* Fixed combinations of low-molecular weight or unfractionated heparin plus dihydroergotamine in the prevention of postoperative deep vein thrombosis. *Am J Surg* 1989; **157:** 413–18.
70 Adolf J, Knee H, Roder JD, van de Flierdt E, Siewert JR. Thromboembolism prophylaxis with low molecular heparin in abdominal surgery. *Dtsch Med Wochenschr* 1989; **114:** 48–53.
71 Heilmann L, Kruck M, Schindler AE. Prevention of thrombosis in gynecology: double-blind comparison of low molecular weight heparin and unfractionated heparin. *Geburtshilfe Frauenheilkd* 1989; **49:** 803–7.
72 Baumgartner A, Jacot N, Moser G, Krahenbuhl B. Prevention of postoperative deep vein thrombosis by one daily injection of low molecular weight heparin and dihydroergotamine. *Vasa* 1989; **18:** 152–6.
73 Dahan M, Levasseur Ph, Bogaty J, Boneu B, Samama M.

Prevention of post-operative deep vein thrombosis (DVT) in malignant patients by Fraxiparine (a low molecular weight heparin). A cooperative trial. *Thromb Haemost* 1989; **62:** 519 (Abstract).
74 Verardi S, Cortese F, Baroni B, Boffo V, Casciani CU. Role of low molecular weight heparin in the prevention of postoperative deep venous thrombosis. Our experience in 88 cases. *G Chir* 1989; **10:** 674–8.
75 Creperio G, Marabini M, Ciocia G, Bergonzi M, Fincato M. Evaluation of the effectiveness and safety of Fragmin (Kabi 2165) *versus* calcium heparin in the prevention of deep venous thrombosis in general surgery. *Minerva Chir* 1990; **45:** 1101–6.
76 Hartl P, Brücke P, Dienstl E, Vinazzer H. Prophylaxis of thromboembolism in general surgery: comparison between standard heparin and Fragmin. *Thromb Res* 1990; **57:** 577–84.
77 Hoffmann R, Largiader F. Perioperative thromboembolic prophylaxis with low molecular weight heparin and postoperative bleeding complications. *Langenbecks Arch Chir* 1990; **Suppl II:** 1179–84.
78 Koppenhagen K, Matthes M, Haering R, Troester E, Wolf H, Welzel D. Prophylaxis of thromboembolism in elective abdominal surgery. Comparison of efficacy and safety of low molecular weight heparin and unfractionated heparin. *Munch Med Wochenschr* 1990; **132:** 677–80.
79 Barbui T, Cassinelli G, Cortelazzo S, D'Alonzo U, Fantoni P, Lavorato F *et al.* Comparison of low molecular weight heparin CY 216 and unfractionated heparin in preventing post-operative venous thromboembolism in general surgery: a preliminary results of a cooperative study. *Fibrinolysis* 1990; **4**(Suppl 1)**:** 79 (Abstract).
80 Leizorovicz A, Picolet H, Peyrieux JC, Boissel JP, HBPM Research Group. Prevention of perioperative deep vein thrombosis in general surgery: a multicentre double blind study comparing two doses of Logiparin and standard heparin. *Br J Surg* 1991; **78:** 412–16.
81 Schielke DJ, Staib I, Wolf H, Mankel T. Prophylaxis of thromboembolism in abdominal surgery. Effectiveness and tolerance of low molecular weight heparin in combination with dihydroergotamine. *Med Welt* 1991; **42:** 346–9.
82 Kaaja R, Lehtovirta P, Venesmaa P, Kajanoja P, Halonen P, Gummerus M *et al.* Comparison of enoxaparin, a low-molecular-weight heparin, and unfractionated heparin, with or without dihydroergotamine, in abdominal hysterectomy. *Eur J Obstet Gynecol Reprod Biol* 1992; **47:** 141–5.
83 Koppenhagen K, Adolf J, Matthes M, Troster E, Roder JD, Hass S *et al.* Low molecular weight heparin and prevention of postoperative thrombosis in abdominal surgery. *Thromb Haemost* 1992; **67:** 627–30.
84 Borstad E, Urdal K, Handeland G, Abildgaard U. Comparison of low molecular weight heparin *vs.* unfractionated heparin in gynecological surgery. II: Reduced dose of low molecular weight heparin. *Acta Obstet Gynecol Scand* 1992; **71:** 471–5.
85 Hoffmann R, Largiader F. Perioperative prevention of thromboembolism with standard heparin and low molecular weight heparin, evaluation of postoperative hemorrhage. A double-blind prospective, randomized and mono-center study. *Langenbecks Arch Chir* 1992; **377:** 258–61.
86 Garcea D, Martuzzi F, Santelmo N, Savoia M, Casertano MG, Furno A *et al.* Post-surgical deep vein thrombosis prevention: evaluation of the risk/benefit ratio of fractionated and unfractionated heparin. *Curr Med Res Opin* 1992; **12:** 572–83.
87 Kakkar VV, Boeckl O, Boneu B, Bordenave L, Brehm OA, Brucke P *et al.* Efficacy and safety of a low-molecular-weight heparin and standard unfractionated heparin for prophylaxis of postoperative venous thromboembolism: European multicenter trial. *World J Surg* 1997; **21:** 2–9.
88 Boneu B. An international multicentre study: Clivarin in the prevention of venous thromboembolism in patients undergoing general surgery. Report of the International Clivarin Assessment Group. *Blood Coagul Fibrinolysis* 1993; **4**(Suppl 1)**:** S21–2.
89 Kakkar VV, Cohen AT, Mohamed MS. Patients at risk of venous thromboembolism – clinical results with reviparin. *Thromb Res* 1996; **81**(Suppl 2)**:** S39–45.
90 Kakkar VV, Cohen AT, Edmonson RA, Phillips MJ, Cooper DJ, Das SK *et al.* Low molecular weight *versus* standard heparin for prevention of venous thromboembolism after major abdominal surgery. The Thromboprophylaxis Collaborative Group. *Lancet* 1993; **341:** 259–65.
91 Godwin JE, Comp P, Davidson B, Rossi M, the Normiflo Cancer Clinical Trial Group. Comparison of the efficacy and safety of subcutaneous RD heparin *vs* subcutaneous unfractionated heparin for the prevention of deep-vein thrombosis in patients undergoing abdominal or pelvic surgery for cancer. *Thromb Haemost* 1993; **69:** 647 (Abstract).
92 Gazzaniga GM, Angelini G, Pastorino G, Santoro E, Lucchini M, Dal Pra ML, the Italian Study Group. Enoxaparin in the prevention of deep venous thrombosis after major surgery: multicentric study. *Int Surg* 1993; **78:** 271–5.
93 Limmer J, Ellbrück D, Müller H, Eisele E, Rist J, Schütze F *et al.* Prospective randomized clinical study in general surgery comparing a new low molecular weight heparin with unfractionated heparin in the prevention of thrombosis. *Clin Investig* 1994; **72:** 913–19.
94 Eurin B. Efficiency and tolerance of Fraxiparine® in the prevention of deep vein thrombosis in general surgery performed with medullar conduction anesthesia. *Ann Fr Anesth Reanim* 1994; **13:** 311–17.
95 Nurmohamed MT, Verhaeghe R, Haas S, Iriarte JA, Vogel G, van Rij AM *et al.* A comparative trial of a low molecular weight heparin (enoxaparin) *versus* standard heparin for the prophylaxis of postoperative deep vein thrombosis in general surgery. *Am J Surg* 1995; **169:** 567–71.
96 McLeod R, Geerts W, Sniderman K, Greenwood C, Gregoire R, Taylor B *et al.* Thromboprophylaxis in colorectal surgery. A randomized trial comparing low dose heparin and enoxaparin. *Thromb Haemost* 1995; **73:** 979 (Abstract).
97 McLeod R, Geerts W, Sniderman K, Greenwood C, Gregoire R, Taylor B *et al.* Thromboprophylaxis in colorectal

surgery. A randomized trial comparing low dose heparin to enoxaparin. *Haemostasis* 1996; **26**(Suppl 3)**:** AB290 (Abstract).
98 McLeod RS, Geerts WH, Sniderman K, Greenwood C, Gregoire R, Taylor B *et al.* Thromboprophylaxis after colorectal surgery. Results of a randomized, double-blind comparison of low dose heparin and enoxaparin. *Thromb Haemost* 1997; **Suppl:** 753 (Abstract).
99 Gonzalez EM, Fontcuberta J, De la Llama F. Prophylaxis of thromboembolic disease with RO-11 (ROVI), during abdominal surgery. *Hepatogastroenterology* 1996; **43:** 744–7.
100 ENOXACAN Study Group. Efficacy and safety of enoxaparin *versus* unfractionated heparin for prevention of deep vein thrombosis in elective cancer surgery: a double-blind randomized multicentre trial with venographic assessment. *Br J Surg* 1997; **84:** 1099–103.
101 Heilmann L, Von Tempelhoff GF, Herrle B, Hojnacki B, Schneider D, Michaelis HC *et al.* Prevention of postoperative venous thrombosis. A randomized trial comparing low-dose heparin and low molecular weight heparin in gynaecological oncology. *Geburtshilfe Frauenheilk* 1997; **57:** 1–6.
102 Heilmann L, von Tempelhoff GF, Kirkpatrick C, Schneider DM, Hommel G, Pollow K. Comparison of unfractionated *versus* low molecular weight heparin for deep vein thrombosis prophylaxis during breast and pelvic cancer surgery: efficacy, safety, and follow-up. *Clin Appl Thrombosis/Hemostasis* 1998; **4:** 268–73.
103 Haas SK, Wolf H, Encke A, Fareed J. Prevention of fatal postoperative pulmonary embolism by low molecular weight heparin. A double blind comparison of certoparin and unfractionated heparin. *Clin Appl Thromb Hemost* 1999; **Suppl:** 491 (Abstract).
104 Thromboembolic Risk Factors (THRIFT) Consensus Group. Risk and prophylaxis for venous thromboembolism in hospital patients. *BMJ* 1992; **305:** 567–74.
105 Collins R, MacMahon S, Flather M, Baigent C, Remvig L, Mortensen S *et al.* Clinical effects of anticoagulant therapy in suspected acute myocardial infarction: systematic overview of randomised trials. *BMJ* 1996; **313:** 652–9.
106 Hirsh J, Warkentin TE, Shaughnessy SG, Anand SS, Halperin JL, Raschke R *et al.* Heparin and low-molecular-weight heparin. Mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. *Chest* 2001; **119**(Suppl 1)**:** 64–94S.
107 Hyers TM, Agnelli G, Hull RD, Morris TA, Samama M, Tapson V *et al.* Antithrombotic therapy for venous thromboembolic disease. *Chest* 2001; **119**(Suppl 1)**:** 176–93S.

