Low molecular weight heparin in prevention of perioperative thrombosis

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Abstract

***Objective*—To determine whether prophylactic treatment with low molecular weight heparin reduces the incidence of thrombosis in patients who have had general or orthopaedic surgery.**

***Design*—Meta-analysis of results from 52 randomised, controlled clinical studies (29 in general surgery and 23 in orthopaedic surgery) in which low molecular weight heparin was compared with placebo, dextran, or unfractionated heparin.**

***Subjects*—Patients who had had general or orthopaedic surgery.**

***Intervention*—Once daily injection of a low molecular weight heparin compared with placebo, dextran, or unfractionated heparin.**

***Main outcome measures*—Incidence of deep venous thrombosis, pulmonary embolism, major haemorrhages, and death.**

***Results*—The results confirm that low molecular weight heparins are more efficacious for the prophylactic treatment of deep venous thrombosis than placebo (common odds ratio 0·31, 95% confidence interval 0·22 to 0·43; $p<0·001$) and dextran (0·44, 0·30 to 0·65; $p<0·001$). The results suggest that low molecular weight heparins are also more efficacious than unfractionated heparin (0·85, 0·74 to 0·97; $p=0·02$), with no significant difference in the incidence of major haemorrhages (1·06, 0·93 to 1·20; $p=0·62$).**

***Conclusions*—Low molecular weight heparins seem to have a higher benefit to risk ratio than unfractionated heparin in preventing perioperative thrombosis. However, it remains to be shown in a suitably powered clinical trial whether low molecular weight heparin reduces the risk of fatal pulmonary embolism compared with heparin.**

Introduction

Patients undergoing surgery with prolonged general anaesthesia or a period of limited mobility postoperatively, or both, face the risk of thromboembolism. From phlebography and measurement of the uptake of fibrinogen labelled with iodine-125 the incidence of deep venous thrombosis in patients over 40 who have undergone general surgery is estimated to be between 20% and 30%; this incidence is much higher in patients who have undergone orthopaedic surgery.[1-3] Although in many cases deep vein thrombosis resolves without sequelae once mobility is re-established, in some cases it can lead to valvar damage and chronic venous insufficiency and in rare cases to non-fatal or fatal pulmonary embolism from displacement of the thrombus.

Heparin, a naturally occurring oligosaccharide, has been used to treat thrombosis since the mid-1930s, and more recently it has been extensively evaluated in numerous clinical trials as a possible prophylactic treatment for deep vein thrombosis and pulmonary embolism in patients undergoing surgery. The incidence of pulmonary embolism is low, thus in many studies the incidence of deep vein thrombosis, which occurs more frequently, has been used as a surrogate end point.

Initially, major haemorrhagic complications were found to be a serious problem, but the use of a low dose regimen—that is, 5000 IU two or three times daily—has reduced these. A recent overview of the results from more than 70 clinical trials with subcutaneously administered unfractionated heparin concluded that patients receiving treatment had a reduced incidence compared with control patients, of both deep vein thrombosis (9·0% *v* 22·4%; reduction of odds 67·0% (±4%); $p<0·001$) and pulmonary embolism (1·7% *v* 3·0%; reduction of odds 47·0% (20%); $p<0·02$).[4]

Dextran has also been used as a prophylactic treatment in this indication, and evidence suggest that it can reduce the incidence of pulmonary embolism in patients undergoing orthopaedic surgery.[5] There is a low risk of anaphylactic reactions, but this is compensated by the haemodilution properties of dextran, which reduce the need for blood transfusion.[5]

In recent years a better understanding of heparin's structure and mechanism of action has led to the development of new molecules of heparin with a lower molecular weight. These are obtained from native, purified heparin by one of four methods,[6] and they have a molecular weight varying from 3000 to 10 000 daltons, depending on the manufacturer (unfractionated heparin is usually a mixture ranging from 5000 to 30 000 daltons, with a mean of 12 000 to 15 000 daltons). These newer molecules have both biological and practical advantages—for example, they have an improved antithrombotic effect to bleeding ratio in animals,[7-9] which is attributed to their ability to inhibit factor Xa, and affect the activated partial thromboplasmin time minimally. Low molecular weight heparins have a smaller disruptive effect on platelets compared with unfractionated heparin,[10] and they are less effectively neutralised by platelet factor 4.[11] From a practical point of view these molecules have an increased bioavailability compared with unfractionated heparin (85% *v* 10%) and a half life that can vary from 3 to 18 hours—for example, in one study the half life for a particular low molecular weight heparin, fragmin, was found to be 3·7 h, with activity remaining after 10 h.[12,13] In clinical medicine these differences enable the newer molecules to be administered once daily, unlike treatment with unfractionated heparin, which requires two or three injections a day.

These results gave rise to a hypothesis that the low molecular weight heparins could be more efficacious than unfractionated heparin for the prophylactic treatment of thrombosis, with a lower incidence of haemorrhagic complications and therefore a higher benefit to risk ratio. Many randomised, clinical trials have been undertaken to compare these molecules with placebo,

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dextran, and unfractionated heparin, and the apparently disparate results obtained may be explained by the low statistical power of the individual studies. Thus, the relative prophylactic efficacy of low molecular weight heparin compared with the other available treatments remains to be established.

We therefore reviewed all the available data from clinical trials comparing a low molecular weight heparin with placebo, unfractionated heparin, or dextran in patients undergoing general or orthopaedic surgery. Our aim was to examine the inherent and relative efficacy of these new heparin molecules in the prophylactic treatment of deep vein thrombosis in patients undergoing general and orthopaedic surgery.

Methods

DATA COLLECTION

We performed a literature search, both manual and computer aided (MEDLINE), for clinical trials evaluating a low molecular weight heparin in patients undergoing either elective or non-elective general or orthopaedic surgery from 1984 to 1991, with no restriction on the language of the paper. We searched meeting abstracts, checked the International Society for Thrombosis and Haemostasis register,[14] scanned the reference lists in reviews and studies, and asked colleagues, investigators, and the manufacturers of these products for any unpublished or missing studies. When studies were published both as an abstract and an original paper, only the paper was considered, and care was taken to eliminate duplicate reports.

Our inclusion criteria selected randomised, controlled studies which had used venous thrombosis of the lower limbs (detected by the fibrinogen uptake test, the thermographic DeVeTherm test, Doppler ultrasonography and phlebography) or pulmonary embolism, or both, as the clinical end point(s). We selected only trials with a control group, either untreated or treated with placebo, unfractionated low dose heparin, or dextran, and therefore dose ranging studies were excluded. Trials with at least one group treated with low molecular weight heparin were selected, but those evaluating the heparinoid OR10172 (Organon) were not because this preparation contains mainly unfractionated heparin sulphate and dermatan sulphate, with only a small proportion of low molecular weight heparin.

The data from the individual trials were extracted independently by two of us (AL and MCH), using the following end points: venous thrombosis of the lower limbs, pulmonary embolism (both non-fatal and fatal), major bleeding, and total mortality. The definitions of venous thrombosis and pulmonary embolism, as specified in each report, were used for the individual studies. The definitions of major bleeding events used in the original papers were heterogeneous and we, therefore, decided to use the author's definition, when given, and to include bleeding requiring blood transfusion, reoperation, permanent discontinuation of treatment, or leading to death, or a combination of these four criteria, when no definition was given in the report. It would have been both impracticable and artificial to have attempted to obtain empirically a more standardised definition for major bleeding and so we chose a more pragmatic approach which we believe is closer to the clinical reality. The definitions of minor bleeding events were even more heterogeneous and thus more difficult to assess; because these events have fewer consequences in terms of therapeutic strategy they were not considered in the analysis.

STATISTICAL METHODS

The results from each trial were summarised on an intention to treat basis in two by two tables for each end point. A comparison of control groups between trials was performed using descriptive statistical methods and χ^2 tests. The meta-analysis was performed using various techniques—that is, the combined logarithm of the odds ratio (both exact and approximate), Mantel-Haenszel, Cochran, Peto, percentage difference (both fixed and random effects models).[15,16] The results obtained from the different methods were similar and therefore only the results from the exact combined logarithm of the odds ratio method, with the corresponding 95% confidence intervals, are presented. An odds ratio equal to 1 indicates no difference between the treatments; less than 1 indicates that low molecular weight heparin is better—that is, an odds ratio of 0·80 indicates a 20% relative risk reduction—and greater than 1 indicates that the control treatment is better. Association and heterogeneity tests were performed for each meta-analysis.[17] A p value of 0·05 or less from an association test is usually taken to be significant in the association test. In a meta-analysis the results of the individual studies may be considered as being heterogeneous when the p value from the heterogeneity test is less than or equal to 0·05. A non-significant value—that is, $p>0{\cdot}05$—does not, however, indicate similarity—that is, homogeneity—but rather failure to detect a difference.

Meta-analyses were performed using data from trials comparing low molecular weight heparin with placebo in general, orthopaedic, and all types of surgery. A comparison of low molecular weight heparin with dextran in orthopaedic surgery was also performed (no trials in general surgery were found). Other meta-analyses were performed comparing low molecular weight heparin with unfractionated heparins with data from general, orthopaedic, and both types of surgery. Another analysis was performed after removal of all data on the doses of low molecular weight heparin that are currently considered to be too high (increased risk of side effects) or too low (decreased efficacy) in the studies involving comparison with unfractionated heparin in both types of surgery. This was done to evaluate the range of doses which are currently recommended by each manufacturer, and therefore the exact dose was dependent on the type of heparin. An additional analysis was performed using the data from results in which the first injection was given at least 12 hours before or after the operation because it has been suggested that this may reduce the incidence of bleeding.

An exploratory analysis of the results in terms of year of publication was performed for all surgery comparing low molecular weight heparin and unfractionated heparin to see when the cumulative result from the studies became stable. This type of analysis can also show the influence of past protocols on new ones—for example, the elimination of particularly high or low doses.

Results

We found nine studies in which low molecular weight heparin was assessed in comparison with placebo[18-26] and 39 with unfractionated heparin[27-32] (M Samama, unpublished data); three of the studies with unfractionated heparin were reported by Samama *et al*.[27] We also found four studies in which the efficacy was compared with that of dextran.[63-66] The 52 studies (29 for general surgery and 23 for orthopaedic surgery) found by our literature search are listed in table I with a summary of the basic characteristics of each study. Two reports were written in French,[20,55] four in German,[34,43,44,46] and the rest in English. Eight of these had appeared only as abstracts,[18,23,24,26,40,53,54,57] one was unpublished, and the rest were original reports. Two

TABLE I—*Brief description of study design and summary of results for clinical trials in meta-analyses*

Comparison for low molecular weight heparin treatment	Name of heparin	Type of surgery	Daily regimen (dose*; first injection†; duration of treatment): LMWH group	Daily regimen (dose*; first injection†; duration of treatment): Control group	End point assessment	End point (no of events/no of patients randomised in group): Deep vein thrombosis: LMWH group	Deep vein thrombosis: Control group	Bleeding: LMWH group	Bleeding: Control group	Pulmonary embolism: LMWH group	Pulmonary embolism: Control group	Total mortality: LMWH group	Total mortality: Control group
				General surgery									
Placebo:													
Le Gagneux 1987[29]	Enoxaparin	Prostatectomy	1×60 mg; 12h before;	Placebo	FUT/phlebography	0/44	0/45	8/44	6/45	0/44	0/45	ND	
Oekelford 1989[30]	Fragmin	General	1×2500; 1-2h before; 5-9 days	Placebo	FUT	4/102	14/95	4/102	4/95	0/102	2/95	0/102	2/95
Pezzuoli 1989[31]	Fraxiparine	General	1×7500; 2h before; 7-21 days	Placebo	Pulmonary embolism	ND		173/2247	69/2251	2/2247	8/2251	8/2247	18/2251
Valle 1988[32]	Fluxum	General	1×7500; 2h before; 7 days	Placebo	Doppler/phlebography	0/50	3/50	6/50	6/50	0/50	0/50	ND	
Unfractionated heparin:													
Samama 1988[33]	Enoxaparin	General	1×6600; 2h before; 7 days 1×4400; 2h before; 7 days 1×2200; 2h before; 7 days	3×5000; 2h before; 7 days 3×5000; 2h before; 7 days 3×5000; 2h before; 7 days	FUT FUT FUT	27/160 24/127 15/168	19/147 16/123 21/167	71/160 45/127 71/168	64/147 48/123 58/167	0/160 0/127 0/168	1/147 0/123 0/167	2/160 1/127 1/168	0/147 0/123 0/167
Verardi 1988[34]	Fluxum	General	1×4000; 2h before; 7 days 1×8000; 2h before; 7 days	2×5000; 2h before; 7 days 3×5000; 2h before; 7 days	FUT/Doppler/SGP	10/308	19/302	3/308	11/302	1/308	3/302	ND	
Bergqvist 1986[35]	Fragmin	Abdominal	1×5000; 2h before; 5-7 days	2×5000; 2h before; 5-7 days	FUT	13/215	9/217	55/215	75/217	0/215	1/217	5/215	5/217
Kofler 1986[36]	Fragmin	Visceral	1×2500; 2h before; ≥5 days	2×5000; 2h before; ≥5 days	FUT/phlebography	2/75	1/75	5/75	2/75	0/75	1/75	0/75	0/75
Onarheim 1986[37]	Fragmin	Abdominal	1×5000; 2h before; 7 days	2×5000; 2h before; 7 days	FUT/phlebography	2/25	2/27	2/25	1/27	0/25	0/27	0/25	0/27
Bergqvist 1988[38]	Fragmin	Abdominal	1×5000; 12h before; ≥6 days	2×5000; 2h before; ≥6 days	FUT/phlebography	28/505	41/497	30/505	15/497	0/505	1/497	10/505	10/497
Borstad 1988[39]	Fragmin	Gynaecological	1×5000; 1h before; 7 days	2×5000; 1h before; 7 days	Plethysmography/phlebography	0/105	0/110	61/105	55/110	0/105	0/110	ND	
Briel 1988[40]	Fragmin	Gynaecological	2×2500 day 1, 1×5000 days 2-8	2×5000+0·5 mg DHE; 8 days	De Ve therm/phlebography	1/99	1/101	3/99	2/101	ND		ND	
Caen 1988[41]	Fragmin	General	1×2500; 2h before; 7 days	2×5000; 2h before; 7 days	FUT/phlebography	6/395	7/190	11/195	8/190	0/195	1/190	2/195	3/190
Fricker 1988[42]	Fragmin	Oncological	2×2500 day 1, 1×5000 days 2-10; 2h before	3×5000; 2h before; 10 days	FUT/phlebography	0/40	0/40	2/40	1/40	0/40	2/40	0/40	0/40
Hartl 1990[43]	Fragmin	Abdominal	1×2500; 2h before; 7 days	2×5000; 2h before; 7 days	FUT/phlebography	6/126	6/124	1/126	3/124	1/126	1/124	5/126	3/124
Kakkar 1985[44]	Fraxiparine	Abdominal	1×7500; 2h before; ≥7 days	2×5000; 2h before; ≥7 days	FUT/phlebography	5/200	15/200	10/200	7/200	0/200	1/200	5/200	6/200
EFS Group 1988[45]	Fraxiparine	Abdominal	1×7500; 2h before; 7 days	3×5000; 2h before; 7 days	FUT/phlebography	27/968	42/941	150/968	144/941	2/968	5/941	11/968	12/941
Dahan 1989[46]	Fraxiparine	Oncological	7500 days 1-3, 10 000 days 4-7; 12h before	3×5000 days 1-3, ND days 3-7; 2h before	FUT/phlebography	0/50	0/50	3/50	2/50	0/50	0/50	ND	
Samama (unpublished)	Logiparin	General	1×2500; 2h before; 7-10 days	2×5000; 2h before; 7-10 days	FUT	0/18	0/19	0/18	1/19	ND		1/18	0/19
Leizorovicz 1991[47]	Logiparin	General	1×2500; 2h before and 12h after; 7-10 days; 1×3500; 2h before to 12h after; 7-10 days	2×5000; 2h before to 12h after; 7-10 days	FUT/phlebography	23/861	7/429	22/861	14/429	5/861	2/429	20/861	9/429
Schmitz-Huebner 1984[48]	Sandoz	Abdominal	2×5100; 2h before; 7 days 2×6700; 2h before; 7 days	3×500; 2h before; 7 days	FUT	3/84	0/42	11/84	0/42	0/84	0/42	1/84	0/42
Adolf 1989[49]	Sandoz	Abdominal	1×6300; 2h before; ≥7 days	3×5000; 2h before; ≥7 days	FUT/phlebography	25/202	24/202	63/202	48/202	0/202	2/202	ND	
Heilmann 1989[50]	Sandoz	Gynaecological	1×6000; 2h before; ≥8 days	3×5000; 2h before; ≥8 days	Phlebography	2/150	6/150	3/150	2/150	ND		0/150	0/150
Sasahara 1986[51]	Sandoz+0·5 mg DHE	Abdominal	1×6300; 2h before; 7-10 days	2×5000; 2h before; 7-10 days	FUT/phlebography	14/137	13/132	19/137	31/132	0/137	2/132	2/137	5/132
Vogt 1986[52]	Sandoz+0·5 mg DHE	Abdominal	1×6300; 2h before; ≥7 days	2×5000; 2h before; ≥7 days	Phlebography	1/103	1/97	3/103	1/97	0/103	1/97	4/103	6/97
Baumgartner 1989[53]	Sandoz+0·5 mg DHE	Abdominal	1×6300; 2h before; 6-10 days	2×2500; 2h before; 6-10 days	FUT/phlebography	6/99	7/102	0/99	0/102	1/99	1/102	1/99	2/102
Kakkar 1989[54]	Sandoz+0·5 mg DHE	Abdominal	1×6300; 2h before; ≥7 days	2×5000; 2h before; ≥7 days	FUT/phlebography	8/88	10/91	0/88	0/91	2/88	0/91	ND	
				Orthopaedic surgery									
Placebo:													
Turpie 1986[55]	Enoxaparin	Elective hip	2×2400; 12-24h after; 14 days	Placebo	FUT/phlebography	6/50	21/50	1/50	2/50	0/50	0/50	0/50	1/50
Leclerc 1991[56]	Enoxaparin	Knee	2×30 mg; 12-24h after; ND	Placebo	FUT/phlebography	11/65	37/64	4/65	5/65	ND		ND	
Jorgensen 1989[57]	Fragmin	Hip fracture	2×2500; 2h before to 12h after; 1×5000; 6 days	Placebo	FUT/phlebography	9/30	22/38	NS		0/30	1/38	0/30	1/38
Torholm 1991[58]	Fragmin	Elective hip	2×2500; 2h before to 12h after; 1×5000; 6 days	Placebo	FUT/phlebography	9/58	19/54	NS		0/58	1/54	1/58	0/54
Lassen 1989[59]	Logiparin	Elective hip	1×50 U/kg; 2h before; ND	Placebo	Phlebography	27/90	45/102	0/90	1/102	ND		1/90	1/102
Dextran:													
DES Group 1991[60]	Enoxaparin	Elective hip	1×3900; 12h before; 7 days	60 mg/ml; 500 ml; twice on day 0, once on days 1 and 3	Phlebography	7/120	24/126	NS		0/120	0/126	1/120	0/126
Eriksson 1988[61]	Fragmin	Elective hip	2×2500; 2h before; 7 days	Dextran 70 2×500 ml day 0, 1×500 ml days 1 and 3	FUT/phlebography	10/50	22/50	0/50	0/50	2/50	2/50	0/50	0/50
Matzsch 1988[62]	Logiparin	Elective hip	1×35 kg; 2h before; 7 days	Dextran 70 500 ml before and after surgery and on days 1, 3, and 5	FUT/phlebography	13/48	19/52	0/48	0/52	0/48	0/52	0/48	0/52
Matzsch 1991[63]	Logiparin	Elective hip	1×50 kg; 2h before; 7 days	Dextran 70 500 ml before and after surgery and on days 1, 3, and 5	FUT/phlebography	22/120	36/123	4/120	10/123	6/120	0/123	0/120	0/123
Unfractionated heparin:													
Planes 1988[64]	Enoxaparin	Elective hip	1×3200; 12h before; ≤14 days	3×5000; 2h before ≤14 days	Phlebography	15/124	27/113	2/124	0/113	0/124	1/113	0/124	0/113
Levine 1991[65]	Enoxaparin	Elective hip	2×2400; 12-24h after; >14 days	2×7500 U; 12 or 24h before; >14 days	FUT/plethysmography/phlebography	57/333	63/332	11/333	19/332	0/333	2/332	0/333	0/332
Chiapuzzo 1988[66]	Fluxum	Elective hip	2×7500; 2h before; 7 days	3×5000; 2h before; 7 days	Doppler/FUT	5/70	7/70	0/70	0/70	0/70	0/70	ND	
Pini 1989[67]	Fluxum	Hip	2×7500; before; ≤14 days	3×5000; before; ≤14 days	FUT/SGP	5/25	7/24	0/25	0/24	0/25	1/24	0/25	1/24
Haas 1985[68]	Fragmin	Elective hip	2×2500 day 0, 1×5000 days 1-15; 2h before	2×5000+DHE; 2h before; 15 days	FUT	6/65	7/65	NS		1/65	0/65	ND	
Binsack 1986[69]	Fragmin	Elective hip	2×2500 day 0; 1×500 ND; 2h before	3×5000; 2h before; ND	FUT/phlebography	5/48	6/47	0/48	0/47	ND		ND	
Barre 1987[70]	Fragmin	Elective hip	2×2500; 2h before; 10 days	3×5000 U; day 0, ND days 1-10; 2h before	Phlebography	7/40	4/40	6/40	4/40	0/40	0/40	0/40	0/40
Dechavanne 1989[71]	Fragmin	Elective hip	2×2500 for 10-13 days, or 2×2500 days 1-2, 1×5000 days 3-13; 2h before	2×5000; days 1-2, ND days 3-13; 2h before	FUT/phlebography	5/82	4/40	0/82	0/40	ND		0/82	0/40
Eriksson 1989[72]	Fragmin	Elective hip	1×5000; 12h before; 10 days	1×5000; 2h before; 10 days	Phlebography	19/67	25/69	1/67	5/69	8/67	19/69	0/67	1/69
Monreal 1989[73]	Fragmin	Hip	1×2500 day 1; 2h before; 1×5000 days 2-9	3×5000; 2h before; 9 days	Phlebography	14/46	6/44	2/46	1/44	6/46	0/44	2/46	3/44
Leyvraz 1991[74]	Fraxiparine	Elective hip	1×41/kg days 1-3, 1×62/kg days 4-10; 12h before	ND; 24h before; 10 days	Phlebography	22/203	28/206	1/203	3/206	1/203	4/206	1/203	2/206
Haas 1987[75]	Sandoz+0·5 mg DHE	Elective hip	1×6200; 2h before; ~7 days	2×5000; 2h before; ~7 days	FUT	15/80	15/80	26/80	13/80	0/80	1/80	0/80	0/80
Lassen 1988[76]	Sandoz+0·5 mg DHE	Elective hip	1×6000; 2h before; 7 days	2×5000; 2h before; 7 days	99m Tc-plasmin/phlebography	35/118	34/122	96/118	98/122	0/118	0/122	0/118	0/122
Lassen 1989[77]	Sandoz+0·5 mg DHE	Hip fracture	1×6300; 2h before; 7 days	2×5000; 2h before; 7 days	99m Tc-plasmin/phlebography	14/68	23/71	NS		1/68	0/71	4/68	2/71

LMWH = low molecular weight heparin; ND = no details given; NS = not significant; FUT = fibrinogen uptake test; DHE = dihydroergotamine; SGP = strain gauge plethysmography.
* IU anti-Xa units except where indicated.
† Time before or after surgery.

studies in which dihydroergotamine was given to only one group were not included[67 68] as this resulted in non-comparable groups.

A summary of the results for the four end points is also given in table I. Although some letters were sent to investigators, not all information was retrievable or available—that is, not given in the reports or indicated as not significant—which is denoted in table I. Data on a total of 18 543 patients were collected; 14 567 had undergone general surgery (29 studies) and 3976 orthopaedic surgery (23 studies). Studies comparing low molecular weight heparin with placebo involved 5479 patients (4884 (four studies) and 595 (five studies) undergoing general and orthopaedic surgery, respectively) and those comparing low molecular weight and unfractionated heparins involved 12 375 patients (9683 (25 studies) and 2692 (14 studies) undergoing general and orthopaedic surgery, respectively). Only 689 patients were included in four studies comparing dextran with low molecular weight heparin in patients undergoing orthopaedic surgery. The total, unadjusted results for the various end points for the different type of surgery and type of control treatment used are summarised in table II.

VERSUS PLACEBO

Only one of the four studies in general surgery showed a significant reduction in deep vein thrombosis (a fifth study did not use deep vein thrombosis as an end point). All five studies in orthopaedic surgery showed a significant reduction between the treated and control groups.

The results obtained from the meta-analyses for the four end points are presented in table III. The incidence of deep vein thrombosis was significantly reduced for both types of surgery, with a common odds ratio of 0·25 (95% confidence interval 0·09 to 0·70; p=0·008) for general surgery and 0·32 (0·22 to 0·46; p<0·001) for orthopaedic surgery (fig 1). The overall odds ratio from the combined data was 0·31 (0·22 to 0·43; p<0·001) (figs 1 and 2). The p value for homogeneity was found to be high for each analysis (p>0·1), indicating that the treatment effect was not different, although the low molecular weight heparins used in the various studies had been produced by different companies, and the study populations were different.[70]

The odds ratio for the incidence of pulmonary embolism in patients having general surgery was 0·33 (0·09 to 1·12) and in those having orthopaedic surgery 0·64 (0·08 to 5·03) (table III), but these results were not significant (p=0·07 and p=0·67, respectively). The analysis for the combined results gave an odds ratio of 0·39 (0·13 to 1·12), which was not significant (p=0·08) because of the very large 95% confidence interval (table III). Although this is a clinically important result, the total number of patients included in these analyses, in other words the statistical power, was not sufficient to show a significant decrease, even if it existed.

The incidence of bleeding was significantly higher in

TABLE II—*Proportions* (percentages) of patients having various outcomes (end points) in studies used for meta-analyses*

Control treatment	End point: Deep vein thrombosis		Pulmonary embolism		Major bleeding		Total mortality	
	LMWH group	Control group	LMWH group	Control group	LMWH group	Control group	LMWH group	Control group
General surgery								
Placebo	4/196 (2·04)	17/190 (8·95)	2/2443 (0·09)	10/2441 (0·41)	191/2443 (7·82)	85/2441 (3·48)	8/2349 (0·34)	20/2346 (0·85)
Unfractionated heparin	248/5108 (4·86)	267/4575 (5·84)	12/4841 (0·25)	25/4305 (0·58)	649/5108 (12·71)	596/4575 (13·03)	71/4253 (1·67)	60/3719 (1·61)
Orthopaedic surgery								
Placebo	62/293 (21·16)	144/308 (46·75)	0/138	2/142 (1·41)	5/205 (2·44)	8/217 (3·69)	2/228 (0·88)	3/244 (1·23)
Unfractionated heparin	224/1369 (17·82)	256/1323 (19·35)	17/1239 (1·37)	28/1236 (2·27)	145/1236 (11·73)	2/351 (12·05)	7/1186 (0·59)	9/1141 (0·79)
Dextran	52/338 (15·38)	101/351 (28·77)	8/338 (2·37)	2/351 (0·57)	4/218 (1·83)	10/225 (4·44)	0/338	0/351

*Number of patients with outcome/total number of patients randomised.
LMWH = Low molecular weight heparin.

TABLE III—*Summary of meta-analyses results with data from studies comparing low molecular weight heparin with placebo, unfractionated heparin, and dextran*

Type of surgery	End point: Deep vein thrombosis		Pulmonary embolism		Bleeding		Total mortality	
	No of studies/No of patients	Odds ratio (95% confidence interval)	No of studies/No of patients	Odds ratio (95% confidence interval)	No of studies/No of patients	Odds ratio (95% confidence interval)	No of studies/No of patients	Odds ratio (95% confidence interval)
Placebo								
General	3/386	0·25 (0·09 to 0·70)	4/4884	0·33 (0·09 to 1·13)	4/4884	2·35 (1·80 to 3·06)	2/4695	0·42 (0·19 to 0·95)
Orthopaedic	5/601	0·32 (0·22 to 0·46)	3/280	0·64 (0·08 to 5·03)	3/422	0·69 (0·22 to 2·11)	4/472	0·92 (0·18 to 4·62)
Both	8/987	0·31 (0·22 to 0·43)	7/5164	0·39 (0·13 to 1·12)	7/5306	2·20 (1·70 to 2·85)	6/5167	0·50 (0·24 to 1·02)
Unfractionated heparin								
General	25/9683	0·86 (0·72 to 1·04)	22/9146	0·62 (0·33 to 1·15)	25/9683	1·02 (0·90 to 1·16)	19/7972	0·96 (0·68 to 1·36)
Orthopaedic	14/2692	0·83 (0·68 to 1·02)	12/2475	0·53 (0·27 to 1·03)	12/2423	1·09 (0·76 to 1·58)	11/2327	0·88 (0·37 to 2·07)
Both	39/12 375	0·85 (0·74 to 0·97)	34/11 621	0·59 (0·37 to 0·93)	37/12 106	1·06 (0·93 to 1·20)	30/10 299	0·95 (0·69 to 1·31)
Dextran								
Orthopaedic	4/689	0·44 (0·30 to 0·65)	3/443	1·88 (0·46 to 7·74)	3/443	0·45 (0·15 to 1·35)		

TABLE IV—*Occurrence of major bleeding in studies with early or late first injection. Values are numbers of patients with outcome/total number of patients randomised*

Reference	Time of injection (before or after surgery)	Low molecular weight heparin group	Control group
General surgery			
v Placebo:			
Le Gagneux[18]	12h before	8/44	6/45
v Unfractionated heparin:			
Bergqvist[42]	12h before	30/505	15/497
Orthopaedic surgery			
v Unfractionated heparin:			
Planes[49]	12h before	2/120	0/108
Eriksson[57]	12h before	1/67	5/69
Leyvraz[58]	12h before	1/203	3/206
v Placebo:			
Turpie[27]	12h after	1/50	2/50
Leclerc[52]	12h after	4/65	5/65
v Unfractionated heparin:			
Levine[60]	12h after	11/333	19/332

the treated group compared with the control group in patients having general surgery (odds radio 2·35 (1·80 to 3·06); p<0·001), whereas in patients having orthopaedic surgery the difference, although indicating an excess in the low molecular weight heparin group, was not significant (odds ratio 0·69 (0·22 to 2·11); p=0·52). The analysis of the incidence of total mortality in both types of surgery gave an odds ratio of 0·50 (0·24 to 1·02; p=0·053), which is on the borderline of significance.

VERSUS DEXTRAN

Only four studies comparing low molecular weight heparin with dextran in 689 patients undergoing orthopaedic surgery were found. Two of these studies showed a significant reduction in the incidence of deep vein thrombosis in the low molecular weight heparin group, but no difference was reported for the other end points. Meta-analysis showed a highly significant reduction for deep vein thrombosis in the patients receiving low molecular weight heparin, with an odds ratio of 0·44 (0·30 to 0·65; p<0·001), and a non-significant trend for a reduction in bleeding (odds ratio 0·45 (0·15 to 1·35); p=0·15). The incidence of pulmonary embolism was higher in the low molecular weight heparin group (odds ratio 1·88), but the 95% confidence interval was large (0·46 to 7·74; p=0·61), the difference seeming to be due to one trial.[66]

VERSUS UNFRACTIONATED HEPARIN

Four of the 25 general surgery studies[28 38 39 41] and three of the 14 orthopaedic surgery studies[49 57 58] showed a significant reduction (p<0·05) in the incidence of deep vein thrombosis, as reported in the publications. The meta-analysis using the results from the trials for both types of surgery combined showed a significant reduction in the incidence of deep vein thrombosis in favour of the low molecular weight heparin group, with an odds ratio of 0·85 (0·74 to 0·97; p=0·02). A non-significant trend towards a reduction in the risk of deep vein thrombosis in patients treated with low molecular weight heparin was observed in patients undergoing general surgery (odds ratio 0·86 (0·72 to 1·04); p=0·12) and in those undergoing orthopaedic surgery (odds radio 0·83 (0·68 to 1·01); p=0·07) (table III).

We also considered the results from trials involving orthopaedic surgery in which phlebography was systematically used for the confirmation of deep vein thrombosis as the fibrinogen uptake test is generally considered to be unsuitable in these patients. After the removal of four trials from the initial analysis,[50-52 59] we found the odds ratio unchanged at 0·83, with a marginally different 95% confidence interval (0·68 to 1·02) and p value (p=0·09).

When the data for general and orthopaedic surgery patients were combined, the odds ratio for pulmonary embolism was 0·59 in favour of the low molecular weight group (0·37 to 0·93; p=0·02). The reduction in the incidence of pulmonary embolism in patients having orthopaedic surgery (odds ratio 0·53 (0·27 to 1·02); p=0·06) was not significant because of the low incidence of the event coupled with the insufficient number of patients. For patients undergoing general surgery the result was similar, and although there were

almost four times as many patients in the analysis, this number was still not sufficient (odds ratio 0·62 (0·33 to 1·15); (p=0·12). No significant differences were found between the two groups for bleeding complications (p>0·6) and total mortality (p>0·55) (table III).

In an analysis performed using data corresponding to the manufacturer's current recommended doses of the various low molecular weight heparins and for both types of surgery we found an odds ratio of 0·83 (0·72 to 0·95; p=0·007) for deep vein thrombosis and an odds ratio of 1·05 (0·93 to 1·20) for major bleeding complications. The results for general surgery were similar, with the result for deep vein thrombosis being significant (odds ratio 0·80 (0·66 to 0·97); p=0·02) whereas that for major bleeding complications was unchanged (odds ratio 1·05 (0·91 to 1·21)) in comparison with the result for all doses (table III).

Five studies, two in general surgery[18 31] and three in orthopaedic surgery[49 57 59] had a first injection 12 hours before surgery and three others[22 23 50] had a first injection 12 hours after orthopaedic surgery (table IV). We performed a meta-analysis using the data on the incidence of major bleeding from three orthopaedic surgery trials in which the first injection was given 12 hours before surgery[49 56 59] and compared the result with that from a meta-analysis using similar data from trials in which this injection was given two hours before surgery.[51 52 54 55 57 58 60 61] The first analysis showed a non-significant trend (p=0·24) in favour of low molecular weight heparin (odds ratio 0·44), but the 95% confidence interval was large (0·11 to 1·77). The second analysis gave an odds ratio of 1·50 (0·96 to 2·32), which is slightly more in favour of unfractionated heparin, compared with the result for all data (odds ratio 1·09 (0·76 to 1·58)) but is non-significant (p=0·07). None the less, the data from these studies were not sufficient to allow any conclusions to be drawn about either the effect of low molecular weight heparin or the treatment schedule on major bleeding events as there were too few patients.

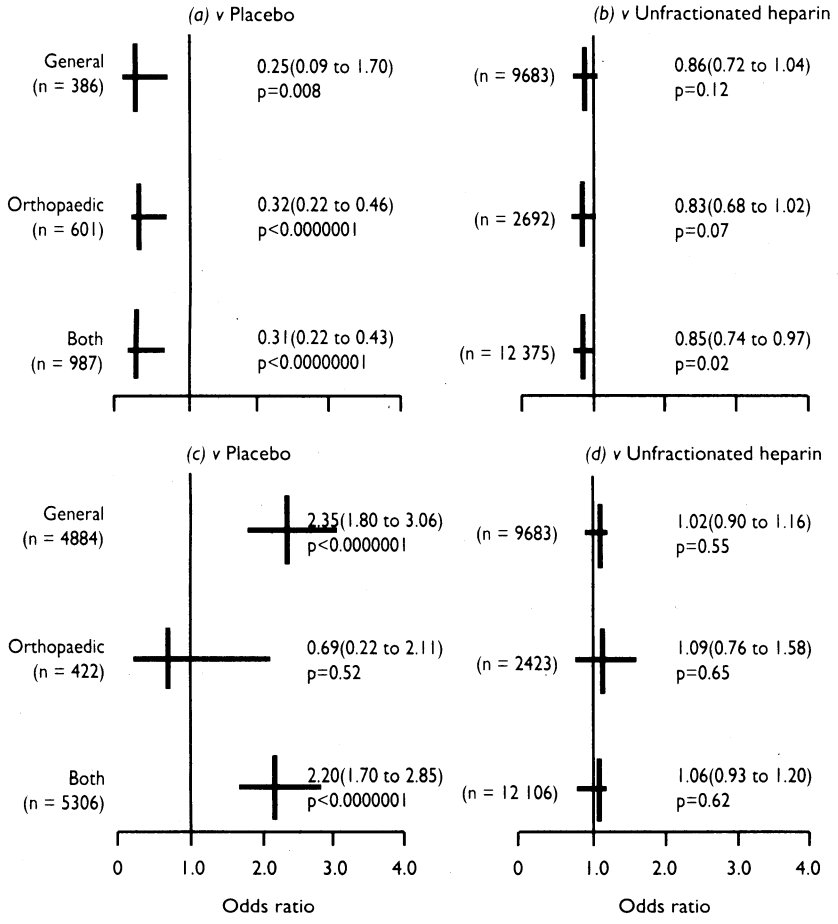

FIG 1—*Graphical representation of results from meta-analyses (exact odds ratio method) for deep venous thrombosis ((a) and (b)) and major bleeding in ((c) and (d)) in general surgery, orthopaedic surgery, and both types of surgery. Odds ratio of <1 indicates that low molecular weight heparin is better than unfractionated heparin and of >1 that unfractionated heparin is better than low molecular weight heparin. Horizontal lines represent 95% confidence intervals; if value of 1 is included results are not significant*

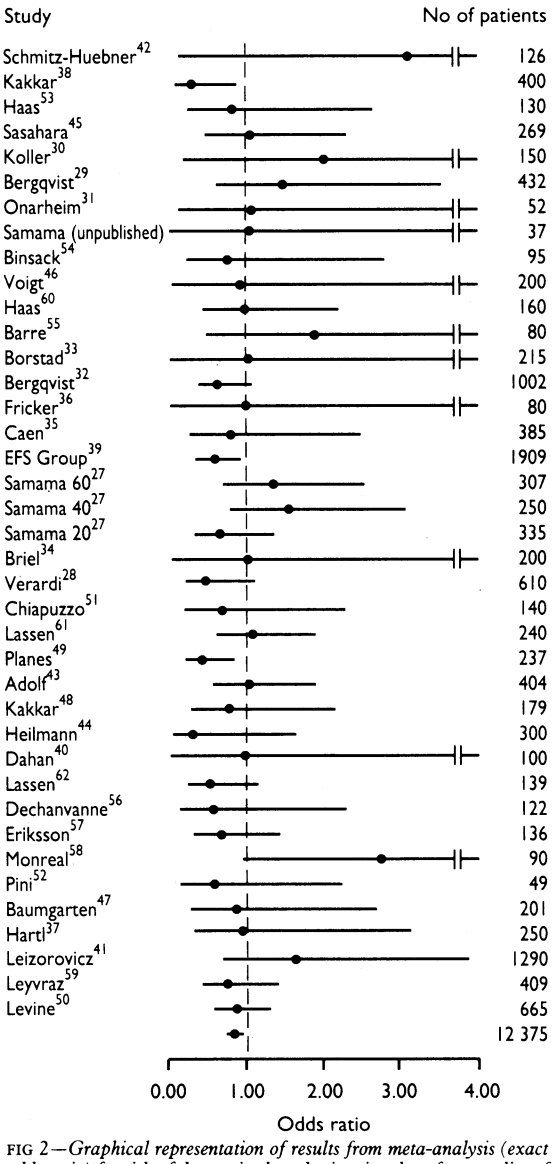

FIG 2—*Graphical representation of results from meta-analysis (exact odds ratio) for risk of deep vein thrombosis using data from studies of general and orthopaedic surgery. Vertical bars represent odds ratios; value of <1 indicates that low molecular weight heparin is better than the unfractionated heparin and >1 that unfractionated heparin is better than low molecular weight heparin. Horizontal lines represent 95% confidence intervals (if value of 1 is included results are not significant) and broken line indicates that upper confidence limit is >4. Common odds ratio=0·85 (0·74 to 0·97), p=0·02.*

CHRONOLOGICAL EVOLUTION OF RESULTS

The chronological evolution of the odds ratios for deep vein thrombosis (both general and orthopaedic surgery) was investigated. After the disappointing results from the first study in 1984 using high doses and few patients the results seemed promising in 1985, and then the cumulative result became less significant in 1986 and 1987. From 1988 onwards the cumulative result showed an improvement, which seems to have remained stable, with the 95% confidence interval becoming smaller (fig 3), the odds ratio decreases drastically from 1984 to 1985 and then remains relatively stable, at between 0·5 to 0·9. The number of patients included in the papers published in 1988 account for about half of the total number of patients and from this year onwards the odds ratio is apparently stable, at about 0·8.

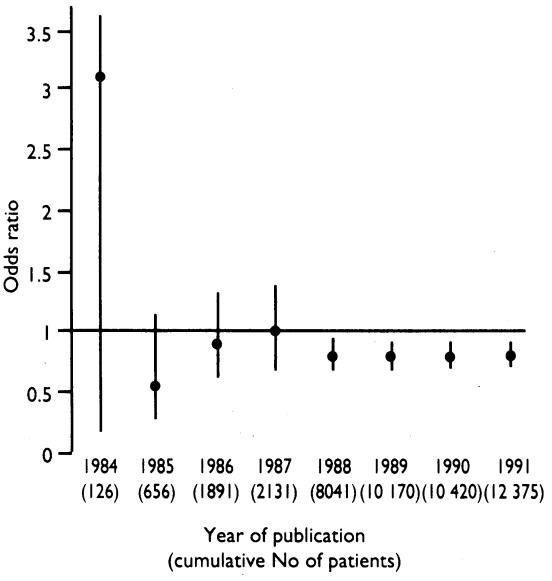

FIG 3—*Graphical representation of results from meta-analysis (exact odds ratio) for risk of deep vein thrombosis in patients undergoing general and orthopaedic surgery. Odds ratio (—●—) is cumulative. From 1988 it is stable, around 0·8, and almost half of all the patients are included in this year. 95% Confidence intervals (horizontal lines) are reduced over time.*

Discussion

The efficacy of low molecular weight heparins has been assessed in comparison with placebo and other prophylactic treatments, but in many cases the results have been ambiguous, often because of an inadequate sample size. If we assume that a clinically significant risk reduction would be a 30% difference in the incidence of deep vein thrombosis between the treatment and control groups for patients receiving general surgery, with a type I (α) error of 5% and a power ($1 - \beta$) of 95% in a two tailed test, we would need 9400 patients, given that the incidence of deep vein thrombosis is 5% with unfractionated heparin and 3·5% with low molecular weight heparin. The number of patients required if these incidences were 4% and 2·8%, respectively, would be 11 900. Thus no single study had a sample size sufficient to be able to detect a significant difference under this hypothesis.

Meta-analysis is a technique that allows the systematic, quantitative summary of data from individual studies, and it may supply the answer which individual trials cannot because of the increased statistical power afforded by the larger number of subjects. Even with the techniques used in meta-analysis, the power may remain too low so that no conclusions can be drawn, as was the case in previous meta-analyses. In our analysis there were insufficient data on the incidence of pulmonary embolism, so the analysis lacks power for this particular end point.

The efficacy of any meta-analysis can be influenced to a large extent by publication bias. This bias can arise when a study gives non-significant results, leading to reluctance by investigators and journal editors to submit and publish the results.[70-73] Many studies are published only in the form of an abstract, which means that the methods are difficult to judge and the results are often only intermediate or not very detailed, or both. This point is important to remember when the results of a meta-analysis are considered. Some manufacturers seem to be reluctant to disclose data that have not already been divulged. In our search, thanks to one pharmaceutical firm, we located only one, small, unpublished study; perhaps others exist, but we were unable to locate them.

COMPARISONS WITH PLACEBO, DEXTRAN, AND UNFRACTIONATED HEPARIN

We identified only four studies comparing low molecular weight heparin with dextran in patients undergoing orthopaedic surgery, whereas placebo controlled studies were found for both general and orthopaedic surgery. Our results confirm previous findings that low molecular weight heparins are superior to placebo for the prophylactic treatment of deep vein thrombosis in patients who have had surgery. The results for pulmonary embolism and total mortality are not as convincing, mainly owing to insufficient numbers of patients.

Dextran has been widely used as a prophylactic treatment in general and orthopaedic surgery in Scandinavian countries. It was significantly superior to placebo in preventing deep vein thrombosis, pulmonary embolism, and death in clinical trials in more than 5000 patients.[74] Dextran has also been compared with unfractionated heparin in a few studies, unfractionated heparin being more effective in patients undergoing general surgery and dextran in those undergoing orthopaedic surgery.[75] Our analysis suggests that low molecular weight heparin is more efficacious than dextran for the prophylactic treatment of deep vein thrombosis. We should be cautious, however, before extrapolating these results to pulmonary embolism and death because of the insufficient amount of data currently available.

We have shown that low molecular weight heparins, compared with unfractionated heparins, reduce the risk of deep vein thrombosis significantly in patients undergoing both general and orthopaedic surgery. This end point was measured using various techniques, but in many general surgery studies the technique used was the fibrinogen uptake test, which is not as accurate a diagnostic procedure as phlebography. The true positive rate for detecting thrombosis has been estimated as 99·6% and the false positive rate as about 9·7% among patients undergoing general surgery.[76] Although we used rates of phlebographically confirmed deep vein thrombosis in our analysis, when available, this close agreement between the methods suggests that the fibrinogen uptake test can give acceptably reliable estimates of the true postoperative rates of deep vein thrombosis. In the majority of the orthopaedic surgery studies phlebography was used for the confirmation of the diagnosis of deep vein thrombosis, which is important as fibrinogen uptake is less reliable in this indication.

DOSAGE

Although the adjusted dose regimen for unfractionated heparin may have a higher efficacy than a fixed dose regimen in orthopaedic surgery patients,[77 78] this technique is not widely used, probably because of its more onerous workload. This explains why we found only a few studies comparing adjusted dose heparin with low molecular weight heparin,[53 54 57] making it impossible to compare these two treatments.

Controversial problems remain about the possibility of a class effect and the lack of a standard for defining the concentrations and comparing the different preparations. The introduction of an international unit system—that is, antifactor Xa units—has reduced the second problem, but this unit system is not always quoted in publications, which can lead to difficulties when comparing results from different studies. The official reference for the determination of the concentration in terms of anti-Xa units, was not always used, especially in the earlier trials, even when the concentration is quoted in these units. The low molecular weight heparins also differ in terms of molecular weight distribution and the ratio of activities of anti-Xa and anti-IIa. This ratio is inversely proportional to the molecular weight and may be related to the antithrombotic activity of these products. Although the clinical relevance of these biochemical differences has not yet been established, it is perhaps incorrect to consider only the anti-factor Xa units when determining the prophylactic dose, but as the reports did not often

give other values, we have used anti-Xa units when possible. The range of the observed p values for heterogeneity (0·18-0·84) does not suggest that the different low molecular weight heparins have quantitatively different effects. However, caution should be used when considering all these products as equal because only direct comparison, in a randomised controlled trial, will enable this hypothesis to be substantiated. Therefore, physicians wishing to use a low molecular weight heparin in their practice should take into consideration the results from the individual study in the choice of the appropriate drug and dose.

The prevention of deep vein thrombosis is important in patients at risk as deep vein thrombosis is a risk factor for pulmonary embolism. Although the incidence of pulmonary embolism is low, an efficient prophylatic treatment is needed because pulmonary embolism is sometimes disabling or fatal. The diagnosis of fatal and non-fatal pulmonary embolism is difficult and so we combined both in one end point. In an overview comparing unfractionated heparin with placebo the reduced incidence of deep vein thrombosis in heparin treated patients was similar to the observed reduction in the incidence of pulmonary embolism when the results were combined but not in individual trials.[4] Therefore, the validity of deep vein thrombosis as a surrogate end point for pulmonary embolism has not yet been firmly established. We should consider the benefit to risk ratio because treatment with any type of heparin leads to increased risk of bleeding complications and, therefore, a patient's risk factors should be carefully examined before taking the decision to administer heparin.

The incidence of major bleeding might be reduced if the first injection is given a long time before or after the operation. In most of the studies identified for this analysis the initial injection was given two hours before surgery, although some had an initial injection at least 12 hours either before or after the operation. No conclusions about the effect of this on the incidence of bleeding could be drawn from the analysis performed with these available data because of the low power of the test, although a non-significant reduction was observed in trials with the first injection given 12 hours before surgery. A comparison of the incidence of bleeding in these different studies would be illegal, so it is not possible to say which is best, giving the first injection 12 or two hours before surgery or 12 hours after surgery; thus a large scale trial should be performed to answer this question.

A single daily dose of low molecular weight heparins certainly offers practical advantages to hospital staff and convenience for the patients. This is not sufficient because treatment is expensive, and therefore, we must also be sure that its efficacy is at least comparable, if not better, than that of existing treatments. Though an unequivocal answer has not been obtained in the individual studies, the results from our meta-analysis suggest that low molecular weight heparins are more efficacious than unfractionated heparins for the prophylactic treatment of deep vein thrombosis and pulmonary embolism.

CONCLUSIONS

Meta-analysis is an undeniably powerful tool, but care should be taken when assessing the results from this type of analysis. In terms of the efficacy for prophylactic treatment of deep vein thrombosis, our results, though indicating the superiority of low molecular weight heparins over unfractionated heparins, cannot be used as a substitute for a large scale clinical trial. This polemic shows the value of meta-analysis when the end point of interest is rare or difficult to measure. A large scale randomised trial to assess the efficacy of this treatment in the prophylactic treatment of venous thrombosis in general and orthopaedic surgery with pulmonary embolism as the main end point needs to be performed. This would require the inclusion of several thousand patients, and two such trials with an expected sample size of 7500 patients are underway[14] and may provide the data to confirm the prophylactic efficacy of heparin for this indication. In addition, a trial to investigate the benefits of low molecular weight heparin in preventing fatal pulmonary embolism and death from other causes is needed. This trial would be even larger, but is, none the less, feasible and well worth performing.

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Correction

The role of non-steroidal anti-inflammatory drugs in acute liver injury

An authors' error occurred in this paper by García Rodríguez *et al* (10 October, p 866). In table II there should be no reference to sulindac in line seven, which should read:

Indomethacin	1	100	1982	M 76	Yes	Hepatocellular§

This does not affect the information in other tables or in the text.