Haematologica 2000; 85:early release
original paper

Do the low molecular weight heparins improve the efficacy and safety in the treatment of deep venous thrombosis? A meta-analysis

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ABSTRACT

Background and Objectives. **We compared the efficacy and safety of low molecular weight heparins (LMWH) and unfractionated heparin (UFH) in the treatement of deep venous thrombosis (DVT). A comparison between two LMWH daily subcutaneous injections against a single injection was also performed.**

Design and Methods**. The study was performed by a meta-analysis. Clot improvement in venography, recurrency, total mortality and major haemorrhages were assessed in 4472 subcutaneous LMWH or UFH-treated DVT patients from 21 studies.**

Results. **An improvement in clot reduction (odds ratio 0.73, 95% confidence interval 0.59 to 0.90, *p* = 0.004), a decrease in total mortality (0.68, 0.50 to 0.91, *p* = 0.012) and a minor haemorrhage incidence (0.65, 0.43 to 0.98, *p* = 0.047) were observed in LMWH patients. There were no differences in recurrency (0.78, 0.59 to 1.04, *p* = 0.10). A single LMWH dose was superior than two in reducing the major bleeding (χ^2 = 4.99, *p* = 0.025); however, the two doses regimen was more effective in clot reduction (χ^2 = 8.56, *p* = 0.004).**

Interpretation and Conclusions. **LMWH is superior than UFH in terms of safety and efficacy. A single LMWH dose is a suitable therapeutical regimen, which could facilitate the outpatient treatment of venous thromboembolism.**

Key words: LMWH; UFH; Deep venous thrombosis; Meta-analysis

Deep vein thrombosis (DVT) is a common complication in patients suffering from a wide variety of processes such as malignancy, spinal injuries, advanced age, hypercoagulability syndromes as well as in patients subjected to major orthopaedic or general surgery[1-3] with an incidence as high as 50% in patient groups not under thromboprophylaxis treatment.[4] Although in many cases DVT resolves without sequelae, in some cases it can lead to valvar damage and chronic venous insufficiency in subsequent years and in rare cases to an immediate threat to life from pulmonary embolism (PE) due to displacement of the thrombus.[5] So, nowadays DVT and PE are considered as the expression of one and the same disease, termed venous thromboembolism (VTE).

Although anticoagulant therapy is the treatment of choice for most patients with VTE, the establishment of a treatment strategy is difficult because the optimum use of this treatment remains to be defined. In this setting, many regimes have been tested over the last decades including the use of oral anticoagulants, antithrombotic drugs, unfractionated heparin (UFH) and aspirin.

In recent years low molecular weight heparins (LMWH) have become available as alternatives to oral anticoagulants and unfractionated heparin for the treatment of VTE. LMWH are derived by controlled chemical or enzymatic depolymerization of standard UFH that yield chains with a mean molecular weight of about 5,000.[6] These heparin molecules with a lower molecular weight inhibit activated coagulation factor Xa more efficiently than they inhibit thrombin because the length of the LMWH does not allow binding to both thrombin and antithrombin III. LMWH have several advantages over UFH based on their high bioavailability and more consistent anticoagulant effect at therapeutic doses, thus enabling them to be administered in fixed doses as a twice or single daily injection without need for laboratory monitoring.[7,8] Furthermore, for an equivalent antithrombotic effect, LMWH are thought to be less likely to cause haemorrhage with a reduced risk of bleeding, especially in surgical patients during the perioperative period.[9]

Some randomised clinical trials have been reported which compare LMWH with UFH in the treatment of DVT showing that LMWH can significantly decrease the risk of recurrency and mortality with minor risk of hemorrhagic events.[10,11] However, most of the published works showed no statistically significant differences. Assuming an α risk of 0.05 and an expected incidence of events similar to the average of published trials, the number of patients needed in a single trial in order to achieve a statistical power of 80% would be approximately as follows: 2,350 patients for comparing the risk of clot impairment, 4,620 for total

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Table 1: Summary of individual trials design.

Study	Sample size (LMWH/UFH)	LMWH used	Route of administration LMWH	Route of administration UFH
Bratt et al, 1985[24]	25/29	Dalteparin	i.v. (sdd)	i.v.
Holm et al, 1986[25]	29/27	Dalteparin	s.c. (tdd)	s.c.
Faivre et al, 1988[26]	33/37	CY 222	s.c. (tdd)	s.c.
Notarbartolo et al, 1988[27]	60/30	OP 2123	s.c. (sdd)	s.c.
Zanghi et al, 1988[28]	40/40	OP 2123	s.c. (sdd)	s.c.
Albada et al, 1989[29]	96/98	Dalteparin	i.v. (sdd)	i.v.
Etude Mult. FranVaise, 1989[30]	33/33	Dalteparin	s.c. (tdd)	i.v.
Bratt et al, 1990[31]	60/60	Dalteparin	s.c. (tdd)	i.v.
Harenberg et al, 1990[32]	24/26	Certoparin	s.c. (tdd)	i.v.
Duroux, 1991[33]	85/81	Nadroparin	s.c. (tdd)	i.v.
Prandoni et al, 1992[34]	85/85	Nadroparin	s.c. (tdd)	i.v.
Lopaciuk et al, 1992[35]	74/72	Nadroparin	s.c. (tdd)	s.c.
Hull et al, 1992[11]	213/219	Logiparin	s.c. (sdd)	i.v.
Simonneau et al, 1993[10]	67/67	Enoxaparin	s.c. (tdd)	i.v.
Tedoldi et al, 1993[36]	20/20	OP 2123	s.c. (sdd)	s.c.
Lindmarker et al, 1994[37]	101/103	Dalteparin	s.c. (sdd)	i.v.
Luomanmaki et al, 1996[38]	110/116	Dalteparin	s.c. (sdd)	i.v.
Fiessinger et al, 1996[39]	120/133	Dalteparin	s.c. (sdd)	i.v.
Levine et al, 1996[40]	247/253	Enoxaparin	s.c. (tdd)	i.v.
Koopman et al, 1996[41]	202/198	Nadroparin	s.c. (tdd)	i.v.
Columbus Investigators, 1997[42]	510/511	Reviparin	s.c. (tdd)	i.v.

LMWH: Low molecular weight heparin; UFH: Unfractionated heparin; i.v.: intravenous; s.c.: subcutaneous; sdd: single dose/day; tdd: two doses/day.

mortality, 8,520 for major bleeding and 11,500 for recurrency. The magnitude of these figures has encouraged some researchers to perform meta-analysis studies in order to achieve definitive conclusions.[12-16] Unfortunately, these meta-analyses have not shown homogeneous results. This could partially be explained by the relatively small number of patients included in these studies (Table 1).

The present study was designed to assess the effectiveness and safety of UFH and LMWH in the treatment of VTE by means of a meta-analysis, taking into account the most recent studies, which had not been included previously in any compilatory study, thus enhancing its analytic power. Furthermore, the treatment of LMWH with two daily subcutaneous injections compared to a single injection with regard to immediate and long term efficacy and side effects was also analysed.

Design and Methods

Data collection

We performed a MEDLINE search of the literature between January 1985 and June 1999 with no restriction on the language of the paper using the following combined key words: low molecular weight heparin (LMWH) and thromboembolic disease; LMWH and deep vein thrombosis; LMWH and treatment; LMWH and clinical trial*; LMWH and meta-analysis; LMWH and review. A search in the Excerpta Medica, in abstracts books of meetings of the *International Society of Thrombosis and Hemostasis* and in the references lists of review and trials papers was also performed to avoid omission of papers that might not have been included in the MEDLINE database. We excluded nonrandomised trials, and we also excluded those which were duplicate reports of data previously published.

Table 2: Summary of individual trials results.

Study	Phlebography: Clot reduction LMWH E/Pts	Clot reduction UFH E/Pts	Clot extension LMWH E/Pts	Clot extension UFH E/Pts	Recurrent event LMWH E/Pts	Recurrent event UFH E/Pts	Total mortality LMWH E/Pts	Total mortality UFH E/Pts	Major bleeding LMWH E/Pts	Major bleeding UFH E/Pts
Bratt et al, 1985 (24)	16/25	14/29	0/25	3/29	0/25	0/29	0/25	0/29	2/13	0/14
Holm et al, 1986 (25)	10/25	12/25	1/25	2/25	1/29	0/27	0/29	0/27	0/27	0/28
Faivre et al, 1988 (26)	19/30	19/29	0/30	2/29	1/33	1/37	0/33	1/37	0/33	0/35
Notarbartolo et al, 1988 (27)	-	-	-	-	0/60	0/30	0/60	0/30	0/60	3/30
Zanghi et al, 1988 (28)	-	-	-	-	0/40	0/40	0/40	0/40	0/40	0/40
Albada et al, 1989 (29)	-	-	-	-	0/96	1/98	0/96	2/98	10/96	13/98
Etude Mult. FranVaise, 1989 (30)	-	-	1/33	2/33	0/33	0/33	0/33	0/33	0/33	0/33
Bratt et al, 1990 (31)	34/45	30/49	2/45	3/9	4/60	6/60	0/60	0/60	0/55	2/55
Harenberg et al, 1990 (32)	13/15	10/13	1/15	0/13	2/24	2/26	-	-	2/24	1/26
Duroux, 1991 (33)	54/77	44/71	5/77	5/71	1/85	2/81	3/78	3/73	2/85	4/81
Prandoni et al, 1992 (34)	50/83	36/85	5/83	14/85	6/85	12/85	5/85	9/85	1/85	3/85
Lopaciuk et al, 1992 (35)	45/68	32/68	10/68	12/68	0/74	3/72	0/74	1/72	0/74	1/72
Hull et al, 1992 (11)	-	-	-	-	6/213	15/219	10/213	21/219	1/213	11/219
Simonneau et al, 1993 (10)	35/60	18/57	1/60	5/57	1/67	7/67	3/67	2/67	0/67	0/67
Tedoldi et al, 1993 (36)	-	-	-	-	0/20	1/20	0/20	0/20	0/20	0/20
Lindmarker et al, 1994 (37)	55/91	56/89	5/91	7/89	5/101	3/103	2/101	3/103	0/101	0/103
Luomanmaki et al, 1996 (38)	47/92	61/98	11/92	7/98	5/110	2/116	-	-	0/110	1/116
Fiessinger et al, 1996 (39)	65/96	62/103	8/96	12/103	6/111	3/120	2/111	4/120	0/120	2/133
Levine et al, 1996 (40)	-	-	-	-	13/247	17/253	11/247	19/253	5/247	3/253
Koopman et al, 1996 (41)	-	-	-	-	14/202	17/198	4/202	7/198	1/202	4/198
Columbus Investigators, 1997 (42)	-	-	-	-	27/510	25/511	36/510	39/511	16/510	12/511
Total events/pts, (%)	443/707 (62.6)	394/716 (55.0)	50/740 (6.75)	74/749 (9.87)	93/2,225 (4.13)	117/2,225 (5.25)	76/2084 (3.64)	111/2075 (5.34)	40/2215 (1.80)	60/2217 (2.70)

LMWH: Low molecular weight heparin; UFH: Unfractionated heparin; E/pts: events/patients.

Information was extracted from studies to assess the following issues:

- proportion of patients with any degree of impairment in the venogram, if pre- and post-treatment evaluations (by phlebography) were done and the assessment was masked with respect to treatment assignment;
- number of patients in each group developing recurrent thromboembolic events (symptomatic recurrent DVT or PE) during the trial period, if reliable diagnosis criteria were used for recurrent thromboembolism, if active follow-up was done prospectively at each center, and if the assessment was masked to treatment assignment. The diagnosis of DVT was accepted if one of the following criteria was met:
  A) a new constant intraluminal filling defect not present on the last available venogram; or
  B) if the venogram was not diagnostic, either an ultrasound result that had been normal before the suspected episode.[17]
  A diagnosis of PE was considered valid if one of the following criteria was met:
  A) a segmental defect on the perfusion lung scan.
  B) positive pulmonary angiography or
  C) PE at autopsy;
- total mortality at the end of follow-up was collected from each report, if any monitoring system for active follow-up was prospectively performed by the researchers;
- the number of patients who presented major hemorrhages during the treatment was also included as an end-point to assess safety. Haemorrhages were considered major if they were fatal, or if any transfusion was needed or they led to the interruption of treatment. In addition all hemorrhagic episodes located inside the brain or into the peritoneum were also considered as major events. All other hemorrhages were considered as minor and were not included as end-points.

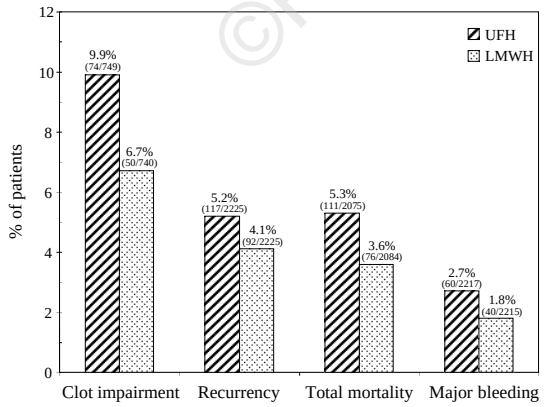

Figure 1: Crude overall incidence of major end-points assessed in the meta-analysis. Number of events / Total patient numbers given in parentheses for each end-point. LMWH: Low molecular weight heparin; UFH: Unfractionated heparin.

Statistical methods

The risks of an impairment in phlebography, developing recurrent thromboembolic events, death from any cause, and major haemorrhages in patients treated with LMWH and patients treated with UFH were compared by calculation of the odds ratio (OR) for each study. These ORs were pooled across studies using the Mantel-Haenszel method to estimate a common OR as an estimator of relative risk (RR). 95% confidence intervals (CI) were computed for the common RR using the Mantel-Haenszel method.[18,19] In addition, the analysis was repeated using a random effect model according to Der Simionian and Laird.[20] ORs were also calculated with the same methodology to compare the risk of an impairment in phlebography, developing recurrent thromboembolic events, major haemorrhages and death stratifying the studies in two groups: those which used two doses of LMWH and those which used a single dose; the comparison group was UFH for both strata. The Schlessemann chi squared was used to compare the ORs between both strata.[21]

We estimated also the number needed to treat using the incidence of events in the UFH group as the reference and applying the ORs provided by the meta-analyses.[22,23]

Results

Comparison between LMWH and UFH

A total of 21 randomised studies[10,11,24-42] comparing the efficacy of LMWH with that of UFH in a total of 4,472 patients were identified. In 15 trials the UFH was given intravenously (i.v.); subcutaneous (s.c.) injection was used in the remaining 6 studies. The patients in the LMWH groups received dalteparin in 8 trials [2 i.v., 3 s.c. at a single dose/day (sdd), 3 s.c. at two doses/day (tdd)], nadroparin in 4 trials (s.c., tdd), OP 2,123 in 3 trials (s.c., sdd), enoxaparin in 2 trials (s.c., tdd), CY 222 (s.c., tdd), certoparin (s.c., tdd), logiparin (s.c., sdd) and reviparin (s.c., tdd) in one trial. Each trial design and results are summarized in tables 1 and 2 respectively. In addition, pooled results of main end-points are given as unadjusted incidences and in terms of odds reduction as well.

Clot reduction in venography. In 13 studies (diagnosis confirmed by phlebography), the unadjusted overall improvement in venography was 55% (394 out of 716 patients) in the UFH group compared with 62.7% (443 out of 707 patients) in the LMWH group. An impairment was assessed in 9.9% of the UFH-treated patients compared with 6.7% in the LMWH group (Figure 1). The results from four of the studies[11, 33-35] showed a significant improvement in clot reduction in favour of LMWH and the results from the meta-analysis (fixed effects model) for this end-point showed that LMWH is significantly more efficient than UFH in terms of thrombus extension [27% reduction, OR 0.73; 95% CI, 0.59 to 0.90; p = 0.004 (Figure 2)]. The random effects model showed very similar results. The number needed to switch from UFH to LMWH in order to achieve one improvement in venography would be 13 patients (95% CI: 8-40)

Incidence of recurrent thromboembolism. The unadjusted overall incidence rates for recurrent thromboem-

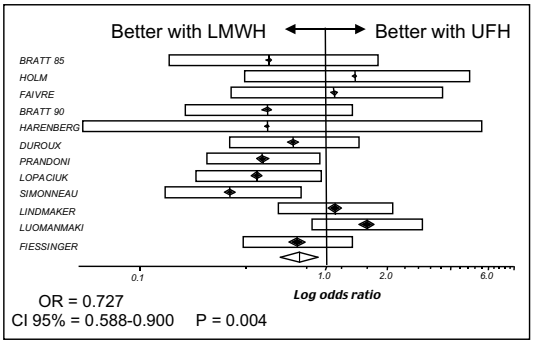

Figure 2: Results from meta-analysis (fixed effects model, Mantel-Haenszel method) for efficacy of treatment evaluated analyzing clot reduction in venography. Results for each trial are given; global results shown at bottom. Odds ratio <1 indicates that low molecular weight heparins performed better than unfractionated heparin, and >1 that unfractionated heparin performed better than low molecular weight heparins. Horizontal lines represent 95% confidence intervals. LMWH: Low molecular weight heparin; UFH: Unfractionated heparin; OR: Odds ratio; CI: Confidence interval.

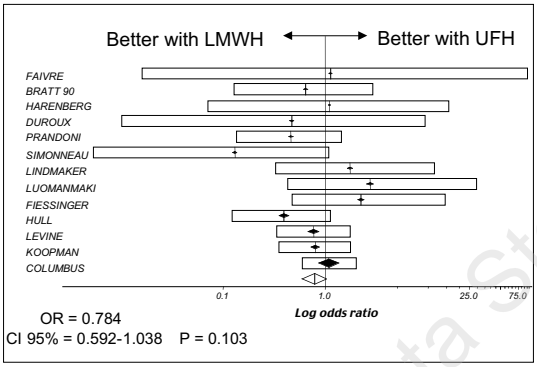

Figure 3: Results from meta-analysis (fixed effects model) for incidence of recurrent thromboembolic events. Results for each trial are given; global results shown at bottom. Odds ratio <1 indicates that low molecular weight heparins did better than unfractionated heparin, and >1 that unfractionated heparin did better than low molecular weight heparins. Horizontal lines represent 95% confidence intervals. LMWH: Low molecular weight heparin; UFH: Unfractionated heparin; OR: Odds ratio; CI: Confidence interval.

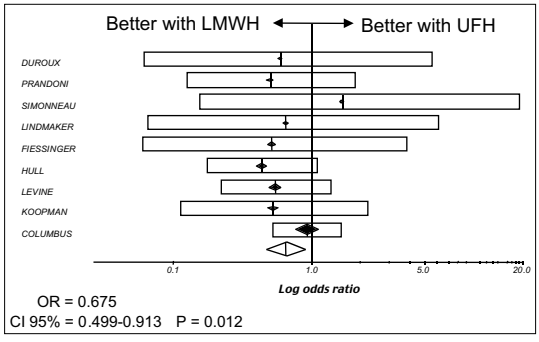

Figure 4: Results from meta-analysis (fixed effects model) for total mortality. Results for each trial are given; global results shown at bottom. Odds ratio <1 indicates that low molecular weight heparins did better than unfractionated heparin, and >1 that unfractionated heparin did better than low molecular weight heparins. Horizontal lines represent 95% confidence intervals. LMWH: Low molecular weight heparin; UFH: Unfractionated heparin; OR: Odds ratio; CI: Confidence interval.

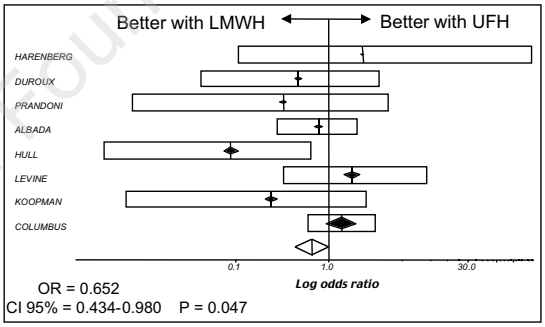

Figure 5: Results from meta-analysis (fixed effects model) for safety of treatments evaluated by analyzing the incidence of major haemorrhagic events. Result for each trial given; global results shown at bottom. Odds ratio <1 indicates that low molecular weight heparins did better than unfractionated heparin, and >1 that unfractionated heparin did better than low molecular weight heparins. Horizontal lines represent 95% confidence intervals. LMWH: Low molecular weight heparin; UFH: Unfractionated heparin; OR: Odds ratio; CI: Confidence interval.

bolic events were 5.2% (117 out of 2225 patients) in the UFH group, and 4.1% (92 out of 2225 patients) in the LMWH group (Figure 1). When taken separately, only one of the studies[11] showed statistically significant differences between both treatments. The results from the meta-analysis (Mantel-Haenszel method) showed a near to significant statistical association with a 22% reduction in the recurrence of thromboembolism in favour of the LMWH group [OR 0.78; 95% CI, 0.59 to 1.04; p = 0.103 (Figure 3)]. Results with the Der Simonian and Laird method were again very similar (OR = 0.814; 95% CI, 0.61 to 1.08).

Total mortality. The unadjusted overall total mortality was higher in the UFH patients (111 out of 2,075, 5.3%) than in the LMWH group (76 out of 2,084, 3.6%) (Figure 1). When taken separately, only one of the studies[10] showed statistically significant differences between both treatments. However, the results from the meta-analysis showed a significant 33% reduction in the total mortality rate in favour of the LMWH group [OR 0.68; 95% CI, 0.50 to 0.91; p = 0.012 (Figure 4)].

Safety and hemorrhagic events. The unadjusted overall incidence of major bleeding was also higher in the patients receiving UFH (60 out of 2,217, 2.7%) than

in the patients assigned to LMWH (40 out of 2,215, 1.8%) (Figure 1). Only one of the individual studies[10] showed significant differences between both treatments. However, the fixed-effects meta-analysis showed again that the risk of major haemorrhage decreased significantly in the LMWH group [35% reduction, OR 0.65; 95% CI, 0.43 to 0.98; $p = 0.047$ (Figure 5)]. This was also true for the random-effects model. The number needed to switch from UFH to LMWH in order to prevent one episode of severe bleeding would be 106 patients (95% CI: 55-1,294)

Comparison between LMWH administered at two doses and LMWH administered at a single dose

Table 3 summarizes the results obtained when we calculated the ORs comparing LMWH and UFH separately in two strata depending on whether one or two doses of LMWH were used. The Schlessemann chi squared for comparisons between ORs was also computed to establish the comparison between both patterns of administering LMWH and UFH. The two doses per day route exhibited a lower OR when it was compared with UFH and therefore it seemed to be more effective than the single dose in terms of thrombus extension ($\chi^2 = 8.56$, $p = 0.004$). In fact, LMWH at a single dose was not significantly more effective than UFH in reducing the clot size as the 95% CI for the OR ranged from 0.77 to 1.51 whereas it ranged from 0.42 to 0.74 in favour of LMWH at two doses when this pattern was compared with UFH. However, the administration of LMWH at a single dose was more effective than the two doses route in reducing the risk of major bleeding ($\chi^2 = 4.99$, $p = 0.025$). In this case the LMWH at two doses per day was not able to reduce the risk of major hemorrhages with respect to UFH (95% CI, 0.47 to 1.32) whereas administered at a single dose, LMWH was clearly safer than UFH (95% CI, 0.01 to 0.54). When analysing the recurrency of thromboembolic events, there were no significant differences between both patterns of administration of LMWH as well as between both of them taken separately with respect to UFH, although LMWH given at two doses was almost significantly more effective than UFH (95% CI, 0.54 to 1.02). Finally, there were no differences between both ways of LMWH administration in terms of total mortality. However, whereas LMWH at a single dose was significantly better than UFH in terms of total mortality (95% CI, 0.26 to 0.96), LMWH at two doses, although superior than UFH, was not better enough to reach statistical significance (95% CI, 0.53 to 1.04).

Table 3. Separate comparison between LMWH and UFH depending on the number of administered doses of LMWH.

	LMWH vs UFH			
	Two doses [O.R. (95% CI)]	*Single dose [O.R. (95% CI)]*	*χ^2**	*p*
Clot reduction	0.56 (0.42-0.74)	1.08 (0.77-1.51)	8.56	0.004
Recurrency	0.74 (0.54-1.02)	1.00 (0.55-1.80)	0.74	0.390
Total mortality	0.74 (0.53-1.04)	0.50 (0.26-0.96)	1.08	0.300
Major bleeding	0.79 (0.47-1.32)	0.07 (0.01-0.54)	4.99	0.025

**Schlesseman chi-squared for the comparison between ORs. LMWH: Low molecular weight heparin; UFH: Unfractionated heparin; OR: Odds ratio; CI: Confidence interval.*

Discussion

Heparin has been the gold standard for the treatment and prophylaxis of venous thrombosis for the past fifty years.[43,44] During the eighties the LMWH underwent extensive evaluation in clinical trials, mainly in those evaluating the prevention of VTE in high-risk patients.[7,45-49] The high effectiveness of LMWH when compared with UFH in the prevention of venous thrombosis in patients undergoing major surgery, in patients with spinal injury, and in patients with stroke shown in these randomised studies led physicians to modify the thromboprophylactic regimen in these patients. In the last decade studies on LMWH have focused on the comparison between these agents and UFH in the treatment of established VTE. There is currently accumulating evidence that these new anticoagulants are also safe and effective in the treatment of acute DVT.[7,44,48,50,51]

In this setting, we have searched and reviewed all randomised trials that compared therapy with UFH versus a LMWH in patients suffering from VTE diagnosed by clinical examination or other objective and valid diagnostic tests. Finally, a total of 4,472 patients were analyzed, thus including the highest number of patients reported so far which substantially increases the statistical power of the comparisons with respect to the previous metaanalysis.

The results of this meta-analysis confirm previous findings and indicate that LMWH preparations seem to be more effective and safer than UFH for the treatment of DVT.[12-16] Some discordances between meta-analyses and subsequent large-scale randomized trials have been used to highlight the caution that must be kept in mind when interpreting a meta-analysis.[52,53] These caveats are always needed, also in our case. Nevertheless, meta-analyses may have substantial advantages, because they can give the best available answer in each moment, can be useful to estimate sample size for a definitive trial and may provide the most reliable treatment recommendation in the situation of conflicting results from some of the trials or in the absence of definitive trials.[54]

Although only a few of the analysed individual studies showed a statistically significant improvement in clot reduction in favour of LMWH when compared with UFH,[11,33-35] our meta-analysis shows that treatment with LMWH can be more effective in reducing thrombus size. Because thrombus extension may be related with morbi-mortality in those patients, one of the short-term objectives for the treatment of VTE is to prevent the extension of thrombus and thus to avoid its sequealae, mainly post-phlebitic syndrome and thrombus recurrence. We can also speculate about the relationship between thrombus extension and an eventually increased embolic risk as Pollak[55] previously suggested.

When efficacy of LMWH was assessed by comparing the appearance of recurrent VTE we could not appreciate statistically significant differences between

treatment with LMWH and UFH. Although an approximately 50% reduction in the relative risk of recurrent venous thrombosis as compared with UFH has been reported in the meta-analysis of early trials of LMWH in the treatment of DVT,[12,14,15] our findings are inconsistent with a reduction of this magnitude and more similar to results of other posterior studies.[13,16] However, the difference seen for this end-point was also in favour of the LMWH in our study. Possibly in the future new and more potent meta-analysis (including new comparative works and thus a higher number of patients) will reach a statistically significant difference in favour of LMWH.

When taken separately, only the study of Hull *et al.*[10] showed statistically significant differences in mortality between both treatments. However, the significant reduction in mortality in the LMWH group shown in our study is consistent with the results of similar meta-analysis reported previously.[14,15] Although mortality might be a pertinent end-point for evaluating the efficacy of an antithrombotic drug, death in patients with VTE usually occurs after the initial treatment period. Moreover, very few deaths of those reported in the studies analyzed are due to fatal PE, which supports the hypothesis proposed by Douketis *et al*.[56] that fatal PE is a rare event in patients who have correctly followed its anticoagulant treatment. So, mortality within the first months seems to be related with underlying diseases. In this setting, although not adding new data to this issue, we agree with other authors suggesting that malignant disease may explain many of the deaths in the studies, as cancer is an important risk factor for VTE and many patients in the trials analysed had an oncologic disease.[10,34] The cause of the reduced mortality in cancer patients treated with LMWH is therefore a finding both intriguing and difficult to explain. We can hypothesize both with the antigrowth tumoral factor activity or with the suppression of the angiogenesis that can be induced more effectively by LMWH than by UFH.[57,58] Nevertheless, further confirmation in prospective randomised trials is required.

Severe bleeding is an important concern when studying the efficacy and safety of an anticoagulant therapy. Although only one study[10] showed a significant difference in the rates of major bleeding between treatment groups for all the studies analysed, when pooled together by means of the meta-analysis, the use of LMWH achieved a statistically significant lower incidence of major bleeding. It is important to note that this reduction in the rate of major haemorrhage when the treatment was performed with LMWH was not at the cost of decreasing the efficacy of the anticoagulation regimen.

Recent studies have demonstrated the possibility and the advantages of outpatient administration of LMWH.[40,41,59,60] However, little is known about the results of the comparison between the patients given LMWH at two doses or at a single dose. With regard to this point, although LMWH given at two doses was better in decreasing phlebographic changes, treatment at single dose was equally effective in terms of recurrence and total mortality, and achieving a statistically significant reduction in major haemorrhage. Thus, our results further substantiate the concept that the effects of a single LMWH dose could be as efficient as and safer than the two-doses regimen, which would facilitate the outpatient treatment of VTE proposed by other authors.[40,41]

Therefore, we conclude that LMWH is superior in terms of safety and efficacy when compared with UFH in unselected patients with DVT. Moreover, LMWH regimes have several practical advantages. They are more comfortable for patients, less time consuming for nurses and produce less work for laboratories. In addition, the fact that the single LMWH dose is a suitable therapeutical regimen would facilitate the outpatient treatment of VTE.

Potential implications for clinical practice

- The results of this meta-analysis indicate that LMWH preparations seem to be more effective and safer than UFH for the treatment of DVT. Our results further substantiae the concept that the effects of a single dose of LMWH could be as efficient and safer than the two-doses regimen, which would facilitate the outpatient treatment of venous thromboembolism.

Contributions and Acknowledgments

ER was the principal clinician involved and responsible for the study design and collection of the data. MAGM performed the statistical analysis. RM and CP contributed to the analysis of the data, and wrote the manuscript. All authors approved the final version of this manuscript.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

Manuscript received May 3, 2000;accepted June 20, 2000.

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