Do the low molecular weight heparins improve efficacy and safety of 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 treatment of deep venous thrombosis (DVT). A comparison between two daily subcutaneous injections of LMWH 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 hemorrhages were assessed in 4,472 patients with DVT from 21 studies treated with subcutaneous LMWH or UFH.

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 lower incidence of hemorrhage (0.65, 0.43 to 0.98, $p = 0.047$) were observed in LMWH treated patients. There were no differences in recurrences (0.78, 0.59 to 1.04, $p = 0.10$). A single dose of LMWH was better than two in reducing major bleeding ($\chi^2 = 4.99, p = 0.025$); however, the two dose regimen was more effective in clot reduction ($\chi^2 = 8.56, p = 0.004$).

Interpretation and Conclusions. LMWH is superior to UFH in terms of safety and efficacy. A single daily dose of LMWH dose is a suitable therapeutic regimen and 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, and hypercoagulability syndromes as well as in patients subjected to major orthopedic or general surgery with an incidence as high as 50% in patient groups not under thromboprophylaxis treatment. Although in many cases DVT resolves without sequelae, in some cases it can lead to valvular 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. 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. 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 the need for laboratory monitoring. Furthermore, for an equivalent antithrombotic effect, LMWH are thought to be less likely to cause hemorrhage with a reduced risk of bleeding, especially in surgical patients during the perioperative period.
LMWH: low molecular weight heparin; UFH: unfractionated heparin; E/pts: events/patients.
The number of patients who presented major hem-
orrhages during the treatment was also included as
an end-point to assess safety. Hemorrhages were
considered major if they were fatal, or if any trans-
mission was needed or they led to the interruption
of treatment. In addition all bleeding inside the
brain or into the peritoneum was also considered
as a major event. All other hemorrhages were con-
sidered as minor and were not included as end-
points.

Statistical methods
The risks of an impairment in phlebography, suf-
fering recurrent thromboembolic events, death from
any cause, and major hemorrhages in patients treat-
ed with LMWH and patients treated with UFH were
calculated by comparison 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).
Then 95% confidence intervals (CI) were computed
for the common RR using the Mantel-Haenszel
method.\[15,19\] In addition, the analysis was repeated
using a random effect model according to Der
Siminian 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 hemorrhages and
death stratifying the studies into 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 test
was used to compare the ORs between both strata.\[21\]
We also estimated the number of patients needed
to be treated using the incidence of events in the UFH
group as the reference and applying the ORs provid-
ed by the meta-analyses.\[22,23\]

Results
Comparison between LMWH and UFH
Overall 21 randomized 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)l], nadroparin in 4 trials (s.c., tdd),
OP 2,123 in 3 trials (s.c., sdd), enoxaparin in 2 trials
(s.c., sdd), CY 222 (s.c., tdd), certoparin (s.c., tdd),
logiparin (s.c., sdd) and reparation (s.c., tdd) in one tri-
al. Each trial's 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 impair-
ment 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\[11,33,35,39\] showed a
significant improvement in clot reduction in favor 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
reducing thrombus extension [27% reduction, OR

![Figure 1. Crude overall incidence of major end-points assessed in the meta-analysis.](image)

<table>
<thead>
<tr>
<th>End-point</th>
<th>LMWH (%)</th>
<th>UFH (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clot impairment</td>
<td>9.9%</td>
<td>6.7%</td>
</tr>
<tr>
<td>Recurrence</td>
<td>4.1%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Total mortality</td>
<td>5.1%</td>
<td>6.7%</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>2.7%</td>
<td>2.7%</td>
</tr>
</tbody>
</table>
The random effects model showed very similar results. The number of patients needed to switch from UFH to LMWH in order to achieve improvement in one venography would be 13 (95% CI: 8-40).

Incidence of recurrent thromboembolism. The unadjusted overall incidence rates for recurrent thromboembolic events were 5.2% (117 out of 2,225 patients) in the UFH group, and 4.1% (92 out of 2,225 patients) in the LMWH group (Figure 1). When taken separately, only one of the studies11 showed a statistically significant difference 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 favor 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 studies20 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 favor 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 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 showed significant differences between both treatments. However, the fixed-effects meta-analysis again showed that the risk of major hemorrhage 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 of patients needed to switch from UFH to LMWH in order to prevent one episode of severe bleeding would be 106 (95% CI: 55-1,294).

Comparison between LMWH administered as two doses and LMWH administered in 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 Schlesseman chi-squared test 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 compared with UFH and therefore seemed to be more effective than the single dose in terms of preventing thrombus extension ($\chi^2 = 8.56$, p = 0.004). In fact, LMWH in 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 favor of LMWH in two doses when this pattern was compared with UFH. However, the administration of LMWH in a single dose was more effective than the two dose regime in reducing the risk of major bleeding ($\chi^2 = 4.99$, p = 0.025). In this case two doses of LMWH 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 as a single dose, LMWH was clearly safer than UFH (95% CI, 0.01 to 0.54). When analyzing the recurrence of thromboembolic events, there were no significant differences between both patterns of administration of LMWH or between either of them taken separately with respect to UFH, although LMWH given as two doses was almost significantly more effective than UFH (95% CI, 0.54 to 1.02). Finally, there were no differences between the two ways of administering LMWH in terms of total mortality. However, whereas a single dose of LMWH was significantly better than UFH in terms of total mortality (95% CI, 0.26 to 0.96), LMWH in two doses, although still better than UFH, was not so to a degree to reach statistical significance (95% CI, 0.53 to 1.04).

Discussion

Heparin has been the gold standard for the treatment and prophylaxis of venous thrombosis for the past fifty years. 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 randomized 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.

In this setting, we searched for and reviewed all randomized 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 previous meta-analyses.

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.

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. Due to the high effectiveness of LMWH in reducing the risk of major bleeding and the acceptable safety profile, the use of LMWH in the treatment of VTE is recommended as the first-choice anticoagulant. However, the choice of the appropriate dosing regimen depends on several factors, including the type of VTE and the duration of treatment.
drome and thrombus recurrence. We can also speculate about the relationship between thrombus extension and an increased embolic risk as Pollak previously suggested.

When efficacy of LMWH was assessed by comparing the appearance of recurrent VTE we were unable to find statistically significant differences between treatment with LMWH and UFH. Although an approximately 50% reduction in the relative risk of recurrent venous thrombosis has been reported in the meta-analysis of early trials of LMWH as compared with UFH in the treatment of DVT, our findings are inconsistent with a reduction of this magnitude and more similar to results of other previous studies. However, the difference seen for this end-point was also in favor of the LMWH in our study. Possibly in the future new and more potent meta-analyses (including new comparative works and thus a higher number of patients) will reach a statistically significant difference in favor of LMWH.

When taken separately, only the study by Hull et al. showed a statistically significant difference in mortality between the two treatments. However, the significant reduction in mortality in the LMWH group shown in our study is consistent with the results of a similar meta-analysis reported previously. 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. that fatal PE is a rare event in patients who have correctly followed anticoagulant treatment. So, mortality within the first months seems to be related to underlying diseases. In this setting, although not adding new data to this issue, we agree with other authors who suggest 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 analyzed had an oncologic disease. The cause of the reduced mortality in cancer patients treated with LMWH is therefore a both intriguing and difficult finding to explain. We can hypothesize that anti-tumor growth factor activity or suppression of angiogenesis could be induced more effectively by LMWH than by UFH. Nevertheless, further confirmation in prospective randomized trials is required.

Severe bleeding is an important concern when studying the efficacy and safety of an anticoagulant therapy. Although, of all the studies analyzed, only one study showed a significant difference in the rates of major bleeding between treatment groups, when pooled together by means of the meta-analysis, the studies showed that the use of LMWH produced a statistically significant lower incidence of major bleeding. It is important to note that this reduction in the rate of major hemorrhage when the treatment was 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. However, little is known about the results of the comparison between the patients given LMWH in two doses or as a single dose. With regard to this point, although LMWH given as two doses was better in decreasing phlebographic changes, treatment as a single dose was equally effective in terms of preventing recurrence and total mortality, and achieving a statistically significant reduction in major hemorrhage. Thus, our results further substantiate the concept that the effects of a single dose of LMWH could be as efficient and safer than the two-dose regimen, which would facilitate the outpatient treatment of VTE proposed by other authors.

We, therefore, 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 dose of LMWH is a suitable therapeutic 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 substantiate the concept that the effects of a single dose of LMWH could be as efficient and safer than the two-dose regimen, which would facilitate the outpatient treatment of venous thromboembolism.

References


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