Enoxaparin in the Treatment of Deep Vein Thrombosis With or Without Pulmonary Embolism*  
An Individual Patient Data Meta-analysis  

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Study objectives: Low-molecular-weight heparins have been compared with unfractionated heparin (UFH) for treatment of deep vein thrombosis (DVT). However, a comparison of their efficacy in the presence or absence of pulmonary embolism (PE) has not been studied. We estimated the efficacy and safety of enoxaparin vs UFH in patients with proximal DVT with/without symptomatic PE using a meta-analysis of individual data from randomized controlled trials.

Design and setting: Randomized controlled trials were identified from MEDLINE, EMBASE, abstracts from international meetings on venous thromboembolism (VTE), previous meta-analyses, and trial data provided by the sponsor.

Participants: For inclusion, randomized controlled trials had to be properly randomized; include patients with objectively diagnosed DVT; compare enoxaparin twice daily with UFH; use objective methods to assess recurrent symptomatic VTE, major bleeding, and death at 3 months; and include blind evaluation of clinical events.

Measurements: A meta-analysis was performed using the logarithm of the relative risk (RR) method. Enoxaparin in DVT treatment with/without symptomatic PE was considered noninferior to UFH for preventing VTE at 3 months if the upper limit of the 95% confidence interval (CI) of the RR (enoxaparin/UFH) was lower than a prespecified noninferiority margin (1.61). No increase in major bleeding or mortality should be observed.

Results: The meta-analysis included individual data from three randomized controlled trials (749 patients and 754 patients in the enoxaparin and UFH groups, respectively). The observed RR (enoxaparin/UFH) of VTE was 0.81 (95% CI, 0.52 to 1.26) for the intention-to-treat population (RR, 0.70; 95% CI, 0.43 to 1.13; for per-protocol analysis). Results did not differ for patients with clinical PE (235 patients; RR, 0.84) and without clinical PE (1,268 patients; RR, 0.71), with a nonsignificant heterogeneity test between groups (p = 0.76). A trend in favor of enoxaparin was observed for reduced mortality and major bleeding.

Conclusions: The efficacy and safety of enoxaparin vs UFH for DVT treatment is not modified by the presence of symptomatic PE.

Key words: deep vein thrombosis; enoxaparin; low-molecular-weight heparin; meta-analysis; noninferiority; pulmonary embolism; unfractionated heparin

Abbreviations: CI = confidence interval; DVT = deep vein thrombosis; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; PREPIC = Prévention du Risque d’Embolie Pulmonaire par Interruption Cave; RR = relative risk; UFH = unfractionated heparin; VTE = venous thromboembolism

Venous thromboembolism (VTE) is a frequent and serious disease1 that encompasses both deep vein thrombosis (DVT) and pulmonary embolism (PE). Unfractionated heparin (UFH) has proved to be effective in the initial treatment of VTE, and the efficacy and safety of low-molecular-weight heparins (LMWHs) for the initial treatment of VTE is well established. Indeed, several meta-analyses2–9 of studies in patients with VTE and one meta-analysis10 in patients with nonmassive PE (including PE trials, PE strata, and PE subgroups of DVT trials) have shown that LMWH treatment is at least as effective and safe for initial treatment as UFH. Finally, LMWHs tend to be prescribed more than UFH11 because they are more convenient to use12 and are feasible in outpatients, thus reducing costs.11,13–20 As noted by the experts of the 2004 American College of Chest Physicians consensus conference,11 recommendations about the initiation of UFH or LMWH for nonmassive PE treatment and DVT are largely based
on the findings in patients with DVT. This is assumed to be appropriate, since DVT and PE are considered to be manifestation of a single clinical entity, often present together and share some risk factors. However, as some products are registered only for patients presenting with DVT, some physicians prefer to systematically check for the absence of PE before treating patients presenting with DVT.

Previous meta-analyses have not been able to address whether the efficacy and safety of LMWH compared to UFH in the treatment of DVT are modified by the presence of PE because they were based on summarized published data. Meta-analyses based on data from individual patients have several advantages over those based on published data. Particularly, by providing greater flexibility in analysis, they allow assessment of the homogeneity of the effects of treatments between patient subgroups. However, a difficulty encountered with these meta-analyses is obtaining exhaustive data when assessing a therapeutic class composed of different preparations from different pharmaceutical companies. To ensure an exhaustive meta-analysis, we focused on enoxaparin, as we had access to individual patient data from all randomized trials comparing enoxaparin with UFH. Furthermore, the number of patients included in these trials afforded important statistical power. Enoxaparin is one of the most prescribed LMWHs worldwide, and it is currently used as the reference treatment to assess new anticoagulants in the treatment of DVT.

The purpose of this individual patient data meta-analysis of randomized trials comparing enoxaparin with UFH was to assess the noninferiority of enoxaparin in the treatment of DVT with or without associated symptomatic PE. This approach enabled assessment of whether the effect of enoxaparin compared with UFH is modified by the presence of symptomatic PE. Some risk factors, however, as some products are registered only for patients presenting with DVT, some physicians prefer to systematically check for the absence of PE before treating patients presenting with DVT.

Methods and Materials

Identification of Randomized Controlled Trials

We attempted to identify all published and unpublished randomized controlled trials that compared enoxaparin with UFH for the treatment of DVT with or without associated symptomatic PE. We searched MEDLINE and EMBASE electronic databases from January 1980 to January 2004 using the following groups of key words: “deep-vein thrombosis” or “thromboembolism” or “pulmonary embolism,” and “randomized” or “randomised” or “controlled trial” or “meta-analysis,” and “UFH” or “LMWH” or “enoxaparin” or “Lovenox” or “Clexane.” We reviewed abstracts from international meetings on VTE. Furthermore, we identified the enoxaparin trials included in the last meta-analyses that compared the efficacy and safety of LMWH with UFH in the treatment of DVT. Finally, the sponsor provided us with information regarding the existence of all such studies.

Selection of Randomized Controlled Trials

Two investigators independently assessed trials for possible inclusion, and a third investigator resolved any disagreements. To be included, trials had to be properly randomized (proper generation of the treatment allocation sequence and proper concealment of the allocation sequence); include patients with objectively diagnosed DVT with or without associated symptomatic PE; compare enoxaparin with UFH; and use objective methods to confirm the diagnosis of the following clinical outcomes: recurrent symptomatic VTE, major bleedings, and death at 3 months. In each trial, clinical events had to be assessed by an independent, blinded, central adjudication committee. Furthermore, individual patient data had to be available. Only patients allocated to enoxaparin, 1 mg/kg bid, were included in this meta-analysis. All other regimens were considered in a sensitivity analysis.

Clinical Events

Clinical events considered of interest for the analysis of efficacy were documented symptomatic VTE recurrences (either DVT or PE) up to 3 months. The definition of events was very similar between trials: DVT was confirmed by ultrasonography and/or venography; PE was confirmed by high-probability lung scan, pulmonary angiography, or autopsy. For analysis of safety, major bleeding was assessed at 10 days and 3 months. Bleeding events were considered to be major when they were clinically overt and associated with a decrease in hemoglobin level of at least 20 g/L or with transfusion of at least 2 U of packed RBCs. Intracranial and retroperitoneal bleeding, and bleeding that required surgical intervention were also considered major. All other bleeding events were considered minor. Finally, we analyzed data on death at 3 months.

Database Composition

After the selection of trials, individual patient data were supplied for analysis by the sponsor or by contacting the main investigator. Then, the database was built up independently of the sponsor. All data were pooled in a common file with information on baseline patient characteristics and occurrence of major clinical events. All data were thoroughly checked for consistency, plausibility, and integrity of randomization and follow-up. All variables were standardized in terms of units, formats, and labels. For this analysis, 3-month clinical events...
were included if they occurred within 92 days of patient enrollment. Therefore, results could differ from those reported in the publications describing each trial because the latter may have considered events to be at 3 months, whereas some may have occurred a few days beyond 92 days after enrollment. Furthermore, because we also standardized definitions of clinical events, the count of clinical events could differ from those reported in publications describing each trial. However, outcome events that were not validated by the independent, blinded, central adjudication committees in each trial were not included in this analysis. Therefore, the meta-analysis presents a high degree of adherence to the specifications in the individual study protocols. Finally, a statistician verified the final database entries.

Statistical Analysis

Individual patient data from each trial were summarized in two-by-two tables for each end point. Meta-analyses were then performed using appropriate software (EasyMA2000, University of Lyon; http://www.spc.univ-lyon1.fr/easyma.dos).32 As a first descriptive approach, adjusted clinical event rates and the associated 95% confidence interval (CI) were estimated by combining the data of each trial weighted by the inverse of the variance. Then a meta-analysis was performed using the logarithm of the relative risk (RR) and Mantel-Haenszel methods.33,34 The results obtained were similar; therefore, only those from the logarithm of the RR method are presented. Heterogeneity between studies was tested with the Cochran Q test, and a random effect model was planned in the event of unexplained heterogeneity between trials.34

Concerning the efficacy criteria (VTE recurrence), the objective was to demonstrate noninferiority, i.e., that the 95% CI of RR (enoxaparin/UFH) did not contain the a priori noninferiority margin. This margin was prespecified when writing the protocol of the meta-analysis, i.e., before pooling the data. The data used to establish this margin were taken from the only available trial assessing UFH vs no treatment or inadequate treatment in the treatment of VTE.35 In this trial, the incidence of VTE at 6 months was 20.0% for placebo and 6.7% for UFH, giving an RR (UFH/placebo) of 0.33 (95% CI, 0.11 to 0.97). The 95% CI was too wide because of the small number of patients (n = 120) included in this trial; therefore, the noninferiority limit was calculated with the average efficacy of UFH relative to placebo that was the observed 67% relative reduction. On the basis of general principles from regulatory guidelines36,37 and previous noninferiority studies38,39,40 comparing LMWH with UFH, we considered clinically acceptable to preserve 70% of the effect size for UFH relative to placebo39, 67% × 0.70 = 47% relative reduction (RR [enoxaparin/placebo] = 0.53). Then, the limit of noninferiority of RR (enoxaparin/UFH) must be equal to RR (enoxaparin/placebo)/RR (UFH/placebo), which is 0.53/0.33 or 1.61. Noninferiority of enoxaparin relative to UFH would be established if the upper limit of the 95% CI of the RR (enoxaparin/UFH) is < 1.61. In addition to the noninferiority analysis, an imputed placebo analysis was used to indirectly validate a treatment superior to the placebo by determining log RR (enoxaparin/placebo) = log RR (enoxaparin/UFH) + log RR (UFH/placebo).40–43

Meta-analyses were performed both on the intention-to-treat population (all randomized patients) and per-protocol population to reinforce the results, as recommended for such a noninferiority approach.44 The per-protocol analysis excluded patients without a proven DVT, patients who were randomized twice, patients who had received heparin for > 48 h before randomization, patients who had received heparin for < 5 days, and patients who had not received the allocated heparin treatment.

The impact of an initial symptomatic PE at entry on the efficacy and safety of enoxaparin compared with UFH was assessed in a subgroup analysis. To verify that the effect of enoxaparin vs UFH was not modified in the absence or presence of symptomatic PE, heterogeneity Cochran Q tests between subgroups were performed.

Sensitivity analyses were also performed to further establish the robustness of our results. First, we examined the impact of an initial PE, whether asymptomatic or symptomatic. Then, we examined the effect of excluding patients who were also randomly allocated to filter placement. Finally, we examined the effect of including another regimen of enoxaparin: 1.5 mg/kg qd. For safety criteria (major bleedings and deaths), results were considered as statistically significant when the upper and lower limits of the 95% CI of the RR were both > 1 or < 1.

Results

Descriptive Results

A total of five studies13,23,45–47 comparing enoxaparin with UFH for the treatment of DVT were identified. Of these, one trial was excluded because clinical events at 3 months were not reviewed blindly by an independent committee.46 Another study was excluded because included patients presented with PE, with or without associated DVT, rather than DVT with or without associated PE, there was no proper generation of the allocation sequence (alternate odd and even numbers) for randomization and clinical events were not reviewed blindly by an independent committee.47 Overall, three studies were selected, including a total of 1,503 patients (Table 1).13,23,45

Baseline characteristics are given in Table 2 for all trials and for the total meta-analysis population. Mean age ± SD was 63 ± 16 years. The initial DVT was mainly proximal, except in the study by Merli et al,45 in which DVT was distal in 19% of patients. All patients included in the study by Levine et al13

<table>
<thead>
<tr>
<th>Table 1—Study Design of Eligible Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trials/Year</td>
</tr>
<tr>
<td>-------------</td>
</tr>
<tr>
<td>Levine et al13/1996</td>
</tr>
<tr>
<td>PREPIC, Decousus et al23/1998</td>
</tr>
<tr>
<td>Merli et al45/2001</td>
</tr>
</tbody>
</table>

*Patients randomly allocated to receive enoxaparin, 1.5 mg/kg qd, were included in a sensitivity analysis.
presented with DVT without clinical PE, because clinical PE was an exclusion criteria. Concomitant, symptomatic, nonmassive PE occurred in 36% of patients included in the Prévention du Risque d’Embolie Pulmonaire par Interruption Cave (PREPIC) study\textsuperscript{23} and 15% of patients included in the study by Merli et al.\textsuperscript{45} Overall, 235 of the 1,503 patients (16%) presented with initial symptomatic PE, 121 in the UFH group and 114 in the enoxaparin twice-daily group. The treatment groups had similar baseline characteristics.

At 3 months, outcomes were assessed in 1,439 of the 1,503 randomized patients (724 patients in the enoxaparin group and 715 patients in the UFH group). Outcome information was missing for 48 patients who died before the end of follow-up and had not experienced recurrent VTE, and for 16 patients who were lost to follow-up. At 3 months, the estimated incidence of VTE recurrence in the UFH group was 5.7% (95% CI, 4.0 to 7.4) [Table 3]. The incidences of DVT and PE were 4.4% (95% CI, 2.9 to 6.0) and 1.8% (95% CI, 0.8 to 2.8), respectively.

Enoxaparin vs UFH in the Treatment of DVT With or Without Associated Symptomatic PE

With respect to VTE, the pooled estimate from all the trials revealed an RR of 0.81 (95% CI, 0.52 to 1.26) on the intention-to-treat population without heterogeneity among studies (p = 0.98). Because the upper limit of the 95% CI was below the prespecified noninferiority margin of 1.61, enoxaparin can be considered to be noninferior to UFH in terms of the prevention of VTE in patients presenting a DVT with or without associated PE. Using the imputed placebo analysis, extrapolation of the efficacy of enoxaparin relative to placebo yields a RR of 0.27 (95% CI, 0.08 to 0.87), indirectly revealing a significant difference between enoxaparin and placebo in terms of VTE.

The observed RR reduction for VTE includes both DVT recurrence (RR, 0.79; 95% CI, 0.48 to 1.30) and PE occurrence (RR, 0.63; 95% CI, 0.27 to 1.44) [Table 4]. On the basis of the per-protocol population including 1,350 patients, enoxaparin was still found to be noninferior to UFH (RR, 0.70; 95% CI, 0.43 to 1.13) because the upper limit of the 95% CI was < 1.61.

Consistency of the Results Between Patients With or Without Associated Symptomatic PE

When considering patients with and without symptomatic PE at entry, 235 of the 1,503 patients presented an initial symptomatic PE. Compared with the group of patients with isolated DVT, this group included a larger percentage of women (52% vs 44%, respectively) and more patients with a history of VTE (33% vs 24%, respectively) [Table 5]. In the UFH group, patients with an initial symptomatic PE were at a nonsignificantly higher risk of

Table 2—Baseline Characteristics of the Patient Population (n = 1,503)*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Levine et al\textsuperscript{13} (n = 501)</th>
<th>PREPIC, Decousus et al\textsuperscript{23} (n = 400)</th>
<th>Merli et al\textsuperscript{45} (n = 602)</th>
<th>Meta-analysis (n = 1,503)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>58 ± 17</td>
<td>72 ± 11</td>
<td>61 ± 16</td>
<td>63 ± 16</td>
</tr>
<tr>
<td>Male gender</td>
<td>303 (60)</td>
<td>190 (48)</td>
<td>331 (55)</td>
<td>824 (55)</td>
</tr>
<tr>
<td>Body mass index &gt; 30 kg/m\textsuperscript{2}</td>
<td>NR</td>
<td>57 (14)</td>
<td>137 (14)</td>
<td>194 (20)</td>
</tr>
<tr>
<td>History of VTE</td>
<td>58 (18)</td>
<td>141 (35)</td>
<td>151 (25)</td>
<td>350 (25)</td>
</tr>
<tr>
<td>Cancer</td>
<td>103 (21)</td>
<td>56 (14)</td>
<td>92 (15)</td>
<td>251 (17)</td>
</tr>
<tr>
<td>Surgery within the past 3 mo</td>
<td>96 (19)</td>
<td>43 (11)</td>
<td>120 (20)</td>
<td>259 (17)</td>
</tr>
<tr>
<td>Chronic cardiac or respiratory insufficiency</td>
<td>NR</td>
<td>86 (22)</td>
<td>63 (10)</td>
<td>149 (15)</td>
</tr>
<tr>
<td>Recent immobilization</td>
<td>NR</td>
<td>85 (21)</td>
<td>78 (13)</td>
<td>163 (16)</td>
</tr>
<tr>
<td>Initial symptomatic DVT</td>
<td>NR</td>
<td>342 (86)</td>
<td>579 (96)</td>
<td>921 (92)</td>
</tr>
<tr>
<td>Proximal DVT</td>
<td>501 (100)</td>
<td>400 (100)</td>
<td>459 (81)</td>
<td>1,360 (93)</td>
</tr>
<tr>
<td>Initial PE</td>
<td>197 (49)</td>
<td>193 (32)</td>
<td>390 (39)</td>
<td></td>
</tr>
<tr>
<td>Symptomatic initial PE</td>
<td>0</td>
<td>145 (36)</td>
<td>90 (15)</td>
<td>235 (16)</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD or No. (%). NR = no recorded data.

Table 3—VTE Recurrences and Major Bleedings at 3 mo According to Treatment in Each Study*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Enoxaparin</th>
<th>UFH</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE recurrences</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levine et al\textsuperscript{13}</td>
<td>13/237</td>
<td>17/247</td>
</tr>
<tr>
<td>PREPIC, Decousus et al\textsuperscript{23}</td>
<td>10/186</td>
<td>12/193</td>
</tr>
<tr>
<td>Merli et al\textsuperscript{45}</td>
<td>11/301</td>
<td>13/275</td>
</tr>
<tr>
<td>Adjusted incidence, % (95% CI)</td>
<td>4.5 (3.0 to 6.0)</td>
<td>5.7 (4.0 to 7.4)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levine et al\textsuperscript{13}</td>
<td>8/239</td>
<td>7/239</td>
</tr>
<tr>
<td>PREPIC, Decousus et al \textsuperscript{23}</td>
<td>10/189</td>
<td>11/193</td>
</tr>
<tr>
<td>Merli et al \textsuperscript{45}</td>
<td>6/297</td>
<td>15/278</td>
</tr>
<tr>
<td>Adjusted incidence, % (95% CI)</td>
<td>2.9 (1.6 to 4.1)</td>
<td>4.3 (2.8 to 5.7)</td>
</tr>
</tbody>
</table>

*Data are presented as No. of patients/total patients unless otherwise indicated.
†There was one more bleeding event compared with the original results since events occurring after a thromboembolic event were not considered in the original trial.
VTE recurrence (8.2%; 95% CI, 3.2 to 13.1) than patients without initial symptomatic PE (4.8%; 95% CI, 3.1 to 6.6). In particular, patients with initial symptomatic PE had more PE recurrences than patients without initial symptomatic PE (4.9%; 95% CI, 1.0 to 8.9; vs 1.3%; 95% CI, 0.4 to 2.3, respectively).

When comparing the efficacy of enoxaparin vs UFH, there was no significant difference in patients with an initial symptomatic PE and patients without symptomatic PE (Fig 1). We observed an RR reduction for VTE of 29% for patients with initial DVT and symptomatic PE (RR, 0.71; 95% CI, 0.28 to 1.81) and 16% for patients with DVT alone (RR, 0.84; 95% CI, 0.51 to 1.38), yielding a nonsignificant heterogeneity test between groups (\( p = 0.76 \)). This means that the effect of enoxaparin vs UFH is not modified by the presence of a PE. The per-protocol analysis confirmed this finding (RR, 0.46; 95% CI, 0.15 to 1.47; and RR, 0.78; 95% CI, 0.46 to 1.34, respectively). When considering total PE, whether symptomatic or asymptomatic, results were similar between patients presenting with DVT and PE and patients presenting with DVT alone (data not shown).

### Table 4—Efficacy Results From the Sensitivity Analyses, Enoxaparin vs UFH

<table>
<thead>
<tr>
<th>Variables</th>
<th>Excluding Patients Randomly Allocated to Filter Placement</th>
<th>Including Patients Who Received Enoxaparin, 1.5 mg/kg qd</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE</td>
<td>0.81 (0.52 to 1.26)</td>
<td>0.86 (0.57 to 1.29)</td>
</tr>
<tr>
<td>DVT</td>
<td>0.79 (0.48 to 1.30)</td>
<td>0.87 (0.55 to 1.38)</td>
</tr>
<tr>
<td>PE</td>
<td>0.63 (0.27 to 1.44)</td>
<td>0.60 (0.27 to 1.29)</td>
</tr>
</tbody>
</table>

*Data are presented as RR (95% CI).

### Sensitivity Analyses

Excluding patients who were randomly allocated to filter placement or including patients who received enoxaparin, 1.5 mg/kg qd, did not change the study findings. Enoxaparin was still found to be noninferior to UFH in reducing the incidence of VTE (Table 4).

### Safety Analysis

In the UFH group, 2.0% of patients (95% CI, 1.0 to 3.0) had major bleeding at 10 days and 4.3% of patients (95% CI, 2.8 to 5.7) had major bleeding at 3 months. In the enoxaparin group, 2.2% of patients (95% CI, 1.1 to 3.2) had major bleeding at 10 days and 2.9% of patients (95% CI, 1.6 to 4.1) had major bleeding at 3 months. Enoxaparin at 3 months reduced major bleeding by 26% (RR, 0.74; 95% CI, 0.43 to 1.25) compared with UFH in patients with initial DVT with or without associated PE.

At 3 months, the estimated incidence of death was 5.8% in the UFH group (95% CI, 4.1 to 7.6) and 3.3% in the enoxaparin group (95% CI, 2.0 to 4.5). There was no statistical evidence of heterogeneity among studies. Enoxaparin reduced mortality by 31% (RR, 0.69; 95% CI, 0.43 to 1.10) compared with UFH in patients with initial DVT with or without associated PE.

### Discussion

Results from this meta-analysis suggest that in terms of VTE recurrences, major bleeding, and death, enoxaparin is as effective and safe as UFH in the treatment of DVT with or without associated symptomatic PE. Similar results were found when comparing enoxaparin and UFH in patients presenting with a DVT and PE and in patients presenting with DVT alone. Emphasizing the robustness of our results, estimates of treatment effect were unchanged regardless of population considered (intention-to-treat or per-protocol population, population without patients randomly allocated to filter placement, or population with patients who received enoxaparin, 1.5 mg/kg qd).

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**Table 5—Baseline Characteristics of Patients According to the Presence of an Initial Symptomatic PE**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients With Isolated DVT (n = 1,268)</th>
<th>Patients With DVT and Symptomatic PE (n = 235)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>62 ± 16</td>
<td>68 ± 15</td>
</tr>
<tr>
<td>Male gender</td>
<td>711 (56)</td>
<td>113 (48)</td>
</tr>
<tr>
<td>Body mass index &gt; 30 kg/m²†</td>
<td>151 (20)</td>
<td>43 (19)</td>
</tr>
<tr>
<td>History of VTE</td>
<td>303 (24)</td>
<td>77 (32)</td>
</tr>
<tr>
<td>Cancer</td>
<td>215 (17)</td>
<td>36 (15)</td>
</tr>
<tr>
<td>Surgery within the past 3 mo</td>
<td>234 (18)</td>
<td>25 (11)</td>
</tr>
<tr>
<td>Chronic cardiac or respiratory insufficiency‡</td>
<td>109 (14)</td>
<td>40 (17)</td>
</tr>
<tr>
<td>Recent immobilization‡</td>
<td>132 (17)</td>
<td>31 (13)</td>
</tr>
<tr>
<td>Proximal DVT§</td>
<td>1,146 (93)</td>
<td>212 (93)</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD or No. (%).
†Information was not available for 533 patients.
‡Information was not available for 35 patients in one trial.
§Information was not available for 35 patients in one trial.
These results are consistent with the recommendations of the 2004 American College of Chest Physicians consensus conference on antithrombotic therapy and of the Groupe d’Etude sur l’Hémostase et la Thrombose, which state that patients with DVT or PE would benefit from the same therapeutic approach (UFH or LMWH), with the latter being more attractive because of its good safety profile and its superior convenience.

At 3 months, the incidence of VTE recurrence, PE, and DVT in the UFH group were 5.7%, 4.4%, and 1.8%, respectively. These data are consistent with data from clinical trials assessing UFH, with the exception of data from the Tinzaparine ou Héparine Standard: Évaluations dans l’Embolie pulmonaire study, which reported a lower rate of recurrence (1.9%). The incidence of deaths observed in the meta-analysis is consistent with data from the literature. However, the incidence of major bleeding at 3 months is higher (4.3%) than that reported in clinical trials. This could be explained by the patients of the PREPIC study, who can be considered as patients at higher risk of bleeding. The RRs of VTE recurrence with enoxaparin compared with UFH were 0.81 (95% CI, 0.52 to 1.26) for the whole population and 0.71 (95% CI, 0.43 to 1.13) in the per-protocol population. Considering these results and the a priori noninferiority margin of 1.61, this meta-analysis of three clinical trials showed that enoxaparin is noninferior to UFH in terms of efficacy. In addition, even if there was a trend in favor of enoxaparin in terms of major bleeding and death, no statistically significant difference was detected between treatments.

As previously described in the literature, the estimated incidence of PE and of VTE at 3 months in the UFH group was higher in patients presenting an initial symptomatic PE (4.9% and 8.2%, respectively) than in patients without initial symptomatic PE (1.3% and 4.8%, respectively). The present study indicates that the efficacy of enoxaparin is not modified by the presence of an initial symptomatic PE. However, because of the modest number of patients presenting with initial symptomatic PE (275 patients), estimates of efficacy and safety were not very precise. Compared with UFH, enoxaparin reduced the risk for VTE recurrence by 16% in patients with DVT alone and by 29% in patients with DVT plus symptomatic PE. This result is consistent with results of a recent meta-analysis by Quinlan et al, who found that LMWH reduced the risk for VTE recurrence in PE patients by 28% at 3 months with an odds ratio of 0.72 (95% CI, 0.40 to 1.48). In conclusion, our data show that enoxaparin is as effective and safe as UFH for the initial treatment of DVT with or without associated symptomatic PE, apart from massive PE.

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