Long-term therapy with low-molecular-weight heparin in cancer patients with venous thromboembolism

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Summary

Long-term therapy with low-molecular-weight heparin (LMWH) is the treatment of choice for cancer patients with venous thromboembolism (VTE). However, the ideal doses of LMWH have not been thoroughly studied. We used the RIETE Registry data to assess the influence of the daily LMWH dosage on outcome during the first three months after VTE. We used propensity score-matching to compare patients who received <150 vs. those receiving ≥150 IU/kg/day LMWH. Up to July 2010, 3,222 cancer patients with VTE received long-term therapy with fixed doses of LMWH. Of these, 1,472 (46%) received <150 IU/kg/day (mean, 112 ± 28), and 1,750 received ≥150 IU/kg/day (mean, 184 ± 32). Results of the propensity score matching involved 1269 matched pairs. During follow-up, the incidence of pulmonary embolism (PE) recurrences was similar (1.2% vs. 1.9%), but patients receiving <150 IU/kg/day LMWH had a lower incidence of fatal PE than those treated with ≥150 IU/kg/day (0.2% vs. 1.0%; p=0.004). Multivariate analysis confirmed that patients receiving <150 IU/kg/day LMWH had a lower risk for fatal PE (odds ratio [OR]: 0.2; 95% confidence interval [CI]: 0.06–0.8) and for major bleeding (OR: 0.6; 95% CI: 0.3–1.0) than those treated with ≥150 IU/kg/day. In real life, one in every two cancer patients with VTE received lower doses of LMWH than those used in randomised trials, with large variations from patient to patient. Unexpectedly, patients treated with <150 IU/kg/day LMWH had fewer fatal PE cases and fewer major bleeding events than those receiving ≥150 IU/kg/day LMWH. This finding, however, should be validated in prospective clinical trials.

Keywords
Cancer, heparins, venous thrombosis, pulmonary embolism

Introduction

In cancer patients with venous thromboembolism (VTE), long-term therapy with low-molecular-weight heparin (LMWH) is the treatment of choice. Four clinical trials enrolling cancer patients with VTE found that, compared to treatment with vitamin K antagonists (VKA), three or six months of LMWH (dalteparin at 200 U/kg/day for one month followed by 150 U/kg/day, enoxaparin at 1.5 mg/kg/day, or tinzaparin at 175 U/kg/day) was associated with fewer VTE recurrences or fewer bleeding events (1–4). Consequently, the American College of Chest Physicians (ACCP) (5), the National Comprehensive Cancer Network (NCCN) (6), the American Society of Clinical Oncology (ASCO) (7), the French guidelines (8, 9), and the European Society of Medical Oncology (ESMO) (10) recommend the use of long-term therapy with LMWH for at least three months over VKA in this clinical setting. However, the ideal doses of LMWH have not been thoroughly studied.

The RIETE registry is an ongoing, international, multi-centre, registry of consecutive patients with symptomatic, acute deep-vein thrombosis (DVT) or pulmonary embolism (PE) (11, 12). We have previously reported the frequency of VTE recurrences and major bleeding complications, and risk factors for these outcomes, in cancer patients with VTE (13). The current analysis compared the clinical outcome during long-term therapy (from Day 8 to Day 90) in cancer patients who received long-term therapy with fixed doses of LMWH. We were especially interested to assess whether lower than recommended doses of LMWH were associated with different outcomes, and to determine which factors may label patients as having a particularly high risk of dying of PE or bleeding.

Methods

Consecutive patients with symptomatic, acute DVT or PE, confirmed by objective tests (contrast venography or ultrasonography for suspected DVT; pulmonary angiography, lung scintigraphy, or helical computed tomography [CT] scan for suspected PE), were enrolled in RIETE. Patients were excluded if they were currently...
participating in a therapeutic clinical trial with a blinded therapy. All patients provided written or oral consent for participation in the registry, in accordance with local ethics committee requirements.

In the RIETE registry, participating physicians ensure that eligible patients were consecutively enrolled. Data are recorded on to a computer-based case report form at each participating hospital and submitted to a centralised coordinating centre through a secure website. The study coordinating centre assigns patients with a unique identification number to maintain patient confidentiality and is responsible for all data management. Data quality is regularly monitored electronically, including checks to detect inconsistencies or errors, which are resolved by the local coordinators. Data quality is also monitored by periodic visits to participating hospitals by contract research organisations that compare medical records with the submitted data.

Study design and outcomes

For this analysis, only patients with active cancer (defined as newly diagnosed cancer or cancer that is being treated [i.e. surgery, chemotherapy, radiotherapy, hormonal, support therapy, or combined treatments]) who received long-term therapy with fixed doses of LMWH were considered. Patients dying during the first seven days since VTE diagnosis were excluded, since the study was aimed to evaluate the effect of long-term therapy. Patients receiving long-term therapy with VKA drugs, and those treated with varying doses of LMWH during the study period were not included in this analysis.

Patients were categorised into two subgroups according to the daily doses of LMWH per body weight (<150 or ≥150 IU/kg/day), and their event rates from Day 8 to Day 90 of VTE diagnosis were compared. The major outcomes were fatal PE and fatal bleeding. Secondary outcomes were VTE recurrences and major bleeding.

The causes of death were determined by the attending physicians. Fatal PE, in the absence of autopsy, was defined as any death appearing during the first 10 days after PE diagnosis, in the absence of any alternative cause of death. Fatal bleeding was defined as any death occurring within 10 days of a major bleeding episode, in the absence of an alternative cause of death. Bleeding complications were classified as ‘major’ if they were overt and required a transfusion of two units of blood or more, or were retroperitoneal, spinal or intracranial, or when they were fatal.

Baseline variables

The following parameters were recorded when the qualifying episode of VTE was diagnosed: patient’s sex, age, and body weight; presence of coexisting conditions such as chronic heart or lung disease; recent (<30 days prior to VTE) major bleeding; presence of risk factors for VTE including recent immobilisation (defined as non-surgical patients who were confined to bed with bathroom privileges for ≥24 days in the two months prior to VTE diagnosis), surgery (defined as those who had undergone an operation in the two months prior to VTE); extension of the DVT (distal DVT was considered when located in the infra-popliteal veins of the lower limbs); and laboratory data on admission, including serum creatinine levels.

Treatment and follow-up

Patients were managed according to the clinical practice of each participating hospital (i.e. there was no standardisation of treatment). The type and dose of anticoagulant therapy, as was the insertion of an inferior vena cava filter, were recorded. After hospital discharge, all patients were followed-up for at least three months in the outpatient clinic. During each visit, any signs or symptoms suggesting either DVT or PE recurrences or bleeding complications were noted. Each episode of clinically suspected recurrent DVT or PE was investigated by repeat ultrasonography, venography, lung scanning, helical CT scan or pulmonary angiography as appropriate.

Most outcomes were classified as reported by the clinical centres. However, if staff at the coordinating centre were uncertain how to classify a reported outcome, that event was reviewed by a central adjudicating committee (less than 10% of events). Patients who had major bleeding or recurrent VTE within three months of enrollment remained under surveillance until three months of follow-up was completed.

Statistical analysis

Student’s t test and Chi² test were used to compare continuous and categorical variables, respectively, between patients receiving LMWH at <150 IU/kg/day vs. those treated with LMWH ≥150 IU/kg/day. A propensity score matching analysis was carried out using a logistic regression model for LMWH therapy <150 IU/kg/day vs. ≥150 IU/kg/day, including variables such as the patient’s gender, age, body weight, clinical presentation of VTE (PE vs. DVT), presence of metastases, diagnosis of cancer <3 months before VTE presentation, recurrent VTE or major bleeding less than seven days of VTE treatment, prior surgery or immobilisation, and major bleeding within one month before VTE diagnosis. The goal of the propensity score matching was to find pairs of patients receiving <150 IU/kg/day or ≥150 IU/kg/day sharing similar propensities. Using a SPSS macro, of the 1,750 patients receiving ≥150 IU/kg/day LMWH, 1,269 (72.5%) were matched with 1,269 of 1,472 patients receiving <150 IU/kg/day LMWH (86.2%) who received <150 IU/kg/day LMWH. We included in the bivariate and multivariate analysis (Cox proportional hazard model) the matched pairs with a delta <0.1 in order to determine the variables independently associated with fatal PE, fatal bleeding, recurrent VTE or major bleeding during the study period.
Covariates entering in the model were selected by a significance level of $p < 0.10$ in the univariate analysis, or by a well known association reported in the literature: gender, age, body weight $< 65$ kg, initial presentation (PE vs. DVT), initial therapy with LMWH, prior bleeding or VTE recurrences during initial therapy, recent surgery, anaemia, diagnosis of cancer $> 3$ months earlier, site of cancer, and presence of metastases. Any variables obtained during follow-up and that were not available at baseline were not included as potential predictors of fatal PE or fatal bleeding. SPSS software (version 15, SPSS Inc., Chicago, IL, USA) was used for the statistical management of the data, and a two-sided $p < 0.05$ was considered to be statistically significant.

### Results
Up to July 2010, 3222 VTE patients with active cancer receiving long-term therapy with fixed doses of LMWH had been enrolled in RIETE. There were 1,702 males and 1,520 females, aged 21–94
years (mean, 67 years). Of these, 1,472 patients (46%) received <150 IU/kg/day LMWH (mean, 112 ± 28), and 1,750 (54%) received ≥150 IU/kg/day LMWH (mean, 184 ± 32). The first patient was included in 2001, and there were no differences in the LMWH doses between patients included early and those included more recently. Patients treated with <150 IU/kg/day LMWH weighed more and more likely had recent bleeding, recent surgery or brain cancer compared with those receiving ≥150 IU/kg/day (Table 1).

During the first week they also received lower LMWH doses as initial therapy, but a higher proportion of patients receiving <150 IU/kg/day LMWH underwent insertion of a vena cava filter (Table 2).

The incidence of VTE recurrences or major bleeding events was non-significantly different than in those treated with ≥150 IU/kg/day LMWH. Unexpectedly, the incidence of fatal PE was significantly lower in patients receiving <150 IU/kg/day LMWH. The all-cause mortality rate also was significantly lower in patients receiving <150 IU/kg/day LMWH. Thirty patients who died underwent autopsy studies, which confirmed the diagnosis of fatal PE in six of them.

Results of the propensity score matching involved 1,269 matched pairs. After matching, baseline covariates were balanced between the two groups, with the exception of recent surgery (Table 1) and the use of heparin as initial therapy (Table 2). Any difference in the LMWH doses during initial therapy or in the proportion of patients in whom a vena cava filter was inserted had disappeared. During follow-up, patients receiving <150 IU/kg/day LMWH had a significantly higher incidence of recurrent DVT than those treated with ≥150 IU/kg/day, but the incidence of PE re-

### Table 2: Initial therapy and three-month outcome.

<table>
<thead>
<tr>
<th></th>
<th>LMWH doses &lt;150 IU/kg/day</th>
<th>LMWH doses ≥150 IU/kg/day</th>
<th>P-value</th>
<th>LMWH doses &lt;150 IU/kg/day</th>
<th>LMWH doses ≥150 IU/kg/day</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, N</td>
<td>1,472</td>
<td>1,750</td>
<td></td>
<td>1,269</td>
<td>1,269</td>
<td></td>
</tr>
<tr>
<td><strong>Initial therapy</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>LMWH</td>
<td>1,428 (97%)</td>
<td>1,665 (95%)</td>
<td>0.009</td>
<td>1,234 (97%)</td>
<td>1,208 (95%)</td>
<td>0.009</td>
</tr>
<tr>
<td>Mean LMWH dose (IU/kg/day)</td>
<td>185±60</td>
<td>203±70</td>
<td>&lt;0.001</td>
<td>187±60</td>
<td>190±65</td>
<td>0.19</td>
</tr>
<tr>
<td>LMWH dose (median, IQR)</td>
<td>179 (72)</td>
<td>198 (80)</td>
<td></td>
<td>181 (76)</td>
<td>184 (67)</td>
<td>0.21</td>
</tr>
<tr>
<td>Unfractionated heparin</td>
<td>44 (3.0%)</td>
<td>85 (4.9%)</td>
<td>0.009</td>
<td>35 (2.8%)</td>
<td>61 (4.8%)</td>
<td>0.009</td>
</tr>
<tr>
<td>Inferior vena cava filter</td>
<td>74 (5.0%)</td>
<td>54 (3.1%)</td>
<td>0.006</td>
<td>61 (4.8%)</td>
<td>41 (3.2%)</td>
<td>0.054</td>
</tr>
<tr>
<td><strong>Long-term therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean LMWH dose (IU/kg/day)</td>
<td>112 ± 28</td>
<td>184 ± 32</td>
<td>&lt;0.001</td>
<td>111 ± 27</td>
<td>182 ± 25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LMWH dose (median, IQR)</td>
<td>118 (39)</td>
<td>179 (32)</td>
<td></td>
<td>118 (40)</td>
<td>177 (30)</td>
<td></td>
</tr>
<tr>
<td><strong>Outcome, Days 0 to 7</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent DVT</td>
<td>1 (0.1%)</td>
<td>0</td>
<td>0.41</td>
<td>1 (0.1%)</td>
<td>0</td>
<td>0.32</td>
</tr>
<tr>
<td>Recurrent PE</td>
<td>0</td>
<td>3 (0.2%)</td>
<td>0.18</td>
<td>0</td>
<td>3 (0.2%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>1 (0.1%)</td>
<td>3 (0.2%)</td>
<td>0.48</td>
<td>1 (0.1%)</td>
<td>3 (0.2%)</td>
<td>0.37</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0</td>
<td>2 (0.1%)</td>
<td>0.31</td>
<td>0</td>
<td>2 (0.2%)</td>
<td>0.16</td>
</tr>
<tr>
<td><strong>Outcome, Days 8 to 90</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent DVT</td>
<td>38 (2.6%)</td>
<td>18 (1.0%)</td>
<td>0.001</td>
<td>34 (2.7%)</td>
<td>13 (1.0%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Recurrent PE</td>
<td>17 (1.2%)</td>
<td>34 (1.9%)</td>
<td>0.08</td>
<td>15 (1.2%)</td>
<td>24 (1.9%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>29 (2.0%)</td>
<td>48 (2.7%)</td>
<td>0.16</td>
<td>24 (1.9%)</td>
<td>31 (2.4%)</td>
<td>0.34</td>
</tr>
<tr>
<td>Overall death</td>
<td>299 (20%)</td>
<td>428 (25%)</td>
<td>0.005</td>
<td>264 (21%)</td>
<td>290 (23%)</td>
<td>0.21</td>
</tr>
<tr>
<td><strong>Causes of death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>3 (0.2%)</td>
<td>21 (1.2%)</td>
<td>&lt;0.001</td>
<td>2 (0.2%)</td>
<td>13 (1.0%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Respiratory insufficiency</td>
<td>15 (1.0%)</td>
<td>20 (1.1%)</td>
<td>0.75</td>
<td>12 (0.9%)</td>
<td>13 (1.0%)</td>
<td>0.84</td>
</tr>
<tr>
<td>Sudden, unexpected</td>
<td>3 (0.2%)</td>
<td>2 (0.1%)</td>
<td>0.53</td>
<td>3 (0.2%)</td>
<td>1 (0.1%)</td>
<td>0.37</td>
</tr>
<tr>
<td>Bleeding</td>
<td>15 (1.0%)</td>
<td>14 (0.8%)</td>
<td>0.51</td>
<td>13 (1.0%)</td>
<td>7 (0.6%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Disseminated cancer</td>
<td>183 (12%)</td>
<td>249 (14%)</td>
<td>0.14</td>
<td>167 (13%)</td>
<td>171 (13%)</td>
<td>0.82</td>
</tr>
<tr>
<td>Other</td>
<td>80 (5.4%)</td>
<td>122 (7.0%)</td>
<td>0.07</td>
<td>67 (5.3%)</td>
<td>85 (6.7%)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

1 before propensity score matching. 2 after propensity score matching. LMWH, low-molecular-weight heparin; IU, international units; IQR, interquartile range; DVT, deep-vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.
currences was similar. Unexpectedly, patients receiving <150 IU/kg/day LMWH had a significantly lower incidence of fatal PE than those treated with ≥150 IU/kg/day (Table 2). Multivariate analysis confirmed that patients receiving <150 IU/kg/day LMWH had a lower risk for fatal PE and for major bleeding than those treated with ≥150 IU/kg/day (Table 3).

**Discussion**

The findings in the current study reveal that one in every two cancer patients with VTE in RIETE received lower daily doses of LMWH than those used in the randomised trials (1–4), with large variations from patient to patient, probably reflecting the absence of firm recommendations on this issue. As it could be expected, patients receiving <150 IU/kg/day LMWH had more DVT recurrences than those treated with ≥150 IU/kg/day. However, patients receiving <150 IU/kg/day unexpectedly had fewer fatal PEs. This lower frequency of fatal PE was due to both a non-significantly lower frequency of PE recurrences (1.2% vs. 1.9%), and a lower probability of dying (i.e. case-fatality) when recurrent PE occurred (13% vs. 54%). This is an unexpected finding, which might not be explained because these patients were probably sicker, since any difference in their baseline characteristics had likely disappeared after propensity score matching. In addition, patients receiving <150 IU/kg/day had a lower incidence of major bleeding complications.

A number of randomised trials have compared VKA with LMWH in the long-term treatment of patients with VTE, with or without cancer (13–20). In a meta-analysis of these studies (21), there were trends towards less recurrent VTE (odds ratio [OR]: 0.66; 95% confidence interval [CI]: 0.41–1.07) and less major bleeding (OR: 0.45; 95% CI: 0.18–1.11) with three months of LMWH compared with VKA. At variance of what happened in the four trials selectively enrolling patients with cancer, the daily LMWH dose in these studies broadly ranged. It was as low as 4,000 IU to as high as 200 IU/kg; approximately a 3.5-fold difference. Between-study differences of mean daily dose of LMWH had little effect on efficacy (21).

In our study, adherence to treatment guidelines for patients with cancer was poor, and VTE patients receiving <150 IU/kg/day LMWH differed from those receiving ≥150 IU/kg/day in mean body weight, frequency of recent bleeding, mean LMWH doses during initial therapy, or the proportion of patients in whom an inferior vena cava filter was inserted. Since these characteristics most likely had an influence on outcome, and we expected bias in a direct comparison between the two treatment groups, we used a propensity score adjustment to compare treatment effects for patients with similar predicted probabilities of receiving different doses of LMWH (22).

Accumulating evidence suggests that the intensity of anticoagulant therapy should be tailored to the risk of VTE recurrences or bleeding in an individual patient. Using data from the RIETE Registry, we recently reported that some variables on admission may reliably identify those patients at an increased risk for bleeding (23,
24), while others may identify those at an increased risk for fatal PE (12). However, in these studies the treatment received by the patients was not included in the multivariate models. Thus, our findings may be of added value in comparison with a model applicable to all cancer patients with VTE.

The present study has potential limitations. First, retrospective studies are susceptible to selection bias if a non-representative sample of patients is selected for analysis. However, the RIETE registry captures a broad range of consecutive patients with symptomatic VTE from multiple medical centres, countries, and treatment settings, making it less likely that the study cohort is made up of a skewed population. Second, the study cohort may have received LMWH therapy based on certain baseline and prognostic characteristics, and this could significantly bias the study findings. The selection of propensity score-matched cohorts for direct comparison allowed us to address the imbalance in distribution of characteristics that existed between patients receiving <150 IU/kg/day or ≥150 IU/kg/day LMWH. However, although we accounted for many of the relevant potential confounding variables available to us in our propensity score model, the possibility of residual confounding remains. Third, data were not available to enable us to assess the influence of additional variables (i.e. chemo- or radiotherapy, the presence of inter-current illnesses, additional medications,…) on outcome. Fourth, we studied only the initial three-month period of treatment, and it is likely that the risk of fatal bleeding will decrease with time, which may, however, also apply to the risk of fatal PE. This emphasises the need for additional studies with longer follow-up data. Finally, the small percentage of events may imply over-fitting, and hence over-optimistic results.

The main strength of our observation is that it pertains to undatable clinically relevant outcomes, namely fatal PE and fatal bleeding. These two outcomes are fully comparable unlike other symptomatic VTE recurrences or bleeding, which may have very dissimilar clinical relevance (e.g. a recurrent symptomatic distal DVT and a non-fatal intracranial bleed). Previous studies and meta-analyses used surrogate and/or combined endpoints, whereas our study focused on the clinically relevant question of whether different LMWH dosages influence mortality. Additionally, the population based sample we used describes the effects of LMWH therapy in “real world” clinical care, as opposed to in a protocol driven randomised trial, and enhances the generalisability of our findings.

In conclusion, cancer patients receiving long-term therapy with LMWH at doses <150 IU/kg/day had fewer fatal PEs than those receiving ≥150 IU/kg/day LMWH. Our findings suggest that LMWH at doses lower than recommended might be at least equally effective and safer. This hypothesis, however, should be assessed in prospective clinical trials.

Conflict of interest
None declared.

References