Identification of Risk Factors for Bleeding During Treatment of Acute Venous Thromboembolism With Heparin or Low Molecular Weight Heparin

By H. Karel Nieuwenhuis, Johannes Albada, Jan Dirk Banga, and Jan J. Sixma

In a prospective double-blind trial, we treated 194 patients with acute venous thromboembolism with heparin or low molecular weight heparin (LMWH; Fragmin). To evaluate the most important prognostic factors for bleeding, the presenting clinical features of the patients, the patients' anticoagulant responses, and the doses of the drugs were analyzed using univariate and multivariate regression analyses. No significant differences in clinical risk factors associated with bleeding were observed between heparin and LMWH. The univariate analyses ranked the parameters in the following order of importance: World Health Organization (WHO) performance status, history of bleeding tendency, cardiopulmonary resuscitation, recent trauma or surgery, leukocyte counts, platelet counts, duration of symptoms, and body surface area. Patients with WHO grade 4 had an eightfold increase in risk of bleeding compared with WHO grade 1.

Assessment of the individual contribution of each variable using multivariate regression analysis showed that the WHO performance status was the most important independent factor predicting major bleeding. A history of a bleeding tendency, recent trauma or surgery, and body surface area were also independent risk factors. The risk of bleeding was influenced by two factors related to the treatment, the patient's anticoagulant response as measured with the anti-Xa assay and the dose of the drug expressed as U/24 h/m². An increased risk of bleeding was only observed at mean anti-Xa levels greater than 0.8 U/mL for both drugs. Significantly more major bleedings occurred in patients treated with high doses of the drugs, an observation that was independent of the concomitant anti-Xa levels. It should be considered whether choosing an appropriate initial dose adapted to the patient's body surface area and clinical risk factors can improve the efficacy to safety ratio of heparin treatment.

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MATERIALS AND METHODS

Subjects. All 194 patients who participated in a prospective, randomized, double-blind study comparing LMWH (Fragmin; KabiVitrum AB, Stockholm, Sweden) with standard heparin in the treatment of acute venous thromboembolism were studied. Included in the study were 115 patients with deep venous thrombosis, 70 with pulmonary embolism, and nine with axillary vein thrombosis. Criteria for exclusion were allergy for heparin, pregnancy, and objection by the patient's physician to the heparin levels of the study. The study protocol and results have been reported. Ninety-eight patients received continuous intravenous (IV) heparin, and 96 patients received Fragmin for 5 to 10 days. All patients received an IV bolus injection of 2,500 U of the drug. Doses were adjusted twice daily to maintain anti-Xa levels between 0.3 and 0.6 U/mL for patients with a high risk for a bleeding complication and between 0.4 and 0.9 U/mL for patients with a low risk for bleeding. The high-risk group (n = 100) was defined as women greater than 60 years of age, men greater than 70 years, surgery within the preceding 10 days, renal insufficiency (creatinine level > 45 mg/L [400 μmol/L]), recent intracranial bleeding or stroke, active peptic disease, hypertension (diastolic pressure > 120 mm Hg or fundal changes greater than stage 2), recent cardiopulmonary resuscitation (< 10 days), history of subarachnoidal bleeding, and history of bleeding diathesis and general disability (World Health Organization [WHO] score ≥ 4). The low-risk group contained all other patients (n = 94).

Anti-Xa activity was assayed with the Coatest (KabiVitrum AB) according to the manufacturer's recommendations, with a modification using 200 μL factor Xa instead of 100 μL, producing a steeper curve for anti-Xa levels between 0.2 and 0.8 U/mL. The test is based on the antifactor Xa assay of Teien and Lie. Anti-Xa assays were calibrated against the fourth International Heparin Standard and the first International Standard for LMWH.
Table 1. Estimated Relationship Between Individual Variables and Major Bleedings: Univariate Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Discriminant</th>
<th>No. of Patients</th>
<th>No. of Major Bleedings (%)</th>
<th>P Value</th>
<th>Relative Risk</th>
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<tr>
<td>≤ 28</td>
<td>159</td>
<td>22 (14)</td>
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<td>.069</td>
<td>4.8</td>
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</table>

(Continued on following page)
The body mass index was calculated from the weight in kilograms divided by the square of the height in meters.

The study end point, major bleeding, was defined as bleeding that leads to death, to interruption of treatment, to blood transfusion, or to a decrease in hemoglobin level of greater than 2.42 g/dL (1.5 mmol/L). Minor bleeding was defined as any overt bleeding that does not meet the criteria of a major bleeding.

Nine patients had a history of a bleeding tendency, including history of an intracranial bleeding (1 patient), hemorrhagic peri-carditis (1), hematuria (1), intestinal bleeding in Crohn's disease (1) and ischemic colitis (1), bleeding in multiple myeloma (1) and chronic granulocytic leukemia (1), postoperative bleeding (1) and easy bruising (1).

Risk factors were furthermore analyzed according to the scoring system as described by Landefeld et al,\(^\text{2}\) with two modifications: macrocytosis (mean corpuscular volume > 95 fL) was not considered a characteristic for liver dysfunction in our study population, and anticoagulant effects outside the therapeutic range were measured with anti-Xa levels instead of partial thromboplastin times.

**Statistical analysis.** Categoric variables were compared using the chi-square test statistic with appropriate degrees of freedom. Continuous variables were assessed using logistic regression and were also categorized for chi-square analysis. Variables with a \(P\) value less than .1 in the univariate analysis were candidates for multivariate analysis using the stepwise logistic regression method to identify the variables capable of being independently predictive. According to this method, the predictor with the highest level of statistical significance is used to initiate the model; other variables are then evaluated for further predictive information and added in turn, beginning with the variables with the highest level of statistical significance (ie, the lowest \(P\) values) and continuing until the \(P\) value for the variable added exceeds .05. Variables were entered into the model both as continuous and dichotomous parameters. Log-rank tests were used to compare times up to the moment of bleeding.

Use was made of the STATA (Computing Resource Center, Santa Monica, CA) and BMDP (Biomedical Computer Programs, BMDP Statistical Software, University of California, Berkeley) statistical software packages.

**RESULTS**

**Univariate analysis.** The variables listed in Table 1 were studied by univariate analysis for possible association with major bleeding. The most significant risk factor for major bleeding was the WHO performance status classification\(^3\) (Fig 1). The incidence of major bleeding was 4% for patients with a WHO grade 1 (restricted in physically strenuous activity, but ambulatory and able to do light work), 12% for WHO grade 2 (ambulatory and capable of all self-care, but unable to carry out any work), 25% for WHO grade 3 (capable of only limited self-care, confined to bed or chair 50% of waking hours), and 29% for WHO grade 4 (completely disabled, cannot carry on any self-care). Patients with WHO grade 0 (able to carry out all normal activity without restriction) were not included in the study. The WHO performance status was significantly
associated with major bleeding in both treatment groups and differences between the drugs could not be found. Minor bleedings also occurred more often in patients with WHO grades 3 and 4.

Of the other parameters investigated, history of bleeding diathesis, cardiopulmonary resuscitation, recent trauma or surgery, platelet levels, leucocyte levels, duration of symptoms, and body surface area also influenced the occurrence of major bleeding. In contrast, no such relationship was found for age, sex, presence of malignancy or alcohol abuse, or treatment with nonsteroidal antiinflammatory drugs.

**Relationship between dose and bleeding.** Large patients had a very low probability of getting bleedings, and the total body surface area was a better predictor than weight, height, or body mass index. Patients with a total body surface area less than 2 m² had a 7.3-fold higher risk of bleeding. We studied whether this was related to the anti-Xa levels of the drugs in the patients or to the doses of the drugs. The mean anti-Xa levels did not show any correlation with the body surface area ($r = 0.25$). Using logistic regression, it was found that the total dose of the drug per 24 hours was not associated with bleeding ($P = 0.781$). When the total dose expressed as U/24 h/m² body weight was related to bleedings, a relationship was observed ($P = 0.045$). The risk of major bleeding increased from 6% to 25% in the heparin group if the total dose of heparin exceeded 20,000 anti-Xa U/24 h/m² ($P = 0.009$), and from 8% to 22% in the Fragmin group if the total Fragmin dose exceeded 10,000 anti-Xa U/24 h/m² ($P = 0.069$). These increases in risk were not caused by higher anti-Xa levels. Patients treated with high doses ($n = 54$) or low doses ($n = 140$) had similar mean anti-Xa levels: 0.48 U/mL.

**Table 2. Relationship Between Anti-Xa Levels and Major Bleeding**

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<th>$1.0 &gt; P$</th>
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<tr>
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<td>17/150</td>
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<tr>
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<td>60</td>
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<td>Heparin group</td>
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<td>Fragmin group</td>
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<td>27</td>
</tr>
<tr>
<td>Fragmin group</td>
<td>Bleeding present/absent</td>
<td>7/47</td>
<td>2/24</td>
<td>1/15</td>
</tr>
<tr>
<td></td>
<td>Risk (%)</td>
<td>13</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Mean anti-Xa level</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>Bleeding present/absent</td>
<td>21/167</td>
<td>2/3</td>
<td>0/0</td>
</tr>
<tr>
<td></td>
<td>Risk (%)</td>
<td>11</td>
<td>40</td>
<td>—</td>
</tr>
<tr>
<td>Heparin group</td>
<td>Bleeding present/absent</td>
<td>12/83</td>
<td>1/1</td>
<td>0/0</td>
</tr>
<tr>
<td></td>
<td>Risk (%)</td>
<td>13</td>
<td>50</td>
<td>—</td>
</tr>
<tr>
<td>Fragmin group</td>
<td>Bleeding present/absent</td>
<td>9/84</td>
<td>1/2</td>
<td>0/0</td>
</tr>
<tr>
<td></td>
<td>Risk (%)</td>
<td>10</td>
<td>33</td>
<td>—</td>
</tr>
</tbody>
</table>

**Relationship between anti-Xa level and bleeding.** The anti-Xa levels on the day of the bleeding complication are shown in Fig 2. The median level in patients with a bleeding complication in the heparin group was 0.53 U/mL, and in the Fragmin group 0.43 U/mL. These levels were not significantly different from anti-Xa levels in patients who did not bleed.

Analysis of the first anti-Xa level, performed 4 hours after the bolus injection and the start of the continuous infusion, showed that patients with a high first anti-Xa level had more major bleedings (Table 2). The risk increased from 10% at an anti-Xa level less than 0.8 U/mL to 14% at greater than 0.8 U/mL, and to 60% at greater than 1.0 U/mL; this trend was found for both drugs.

A relationship between the patient’s highest anti-Xa level during the study period and bleeding complications could not be established. Analysis of the patient’s mean anti-Xa levels over the study period showed an increased risk of bleeding from 11% to 40% at levels greater than 0.8 U/mL.

**Relationship between international normalized ratio and bleeding.** Treatment with oral anticoagulants was begun on the first day. The median international normalized ratio (INR) was 2.0 on the day of a bleeding complication in patients with major bleedings. This level was significantly lower than the maximum INR in patients who did not get a bleeding complication, indicating that the treatment with
risk factors for heparin-induced bleeding

Table 3. Multivariate Analysis of Prognostic Factors for Major Bleeding

<table>
<thead>
<tr>
<th>Variable</th>
<th>Continuous Univariate</th>
<th>Continuous Multivariate</th>
<th>Dichotomous Univariate</th>
<th>Dichotomous Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.001</td>
<td>-</td>
<td>0.000</td>
<td>0.025</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>0.278</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>0.026</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td>Bleeding diathesis</td>
<td></td>
<td></td>
<td>0.002</td>
<td>0.012</td>
</tr>
<tr>
<td>Cardiopulmonary</td>
<td></td>
<td></td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>resuscitation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent trauma or</td>
<td></td>
<td></td>
<td>0.005</td>
<td>0.028</td>
</tr>
<tr>
<td>surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukocytes</td>
<td>0.000</td>
<td>-</td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>0.360</td>
<td>-</td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td>Duration of symptoms</td>
<td>0.018</td>
<td>-</td>
<td>0.012</td>
<td></td>
</tr>
<tr>
<td>Body surface area</td>
<td>0.014</td>
<td>0.045</td>
<td>0.016</td>
<td></td>
</tr>
</tbody>
</table>

Variables were entered both as continuous and dichotomous parameters, using the following cut-off levels: WHO grade 1-2 v grade 3-4; platelets, > or <150 x 10^9/L; leukocytes, > or <10 x 10^9/L; duration of symptoms, > or <2 d; body surface area, > or <2 m^2.

...coumarins did not have a major impact on the bleeding risk. Analysis of the INR by the use of logistic regression or the categorizing of the INR did not show any relationship between INR and bleeding complications.

Multivariate analysis. Multivariate analysis using stepwise logistic regression (Table 3) showed the WHO performance score, a history of a bleeding tendency, recent trauma or surgery, and the body surface area as independent prognostic factors. Including the drug in the regression analysis did not increase the log likelihood.

Other findings. The bleeding complications were analyzed according to the criteria for high or low risk of bleeding that were assigned before the study began (Table 4). Major bleedings occurred in 6% of the patients classified as being at low risk, as compared with 17% of the patients at high risk for bleeding (P = .045). The anti-Xa levels were similar in these groups, median 0.48 U/mL, and the doses (U/24 h/m^2) were not significantly different either.

To evaluate the scoring system as described by Landefeld et al, point scores were calculated for each patient. Table 5 shows that this scoring system did not identify patients with major bleeding in our study.

On the basis of our multivariate analysis, we developed a new scoring system: WHO grade 2, 1 point; WHO grade 3 or 4, 2 points; history of a bleeding diathesis, 2 points; recent (<2 months) trauma or surgery, 1 point; body surface area less than 2 m^2, 2 points. Using this scoring system, we found that a score 5 or greater identified 44% of the patients with a major bleeding, with a false-positive rate of 9% (Table 5).

To determine the relationship between onset of bleeding and the duration of treatment, the risk of bleeding was calculated from the number of first bleedings and the number of patients at risk at the time of bleeding. Figure 3 shows that the risk of bleeding (major plus minor complications) was high on the first 3 days of treatment. Patients treated with Fragmin had fewer bleedings after day 3 as compared with the heparin group. This difference was not statistically significant, by comparing the cumulative incidences of bleedings with the log-rank test.

DISCUSSION

In this study, we recognized two new independent prognostic factors for major bleeding during heparin treatment: the WHO performance score and the total body surface area. We confirmed the previously noted prognostic value of two other clinical factors at diagnosis: history of a bleeding tendency and recent trauma or surgery. We could not confirm the reported prognostic relevance of age, sex, anemia, and cancer.

The performance status classification according to a 5-grade scale has not been included in any previous analysis of heparin treatment. It is a well-known, helpful parameter in reporting results of cancer treatment. The score was the most powerful predictor of bleeding in this study. If the relevance of the predictor will be confirmed in subsequent prospective studies, it will provide a very simple parameter for routine clinical use.

The previously reported risk factors age, sex, anemia, and cancer were not supported in the present study. This cannot be explained by the sample size for the variables age, sex, and cancer. For the variable anemia, it could be relevant that we had very few patients with a severe anemia. In severe anemia, the platelet-vessel wall interaction is disturbed, since red blood cells enhance platelet adhesion. Furthermore, correction of anemia in patients with uremia shortens the bleeding time. This would support severe anemia as a risk factor for bleeding. Age and sex were not consistent risk factors in other studies, and the differences among the studies are difficult to explain. There is no support from the pathophysiology that age and sex have a major impact on hemostasis. The differences that have been reported for the risk factor cancer may be explained by patient selection. Depending on the type and the stage of the malignancy, cancer influences hemostasis.

In this study, which is the first analysis that also includes patients treated with therapeutic doses of LWMH, we could not find a difference in risk factors for patients treated with heparin or LMWH. The only difference was a relative decrease in LMWH-induced bleedings after 3 days of treatment. However, this difference was not statistically significant. These data suggest that the mechanisms that cause bleeding are similar for heparin and LMWH. Possible differences are most likely due to quantitative differ-
bleeding rate in our study was significantly related to higher thromboembolism.

Capacity to induce bleeding that influence hemostasis by other mechanisms, eg, inhibition of thrombin activity and platelet function. The observed bleedings for patients treated with heparin dose adjustments on the basis of anti-Xa assays, most of the unidentified mechanisms. LMWHs inhibit platelet function less than standard heparin and have a decreased ability to surface area. This suggests that heparin and LMWH have a contrast to Levine et al, we did not observe a relationship effects can be mediated by one of these, or by as yet unidentified mechanisms. LMWHs inhibit platelet function less than standard heparin and have a decreased ability to potentiately thrombin inhibition. However, the similar bleeding rates in this study do not support the hypothesis that the bleeding-inducing activity of heparin and LMWH are attributable to one of both mechanisms. The results indicate that monitoring treatment with anti-Xa levels will not prevent all bleedings, since anti-Xa levels within a certain range are not a good marker for the other effects of heparin and LMWH on hemostasis.

This study has one limitation related to the prestudy selection of a high- and low-risk group. The therapeutic range assessed before the study began was 0.4 to 0.9 anti-Xa U/mL for the low-risk group, and 0.3 to 0.6 U/mL for the high-risk group. Treatment according to these prestudy criteria could have influenced the outcome and the analysis of the risk factors. However, it is unlikely that this is the case, since it appeared at the end of the trial that both risk groups had been treated with similar doses and that the median anti-Xa levels did not differ between the groups.

The results of this study should be proven in prospective studies. So far, one scoring system for the prediction of major bleeding has been published by Landefeld et al, and we decided to examine its predictive capacity in our series. This scoring system was not effective, probably due to differences in study population; 70% of the patients in their study received heparin to prevent arterial thromboembolism, including patients who underwent aortic or mitral valve replacement and patients with atrial fibrillation. The new scoring system that we developed on basis of the multivariate analysis may be useful in further studies in patients with venous thromboembolism.

If our results are validated, what implications would these have for the management of patients with deep venous thromboembolism? The narrow therapeutic range and the wide individual variability in heparin sensitivity necessitate monitoring of high doses with a laboratory test despite the limitations of the tests. In high-risk patients, monitoring will not prevent all major bleedings. Since most bleedings occur in the first days of treatment, it should be studied whether choosing an appropriate initial dose adapted to the patient's body surface area or weight can improve the safety of heparin and LMWH treatment.

ACKNOWLEDGMENT

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REFERENCES

Identification of risk factors for bleeding during treatment of acute venous thromboembolism with heparin or low molecular weight heparin

HK Nieuwenhuis, J Albada, JD Banga and JJ Sixma