Blood Coagulation, Fibrinolysis and Cellular Haemostasis

Predictive variables for major bleeding events in patients presenting with documented acute venous thromboembolism. Findings from the RIETE Registry

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Summary
A score that can accurately determine the risk of major bleeding during anticoagulant therapy may help to make decisions on anticoagulant use. RIETE is an ongoing registry of consecutive patients with acute venous thromboembolism (VTE). We composed a score to predict the risk for major bleeding within three months of anticoagulant therapy. Of 19,274 patients enrolled, 13,057 (67%) were randomly assigned to the derivation sample, 6,572 to the validation sample. In the derivation sample 314 (2.4%) patients bled (fatal bleeding, 105). On multivariate analysis, age >75 years, recent bleeding, cancer, creatinine levels >1.2 mg/dl, anemia, or pulmonary embolism at baseline were independently associated with an increased risk for major bleeding. A score was composed assigning 2 points to recent bleeding, 1.5 to abnormal creatinine levels or anemia, 1 point to the remaining variables. In the derivation sample 2,654 (20%) patients scored 0 points (low risk); 9,645 (74%) 1–4 points (intermediate); 758 (5.8%) >4 points (high risk). The incidences of major bleeding were: 0.3% (95% confidence interval [CI]: 0.1–0.6), 2.6% (95% CI: 2.3–2.9), and 7.3% (95% CI: 5.6–9.3), respectively. The likelihood ratio test was: 0.14 (95% CI: 0.07–0.27) for patients at low risk; 2.96 (95% CI: 2.18–4.02) for those at high risk. In the validation sample the incidence of major bleeding was: 0.1%, 2.8%, and 6.2%, respectively. In conclusion, a risk score based on six variables documented at entry can identify VTE patients at low, intermediate, or high risk for major bleeding during the first three months of therapy.

Keywords
Venous thromboembolism, bleeding complications, prediction

Introduction
Bleeding is the major side effect of anticoagulant therapy in patients with venous thromboembolism (VTE) (1–4). Reliable information on the factors determining the risk for major bleeding may facilitate better use of therapy by improving selection of patients in whom its benefit will likely outweigh the risk, and by identifying those who may benefit from careful management. In addition, early detection and prompt treatment of major bleeding with supportive measures might reduce mortality.

So far two prospectively validated prediction rules have been published for assessing individual risk of major bleeding during the first three months, both with several limitations in clinical practice. Over 50% of patients in one study received anticoagulant therapy to prevent arterial thromboembolism (i.e. cardiac valve replacement, atrial fibrillation) (5). The other study was constructed and validated with VTE patients participating in a randomized clinical trial (6). Since patients with contraindications for anticoagulant therapy were not included in that trial, their findings may hardly be translated to real world.

The RIETE Registry is an ongoing, international (Spain, France, Italy, Israel, Argentina), multicenter, prospective registry of consecutive patients presenting with symptomatic acute VTE confirmed by objective tests (7–11). In this analysis, the inci-
Table 1: Clinical characteristics, treatment details and three-month outcome of the two samples of patients with VTE.

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Derivation sample (N=13,057)</th>
<th>Validation sample (N=6,572)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (males)</td>
<td>6432 (49%)</td>
<td>3264 (50%)</td>
<td>0.593</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>66 ± 17</td>
<td>66 ± 17</td>
<td>0.772</td>
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<tr>
<td>Body weight (mean ± SD)</td>
<td>74 ± 15</td>
<td>74 ± 16</td>
<td>0.527</td>
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<tr>
<td>Risk factors for VTE</td>
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<tr>
<td>Previous VTE</td>
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<tr>
<td>Chronic lung disease</td>
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<td>Recent major bleeding</td>
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<tr>
<td>Antiplaetc (AID) therapy</td>
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<td>Corticosteroid therapy</td>
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<td>Laboratory tests</td>
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<tr>
<td>Abnormal creatinine levels</td>
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<tr>
<td>Platelet count &lt;100,000/mm³</td>
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<td>Anemia</td>
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<td>VTE characteristics</td>
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<td>Clinically overt PE</td>
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<td>Initial therapy</td>
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<tr>
<td>LMWH</td>
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<td>LMWH, mean doses (IU/kg/day)</td>
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<td>UFH</td>
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<td>Inferior vena cava filter</td>
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<td>Long-term therapy</td>
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<td>LMWH</td>
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<td>AVK drugs</td>
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<td>3-month outcome</td>
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<tr>
<td>Recurrent VTE</td>
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<td>Fatal PE</td>
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<td>Minor bleeding</td>
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<tr>
<td>Major bleeding</td>
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<tr>
<td>Fatal bleeding</td>
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<td>Overall death</td>
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VTE, venous thromboembolism; NSAIDs, nonsteroidal anti-inflammatory drugs; PE, pulmonary embolism; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; IU, international units; AVK, anti-vitamin K drugs; CI, confidence intervals; NS, non significant.

dence of major bleeding within three months of anticoagulant therapy was evaluated first. Then, a bleeding risk prediction score based on variables that can be obtained before the institution of anticoagulant therapy was composed. The aim of the study was to propose a risk score based on VTE patients included in a large registry reflecting real-life current clinical practice.

Patients and methods

Inclusion criteria

Consecutive patients with symptomatic, acute deep vein thrombosis (DVT) or pulmonary embolism (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 blind therapy or if they will not be available for a three-month follow-up. All patients provided oral consent to their participation in the registry, according to the requirements of the ethics committee within each hospital.

The attending physicians ensure that eligible patients were consecutively enrolled. Data are recorded on a computer-based case report form at each participating hospital and submitted to a centralized coordinating center through a secure website. Patient identities remain confidential because they are identified by a unique number assigned by the study coordinating center, which is responsible for all data management. Data quality is regularly monitored and documented electronically 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 organizations, who compare the medical records with the data in the web. A full data audit is performed at periodic intervals.


Study design
The major outcome for this study was the ability to distinguish between patients at low, mild or high risk of experiencing major bleeding during the first 90 days of therapy. 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.

Study variables and definitions
The following parameters are recorded: patient's baseline characteristics (gender, age, body weight); clinical status including any coexisting or underlying conditions such as chronic heart or lung disease, or renal insufficiency; recent (<15 days prior to VTE) major bleeding; risk factors for VTE (cancer, immobilization, surgery); use of antiplatelets, corticosteroids or nonsteroidal anti-inflammatory drugs; biological data (serum creatinine levels, platelet count and anemia); the type and dose of treatment received upon VTE diagnosis; and the outcome during the first three months of therapy. Immobilized patients are defined as non-surgical patients who had been immobilized (i.e. total bed rest with bathroom privileges) for ≥4 days in the two-month period prior to VTE diagnosis. Surgical patients are defined as those who had undergone an operation in the two months prior to VTE.

Anemia was defined as an haemoglobin content <13 g/dl for men and <12 g/dl for women.

Follow-up
Patients were managed according to the clinical practice of each participating hospital and were not subject to any predetermined intervention. After hospital discharge, all patients were followed-up for three months. 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 documented by repeat ultrasonography, venography, lung scanning, helical-CT scan or pulmonary angiography.

Statistical analysis
A commercial software package (SPSS 13.5, SPSS Inc., Chicago, IL, USA) was used to calculate odds ratios and corresponding 95% confidence intervals (CI), and a p-value <0.05 was considered to be statistically significant. The predictive value of selected variables for major bleeding during the first three months of therapy was evaluated by logistic regression. Candidate variables available at entry were based on published literature or in expert opinion. Multivariate logistic analysis was carried out to
identify independent predictors of bleeding after adjustment for interactions between characteristics, in order to predict any bleeding event, and the corresponding Kaplan-Meier survival curves were constructed. Significance level of p < 0.10 was considered to include and exclude variables in the final multivariate model. The long-term treatment received by the patients was not included in the multivariate models as it has been performed using variables available at entry. Variables after entry into the registry were not included for the predictive bleeding score.

We composed a risk scoring system in which we assigned points to each risk factor according to the regression coefficients \( \beta \), rounding to the nearest integer. A risk score was assigned to each patient by adding up the points for each risk factor present. Then, we selected the best cut-off score discriminating between low-, intermediate- and high-risk patients for major bleeding. We performed a cross-validation procedure by selecting the sample randomly into 67% of patients for the derivation sample and 33% for the internal validation sample. The likelihood ratio for each stratum was calculated by dividing the percentage of patients with major bleeding in that subgroup by the percentage without bleeding in that subgroup.

### Results

As of June 2007, 19,274 patients with acute VTE were enrolled at 123 participating hospitals. Of them, 13,057 (67%) were randomly assigned to the derivation sample, 6,572 to the validation sample. Both samples had similar clinical characteristics at baseline, treatment details and three-month outcome (Table 1).

### Derivation patient group

During the study period 314 patients (2.4%) had major bleeding (fatal in 105). The most frequent sites of bleeding were the gastrointestinal tract (34%), muscular (15%), genitourinary (12%), and brain (11%). In the univariate analysis age > 75 years, body weight < 70 kg, cancer, recent immobility, recent bleeding, use of antiplatelets or corticosteroids, creatinine levels > 1.2 mg/dl, abnormal prothrombin time, thrombocytopenia, anemia, and PE diagnosis at baseline were associated with an increased risk for major bleeding (Table 2). Multivariate analysis confirmed that only age > 75 years, recent bleeding, cancer, abnormal creatinine levels, anemia, and PE diagnosis at baseline were independently associated with an increased risk for major bleeding (Table 3). Patients with recent bleeding were assigned 2 points, those with creatinine levels > 1.2 mg/dl or anemia 1.5 points each, age > 75 years, cancer or PE diagnosis at baseline 1 point each.

### Clinical score

When these six independent variables were added into the derivation patient group, patients with a risk score of 0 points had a 0.3% (95% CI: 0.1–0.6) incidence of major bleeding (9 in 2,654 patients) and they were identified as low-risk, compared to the 2.6% (95% CI: 2.3–2.9) incidence in 9,645 (75%) patients at intermediate-risk (score 1–4), and the 7.3% (95% CI: 5.6–9.3) in 758 (5.8%) patients at high-risk, as shown in Table 4a. The incidence of major bleeding in the three groups were statistically different (p < 0.001) as shown in Table 4b and in Figure 1. The likelihood ratio test was 0.14 (95% CI: 0.07–0.27) for patients at low

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### Table 3: Multivariate analysis for major bleeding in the derivation sample.

<table>
<thead>
<tr>
<th></th>
<th>( \beta )</th>
<th>Odds ratio (95% CI)</th>
<th>P-value</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent major bleeding</td>
<td>0.996</td>
<td>2.7 (1.6–4.6)</td>
<td>&lt;0.001</td>
<td>2</td>
</tr>
<tr>
<td>Creatinine levels &gt;1.2 mg/dl</td>
<td>0.761</td>
<td>2.1 (1.7–2.8)</td>
<td>&lt;0.001</td>
<td>1.5</td>
</tr>
<tr>
<td>Anemia</td>
<td>0.739</td>
<td>2.1 (1.7–2.7)</td>
<td>&lt;0.001</td>
<td>1.5</td>
</tr>
<tr>
<td>Cancer</td>
<td>0.533</td>
<td>1.7 (1.4–2.2)</td>
<td>&lt;0.001</td>
<td>1</td>
</tr>
<tr>
<td>Clinically overt PE</td>
<td>0.545</td>
<td>1.7 (1.4–2.2)</td>
<td>&lt;0.001</td>
<td>1</td>
</tr>
<tr>
<td>Age &gt;75 years</td>
<td>0.504</td>
<td>1.7 (1.3–2.1)</td>
<td>&lt;0.001</td>
<td>1</td>
</tr>
</tbody>
</table>

PE, pulmonary embolism; CI, confidence intervals.

### Table 4: Application of the clinical score (a) and Bleeding risk Index classification (b).

<table>
<thead>
<tr>
<th>Score</th>
<th>Derivation sample (N=13,057)</th>
<th>Validation sample (N=6,572)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Points</td>
<td>Patients, N (%)</td>
<td>Major bleeding, % (95% CI)</td>
</tr>
<tr>
<td></td>
<td>Major bleeding N</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2654 (20%)</td>
<td>9 (0.3–1.0)</td>
</tr>
<tr>
<td>1</td>
<td>3169 (24%)</td>
<td>34 (1.1–0.7)</td>
</tr>
<tr>
<td>1.5–2</td>
<td>2495 (19%)</td>
<td>59 (2.4–1.8)</td>
</tr>
<tr>
<td>2.5–3</td>
<td>2251 (17%)</td>
<td>66 (2.9–2.2)</td>
</tr>
<tr>
<td>3.5–4</td>
<td>1730 (13%)</td>
<td>91 (5.3–4.2)</td>
</tr>
<tr>
<td>4.5–5</td>
<td>611 (4.7%)</td>
<td>39 (6.4–4.4)</td>
</tr>
<tr>
<td>5.5–6</td>
<td>124 (0.9%)</td>
<td>13 (10.5–1.6)</td>
</tr>
<tr>
<td>&gt;6</td>
<td>23 (0.2%)</td>
<td>3 (13.0–0.28)</td>
</tr>
</tbody>
</table>

#### a) Application of clinical score

<table>
<thead>
<tr>
<th>Score</th>
<th>Derivation sample (N=13,057)</th>
<th>Validation sample (N=6,572)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Points</td>
<td>Patients, N (%)</td>
<td>Major bleeding, % (95% CI)</td>
</tr>
<tr>
<td></td>
<td>Major bleeding N</td>
<td></td>
</tr>
<tr>
<td>Low risk (0)</td>
<td>2654 (20%)</td>
<td>9 (0.3–1.0)</td>
</tr>
<tr>
<td>Intermediate risk (1–4)</td>
<td>9645 (74%)</td>
<td>250 (2.6–2.3)</td>
</tr>
<tr>
<td>High risk (&gt;4)</td>
<td>758 (5.8%)</td>
<td>55 (7.3–5.6–9.3)</td>
</tr>
</tbody>
</table>

#### b) Bleeding risk index classification

N, number; CI, confidence intervals.
risk; 1.08 (95% CI: 0.91–1.28) for those at intermediate risk; 2.96 (95% CI: 2.18–4.02) for those at high risk. Within the high-risk subgroup of patients, those scoring >5 (147 patients, 1.1%) had an 11% incidence of bleeding.

Validation patient group
In this group 159 patients (2.4%) had major bleeding (fatal in 41). The most frequent sites of bleeding were the gastrointestinal tract (37%), brain (15%), and muscle (12%). When we cross-validated the predictive model into the validation patient group, the incidence of major bleeding was 0.1% (95% CI: 0.0–0.2) in low-risk patients; 2.8% (95% CI: 2.4–3.3) in those at intermediate risk, and 6.2% (95% CI: 4.0–9.1) in high-risk patients. The incidence of major bleeding in the three groups were statistically different (p <0.001) as shown in Figure 2. The likelihood ratio test was: 0.03 (95% CI: 0.01–0.20) for patients at low risk; 1.16 (95% CI: 0.92–1.48) for those at intermediate risk; 2.65 (95% CI: 1.61–4.32) for those at high risk.

Discussion
Our data, obtained from a large prospective series of consecutive patients in the RIETE registry, reveal that with six clinical variables documented at entry, it is possible to identify VTE patients at low, intermediate, or high risk for major bleeding during the first three months of therapy. Major bleeding occurred in 2.4% of patients, and in one in every three cases major bleeding was fatal. Thus, its clinical impact is considerable. The frequency of major bleeding in our study was similar to that reported in several randomized clinical trials (2, 12–14), and this is important because, unlike the careful patient selection that characterizes clinical trials, our patient population reflects routine, unmonitored medical practice involving a broad spectrum of patients with VTE. We found elderly patients, or those with co-morbid diseases such as cancer, recent bleeding, anemia or renal insufficiency, to be more likely to have major bleeding than those without these features. Such data are not usually available from the published randomized clinical trials of anticoagulant therapy, because these “high-risk” patients are typically excluded from such studies. However, recent reports have demonstrated their influence on the risk for bleeding (15–18). The Outpatient Bleeding Risk Index included four independent risk factors: age ≥65 years, history of gastrointestinal bleeding, history of stroke, and one or more of four specific comorbid conditions: recent myocardial infarction, haematocrit <30%, creatinine levels >1.5 mg/dl, or diabetes mellitus (5). However, over 50% of patients received warfarin to prevent arterial thromboembolism instead of VTE. The Dutch score was constructed and validated with VTE patients participating in a clinical trial, and included three variables: age, gender and cancer (6). However, patients with recent gastrointestinal bleeding, stroke, or contraindications for anticoagulant therapy were ineligible for the study. Other clinical scores have been developed, but not in patients with VTE (10, 19).

The present study has potential limitations that should be addressed. First, the study is limited by the lack of information on international normalised ratio (INR) control and details relating to type of vitamin K antagonists (VKA) used. Second, the risk of bleeding is also probably modified by characteristics that change during the course of therapy, such as the use of concomitant medications, or the presence of intercurrent illnesses. Third, we composed a risk prediction score based on registry data, which was used for both the derivation and the validation patient group, although not the same patients, and this methodology reduces the external validity of the score. Finally, VTE patients for whom a follow-up of three months would not be feasible are not included in RIETE. These may have been the sickest patients with an even higher risk of bleeding.

In summary, we composed a simple risk score based on variables available at entry, that can reliably identify VTE patients at
low, mild or high risk for major bleeding. This information may be useful for clinicians weighing the risks and benefits of prescribing long-term anticoagulant therapy.

Acknowledgements

We express our gratitude to Sanofi-Aventis for supporting this Registry, with an unrestricted educational grant and the Registry Coordinating Center, S & H Medical Science Service, for their logistic and administrative support. We also express our gratitude to Salvador Ortiz for statistical advice.

Members of the RIETE Group


References
