The Outpatient Bleeding Risk Index

Validation of a Tool for Predicting Bleeding Rates in Patients Treated for Deep Venous Thrombosis and Pulmonary Embolism

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Background: Long-term anticoagulation prevents recurrent thrombosis in patients with idiopathic deep venous thrombosis or pulmonary embolism, but with a risk of clinically important so-called major bleeding. Physician- and patient-based decisions on the optimal duration of therapy are sensitive to the bleeding risk. The Outpatient Bleeding Risk Index potentially provides a means of calculating the potential risk of bleeding using easily elicited clinical findings, but, to our knowledge, the authors of the index have provided the only published validation of it. We sought to determine the accuracy of the index in our population of patients.

Methods: We prospectively applied the Outpatient Bleeding Risk Index to consecutive patients in our clinic who had been objectively diagnosed as having pulmonary embolism or deep venous thrombosis and who were about to undergo standard therapy. Standard therapy consisted of a minimum of 5 days of low-molecular-weight heparin therapy overlapped with warfarin sodium therapy, and continuation of warfarin therapy for at least 3 months, with a target international normalized ratio of 2.5. Patients were placed in 3 risk groups (low, moderate, or high), as defined by the index. The survival curves of the groups, using major hemorrhages as the events, were then compared by the log-rank test.

Results: Bleeding rates were lower than expected, but the index did discriminate between low- and moderate-risk groups ($P = .03$, log-rank test). The rate of major hemorrhage per 100 person-years was 0% (95% confidence interval, 0%-2.8%) in the low-risk group and 4.3% (95% confidence interval, 1.1%-11.1%) in the moderate-risk group. The rate in the high-risk group could not be defined because only 2 patients were at high risk.

Conclusion: The Outpatient Bleeding Risk Index discriminates between low- and moderate-risk patients, and could be used to guide decisions on the optimal duration of anticoagulant therapy.

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It is apparent that long-term anticoagulation for patients with idiopathic deep venous thrombosis or pulmonary embolism prevents recurrent thrombosis. Recent studies suggest that the recurrent thrombosis rate may be as high as 27% per year, but the risk of major hemorrhage is 3.7% per year.1 In patients untreated, the major hemorrhage rate was 0%. Clearly, the trade-off to ongoing anticoagulation is the risk of major bleeding. Recent decision analyses2,3 suggest that rates of major hemorrhage have a significant impact on determining the optimal duration of anticoagulant therapy, from a patient and a physician perspective. The decision analysis performed by our group demonstrated that patient decisions are most sensitive to the rate of major bleeding and the burden of anticoagulant therapy. If major bleeding rates are less than approximately 2.5% per year, lifelong therapy is favored in patients with idiopathic deep venous thrombosis. A valid predictive index to determine bleeding risks would, therefore, be of benefit.

To estimate the risk for major bleeding during anticoagulant therapy, a few prediction rules have been published. One of the more promising indexes was based on a study by Landefeld et al4 that identified 5 independent risk factors for major bleeding—65 years or older, history of stroke, history of gastrointestinal (GI) tract bleeding, a serious comorbid condition (recent myocardial infarction, renal insufficiency, or severe anemia), and atrial fibrillation. Beyth et al5 developed a modified Outpatient Bleeding Risk Index, and found that cumulated rates of major bleeding at 12 months were 3%, 12%, and 48% in pa-
METHODS

We prospectively applied the Outpatient Bleeding Risk Index of Beyth et al14 to patients in our clinic diagnosed as having a pulmonary embolism or deep venous thrombosis, treated with low-molecular-weight heparin therapy followed by prolonged warfarin sodium therapy. Our thrombosis unit serves as a secondary and tertiary care center, with most patients in a 700,000-population region receiving treatment from our unit. Patients were enrolled in treatment studies approved by the local research ethical board, and they signed informed consent forms. Major bleeding in this group of patients was defined as bleeding that led to a loss of 2 U of blood in a 7-day period or bleeding that was otherwise life threatening (ie, the same definition used by Beyth et al). All other hemorrhages were considered minor. Deep venous thrombosis was diagnosed objectively with ultrasonography or phlebography. Pulmonary emboli were diagnosed by a high-probability ventilation-perfusion lung scan with a moderate to high pretest clinical probability, a spiral computed tomographic scan with contrast medium, or pulmonary angiography.

Using the Outpatient Bleeding Risk Index, 1 point was scored for each of the following: (1) 65 years or older, (2) history of GI tract bleeding, (3) history of stroke, and (4) one or more comorbid conditions (recent myocardial infarction, severe anemia, renal impairment, or diabetes mellitus). The patient was low risk if the score was 0, moderate risk if the score was 1 or 2, and high risk if the score was 3 or more.

Table 1. Frequency of Each Risk Factor According to Risk Category

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Moderate</td>
<td>53</td>
<td>2</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td>High</td>
<td>71</td>
<td>2</td>
<td>1</td>
<td>36</td>
</tr>
</tbody>
</table>

*Data are given as number of patients.
†Patients were low risk if their Outpatient Bleeding Risk Index score was 0 (n = 128), moderate risk if their score was 1 or 2, and high risk if their score was 3 or more.
‡The risk factors were as follows: 1, 65 years or older; 2, history of stroke; 3, history of gastrointestinal tract bleeding; and 4, the presence of one or more comorbid conditions (recent myocardial infarction, severe anemia, renal impairment, or diabetes mellitus).

Table 2. Number of Bleeding Events per Risk Category

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Total No. of Patients</th>
<th>Type of Hemorrhage</th>
<th>Minor</th>
<th>Major</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>128</td>
<td></td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>74</td>
<td></td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>18</td>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Overall</td>
<td>92</td>
<td></td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>High</td>
<td>2</td>
<td></td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

*The risk categories are described in the second footnote to Table 1.

We observed 222 patients for a mean of 18.5 months (SD, 14.9 months; range, 3-70 months). There were 342 patient-years of observation. The mean age of the patients was 58.4 years; 35.1% of the patients had cancer, 58.1% had idiopathic venous thromboembolism, and 6.8% had venous thromboembolism due to transient risk factors. There were 95 women and 127 men. Table 1 summarizes the frequency of each point in the index according to risk category. The most frequent point by far was 65 years or older. Of the 222 patients, 128 (57.7%) were low risk. This group had 7 minor hemorrhages (5.5%), but no major hemorrhages. Overall, 41.4% (92/222) of the patients were at moderate risk, and 5 (5.4%) (95% confidence interval, 1.8%-12.2%) had a major hemorrhage over a mean follow-up of 15.2 months, for an annualized risk of 4.3% (95% confidence interval, 1.1%-11.1%), or 4.3 events per 100 patient-years of observation. In the moderate-risk group, 74 patients (33.3%) had a score of 1. This group had 4 major hemorrhages (5.4%; 95% confidence interval, 1.5%-13.3%) and 5 minor bleeding events (6.7%) over a mean follow-up of 17 months. There were an additional 18 (8.1%) of the 222 patients at moderate risk, but they had a score of 2. One had a major hemorrhage (5.6%; 95% confidence interval, 1.4%-27.0%) and no minor bleeding events over a mean follow-up of 14 months. Only 2 patients of the 222 followed up were at high risk. Only 1 of the 2 had a minor hemorrhage after a mean ± SD follow-up of 12 ± 6 months. Bleeding events by score are summarized in Table 2.

RESULTS

The differences between the low- and moderate-risk groups were statistically significant (P = .03, log-rank test) (Figure). The 5 major hemorrhages varied in the time of occurrence; they occurred after 1, 3, 11, 12, and 36 months of treatment. All the major bleeding events were in the GI tract, with 2 in the upper GI tract and 3 in the lower GI tract (Table 3).
To estimate the risk for major bleeding during anticoagulant therapy, a few prediction rules have been published. Landefeld and Beyth\textsuperscript{6} reported that the average annual frequencies of fatal, major, and minor bleeding during warfarin therapy were 0.6\%, 3.0\%, and 9.6\%, respectively. These frequencies are approximately 5 times those expected without warfarin therapy. It was suggested that an individual patient’s risk for major anticoagulant-related bleeding could be estimated based on specific risk factors, such as the intensity of the anticoagulant effect achieved and the presence of serious comorbid diseases. They also concluded that during the first month of warfarin therapy, the risk for major bleeding is approximately 10 times the risk after the first year of therapy, but this is of little help in patients who require at least 3 months of oral anticoagulation. Beyth et al\textsuperscript{5} have more recently promoted the Outpatient Bleeding Risk Index. We believed the major bleeding event rates they reported were much higher than those we observed in our patients, so we conducted a prospective evaluation of the index. Major bleeding event rates using the Outpatient Bleeding Risk Index in our patient population were lower than previously published rates, with no major bleeding in the low-risk group and 4.3 events per 100 patient-years of observation in the moderate-risk group. These rates are much lower than those in the validation study published by Beyth et al. It is possible our rates were lower because we have an anticoagulation service that provides care similar to that described recently by Beyth et al.\textsuperscript{7} In that study, the rates were almost half those previously published. Regardless, we have demonstrated that the index did discriminate between low- and moderate-risk groups (P = .03, log-rank test). Given that the major bleeding event rate was greater than 4\% per year of patient observation in this group, the Outpatient Bleeding Risk Index should be a useful tool to use in decisions regarding the optimal duration of anticoagulation therapy. The definition of major bleeding used by Beyth et al is not that used in many trials evaluating the treatment of patients with venous thromboembolic diseases. However, using other definitions did not change the results (data not shown); thus, our results are probably generalizable to centers similar to ours.

Nieuwenhuis et al\textsuperscript{8} recognized 2 independent prognostic factors for major bleeding during heparin treatment: the World Health Organization performance score and the total body surface area. They found that the scoring system, as described by Landefeld et al,\textsuperscript{5} did not identify patients with major bleeding in their study, leading them to develop a new scoring system. Nieuwenhuis et al determined World Health Organization performance status, history of a bleeding diathesis, recent trauma or surgery, and body surface area less than 2 m\textsuperscript{2} to be risk factors. A score of 5 or greater identified 44\% of the patients with major bleeding, with a false-positive rate of 9\%. Patients with World Health Organization grades 3 and 4 experienced minor hemorrhages more often. Major hemorrhages occurred in 6\% of the patients classified as low risk, compared with 17\% of the patients at high risk for bleeding (P = .04). We did not apply the scale of Nieuwenhuis et al to all our patients, but in a recent randomized treatment trial,\textsuperscript{10} the scale was not predictive of bleeding. Van der Meer et al\textsuperscript{11} have reported that age, type of coumarin used, and achieved intensity of anticoagulation are important predictors of major hemorrhage. We could not evaluate the influence of different coumarin derivatives because in Canada, most patients (all patients in our study) receive warfarin. Also, we have not looked at achieved intensity of anticoagulation because all patients had a target international normalized ratio of 2.0 to 3.0.

Because the major complication of anticoagulant therapy is the risk of bleeding, the Outpatient Bleeding Risk Index could prove useful in assessing the potential risk to patients commencing or currently undergoing anticoagulation therapy. Patient risk could be assessed in conjunction with the potential benefit of preventing recurrent thrombosis. In addition, knowledge of the risk category could indicate those in whom closer monitoring of anticoagulant therapy, including vigilant observation for signs and symptoms of bleeding, may be of benefit. The ability to classify patients with venous thrombosis at a greater risk for a hemorrhage could be beneficial in guiding anticoagulant therapy and could be incorporated in decision aids. Beyth et al\textsuperscript{7} recently demonstrated lower bleeding rates in patients who were better educated and more closely observed during anticoagulant therapy.

At our institution, patients commencing or considering anticoagulation therapy are assessed for their risk of major hemorrhage using the Outpatient Bleeding Risk Index.
The risk is assessed at 4.3% per year for moderate-risk patients and considered to be higher if patients score high risk by the index. The risk is factored into decisions on the optimal duration of anticoagulant therapy. We are evaluating whether the Outpatient Bleeding Risk Index can be used as a preventive measure for patients who have a greater risk for a major hemorrhage by subjecting them to more intense monitoring of the oral anticoagulation therapy. The Outpatient Bleeding Risk Index could prove effective in decreasing the rates of major hemorrhage and death in patients undergoing or commencing anticoagulant therapy.

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REFERENCES