


Research Correspondence

Comparative Analysis of the HAS-BLED Score With Other Bleeding Risk Scores, Using Estimates of Net Reclassification Improvement and Integrated Discrimination Improvement

To the Editor: We thank Drs. Rosenstein and DiMaggio for their comments. We agree that estimates of net reclassification improvement (NRI) and integrated discrimination improvement (IDI) offer potentially useful analytic methods offering incremental information relative to the c-statistic. Based on their suggestions, we have calculated these statistics to complement the results provided in Table 7 of our paper (1), based on the low-, moderate-, and high-risk categorizations resulting from the different bleeding risk schema. Table 1 summarizes the results in terms of NRI and IDI, which together with our other analyses presented in the original paper, would reinforce the incremental utility of the HAS-BLED index over these other schemas, with the exception of the score by Shireman et al. (2), which is based on the NRI. As emphasized, the HAS-BLED score also has the advantage of simplicity. We concur with Drs. Rosenstein and DiMaggio that the NRI and IDI methodology should be considered in the assessment of future contributions as we seek to optimize the predictive accuracy of bleeding risk prediction for patients with atrial fibrillation undergoing anticoagulation.

We also agree that bleeding risk with the new oral anticoagulants may be different from warfarin, and our original paper presents the risk factors for bleeding in warfarin-only patients (Table 6 [1]) and the comparison against other scores in warfarin-only patients (and not in combination with ximelagatran users, as implied in their letter).

As Drs. Rosenstein and DiMaggio suggest, further analyses of the HAS-BLED scores in “real-world” nontrial populations would reinforce the usefulness of this score in the nontrial cohorts, and our ongoing analyses in such ‘real world’ cohorts again confirm the consistency of the usefulness of this score in assessing bleeding risk in patients with atrial fibrillation (6).

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Please note: This is a reply for the letter “Predicting Bleeding Risk in Anticoagulated Patients with Atrial Fibrillation” in this issue. Dr. Lip has served as a consultant for Bayer, Astella, Merck, AstraZeneca, Sanofi, BMS/Pfizer, Boitronik, Portola, and Boehringer Ingelheim; and is on the speakers’ bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, and Sanofi-Aventis. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

REFERENCES

1. Lip GY, Frison L, Halperin JL, Lane DA. Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: the HAS-BLED (Hypertension, Abnormal

<table>
<thead>
<tr>
<th>HAS-BLED Versus</th>
<th>Difference in Predicted Probability of an Event</th>
<th>NRI</th>
<th>SE</th>
<th>z-score</th>
<th>p Value</th>
<th>IDI</th>
<th>SE</th>
<th>z-score</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shireman et al. (2)</td>
<td>0.644</td>
<td>-0.025</td>
<td>0.089</td>
<td>0.077</td>
<td>1.15</td>
<td>0.25</td>
<td>0.668</td>
<td>0.163</td>
<td>4.10</td>
</tr>
<tr>
<td>HEMORR_HAGES (3)</td>
<td>0.400</td>
<td>-0.015</td>
<td>0.152</td>
<td>0.078</td>
<td>1.95</td>
<td>0.05</td>
<td>0.416</td>
<td>0.135</td>
<td>3.07</td>
</tr>
<tr>
<td>Beyth et al. (4)</td>
<td>0.797</td>
<td>-0.031</td>
<td>0.262</td>
<td>0.054</td>
<td>4.85</td>
<td>&lt;0.0001</td>
<td>0.828</td>
<td>0.139</td>
<td>5.96</td>
</tr>
<tr>
<td>Kulier et al. (5)</td>
<td>0.850</td>
<td>-0.033</td>
<td>0.306</td>
<td>0.060</td>
<td>5.10</td>
<td>&lt;0.0001</td>
<td>0.883</td>
<td>0.143</td>
<td>6.17</td>
</tr>
</tbody>
</table>

HAS-BLED score = Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly score; IDI = integrated discriminant improvement; NRI = net reclassification improvement.
Predicting Bleeding Risk in Anticoagulated Patients With Atrial Fibrillation

We read with interest the paper by Lip et al. (1) describing the comparative validation of the HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) score. There are difficulties in evaluating the usefulness of new risk models, and a simple increase of the c-statistic does not necessarily reflect a clinically relevant improvement in describing a patient's risk status. Newer modeling has suggested that the net reclassification improvement (NRI) and integrated discrimination improvement (IDI) be evaluated in the assessment of the usefulness of potential biomarker(s) within an established risk-stratifying tool (2). When comparing models, using the NRI may reveal the advantages obtained by reclassifying a patient from one risk category to another. Although the model in the HAS-BLED comparative analysis seemed to be properly calibrated with the Hosmer-Lemeshow test, the actual number of patients who were reclassified into a different risk category (which subsequently resulted in a change of therapy) is not specified. Therefore, the number of reclassified patients who either were spared or experienced a bleeding event was not reported. Thus, without the NRI, it remains questionable if the reclassification yielded an improvement or whether the HAS-BLED model over the other schemas. If an increase in the c-statistic does not yield a meaningful change in a patient's therapeutic strategy, then the utility of such testing is not apparent. Proclaiming that the HAS-BLED score offers useful predictive capacity for bleeding risk should not be based solely on the area under the curve but should also include integrated sensitivity and specificity, both components of the IDI, as well as improvements in the reclassification tables. Therefore, although we agree with the authors that the HAS-BLED score may provide a valuable tool in discriminating patients based on bleeding risk, these additional measures will offer an incremental improvement over the c-statistic, and validate the usefulness of this score.

In addition, this combined analysis included patients treated with ximelagatran, a direct thrombin inhibitor found to have adverse effects on liver function testing (3). We suggest that the bleeding risk associated with other newer antithrombotic agents might be different and also may vary according to specific anatomic sites. For example, dabigatran was associated with less intracranial hemorrhage yet a greater risk of gastrointestinal bleeding compared with warfarin in the RE-LY (Randomized Evaluation of Long Term Anticoagulant Therapy With Dabigatran Etexilate) study (4). This variability has implications for any future risk model and suggests that each agent may require independent validation in separate cohorts.

Finally, the limitation of analysis of all major bleeding in this study to the on-treatment analysis may be less reflective of the world outside of the clinical trial than a protocol that strictly adheres to intention-to-treat analysis (5).

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