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COMMENTARY

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Disclosures

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Abstract

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In a total of 210,299 AF patients, we observed an event rate for major bleeding of 4.3 per 100 person-years. The C-statistics for the two scores were modest: 0.613 (95%CI, 0.607-0.619) for the original and 0.616 (95%CI, 0.610-0.622) for the recalibrated. The NRI was 10.0% (95%CI 7.6%-12.4%). When assessing the NRI in less than 6 months follow-up, we observed a markedly higher NRI of 34.2%. The relative IDI was 23.6% (95%CI, 15.7%-31.5%) reflecting that the recalibrated HAS-BLED score more accurately predicted bleeding events.

Recalibration of the “S” component in the HAS-BLED score, counting 2 points for a haemorrhagic stroke, resulted in an increase in the C-statistics, NRI and IDI. This approach could potentially aid physicians in a more accurate bleeding risk assessment in AF patients.
Introduction

Oral anticoagulant (OAC) treatment substantially reduces the risk of stroke and all-cause mortality in atrial fibrillation (AF) patients. However, the decision to treat these patients relies on the expected risk of stroke weighed against the expected risk of bleeding. Contemporary guideline recommendations on OAC treatment are based on the CHA₂DS₂-VASc score (assessing the risk of thromboembolism) to initiate treatment or not. The European Society of Cardiology further recommends formal assessment of the bleeding risk by the HAS-BLED score. The HAS-BLED score summarizes to a maximum of 9 points (hypertension, abnormal renal/liver function [1 or 2 points], stroke, bleeding history or predisposition, labile INR, elderly [>65], drugs/alcohol concomitantly [1 or 2 points]). A stroke currently contributes 1 point, and prior major bleeding (or its predisposition) contributes 1 point. Accurate bleeding risk assessment and optimal treatment guidance is pivotal in this frail population of AF patients who sustain an intracranial bleeding, especially given the strong associations to disability and mortality.

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We calculated two different HAS-BLED scores (original and recalibrated) at hospital discharge; only patients with a haemorrhagic stroke (non-traumatic intracranial bleeds) were reclassified in the recalibrated HAS-BLED score. Crude event rates (total number of events divided by accrued person-time) stratified by score ranging from 0-8 were reported. We did not have information on INR values; hence the “L” component was excluded from the calculations. To compare the predictive power of the scores we calculated and compared the (Harrell’s) C-statistics. We obtained estimates of bleeding risk in a competing risk of death setting, by using information directly from the cumulative incidence function. Use of competing risk analyses are advised - especially in an elderly and fragile population - to obtain adequate risk estimates, which are not biased due to the competing risk. To further compare the individual level changes in risk assessment from the two scores, we calculated a Net Reclassification Index (NRI), also in a competing risk setting. In short, the NRI evaluates the proportion of patients with a
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Results

The study population comprised 210,299 AF patients (5,898 patients were excluded due to a thromboembolic/bleeding event within 7 days after discharge) with a median age of 74 [IQR: 65-82] and 46.6% were women. During one year of follow-up we observed 7,602 (3.62%) bleeding events. The mean HAS-BLED scores were 2.13 for the original score and 2.14 for the recalibrated score. The overall crude event rate of the primary endpoint was 4.3 per 100 person-years; Table 1 shows the event rates stratified according to points for the two scores. A total of 1,479 patients were reclassified in the recalibrated HAS-BLED score based on having sustained a haemorrhagic stroke when the observation time commenced. The predictive accuracy of the two scores in terms of the C-statistics was moderate, 0.613 (95%CI, 0.607-0.619) for the original and 0.616 (95%CI, 0.610-0.622) for the recalibrated HAS-BLED score, respectively. The NRI was 10.0% (95%CI, 7.6%-12.4%) displaying a significant improvement of correct classification by the recalibrated HAS-BLED scored compared to the original score. The relative IDI was 23.6% (95%CI, 15.7%-31.5%) reflecting that the recalibrated HAS-BLED score more accurately predicted bleeding events.

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Discussion

In this nationwide cohort study reflecting clinical practice, we recalibrated the original HAS-BLED score to account for 2 points if the stroke type was a haemorrhagic stroke. We observed an improved accuracy of the recalibrated HAS-BLED score as displayed by an improved NRI of 10.0% and a relative IDI of 23%.

Although the recalibration only resulted in a modest increase in the C-statistics, the potential of improved accuracy could be higher, as we only reclassified a very small proportion of this large cohort: of 2,218 patients who sustained an ICH event, we reclassified 1,479 (0.7% of total study population). The remaining 739 patients who were not reclassified all had prior events of ischemic stroke/TIA and a major bleeding event (or anaemia).

The recalibrated HAS-BLED score could potentially be more complicated to count than the original score. The physician who is presented with a patient who has sustain an haemorrhagic stroke has to take into account if this patient already has 1 point attributing prior bleeding and prior stroke. On the other hand, counting a haemorrhagic stroke as two points (1 for stroke and 1 for bleeding) appears intuitively applicable given the nature of the outcome. Importantly, the recalibrated score performs best within short follow-up time in terms of NRI, which could be related to the patients who were actually reclassified (those with a haemorrhagic stroke); however, this could represent the early excess risk associated with such ‘high risk’ patients.

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however risk assessment in AF patients is a continuum and risk (both for bleeding and thromboembolic events) does not remain static in these patients.

In conclusion, recalibration of the HAS-BLED score, counting 2 points for a haemorrhagic stroke, resulted in an improved accuracy of predicting major bleeding events. This approach could potentially aid physicians in a more accurate bleeding risk assessment in AF patients.
References


**Table 1:** Major bleeding event rates per 100 person-years for major bleeding events according to HAS-BLED scores for 1-year follow-up in incident atrial fibrillation patients.

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<th>Recalibrated HASBLED</th>
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<td>7602</td>
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<table>
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<tr>
<td>≥3 (High risk)</td>
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<td>4103</td>
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Observation time starts after a quarantine period of 7 days relative to AF discharge.
List of abbreviations:

OAC: Oral anticoagulant
AF: Atrial fibrillation
ICD-10: International classification of disease version 10
INR: International normalized ratio
NRI: Net reclassification index
IDI: Integrated discrimination improvement
CI: Confidence interval
IQR: Interquartile range
TIA: Transient ischemic attack
Recalibration of the HAS-BLED score – should haemorrhagic stroke account for 1 or 2 points?

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<td>Complete List of Authors:</td>
<td>Nielsen, Peter; Aalborg University, Aalborg Thrombosis Research Unit Larsen, Torben; Aalborg University Hospital, Aalborg Hospital, Department of Cardiology &amp; Center for Thrombosis Research; Aalborg University, Department of Clinical Medicine Lip, Gregory; City Hospital, Centre for Cardiovascular Sciences; Aalborg University, Thrombosis Research Unit, Dept of Clinical Medicine</td>
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<td>17359</td>
<td>1294</td>
</tr>
<tr>
<td>5</td>
<td>3692</td>
<td>361</td>
</tr>
<tr>
<td>6</td>
<td>425</td>
<td>52</td>
</tr>
<tr>
<td>7</td>
<td>22</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>9 (Labile INR)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Any score</td>
<td>178676</td>
<td>7602</td>
</tr>
</tbody>
</table>

Categorised risk

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>0-2 (low risk)</td>
<td>113408</td>
<td>3499</td>
</tr>
<tr>
<td></td>
<td>3.09</td>
<td>113113</td>
</tr>
<tr>
<td>≥3 (High risk)</td>
<td>65268</td>
<td>4103</td>
</tr>
<tr>
<td></td>
<td>6.29</td>
<td>65563</td>
</tr>
<tr>
<td></td>
<td>4149</td>
<td>6.33</td>
</tr>
</tbody>
</table>

Observation time starts after a quarantine period of 7 days relative to AF discharge.
### e-Table 1: ICD codes and ATC codes used in the study.

<table>
<thead>
<tr>
<th>Condition</th>
<th>International Classification of Diseases 10th revision (ICD-10) code</th>
<th>Anatomical Therapeutic Chemical (ATC) code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>E10.0; E10.1; E10.9; E11.0; E11.1; E11.9</td>
<td>A10</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>I63; I64</td>
<td></td>
</tr>
<tr>
<td>Transient ischemic disease</td>
<td>G45</td>
<td></td>
</tr>
<tr>
<td>Abnormal ischemic function</td>
<td>I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61</td>
<td></td>
</tr>
<tr>
<td>Abnormal renal function</td>
<td>B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85</td>
<td></td>
</tr>
<tr>
<td>Prior Bleeding</td>
<td>I60-I62; D62; J94.2; H11.3; H35.6; H43.1; N02; N95; R04; R31; R58; K25.0; K26.0; K27.0; K28.0; K29.0; S06.3C; S06.4; S06.5; S06.6</td>
<td></td>
</tr>
<tr>
<td>Alcohol intake</td>
<td>E22.4; E52.9A; F10; G31.2; G62.1; G72.1; I42.6; K29.2; K70; K86.0; L27.8A; O35.4M; T51; Z71.4; Z72.1</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>I48</td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>D62 J942 H113 H356 H431</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>K250 K260 K270 K280 K290</td>
<td></td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>I60 I61 I62</td>
<td></td>
</tr>
<tr>
<td>Traumatic intracranial bleeding</td>
<td>S063C S064 S065 S066</td>
<td></td>
</tr>
<tr>
<td>Retinal bleeding</td>
<td>H356</td>
<td></td>
</tr>
</tbody>
</table>

* We identified subjects with hypertension from combination treatment with at least two of the following classes of antihypertensive Drugs:
1. Alpha adrenergic blockers (C02A, C02B, C02C)
2. Non-loop diuretics (C02DA, C02L, C03A, C03B, C03D, C03E, C03X, C07C, C07D, C08G, C09BA, C09DA, C09XA52)
3. Vasodilators (C02DB, C02DD, C02DG, C04, C05)
4. Beta blockers (C07)
5. Calcium channel blockers (C07F, C08, C09BB, C09DB)
6. Renin-angiotensin system inhibitors (C09).
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