The HEMORR$_2$HAGES, ATRIA and the HAS-BLED bleeding risk prediction scores in anticoagulated atrial fibrillation patients: The AMADEUS study

Apostolakis S$^1$, Lane DA$^1$, Buller H$^2$, Lip GY$^1$

$^1$University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, UK; $^2$Department of Vascular Medicine, Academic Medical Centre, Amsterdam, Netherlands
Why is bleeding risk estimation important?

- Anticoagulation increases the incidence of bleeding.
- Net clinical benefit of OAC is clearly affected by the risk of bleeding.
- Major bleeding events are associated with prolonged hospitalization, permanent disability and increased mortality.
- Less severe bleeding events can also have clinical implications.
- Bleeding risk can be reduced by simple measures.

Why is bleeding risk estimation important?

- Bleeding is a much less common event than thromboembolism.
- Multiple clinical and demographic risk factors affect bleeding risk.
- Risk factors can cluster together in significant patterns with cumulative effect on individuals overall bleeding risk.
- Bleeding and thromboembolic risk factors overlap.

Estimation of bleeding risk: the options

- Risk estimation tools
  - Collection of information
  - Interpretation based on a validated algorithm
  - Decision

- Clinical judgment
  - Collection of information
  - Interpretation based on knowledge and professional experience
  - Decision
Estimation of bleeding risk

- **Risk estimation tools**
  - **Pros**
    - Validated
    - Reproducible
    - Easily learned
  - **Cons**
    - Limited variables
    - One-size fits all philosophy
    - Depend on the validity of the collected information

- **Clinical judgment**
  - **Pros**
    - Multivariable
    - Individualized
    - Flexible
  - **Cons**
    - Cannot be validated
    - Non reproducible
    - Time consuming
Objectives: Which is the best score?

- Three scores developed and validated in AF population

<table>
<thead>
<tr>
<th>ATRIA</th>
<th>HAS-BLED</th>
<th>HEMORR$_2$HAGES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia</td>
<td>3 Hypertension</td>
<td>1 Hepatic or Renal disease</td>
</tr>
<tr>
<td>Severe renal disease</td>
<td>3 Abnormal Renal or Liver function</td>
<td>1 Ethanol abuse</td>
</tr>
<tr>
<td>Age ≥75 yrs</td>
<td>2 Stroke</td>
<td>1 Malignancy</td>
</tr>
<tr>
<td>Any prior hemorrhage</td>
<td>1 Bleeding</td>
<td>1 Older Age (&gt;75 yrs)</td>
</tr>
<tr>
<td>Hypertension$^3$</td>
<td>1 Labile INR</td>
<td>1 Reduced platelet number or function</td>
</tr>
<tr>
<td>Elderly (&gt;65 yrs)</td>
<td></td>
<td>1 Rebleeding</td>
</tr>
<tr>
<td>Drugs or Alcohol</td>
<td>1 Hypertension</td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Genetic factors</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Excessive fall risk</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

Objectives: Which is the best score?

- The objective of this study was to compare the predictive performance of bleeding risk estimation tools in a cohort of anticoagulated AF patients.

- This is the first direct comparison between the HAS-BLED and ATRIA scores and the first external validation of the ATRIA score.
Methods: comparison of risk estimation scores

Score 1

Total population: 24  
True positive: 2  
False positive: 1  
True negative: 18  
False negative: 2

Score 2

Total population: 24  
True positive: 3  
False positive: 3  
True negative: 17  
False negative: 1
Methods: comparison of risk estimation scores
Methods: comparison of risk estimation scores

Reclassification Table

<table>
<thead>
<tr>
<th></th>
<th>True Positive</th>
<th>Score 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>True Negative</td>
<td>Score 1</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Positive</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Negative</td>
<td>1</td>
<td>3</td>
<td>16</td>
</tr>
</tbody>
</table>
**Methods: comparison of risk estimation scores**

**Net Reclassification improvement (NRI)** Compare classifications from 2 models for changes by outcome for a net calculation of changes in the right direction.

\[
NRI = \frac{\text{Number of True positive correctly reclassified}}{\text{True positive}} + \frac{\text{Number of True negative correctly reclassified}}{\text{True negative}}
\]

<table>
<thead>
<tr>
<th>Score 1</th>
<th>Score 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Score 1</strong></td>
<td><strong>Score 2</strong></td>
</tr>
<tr>
<td><strong>True Positive</strong></td>
<td><strong>Positive</strong></td>
</tr>
<tr>
<td><strong>True Negative</strong></td>
<td>2</td>
</tr>
<tr>
<td><strong>Positive</strong></td>
<td>0</td>
</tr>
<tr>
<td><strong>Negative</strong></td>
<td>1</td>
</tr>
</tbody>
</table>

Methods: comparison of risk estimation scores

- **Net benefit**: Net number of true positives gained by using a model compared to no model or a different model at a single threshold probability.

- **Decision curve analysis**: Net number of true positives gained by using a model compared to no model or a different model over a range of thresholds.

\[
\text{Net benefit} = \frac{\text{True positive}}{n} - \frac{\text{False positive}}{n} \cdot \frac{1 - \text{pt}}{1 - \text{pt}}
\]

**Threshold probability:** The probability of disease that is considered high enough to require action

Methods: comparison of risk estimation scores

Materials and Methods: The AMADEUS study

- Multicentre, randomised, open-label non-inferiority study
- Fixed-dose idraparinux vs. oral VKA therapy for prevention of thromboembolism in patients with AF.
Materials and Methods: The AMADEUS study

Outcomes

• Events that occurred in the randomization/on treatment/observational period.
• Primary outcome: Clinically relevant bleeding including:
  • major bleeding:
    – bleeding that was fatal
    – intracranial or affecting another critical anatomical site
    – overt bleeding with a drop of haemoglobin ≥20 g/L or requiring transfusion of two or more units of erythrocytes
  • clinically relevant non-major bleeding:
    – Overt bleeding that did not satisfy the criteria for major bleeding
    – Epistaxis for more than 5 min at least twice in 24 h,
    – Haematuria spontaneous or lasting more than 24 h
    – Haematemesis
    – Subcutaneous haematomas of more than 25 cm² if spontaneous, or more than 100 cm² if after trauma.

• 2293 patients randomised to the VKA arm
• 65% men, mean age 70.2±9.1
• In total, 251 (11%) clinically relevant bleeding event.
• Thirty nine (1.7%) major bleedings
Receiver operator characteristic analysis

Major Bleeding

- C-index: 0.60
- Sensitivity: 0.5
- Specificity: 0.5

Any Clinically Relevant Bleeding

- C-index: 0.55
- Sensitivity: 0.65
- Specificity: 0.5

All Cause Mortality

- C-index: 0.57
- Sensitivity: 0.6
- Specificity: 0.5

Legend:
- HEMORRHAGES
- HAS-BLED
- ATRIA
- Reference line
### Comparing C-indexes

<table>
<thead>
<tr>
<th>AUC analysis</th>
<th>Any Clinically Relevant Bleeding</th>
<th>Major Bleeding</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC Difference (95%CI) z p</td>
<td>AUC Difference (95%CI) z p</td>
<td>AUC Difference (95%CI) z p</td>
</tr>
<tr>
<td>HAS-BLED vs.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HEMORR²HAGES</td>
<td>0.04 (0.52 to 0.59) 2.95 0.003</td>
<td>0.04 (-0.03-0.12) 1.19 0.23</td>
<td>0.09 (-0.14 to -0.05) 4.33 &lt;0.0001</td>
</tr>
<tr>
<td>HAS-BLED vs.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>vs. ATRIA</td>
<td>0.09 (0.03 to 0.15) 3.14 0.002</td>
<td>0.04 (-0.06-0.14) 0.85 0.4</td>
<td>0.04 (-0.03 to 0.11) 1.17 0.2</td>
</tr>
<tr>
<td>ATRIA vs.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HEMORR²HAGES</td>
<td>-0.05 (-0.01 to 0.11) 1.54 0.1</td>
<td>0.0 (-0.09-0.09) 0.04 0.97</td>
<td>0.05 (-0.12 to 0.02) 1.5 0.1</td>
</tr>
<tr>
<td>Event</td>
<td>No Event</td>
<td>HAS-BLED</td>
<td>Total</td>
</tr>
<tr>
<td>-------------</td>
<td>----------</td>
<td>----------------</td>
<td>---------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>ATRIA</td>
<td></td>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>67</td>
<td>135</td>
</tr>
<tr>
<td></td>
<td></td>
<td>74</td>
<td>146</td>
</tr>
<tr>
<td></td>
<td></td>
<td>393</td>
<td>1425</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>92</td>
<td>156</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>460</td>
<td>1560</td>
</tr>
<tr>
<td>HEMORR₂HAGES</td>
<td></td>
<td>54</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>306</td>
<td>154</td>
</tr>
<tr>
<td></td>
<td></td>
<td>38</td>
<td>144</td>
</tr>
<tr>
<td></td>
<td></td>
<td>158</td>
<td>1402</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>92</td>
<td>156</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>464</td>
<td>1556</td>
</tr>
</tbody>
</table>
Reclassification analysis

<table>
<thead>
<tr>
<th>NRI analysis</th>
<th>Any Clinically Relevant Bleeding</th>
<th>Major Bleeding</th>
<th>All cause mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NRI</td>
<td>z</td>
<td>p</td>
</tr>
<tr>
<td>HAS-BLED vs. HEMORR₂HAGES</td>
<td>0.103</td>
<td>3.45</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HAS-BLED vs. ATRIA</td>
<td>0.13</td>
<td>3.37</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ATRIA vs. HEMORR₂HAGES</td>
<td>0.021</td>
<td>0.596</td>
<td>0.55</td>
</tr>
</tbody>
</table>

- HAS-BLED vs. ATRIA: more than 25% of the ‘event positive population’ reclassified correctly with a cost of less than 13% misclassification in ‘event negative’ patients.
- HAS-BLED vs. HEMORR₂HAGES: more than 10% of the ‘event positive population’ reclassified correctly without a net loss in the event-free group.
Cox regression survival plots for cumulative major bleeding free survival* in AF patients stratified by the three bleeding risk schemes (*analysis also included the observational period of the AMADEUS study)
“High risk” classification by one of the tests will result in alternative treatment. If it is considered efficient to apply alternative treatment for 11 patients - or less - to prevent 1 event then HAS-BLED is superior to the “treat all alternatively” strategy (grey line) and the “treat none alternatively strategy “(black dotted line). The HAS-BLED score was superior to the HEMORR2HAGES and ATRIA score for any threshold probability.
Conclusions

• All tested bleeding scores performed less than modestly in predicting endpoints.

• Among the AMADEUS population, the HAS-BLED score performed better than either the HEMORR\textsubscript{2}HAGES or ATRIA scores in predicting any clinically relevant bleeding.
Conclusions

• Despite modest predictive performance bleeding risk estimation tools are the only alternative to implicit clinical judgment.

• Given its simplicity and superior performance HAS-BLED score seems to be an attractive method for the estimation of OAC-related bleeding.

• These results support international guideline recommendations:
  – European Society of Cardiology and
  – Canadian guidelines.
  – RCPE
Performance of the HEMORR\textsubscript{2}HAGES, ATRIA, and HAS-BLED Bleeding Risk–Prediction Scores in Patients With Atrial Fibrillation Undergoing Anticoagulation

The AMADEUS (Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation) Study

Stavros Apostolakis, MD, PhD,* Deirdre A. Lane, PhD,* Yutao Guo, MD,* Harry Buller, MD, PhD,† Gregory Y. H. Lip, MD*

*Birmingham, United Kingdom; and Amsterdam, the Netherlands

Expedited publication JACC in press
Thank you for your attention

- **COMPETING INTERESTS**
  Dr Lane has received research funding and/or honoraria for educational symposia from Boehringer Ingelheim, Bayer Healthcare and Bristol Myers Squibb/Pfizer in relation to atrial fibrillation. Professor Buller has served as a consultant to Sanofi-Aventis, Bayer, Pfizer, Glaxo-Smith-Kline, Astellas, Boehringer-Ingelheim and Daiichi-Sankyo. Professor Lip has served as a consultant for Bayer, Astellas, Merck, Astra-Zeneca, Sanofi Aventis, Aryx, Portola, Biotronic, and Boehringer Ingelheim and has been on the speaker bureau for Bayer, Boehringer Ingelheim, and Sanofi Aventis. Dr Apostolakis—none declared in relation to the present work.
- **AMADEUS study was funded by Sanofi-Aventis**