Development and Validation of the DOAC Score
A Novel Bleeding Risk Prediction Tool for Patients with Atrial Fibrillation on Direct-Acting Oral Anticoagulants

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Our Goal

• Anticoagulation is recommended for many patients with **atrial fibrillation**

• We develop a **bleeding risk score** for patients with **atrial fibrillation** on DOACs (apixaban, dabigatran, edoxaban, rivaroxaban)

• We compare this bleeding risk score to **HAS-BLED**
Four Cohorts Were Identified

<table>
<thead>
<tr>
<th>Data Type</th>
<th>DOAC Agent</th>
<th>Final Sample Size (N)</th>
<th>Major Bleeding Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY Clinical Trial</td>
<td>Dabigatran (100%)</td>
<td>5,684</td>
<td>386</td>
</tr>
<tr>
<td>GARFIELD-AF Registry</td>
<td>Apixaban (29%) Dabigatran (10%) Edoxaban (3%)</td>
<td>12,296</td>
<td>131</td>
</tr>
<tr>
<td>COMBINE-AF* Pooled Clinical Trials</td>
<td>Apixaban (46%) Edoxaban (27%) Rivaroxaban (28%)</td>
<td>25,586</td>
<td>692</td>
</tr>
<tr>
<td>RAMQ** Administrative Database</td>
<td>Apixaban (59%) Rivaroxaban (41%)</td>
<td>11,945</td>
<td>258</td>
</tr>
</tbody>
</table>

†Patients on warfarin were excluded from all trials
*Patients in RE-LY and on low dose edoxaban were excluded
**Only patients on full dose apixaban and rivaroxaban were included
Candidate variables for bleeding prediction are identified

Stepwise regression to determine final variables in first cohort

Model fit and then refined in second cohort

Converted to a points system

Validated in third and fourth cohorts
**Key inclusion criteria:**
- Atrial Fibrillation
- DOAC Therapy

**Outcome:**
- Major Bleeding
  - 20 g/L reduction in Hb, 2-unit transfusion, fatal bleeding, or symptomatic bleeding in a critical area or organ

*Patients in RE-LY and on low dose edoxaban were excluded
**Major bleeding defined by billing codes
Final Risk Score

- 10 variables

- Total score range: 0-10 (maximum 10 points)
Major Bleeding Rates by Score in RE-LY

- Higher scores associated with increased bleeding rates (P<0.001)

- Clinical Categories:
  - Very Low: 0-3
  - Low: 4-5
  - Moderate: 6-7
  - High: 8-9
  - Very High: ≥10
Performance in Development Cohorts

**RE-LY**

- Cumulative Incidence
- Events = 386
- C-Statistic: 0.72 (0.71-0.74)

**GARFIELD-AF**

- Cumulative Incidence
- Events = 131
- C-Statistic: 0.71 (0.67-0.75)

Note: Y-axis has differing bleeding rates by cohort
Performance in Validation Cohorts

COMBINE-AF

Cumulative Incidence

Events = 692

C-Statistic: 0.67 (0.64-0.69)

Note: Y-axis has differing bleeding rates by cohort

RAMQ

Cumulative Incidence

Events = 258

C-Statistic: 0.65 (0.61-0.68)
### DOAC Score vs HAS-BLED

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Number of Events</th>
<th>DOAC Score, C-Statistic</th>
<th>HAS-BLED, C-Statistic</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY</td>
<td>5,684</td>
<td>386</td>
<td>0.72 (0.71-0.74)</td>
<td>0.60 (0.58-0.62)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GARFIELD-AF</td>
<td>12,296</td>
<td>131</td>
<td>0.71 (0.67-0.75)</td>
<td>0.66 (0.62-0.71)</td>
<td>0.025</td>
</tr>
<tr>
<td>COMBINE-AF</td>
<td>25,586</td>
<td>692</td>
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<td>0.58 (0.55-0.62)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Improved predictive performance compared to HAS-BLED in all cohorts.
### Major Bleeding Rates by DOAC Score in Each Cohort

<table>
<thead>
<tr>
<th>Risk Category (Risk Score)</th>
<th>RE-LY (N=5,684)</th>
<th>GARFIELD-AF (N=12,296)</th>
<th>COMBINE-AF (N=25,586)</th>
<th>RAMQ (N=11,945)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>1-Year Rate</td>
<td>N</td>
<td>1-Year Rate</td>
</tr>
<tr>
<td>Very Low (0-3)</td>
<td>767 (2)</td>
<td>0.8%</td>
<td>4360 (14)</td>
<td>0.3%</td>
</tr>
<tr>
<td>Low (4-5)</td>
<td>1249 (21)</td>
<td>1.6%</td>
<td>3735 (33)</td>
<td>0.9%</td>
</tr>
<tr>
<td>Moderate (6-7)</td>
<td>1727 (53)</td>
<td>3.4%</td>
<td>3263 (60)</td>
<td>1.9%</td>
</tr>
<tr>
<td>High (8-9)</td>
<td>1296 (87)</td>
<td>6.9%</td>
<td>748 (17)</td>
<td>2.4%</td>
</tr>
<tr>
<td>Very High (10)</td>
<td>645 (73)</td>
<td>13.9%</td>
<td>190 (7)</td>
<td>3.7%</td>
</tr>
</tbody>
</table>

Increased **bleeding rates** by score but variation in bleeding rates by cohort.
Conclusions

• In patients with atrial fibrillation on DOAC therapy, the DOAC Score can personalize predictions for major bleeding

• The DOAC Score had stronger predictive performance than HAS-BLED

• Limitations:
  • Labile INR was not applicable to DOACs
  • Differing bleeding rates in each cohort
Fantastic Co-Authors

Christian T. Ruff, MD, MPH, Saverio Virdone, MSc, Sylvie Perreault, BPharm, PHD, Ajay K. Kakkar, MBBS, PhD, Michael G. Palazzolo, MPH, Marc Dorais, MSc, Gloria Kayani, BSc, Daniel E. Singer, MD, Eric Secemsky, MD, Jonathan Piccini, MD, MHS, Usman A. Tahir, MD, MBI, Changyu Shen, PhD, Robert W. Yeh, MD, MSc

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