Atrial Fibrillation: Stratifying Stroke Risk and Determining Anticoagulant Therapy

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Disclosure Statement of Financial Interest

I, Asma Hussaini DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.
Atrial Fibrillation and Stroke

• AF is a very common, often asymptomatic condition that can present for the first time as a devastating stroke.

• Stroke rate with atrial fibrillation (AF) varies between 1% and 20% annually (mean 4.5% per year) depending on comorbidities and history of prior cerebrovascular events.¹

• Stratification of stroke risk important, as the major risk of anticoagulation therapy is bleeding.

LAA is the source of thrombus in over 90% of AF patients

**CHADS₂ Score**

<table>
<thead>
<tr>
<th>Item</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C</strong>ongestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td><strong>H</strong>ypertension</td>
<td>1</td>
</tr>
<tr>
<td><strong>A</strong>ge ≥75 years</td>
<td>1</td>
</tr>
<tr>
<td><strong>D</strong>iabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td><strong>S</strong>troke/TIA</td>
<td>2</td>
</tr>
</tbody>
</table>

*Add points together*

<table>
<thead>
<tr>
<th>CHADS₂</th>
<th>Stroke rate (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>18.2 (10.5–27.4)</td>
</tr>
<tr>
<td>5</td>
<td>12.5 (8.2–17.5)</td>
</tr>
<tr>
<td>4</td>
<td>8.5 (6.3–11.1)</td>
</tr>
<tr>
<td>3</td>
<td>5.9 (4.6–7.3)</td>
</tr>
<tr>
<td>2</td>
<td>4.0 (3.1–5.1)</td>
</tr>
<tr>
<td>1</td>
<td>2.8 (2.0–3.8)</td>
</tr>
<tr>
<td>0</td>
<td>1.9 (1.2–3.0)</td>
</tr>
</tbody>
</table>

*Per 100 patient-years without antithrombotic therapy

Gage et al, *JAMA* 2001
**ACC/AHA/HRS 2012 guidelines: based on CHADS\(_2\) Score**

<table>
<thead>
<tr>
<th>CHADS(_2) score</th>
<th>Recommended therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>ASA 81–325 mg/day</td>
</tr>
<tr>
<td>1</td>
<td>WF (INR 2–3) or ASA 81–325 mg/day</td>
</tr>
<tr>
<td>≥2</td>
<td>WF (INR 2–3)</td>
</tr>
</tbody>
</table>

**CHADS₂-VASc:**
*a further refinement of CHADS₂*

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure/LV dysfunction*</td>
<td>+1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>+1</td>
</tr>
<tr>
<td>Age ≥75 years</td>
<td>+2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>+1</td>
</tr>
<tr>
<td>Previous stroke/TIA/thromboembolism</td>
<td>+2</td>
</tr>
<tr>
<td>Vascular disease (MI, aortic plaque, peripheral artery disease)</td>
<td>+1</td>
</tr>
<tr>
<td>Age 65–74 years</td>
<td>+1</td>
</tr>
<tr>
<td>Sex category (female)</td>
<td>+1</td>
</tr>
<tr>
<td>Maximum score</td>
<td>9</td>
</tr>
</tbody>
</table>

*Left ventricular ejection fraction ≤40%; Including prior revascularization, amputation due to peripheral artery disease or angiographic evidence of peripheral artery disease

Camm *et al*, Eur Heart J 2010; Lip *et al*, Chest 2010
Many stroke risk factors are also risk factors for bleeding

<table>
<thead>
<tr>
<th>Risk factor for stroke*</th>
<th>Risk factor for anticoagulant-related bleeding*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced age^1−4</td>
<td>✓</td>
</tr>
<tr>
<td>History of hypertension^1,3,4</td>
<td>✓</td>
</tr>
<tr>
<td>History of MI or ischemic heart disease^1,3</td>
<td>✓</td>
</tr>
<tr>
<td>Cerebrovascular disease^1−4</td>
<td>✓</td>
</tr>
<tr>
<td>Anemia^3,4</td>
<td>✓</td>
</tr>
<tr>
<td>Previous history of bleeding^3,4</td>
<td>✓</td>
</tr>
<tr>
<td>Kidney or liver dysfunction^4</td>
<td>✓</td>
</tr>
<tr>
<td>Concomitant use of antiplatelets^3,4</td>
<td>✓ *Not exhaustive</td>
</tr>
</tbody>
</table>

The relationship between stroke risk and bleeding risk complicates the evaluation of benefit–risk

## HAS-BLED score

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (SBP &gt;160 mm Hg)</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal renal or liver function</td>
<td>1 + 1</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1</td>
</tr>
<tr>
<td>Labile INRs</td>
<td>1</td>
</tr>
<tr>
<td>Elderly (age &gt;65 years)</td>
<td>1</td>
</tr>
<tr>
<td>Drugs or alcohol</td>
<td>1 + 1</td>
</tr>
<tr>
<td><strong>Cumulative score</strong></td>
<td>Range 0–9</td>
</tr>
</tbody>
</table>

Pisters et al, *Chest* 2010
1-year risk of major bleeding increases with HAS-BLED score

<table>
<thead>
<tr>
<th>Score</th>
<th>No</th>
<th>No of Bleed</th>
<th>Bleeds Per 100 Patient-Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>798</td>
<td>9</td>
<td>1.13</td>
</tr>
<tr>
<td>1</td>
<td>1286</td>
<td>13</td>
<td>1.02</td>
</tr>
<tr>
<td>2</td>
<td>744</td>
<td>14</td>
<td>1.88</td>
</tr>
<tr>
<td>3</td>
<td>187</td>
<td>7</td>
<td>3.74</td>
</tr>
<tr>
<td>4</td>
<td>46</td>
<td>4</td>
<td>8.70</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>1</td>
<td>12.50</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Pisters et al, Chest 2010
HAS-BLED score

• Should not be used to exclude patients from OAC therapy.
• Allows clinician to identify bleeding risk factors and to correct those that are modifiable, ie, controlling blood pressure, and reducing alcohol.
• Can be used to highlight those patients on OACs in whom caution and regular review is warranted.
Vitamin K Antagonists (Warfarin)

- Multiple trials demonstrate superiority of vitamin K antagonists over antiplatelet therapies for stroke prevention in AF patients.
- Data shows consistent benefit of warfarin across studies with absolute reduction in annual stroke rate from 4.5% for control patients to 1.4% in patients assigned to adjusted-dose warfarin.¹
- This absolute risk reduction translates to 31 ischemic strokes prevented each year for every 1000 patients treated.
Vitamin K Antagonists

- Warfarin is relatively safe, annual rate of major bleeding of 1.3% compared with 1% for placebo or aspirin.\(^1\)
- No data to support that increasing intensity of anticoagulation or adding antiplatelet agent provides additional protection against second event for patients who have a stroke while on therapeutic anticoagulation.

For high-risk patients with AF deemed unsuitable for anticoagulation, dual-antiplatelet therapy with Clopidogrel and aspirin offers more protection against stroke than aspirin alone but with an increased risk of major bleeding.

New Oral Anticoagulants (NOACs)

- No published data comparing Dabigatran, Rivaroxaban, and Apixaban to one another, only comparisons to warfarin.
- The duration of follow-up in the clinical trials was limited.
- Due to their short half-lives, noncompliant patients may be at risk for thromboembolism.
New Oral Anticoagulants (NOACs)

- Treatment decisions should account for differences in costs, which may affect compliance.
- Drug activity presently cannot be assessed in routine clinical practice, this can lead to risk of undertreating or overtreating.
- There are no antidotes to emergently reverse these medications in the setting of hemorrhage.
<table>
<thead>
<tr>
<th></th>
<th>RE-LY&lt;sup&gt;26&lt;/sup&gt;</th>
<th>ROCKET-AF&lt;sup&gt;52&lt;/sup&gt;</th>
<th>ARISTOTLE&lt;sup&gt;58&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agent</strong></td>
<td>Dabigatran 150 mg BID</td>
<td>Rivaroxaban 20 mg QD</td>
<td>Apixaban 5 mg or 2.5 mg BID*</td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
<td>Warfarin</td>
<td>Warfarin</td>
<td>Warfarin</td>
</tr>
<tr>
<td><strong>Blinding</strong></td>
<td>Open label</td>
<td>Double blind</td>
<td>Double blind,</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>18 113</td>
<td>14 264</td>
<td>18 201</td>
</tr>
<tr>
<td><strong>Mean age, y</strong></td>
<td>72</td>
<td>73</td>
<td>70</td>
</tr>
<tr>
<td><strong>Female, %</strong></td>
<td>36</td>
<td>40</td>
<td>35</td>
</tr>
<tr>
<td><strong>CHADS score</strong></td>
<td>2.1</td>
<td>3.5</td>
<td>2.1</td>
</tr>
<tr>
<td><strong>0–1, %</strong></td>
<td>32</td>
<td>0</td>
<td>34</td>
</tr>
<tr>
<td><strong>2, %</strong></td>
<td>35</td>
<td>13</td>
<td>36</td>
</tr>
<tr>
<td><strong>3–6, %</strong></td>
<td>33</td>
<td>87</td>
<td>30</td>
</tr>
<tr>
<td><strong>Previous stroke, %</strong></td>
<td>20</td>
<td>34</td>
<td>19</td>
</tr>
<tr>
<td><strong>Event rate vs comparator, %</strong></td>
<td>1.1 vs 1.7 (P&lt;0.001)</td>
<td>2.1 vs 2.4 (P=0.12‡)</td>
<td>1.3 vs 1.6 (P&lt;0.001)</td>
</tr>
<tr>
<td><strong>HR vs comparator</strong></td>
<td>0.66 (0.53–0.82)</td>
<td>0.88 (0.74–1.03)‡</td>
<td>0.79 (0.66–0.95)</td>
</tr>
<tr>
<td><strong>No. needed to treat</strong></td>
<td>167</td>
<td>Noninferior</td>
<td>303</td>
</tr>
<tr>
<td><strong>Major bleeding vs comparator, %</strong></td>
<td>3.1 vs 3.4</td>
<td>3.6 vs 3.4</td>
<td>2.1 vs 3.1</td>
</tr>
<tr>
<td><strong>ICH vs comparator, %</strong></td>
<td>0.3 vs 0.7</td>
<td>0.5 vs 0.7</td>
<td>0.2 vs 0.5</td>
</tr>
</tbody>
</table>

Total Mortality Relative Reduction (vs warfarin)

- Total Mortality Relative Reduction (

- 1 Connolly, S. NEJM 2009; 361:1139-1151 – 2 yrs f-up
- 2 Patel, M. NEJM 2011; 365:883-891 – 1.9 yrs f-up, ITT
- 3 Granger, C NEJM 2011; 365:981-992 – 1.8 yrs f-up

- RE-LY¹
- ROCKET-AF²
- ARISTOTLE³

- % Relative Reduction
- All-Cause Mortality

- Dabigatran 110
- Dabigatran 150
- Rivaroxaban
- Apixaban
**Dabigatran**

- Dabigatran is useful as an alternative to warfarin for the prevention of stroke in AF patients who do not have a prosthetic heart valve or hemodynamically significant valve disease, severe renal failure (CrCl <15 mL/min), or advanced liver disease (impaired baseline clotting function).

Apixaban 5 mg twice daily is a relatively safe and effective alternative to warfarin in patients with nonvalvular AF deemed appropriate for vitamin K antagonist therapy who have at least 1 additional risk factor and no more than 1 of the following characteristics: Age ≥80 years, weight ≤60 kg, or serum creatinine ≥1.5 mg/dL.

Rivaroxaban

- Rivaroxaban 20 mg/d is reasonable as an alternative to warfarin.
- Should not be used if CrCl<25 mL/min.
- Also approved for treatment and prophylaxis of DVT/PE

Conclusions

• Warfarin and the newer anticoagulant agents (Dabigatran, Rivaroxaban, Apixaban) are effective in reduction of ischemic stroke risk in AF patients.
• Clinicians often overestimate the risk of bleeding with OACs, and underestimate risk of stroke in AF.
• Stroke and bleeding risk assessment tools such as CHADS\textsubscript{2} and HAS-BLED can help guide the decision of OAC to use and the management plan.