Stroke Prevention with Atrial Fibrillation

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Disclosures

- I have no actual or potential conflict of interest in relation to this program/presentation
Epidemiology of Atrial Fibrillation

- Prevalence
  - Most common cardiac arrhythmia
  - US Prevalence about 1%
  - Increases significantly with age
- If you are older than 65, AF prevalence is 5%
- Over age 85, prevalence is 10%
Epidemiology of Atrial Fibrillation

Quinn and Fang, 2012
We have all seen a lot of Atrial Fibrillation, is it really bad for you?
Atrial Fibrillation and Death

RR men 1.5; RR women 1.9
AF diminished ♀ survival advantage


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What is the cause for excess mortality?
### Cause-Specific Death Rates

<table>
<thead>
<tr>
<th>Follow-up interval</th>
<th>CHD</th>
<th>Stroke</th>
<th>Other CVD</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 d</td>
<td>10 (3.4)</td>
<td>6 (2.0)</td>
<td>4 (1.4)</td>
<td>23 (7.8)</td>
</tr>
<tr>
<td>30 d–1 y</td>
<td>19 (6.4)</td>
<td>2 (0.7)</td>
<td>5 (1.7)</td>
<td>24 (8.1)</td>
</tr>
<tr>
<td>No, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 d</td>
<td>0</td>
<td>0</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>30 d–1 y</td>
<td>10 (1.7)</td>
<td>2 (0.3)</td>
<td>2 (0.3)</td>
<td>21 (3.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AF Status, Men</th>
<th>Yes, n (%)</th>
<th>No, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>296</td>
<td>592</td>
</tr>
<tr>
<td>Follow-up interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 d</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>30 d–1 y</td>
<td>30</td>
<td>30</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AF Status, Women</th>
<th>Yes, n (%)</th>
<th>No, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>325</td>
<td>650</td>
</tr>
<tr>
<td>Follow-up interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 d</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>30 d–1 y</td>
<td>30</td>
<td>30</td>
</tr>
</tbody>
</table>

Is this a realistic estimate?

What about subclinical AF?
2580 Patients > 65
Dx of hypertension and no clinical AF
Recent pacemaker or implantable defibrillator
Used devices to monitor for AF over 3 mos
Then determined outcome over 2.5 years

Healey et al., *NEJM* 2012;366:2
# Stroke in AF: Implications

**Table 2. Clinical Outcomes Occurring after the 3-Month Visit, According to Whether Subclinical Atrial Tachyarrhythmias Were or Were Not Detected between Enrollment and the 3-Month Visit.**

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>Subclinical Atrial Tachyarrhythmias between Enrollment and 3 Months</th>
<th>Hazard Ratio with Subclinical Atrial Tachyarrhythmias (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present (N = 261)</td>
<td>Absent (N = 2319)</td>
<td>no. of events</td>
</tr>
<tr>
<td>Ischemic stroke or systemic embolism*</td>
<td>11</td>
<td>40</td>
<td>1.69</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>10</td>
<td>36</td>
<td>1.54</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>1</td>
<td>4</td>
<td>0.15</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>7</td>
<td>39</td>
<td>1.07</td>
</tr>
<tr>
<td>Death from vascular causes</td>
<td>19</td>
<td>153</td>
<td>2.92</td>
</tr>
<tr>
<td>Stroke, myocardial infarction, or death from vascular causes</td>
<td>29</td>
<td>206</td>
<td>4.45</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>20</td>
<td>131</td>
<td>3.07</td>
</tr>
<tr>
<td>Clinical atrial fibrillation or flutter on surface electrocardiogram</td>
<td>41</td>
<td>71</td>
<td>6.29</td>
</tr>
</tbody>
</table>

*Ischemic stroke or systemic embolism includes both ischemic stroke and systemic embolism.

Healey et al., *NEJM* 2012;366:2
Key Points

- Atrial fibrillation is a prevalent condition
- Increases with age, so demographics predict more AF in your patient population
- AF confers increased morbidity and mortality, with stroke being a chief cause
- 10 – 25% of AF is undetected, so the above estimates are likely LOW
Clinical Quiz: Who needs anticoagulation?
Clinical Quiz: Who needs anticoagulation?

- **MAT**  Warfarin not indicated for multifocal atrial tach
- **AFL**  Warfarin IS indicated for atrial flutter
- **AF**  Warfarin IS indicated for atrial fibrillation
What are the choices for anticoagulation?

- Aspirin
- Warfarin
- Dabigatran
- Rivaroxiban
- Apixaban
What are the choices for anticoagulation?

- Aspirin
- Warfarin
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Aspirin in AF: Better than Nothing

- Irreversible Cox1 inhibition
- Preferentially acts upon platelets
- Only need 81 mg/d

JACC Vol. 57, No. 11, 2011

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What are the choices for anticoagulation?

- Aspirin
- Warfarin
- Dabigatran
- Rivaroxiban
- Apixaban
Coumadin in AF: Gold Standard

- Vitamin K antagonist
- 50 yrs of experience
- Sensitive to diet and gut flora
- Target INR 2.0 – 3.0 in absence of other conditions
- Universally hated by patients

JACC Vol. 57, No. 11, 2011
Why close follow-up?
Cournadin: Narrow Therapeutic Window

Incidence Rate of First Ischemic or Hemorrhagic Complication

INR = international normalized ratio.

INR Range

0 1.0–1.9 2.0–2.4 2.5–2.9 3.0–3.4 3.5–3.9 4.0–4.4 4.5–4.9 >5.0

Incidence rate (per 100 person-years)
How do we balance embolic vs. hemorrhagic complications?
# Risk Scoring for Thrombotic Complications

<table>
<thead>
<tr>
<th>CHADS2</th>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Congestive Heart Failure</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Age &gt; 75 years</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Stroke or TIA history</td>
<td>2</td>
</tr>
</tbody>
</table>

CHADS2 = 0, ASA
1, ASA or Warfarin
2, Warfarin
What do you do if CHADS2 is 1?
European Society Recommendations

→ Calculating CHADS2 score for AF patients
→ If CHADS2 ≥ 2, oral anticoagulant
→ If CHADS2 < 2, check CHADS2-VASc
  • If CHADS2VASc = 0, ASA
  • If CHADS2VASc = 1, oral anticoagulant preferred
  • If CHADS2VASc ≥ 2, oral anticoagulant
<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</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 y</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/TIA/TE</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque)</td>
<td>1</td>
</tr>
<tr>
<td>Age 65-74 y</td>
<td>1</td>
</tr>
<tr>
<td>Sex category (ie female gender)</td>
<td>1</td>
</tr>
</tbody>
</table>

LV = left ventricular; TE = thromboembolism. See Table 1 for expansion of other abbreviations.
What are the choices for anticoagulation?

- Aspirin
- Warfarin
- Dabigatran
- Rivaroxiban
- Apixaban
What are the choices for anticoagulation?

- Aspirin
- Warfarin
- Dabigatran
- Rivaroxiban
- Apixaban
Dabigatran: Mechanism and Pharmacology

- Direct thrombin inhibitor
- 80% Renal excretion
- $T_{1/2} 12 – 17$ hrs
- No good monitoring mechanism
- Orally active
Dabigatran: RE-LY Trial

- 18,113 randomized to dabigatran (110 or 150 mg) vs. warfarin
- Non-inferiority
- Warfarin non-blinded
- Follow-up 2.0 years
- Endpoint stroke or systemic embolization

Healy et al. *NEJM* 2009

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Issues with Dabigatran Use

- Increased risk of bleeding in patients with renal insufficiency (Cr Cl<30 ml/min)
- In patients >75 years; increased risk of GI bleeding
- Signal of increased MI, but likely that warfarin is protective
What are the choices for anticoagulation?

- Aspirin
- Warfarin
- Dabigatran
- Rivaroxiban
- Apixaban
What are the choices for anticoagulation?

- Aspirin
- Warfarin
- Dabigatran
- **Rivaroxiban**
- Apixaban
Rivaroxaban: Mechanism and Pharmacology

- Direct factor Xa inhibitor
- Orally active
- T$_{1/2}$ 8 - 12hrs
- Factor Xa inhibited for 24h
- No good monitoring mechanism
- No reversal agent.
Rivaroxiban: Rocket AF Trial

- 14,264 randomized to rivaroxiban (20mg) vs. warfarin
- Non-inferiority
- Blinded
- Event-driven
- Endpoint stroke or systemic embolization

Patel et al. *NEJM* 2011
What are the choices for anticoagulation?

- Aspirin
- Warfarin
- Dabigatran
- Rivaroxiban
- Apixaban
What are the choices for anticoagulation?

- Aspirin
- Warfarin
- Dabigatran
- Rivaroxiban
- Apixaban
- Direct factor Xa inhibitor
- Orally active
- $T_{1/2} \sim 12$ hrs
- Twice daily dosing
- 25% renal elimination
- No good monitoring mechanism
- No reversal agent.
Apixaban: Aristotle Trial

- 18,201 subjects randomized to apixaban (5mg twice daily) vs. warfarin
- Non-inferiority
- Blinded
- Endpoint of stroke or systemic embolization

Granger et al. *NEJM* 2011;365:11
### Aristotle: All Endpoints

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Apixaban Group (N=9120)</th>
<th>Warfarin Group (N=9081)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients with Event no.</td>
<td>Event Rate %/yr</td>
<td>Patients with Event no.</td>
<td>Event Rate %/yr</td>
</tr>
<tr>
<td>Primary outcome: stroke or systemic embolism</td>
<td>212</td>
<td>1.27</td>
<td>265</td>
<td>1.60</td>
</tr>
<tr>
<td>Stroke</td>
<td>199</td>
<td>1.19</td>
<td>250</td>
<td>1.51</td>
</tr>
<tr>
<td>Ischemic or uncertain type of stroke</td>
<td>162</td>
<td>0.97</td>
<td>175</td>
<td>1.05</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>40</td>
<td>0.24</td>
<td>78</td>
<td>0.47</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>15</td>
<td>0.09</td>
<td>17</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>Key secondary efficacy outcome: death from any cause</strong></td>
<td>603</td>
<td>3.52</td>
<td>669</td>
<td>3.94</td>
</tr>
<tr>
<td>Other secondary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke, systemic embolism, or death from any cause</td>
<td>752</td>
<td>4.49</td>
<td>837</td>
<td>5.04</td>
</tr>
<tr>
<td><strong>Myocardial infarction</strong></td>
<td>90</td>
<td>0.53</td>
<td>102</td>
<td>0.61</td>
</tr>
<tr>
<td>Stroke, systemic embolism, myocardial infarction, or death from any cause</td>
<td>810</td>
<td>4.85</td>
<td>906</td>
<td>5.49</td>
</tr>
<tr>
<td>Pulmonary embolism or deep-vein thrombosis</td>
<td>7</td>
<td>0.04</td>
<td>9</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Granger et al. *NEJM* 2011;365:11

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*UMASS Medical School*

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What should we do with our patients?
Non-valvular AF

1. Calculate CHADS₂, If >1, anticoagulation
2. If CHADS₂=1, CHADS-VASC
3. Anticoagulation preferred if >0
4. Consider coumadin vs newer agents
Non-valvular AF

- Coumadin has a long track record.
- Compared to coumadin:
  - Dabigatran prevents embolism with equal bleeding, possible increase in MI
  - Rivaroxiban has similar rates of embolism, but less bleeding
  - Apixaban has similar rates of embolism, less bleeding, less death
Thank You and Questions?