Disclosures

• None
Issues with Anticoagulation for Atrial Fibrillation

Fred Kusumoto MD
Professor of Medicine Mayo Clinic College of Medicine
Kusumoto.Fred@Mayo.edu

2nd Annual Lakeland regional Health Cardiovascular Symposium
February 10, 2018
Management of Atrial Fibrillation

- Symptoms
- Stroke Risk
Case

• 56 year old lawyer comes to your office with a 3 month history of progressive dyspnea on exertion and fatigue, without chest pain.

• He has been on HCTZ 25 mg daily for hypertension

• Physical examination reveals an irregular fast heart rate but is otherwise normal
Initial management for stroke risk
Atrial Fibrillation and Stroke

- Overall Risk/Risk stratification
- Evidence Base
- Clinical cases
Atrial Fibrillation and Stroke

• Overall Risk/Risk stratification
• Evidence Base
• Clinical cases
Stroke Rates in Placebo-Treated Patients With AF*

*This represents patients who are not anticoagulated; †Secondary prevention.

Stroke in AF

Paroxysmal vs Permanent

<table>
<thead>
<tr>
<th>Study</th>
<th>Paroxysmal (%)</th>
<th>Permanent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAATAF</td>
<td>2.5</td>
<td>2.8</td>
</tr>
<tr>
<td>SPAF</td>
<td>5.6</td>
<td>5.9</td>
</tr>
<tr>
<td>Petersen</td>
<td>2.0</td>
<td>5.1</td>
</tr>
<tr>
<td>Roy</td>
<td>5.3</td>
<td>5.4</td>
</tr>
</tbody>
</table>

Relative contributions of different risk factors to the CHADS$_2$ score ("NIH")

- 73,558 patients with AF not treated with OAC (Denmark)

Olesen et al BMJ 2011;342:d124
Relationship Between the CHA$_2$DS$_2$-VASc Score and the Risk of Stroke

• CHA$_2$DS$_2$-VASc: Weights age, adds vascular disease and gender

• Greater granularity at “low and moderate” risk
Atrial Fibrillation and Stroke

• Overall Risk/Risk stratification
  • CHA$_2$DS$_2$-Vasc adds more granularity at the lower levels
  • “Back of the envelope” calculation: Each point corresponds to an incremental 1% annual risk of stroke

• Evidence Base

• Clinical cases
Atrial Fibrillation and Stroke

• Overall Risk/Risk stratification
  • CHA$_2$DS$_2$-Vasc adds more granularity at the lower levels
  • “Back of the envelope” calculation: Each point corresponds to an incremental 1% annual risk of stroke

• Evidence Base

• Clinical cases
Moldy sweet clover was associated with livestock deaths due to hemorrhage
Anticoagulation in AF
Stroke Risk Reductions

Reduction of all-cause mortality
RRR 26%

Reduction of stroke
RRR 62%

Coagulation Cascade

**Inhibition of Thrombolysis**

- Dabigatran
- Rivaroxaban
- Apixaban
- Edoxaban

**Reactivation of Coagulation Cascade**

**Extrinsic Pathway**

- XIIa
- X1a
- IXa
- VIIa
- Tissue Factor

**Intrinsic Pathway**

- Platelet Activation
- Fibrin

Summary of the NOAC Trials:
**Annual Risk of Stroke and Systemic Embolism**

<table>
<thead>
<tr>
<th>Drug</th>
<th>CHADS$_2$ Risk</th>
<th>Annual Rate of Stroke and Systemic Embolism (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>dab</td>
<td>2.1</td>
<td>War: 1.5</td>
</tr>
<tr>
<td>riv</td>
<td>3.5</td>
<td>War: 2.5</td>
</tr>
<tr>
<td>apix</td>
<td>2.0</td>
<td>War: 2.0</td>
</tr>
<tr>
<td>edox</td>
<td>2.8</td>
<td>War: 2.3</td>
</tr>
</tbody>
</table>

Summary of the NOAC Trials: 
Annual Risk of Major bleeding

<table>
<thead>
<tr>
<th>Drug</th>
<th>Annual Rate of Major bleeding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>dab</td>
<td>2.1</td>
</tr>
<tr>
<td>riv</td>
<td>3.5</td>
</tr>
<tr>
<td>apix</td>
<td>2.0</td>
</tr>
<tr>
<td>edox</td>
<td>2.8</td>
</tr>
</tbody>
</table>

CHADS$_2$  
- dab: 2.1
- riv: 3.5
- apix: 2.0
- edox: 2.8

Atrial Fibrillation and Stroke

- Overall Risk/Risk stratification
- Evidence Base
  - Dabigatran (ReLy)
  - Rivaroxaban (Rocket AF)
  - Apixaban (Aristotle)
  - Edoxaban (Engage)
- Clinical Cases
Atrial Fibrillation and Stroke

• Overall Risk/Risk stratification

• Evidence Base
  • Dabigatran (ReLy)
  • Rivaroxaban (Rocket AF)
  • Apixaban (Aristotle)
  • Edoxaban (Engage)
  • LAA occlusion (Protect AF)

• Clinical Cases
  • Preparation for CV?
  • Valvular heart disease?
  • High risk for falls?
Initial Management vs. “Long-term” Recommendations

Preparation for CV?

<table>
<thead>
<tr>
<th>CHA$_2$DS$_2$-VASc</th>
<th>Rec</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No AC (ⅱa)</td>
</tr>
<tr>
<td>1</td>
<td>No AC (ⅱb)AC (ⅱb)</td>
</tr>
<tr>
<td>2</td>
<td>AC (ⅰ)</td>
</tr>
</tbody>
</table>

CHADS$_2$: 1 (Hypertension)

CHA$_2$DS$_2$-VaSC: 1
Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement (RE-ALIGN)

- Stopped prematurely due to significant increased risk of thromboembolism and bleeding associated with dabigatran

Eikelboom et al NEJM 2013
Edoxaban and moderate valvular heart disease

• Excluded mechanical heart valves and moderate to severe MS
• “Valvular HD”
  • MR: 2,250
  • Surgery: 333

**Definition of Valvular Heart Disease**

**Trial data and FDA**

**Contraindication:** Risk clearly outweighs any benefit

**Warning:** Potential safety hazards that are serious or clinically significant

<table>
<thead>
<tr>
<th>Drug</th>
<th>Prosthetic valve</th>
<th>(Mech)</th>
<th>(Bio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>Prosthetic valve “Hemodynamically Significant”</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>PVR (Annuloplasty OK) “Hemodynamically significant” MS</td>
<td>(none)</td>
<td>(Bio and Mech)</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Mech PVR Mod to severe MS</td>
<td>(None)</td>
<td>(Bio and Mech)</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Mech PVR Mod to severe MS</td>
<td>(None)</td>
<td>(Mech PVR and MS)</td>
</tr>
</tbody>
</table>

Proposed NVAF definition: Atrial fibrillation without the presence of hemodynamically relevant mitral valve stenosis or mechanical prosthetic heart valve

EHRA APHRS 2014
AVERROES Study: Apixaban vs. Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who have Failed or are Unsuitable for Vitamin K Antagonist Treatment

- 5,599 warfarin ineligible patients with AF randomized to aspirin (81 mg daily) or apixaban (5 mg BID)
- Primary endpoint: Stroke, non-CNS embolism

<table>
<thead>
<tr>
<th>Age</th>
<th>Persistent AF</th>
<th>CHADS</th>
<th>Reason for warfarin ineligibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>70 yo</td>
<td>70%</td>
<td>21%</td>
<td>CHADS 1 and VKA NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>90%</td>
<td>Poor INR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>38%</td>
<td>Pt Refusal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6%</td>
<td>Adverse bleeding</td>
</tr>
</tbody>
</table>

Hazard ratio with apixaban, 0.45 (95% CI, 0.32-0.62)
P<0.001

Hazard ratio with apixaban, 1.13 (95% CI, 0.74-1.75)
P=0.57

©2011 MFMER
Connolly SJ NEJM 2011
Edoxaban vs. warfarin in patients at risk for falling
ENGAGE AF TIMI-48

• 21,105 patients, 900 patients (4.3%) thought to be at risk for falling

**CENTRAL ILLUSTRATION:** Absolute Risk Reduction of Higher Dose Edoxaban Regimen Compared With Warfarin in Patients at Increased Fall Risk Versus Not at Increased Fall Risk


"More Negative = Better"
34 million people in the world have atrial fibrillation

Prevalence of atrial fibrillation and flutter (per 100,000) by region, 2010

Chugh et al Circ 2013
Mediterranean diet and reduction of cardiac events (PREDIMED)

• 7,447 patients randomized to three diets followed for 5 years
  (Low Fat, Med + Olive Oil, Med + mixed nuts)

Can “upstream” strategies prevent AF?

Martinez Gonzalez Prog CV Dz 2015
Issues with Anticoagulation for Atrial Fibrillation

• Overall Risk/Risk stratification
  • CHA$_2$DS$_2$-VASc
    (more detail: age, gender, vascular disease)

• Evidence Base
  • NOACs

• Cases
  • Cardioversion
  • Valvular heart disease
  • “High risk for falls”