Management of Thromboembolism Risk Related to Atrial Fibrillation

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Chief, Electrophysiology Section
Few Concepts….

- Atrial Fibrillation = Atrial Flutter
  - *Everytime* the word “fibrillation” is used the same rationale applies to “flutter”

- ASA and Clopidogrel (Plavix)
  - Not anticoagulants
  - Net effect is increased complications
Anticoagulation for AF, Protocol #1: Peri-Cardioversion, For Every Patient

- Identical for Electrical CV, Pharmacologic CV or Restoration of SR with Ablation
- 3 consecutive weeks of AC before CV
- 6 weeks AC after CV
- TEE: eliminates the 3 wks AC prior to CV
  - *But* the pt MUST be AC prior / at time of CV
- Once CV, then use CHADS-VASc Score to determine need for long term AC
Anticoagulation for AF, Protocol #2: Thromboembolism Prophylaxis

- Use risk assessment tools
- CHA$_2$DS$_2$-VASc

Anticoagulation is indeed *forever*

- Recognize that decision re AC can change
- In 5 years with new Dx of DM, change to AC
- Reassess if bleeding risk changes
## CHA\textsubscript{2}DS\textsubscript{2}-VASc Score

### Major Risks (2 pts):
- Prior CVA / TIA
- Systemic embolism
- Age \( \geq 75 \) yo

### Non-Major Risks (1 pt):
- CHF / LVEF \( \leq 40\% \)
- HTN
- DM
- Female Sex
- Age 65-74
- Vascular Disease

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive HF</td>
<td>1</td>
</tr>
<tr>
<td>HTN</td>
<td>1</td>
</tr>
<tr>
<td>Age ( \geq 75 )</td>
<td>2</td>
</tr>
<tr>
<td>DM</td>
<td>1</td>
</tr>
<tr>
<td>Stroke / TIA / TE</td>
<td>2</td>
</tr>
<tr>
<td>Vascular Disease</td>
<td>1</td>
</tr>
<tr>
<td>Age 65 - 74</td>
<td>1</td>
</tr>
<tr>
<td>Sex (ie, female)</td>
<td>1</td>
</tr>
</tbody>
</table>

**Maximum Score** 9
Adjusted Annual Stroke Risk
Using CHA$_2$DS$_2$-VASc Score
n = 7329

Stroke in Atrial Fibrillation: Stockholm Cohort of AF

Stroke risk persists and is equal in the asymptomatic AF, low AF burden or high AF burden patient

Stroke risk unchanged despite a strategy of rhythm control!

\[ P = 0.54 \]

\[ HR = 1.10 \ (95\% \ CI \ 0.78-1.56) \]
\[ P = 0.58 \]
Perception is Not Reality......
Use of AAD’s and Maintenance of SR Does *Not* Reduce Stroke Risk.
Anticoagulation is Forever!!!
### COMPARED TO WARFARIN

<table>
<thead>
<tr>
<th></th>
<th>Apixaban (ARISTOTLE)</th>
<th>Dabigatran 150 mg (RE-LY)</th>
<th>Rivaroxaban (ROCKET AF)</th>
<th>Edoxaban (ENGAGE AF-TIMI 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall Mortality</strong></td>
<td>↓ (p 0.047)</td>
<td>↔ (p 0.051)</td>
<td>↓ (p 0.15)</td>
<td>Equal c 60mg ↓ c 30mg (p 0.006)</td>
</tr>
<tr>
<td><strong>Stroke and Systemic Embolism</strong></td>
<td>↓ (No decrease ischemic CVA)</td>
<td>↓ (↓ Ischemic &amp; Hemorrhagic CVA)</td>
<td>↔ (No decrease ischemic CVA)</td>
<td>↔ (No decrease ischemic CVA)</td>
</tr>
<tr>
<td><strong>Major Bleeding</strong></td>
<td>↓</td>
<td>↔</td>
<td>➯</td>
<td>➯</td>
</tr>
<tr>
<td><strong>GI Bleeding</strong></td>
<td>↔</td>
<td>➯</td>
<td>➯</td>
<td>➯</td>
</tr>
<tr>
<td><strong>ICH</strong></td>
<td>↓</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Indication**
- Stroke/embolism prevention in non-valvular AF
- VTE Tx
- VTE 2° prevention
- VTE prevention after hip/knee replacement

**Exclusions from trials**
- Valve disorders
- Stroke within 7 days
- ASA > 100 or ASA+Plavix
- CrCl < 25 OR SCR > 2.5
- Hgb < 9

**Renal Function Subgroup Analysis**
- Significant S/SE redn only in CrCl 50-80
- Major bleeding significantly reduced in CrCl < 80 (no diff CrCl > 80)
- No diff in major bleeding

**Dosage Changes**
- If 2 out of 3: Age ≥ 80, Wt ≤ 60 Kg, SCR ≥ 1.5, ↓ dose to 2.5 mg bid
- Use 75 mg bid for CrCl 15-30
- Use 15 mg daily for CrCl 30-50
- If CrCl > 95 (? >80), AVOID USE (↑ ischemic CVA due to ↓ blood levels by 30-40%)

**Target**
- (Warfarin – VKORC1 – II, VII, IX, X, C, S)
- Factor Xa
- Thrombin
- Factor Xa
- Factor Xa

**DOAC’s are Better**
**But DOAC’s / Warfarin are Supported by Guidelines**
<table>
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<th>Apixaban</th>
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<th>Edoxaban</th>
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<tr>
<td><strong>Bioavailability</strong></td>
<td>50%</td>
<td>3-7% (↑ by 75% when pellets are taken w/o capsule shell (should NOT broken/chewed/opened)) Requires pH 2-3 for absorption (coated with tartaric acid)</td>
<td>60-80% → Dose dependent; Food ↑ bioavailability by another 40%</td>
<td>62%</td>
</tr>
<tr>
<td><strong>Time to peak effect</strong></td>
<td>3-4 hrs $T_{1/2} \sim 12$ hrs</td>
<td>1-2 hrs $T_{1/2} \sim 12-17$ hrs</td>
<td>2-4 hrs $T_{1/2} \sim 5-9$ hrs (healthy) and 11-13 hrs in elderly</td>
<td>1-2 hrs $T_{1/2} \sim 10-14$ hrs</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Liver: CYP3A4 (primary) CYP1A2, 2C8, 2C9, 2C19, 2J2</td>
<td><strong>PRODRUG</strong> → Hydrolyzed to active moiety then further metabolized thru conjugation.</td>
<td>Liver: CYP3A4/5 &amp; CYP2J2</td>
<td>Minimal</td>
</tr>
<tr>
<td><strong>Excretion</strong></td>
<td>Renal 27%; Majority: Feces substrate of transport proteins: P-gp and BRCP</td>
<td>Oral: Renal 7%, Feces 86% Dabigatran etexilate - substrate of the efflux transporter P-gp</td>
<td>~33% unchanged urine (~66% metabolites in urine and feces)</td>
<td>Eliminated primarily as unchanged drug in the urine 50% Renal</td>
</tr>
<tr>
<td><strong>Interactions</strong></td>
<td>↑ - Keto/Itraconazole, HIV protease inhibitors Mild Inc – Diltiazeum ↓ - Rifampin, carbamazepine, Phenytoin, St John’s wort (inducers)</td>
<td>↑ - Dronedarone, Amio, verapamil, Quinidine, keto/Itraconazole, ↓ - Rifampin, carbamazepine, Phenytoin, St John’s wort (inducers) mild decrease c Antacids ↔ - Diltiazem</td>
<td>↑ - Keto/Itraconazole, HIV protease inhibitors ↓ - Rifampin, carbamazepine, Phenytoin, St John’s wort (inducers)</td>
<td>↑ - Dronedarone, Amio, verapamil, Quinidine, keto/Itraconazole, cyclosporine, tacrolimus ↓ - Rifampin, carbamazepine, Phenytoin, St John’s wort (inducers)</td>
</tr>
<tr>
<td><strong>Reversal Agents</strong></td>
<td>Idarucizumab (Praxbind) → Humanized antibody fragment (Fab) → Significantly exceeds thrombin affinity for binding dabigatran (350X higher) → Displaces dabigatran from thrombin and Irreversibly binds dabigatran and metabolites → Dose: 2.5 grams X2 (total dose= 5 grams) IV push or IVPB → Onset- minutes</td>
<td>Andexanet alfa → Recombinant, inactivated FXa decoy protein → Cannot form prothrombinase complex on PLT surface and Cannot bind prothrombin → Binds Xa inhibitors, ATIII complexed with LMWH → Onset: minutes → DOSING: 400mg bolus or 400mg bolus + infusion (30 / 120) minutes</td>
<td>Andexanet alfa → Recombinant, inactivated FXa decoy protein → Cannot form prothrombinase complex on PLT surface and Cannot bind prothrombin → Binds Xa inhibitors, ATIII complexed with LMWH → Onset: minutes → DOSING: 800mg bolus or 800mg bolus + infusion (30 / 120) minutes</td>
<td></td>
</tr>
</tbody>
</table>
Why DOACs are Better

- No variability. Constant Therapy
  - Warfarin – high INR variability & low time in therapeutic window
- Greater compliance
- No monitoring
- Reduce stroke and bleeding
  - Some associated with decreased mortality
- *But…*
  - Not for valve replacement
  - Careful in kidney disease
Even With Successful Ablation of AFib.....Why I Continue Anticoagulation with DOAC but Not Warfarin

AVERROES: >5000 pts
Apixaban 5 mg twice daily, vs ASA in AF pts for whom warfarin was considered unsuitable
Apixaban reduced stroke

Apixaban vs ASA No difference in bleeding
New Thinking

- So why switch from Apixaban to ASA?
- Even for CHADSVASc = 0 or 1?
- Not all anticoagulants are the same
  - DOACs are not warfarin…so everything needs to be carefully reconsidered
Left Atrial Appendage Occlusion

- Occlusion of LAA = Mechanical Anticoagulation
- Wall off the left atrial appendage
**PROTECT–AF: Primary Efficacy Endpoint**

<table>
<thead>
<tr>
<th>Event</th>
<th>Watchman Group (n = 463)</th>
<th>Warfarin Group (n = 244)</th>
<th>Rate Ratio (Watchman/Warfarin) (95% Crl)</th>
<th>Posterior Probabilities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events/Patient-Years</td>
<td>Observed Rate (Events per 100 Patient-Years) (95% Crl)</td>
<td>Events/Patient-Years</td>
<td>Observed Rate (Events per 100 Patient-Years) (95% Crl)</td>
</tr>
<tr>
<td>Primary Efficacy Endpoint</td>
<td>39/1720.2</td>
<td>2.3 (1.7, 3.2)</td>
<td>34/900.8</td>
<td>3.8 (2.5, 4.9)</td>
</tr>
<tr>
<td>Stroke</td>
<td>26/1720.7</td>
<td>1.5 (1.0, 2.2)</td>
<td>20/900.9</td>
<td>2.2 (1.3, 3.1)</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>24/1720.8</td>
<td>1.4 (0.9, 2.1)</td>
<td>10/904.2</td>
<td>1.1 (0.5, 1.7)</td>
</tr>
<tr>
<td>Hemorrhagic Stroke</td>
<td>3/1774.2</td>
<td>0.2 (0.0, 0.4)</td>
<td>10/916.2</td>
<td>1.1 (0.5, 1.8)</td>
</tr>
<tr>
<td>Systemic Embolization</td>
<td>3/1773.6</td>
<td>0.2 (0.0, 0.4)</td>
<td>0/919.5</td>
<td>0.0</td>
</tr>
<tr>
<td>Cardiovascular Death</td>
<td>17/1774.3</td>
<td>1.0 (0.6, 1.5)</td>
<td>22/919.4</td>
<td>2.4 (1.4, 3.4)</td>
</tr>
</tbody>
</table>

No difference in stroke Reduction in hemorrhagic stroke with Watchman resulted in reduction in CV Death
CMS Mandatory Criteria for WATCHMAN

- CHADS2 ≥ 2 or CHA2DS2-VASc ≥ 3
- Documented evidence of a formal shared decision interaction between the patient and an independent, non-interventional physician using an evidenced-based decision making tool on oral anticoagulants
- Short-term warfarin OK, but deemed unable to take long-term oral anticoagulation
  - Not for pts actively bleeding or absolute contraindication
- Must be performed in a hospital with structural heart disease or electrophysiology program.
- Must be trained by the manufacturer
- Patients must be enrolled in a prospective national registry
Thank You
ACTIVE Trials: Clopidogrel + Aspirin

AF + risk factors: Age $\geq$ 75 yrs, HTN, prior stroke/TIA, LVEF $<$ 45%, PAD, age 55–74 yrs + CAD or diabetes

Primary outcome: Stroke, systemic embolism, MI, or CV death

ACTIVE-W

Anticoagulation-eligible

<table>
<thead>
<tr>
<th>Warfarin (INR 2-3)</th>
<th>Clopidogrel + Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open label</td>
<td>N = 6500</td>
</tr>
</tbody>
</table>

ACTIVE-A

OAC Contraindications or Unwilling

<table>
<thead>
<tr>
<th>Aspirin + Placebo</th>
<th>Clopidogrel + Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double-blind</td>
<td>Superiority n~7500</td>
</tr>
</tbody>
</table>

ACTIVE-I

Irbesartan, 300 mg/day vs placebo

N $\approx$ 9000