Atrial Fibrillation 2014: New Anticoagulants and Updates on Ablation

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University of Chicago Medicine
Disclosures

- Dr. Burke receives Research Grant support, Fellowship support as well as consulting and speaking honoraria from St Jude Medical, Boston Scientific and Biosense Webster.
Tough Fellowship
Clinical Considerations

- AF has many mechanisms
- AF has a clear natural history
- Patient substrate is variable
- Patient symptoms should rule the choice of clinical approach
- Hybrid therapies will likely be applied to patients outside of the “lone” AF model
Perpetuation of AF
Electrophysiologic Mechanisms

Burst pacing → AF → Sinus rhythm

Control: 5 seconds

After 24 hours: 20 seconds

After 2 weeks: >24 hours

Case Study

- AR is a 78 yo woman with HTN, DM, CAD, and chronic kidney disease stage III who presents to her doctor’s office with complaints of fatigue and DOE for 4 weeks.
- PE notable for BP = 150/88, P = 108 irregular, normal JVP, clear lungs, no LE swelling
- Echo last year with LVEF = 50%
- Rhythm strip and 12-lead ECG show:
Therapy for AF

Prevent Thromboembolism

Control ventricular response

Restore/Maintain sinus rhythm
and the relative risk and benefit for a given patient. (Level of Evidence: A)

3. For patients without mechanical heart valves at high risk of stroke, chronic oral anticoagulant therapy with a vitamin K antagonist is recommended in a dose adjusted to achieve the target intensity INR of 2.0 to 3.0, unless contraindicated. Factors associated with highest risk for stroke in patients with AF are prior thromboembolism (stroke, TIA, or systemic embolism) and rheumatic mitral stenosis. (Level of Evidence: A)

4. Anticoagulation with a vitamin K antagonist is recommended for patients with more than 1 moderate risk factor. Such factors include age 75 y or greater, hypertension, HF, impaired LV systolic function (ejection fraction 35% or less or fractional shortening less than 25%), and diabetes mellitus. (Level of Evidence: A)

5. INR should be determined at least weekly during initiation of therapy and monthly when anticoagulation is stable. (Level of Evidence: A)

6. Aspirin, 81–325 mg daily, is recommended as an alternative to vitamin K antagonists in low-risk patients or in those with contraindications to oral anticoagulation. (Level of Evidence: A)

7. For patients with AF who have mechanical heart valves, the target intensity of anticoagulation should be based on the type of prosthesis, maintaining an INR of at least 2.5. (Level of Evidence: B)

8. Antithrombotic therapy is recommended for patients with atrial flutter as for those with AF. (Level of Evidence: C)
# Stroke Prevention in AF

<table>
<thead>
<tr>
<th>CHADS2 item</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension (systolic &gt;160 mmHg)</td>
<td>1</td>
</tr>
<tr>
<td>Age greater than 75 years</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
</tr>
<tr>
<td>Prior cerebral ischemia</td>
<td>2</td>
</tr>
</tbody>
</table>

Risk Adjusted by CHAD2 Score

**CHA$_2$DS$_2$-VASc Score**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive HF/LV dysfunction</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age $\geq$ 75</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/TIA/thromboembolism</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 category (ie, female sex)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Maximum score</strong></td>
<td><strong>9</strong></td>
</tr>
</tbody>
</table>

Olesen et al.  BMJ. 2011;342d124
**CHADS\(_2\) -> CHA\(_2\)DS\(_2\)VASc**

<table>
<thead>
<tr>
<th>CHADS2 score</th>
<th>Patients ((n = 1733))</th>
<th>Adjusted stroke rate %/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>120</td>
<td>1.9</td>
</tr>
<tr>
<td>1</td>
<td>463</td>
<td>2.8</td>
</tr>
<tr>
<td>2</td>
<td>523</td>
<td>4.0</td>
</tr>
<tr>
<td>3</td>
<td>337</td>
<td>5.9</td>
</tr>
<tr>
<td>4</td>
<td>220</td>
<td>8.5</td>
</tr>
<tr>
<td>5</td>
<td>65</td>
<td>12.5</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>18.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHA2DS2-VASc score</th>
<th>Patients ((n = 7329))</th>
<th>Adjusted stroke rate %/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>422</td>
<td>1.3</td>
</tr>
<tr>
<td>2</td>
<td>1230</td>
<td>2.2</td>
</tr>
<tr>
<td>3</td>
<td>1730</td>
<td>3.2</td>
</tr>
<tr>
<td>4</td>
<td>1718</td>
<td>4.0</td>
</tr>
<tr>
<td>5</td>
<td>1159</td>
<td>6.7</td>
</tr>
<tr>
<td>6</td>
<td>679</td>
<td>9.8</td>
</tr>
<tr>
<td>7</td>
<td>294</td>
<td>9.6</td>
</tr>
<tr>
<td>8</td>
<td>82</td>
<td>6.7</td>
</tr>
<tr>
<td>9</td>
<td>14</td>
<td>15.2</td>
</tr>
</tbody>
</table>
Warfarin Narrow Therapy Safety

Warfarin: Narrow therapeutic window

- Ischemic stroke
- Intracranial bleeding

International normalized ratio

Odds ratio

Limitations Lead to Underutilization

Warfarin limitations lead to under-treatment of AF

- Warfarin use in eligible patients (%)
  - <55: 44%
  - 55-64: 58%
  - 65-74: 61%
  - 75-84: 57%
  - ≥85: 35%

55% overall use

# HAS-BLED Score

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal renal or liver function (1 each)</td>
<td>1 or 2</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1</td>
</tr>
<tr>
<td>Labile INR</td>
<td>1</td>
</tr>
<tr>
<td>Elderly age</td>
<td>1</td>
</tr>
<tr>
<td>Drugs or alcohol (1 each)</td>
<td>1 or 2</td>
</tr>
</tbody>
</table>

**Maximum Score** 9

Hypertension: SBP > 160 mmHg; Abnormal renal function: Chronic dialysis, renal transplant, serum creatinine ≥ 200μmol/L; Abnormal liver function: Chronic hepatitis, bilirubin > 2x upper limit of normal (ULN) in association with AST/ALT/ALP > 3 x ULN; Bleeding: Previous history, predisposition; Labile INRs: unstable/high INRs, in therapeutic range < 60%; Age > 65 years; Drugs/alcohol: Concomitant use of antiplatelet agents, non-steroidal anti-inflammatory drugs, etc.

Dabigatran (150 mg bid)

**Advantages**
- Works better than warfarin
- Similar rates of major bleeding
- Less intracranial hemorrhage
- No monitoring required
- No drug-drug or diet interactions

**Disadvantages**
- More GI bleeding
- Unclear efficacy in renal insufficiency
- No reversal agent
- Hemodialysis
- New
- Expensive
- Bleeding risk higher in patients > 75 years
RE-LY Study

Cumulative Hazard Rates for the Primary Outcome of Stroke or Systemic Embolism, According to Treatment Group.

34% reduction

**ROCKET-AF Trial**

**Baseline Patient Demographics (cont)**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF or LVEF ≤ 35%</td>
<td>63</td>
<td>32</td>
<td>30</td>
<td>23</td>
<td>39</td>
</tr>
<tr>
<td>Hypertension</td>
<td>90</td>
<td>79</td>
<td>82</td>
<td>77</td>
<td>81</td>
</tr>
<tr>
<td>Age ≥ 75 years</td>
<td>44</td>
<td>–</td>
<td>–</td>
<td>31</td>
<td>42</td>
</tr>
<tr>
<td>Diabetes</td>
<td>40</td>
<td>23</td>
<td>21</td>
<td>10*</td>
<td>19†</td>
</tr>
<tr>
<td>Prior stroke, TIA, or non-CNS SE</td>
<td>55</td>
<td>20</td>
<td>15</td>
<td>24</td>
<td>18</td>
</tr>
</tbody>
</table>

* Diabetes and age 65-75 years
† Diabetes and age ≥ 65 years

**Baseline Patient Demographics: Comparison of ROCKET AF With Previous VKA-controlled Trials**

<table>
<thead>
<tr>
<th>CHADS₂ score (%)</th>
<th>ROCKET AF[a]</th>
<th>RE-LY[b]</th>
<th>ACTIVE W[c]</th>
<th>AMADEUS[d]</th>
<th>SPORTIF V[e]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>&lt;1</td>
<td>32</td>
<td>N/A</td>
<td>41</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>13</td>
<td>36</td>
<td>N/A</td>
<td>32</td>
<td>31</td>
</tr>
<tr>
<td>≥ 3</td>
<td>86</td>
<td>32</td>
<td>N/A</td>
<td>27</td>
<td>44</td>
</tr>
</tbody>
</table>

Median CHADS₂ score: ≥ 3 2 2 2 2
## ROCKET-AF Trial

### ROCKET AF: Primary Safety Outcomes

<table>
<thead>
<tr>
<th>Bleeding</th>
<th>Rivaroxaban event rate</th>
<th>Warfarin event rate</th>
<th>HR 95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major and nonmajor clinically relevant</td>
<td>14.91</td>
<td>14.52</td>
<td>1.03 0.96-1.11</td>
<td>.442</td>
</tr>
<tr>
<td>Major</td>
<td>3.60</td>
<td>3.45</td>
<td>1.04 0.90-1.20</td>
<td>.576</td>
</tr>
<tr>
<td>Nonmajor clinically relevant</td>
<td>11.80</td>
<td>11.37</td>
<td>1.04 0.96-1.13</td>
<td>.345</td>
</tr>
</tbody>
</table>

Event rates are per 100 patient-years
Based on safety on-treatment population

## Table 2. Efficacy Outcomes.*

<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><strong>Hemorrhagic stroke</strong></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>Key secondary efficacy outcome: death from any cause</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>Myocardial infarction</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>

*Analyses were performed on data from the intention-to-treat population and included all events through the cutoff date for efficacy outcomes of January 30, 2011; comparisons of the primary outcome and of death from any cause were analyzed as part of hierarchical sequence testing (starting with testing the primary outcome for noninferiority, then the primary outcome for superiority, then major bleeding, and finally death from any cause), to control the type I error.
ARISTOTLE Study

ARISTOTLE: Summary

Apixaban vs warfarin

- Reduces stroke and systemic embolism by 21% ($P = .01$)
- Reduces major bleeding by 31% ($P < .001$)
- Reduces mortality by 11% ($P = .047$)

Favorable trend for MI
Used in patients with moderate renal disease

Novel Oral Anticoagulants (NOACS)

Pro-thrombin complex concentrate (PCC) shown to reverse effects of rivaroxaban but not dabigatran.
Therapy for AF

Prevent Thromboembolism

Control ventricular response

Restore/Maintain sinus rhythm

Treat Pressure and Volume
The Four Stages of Life
Rate Control vs. Rhythm Control

AFFIRM

RACE

AFFIRM Investigators, NEJM 2002

Van Gelder, et al. NEJM 2002
DUAL SUBSTRATES FOR AF

TRIGGERING

PV PACs
OTHER PACs
AT / SVT

MAINTENANCE

LOCAL ANISOTROPY
FIBROSIS / SCARRING
REPETITIVE TRIGGERING

MODULATORS
STRETCH
AUTONOMIC TONE
ELECTRICAL
REMODELING

PAROXYSMAL AF
“PERSISTENT” AF
Longstanding Persistent
Electrocardiographic and Intracardiac Recordings at the Onset of Atrial Fibrillation.
AF frequently initiated by APDs from PVs

- Ablation of venous foci performed at earliest site of maximal amplitude of EGM spike during conducted or nonconducted ectopic beat
- PAF eliminated in 62% at median 7 months

AF Catheter Ablation

Maintenance of Sinus Rhythm

- No (or minimal) heart disease
  - Dronedarone, Flecaïnid, Propafenone, Sotalol
    - Amiodarone, Dofetilide
    - Catheter ablation
  - Dronedarone, Flecaïnid, Propafenone, Sotalol
    - Amiodarone, Dofetilide
    - Catheter ablation
    - Catheter ablation

- Hypertension
  - Substantial LVH
    - No
      - Amiodarone, Dofetilide
      - Catheter ablation
    - Yes
      - Amiodarone
      - Catheter ablation

- Coronary artery disease
  - Dofetilide, Dronedarone, Sotalol
    - Amiodarone
    - Catheter ablation

- Heart failure
  - Amiodarone, Dofetilide
    - Catheter ablation

Lots to know…without lots of consensus

- **Strategies**
  - Focal
  - Segmental
  - WACA/LACA/WEPV
  - Lines lines lines
  - Non-PV triggers, CFAE, rotors, GPs

- **Procedure/Techniques**
  - Irrigated v. non-irrigated RF
  - Non-RF energy sources
  - Imaging/mapping
  - Sheaths
  - Anesthesia
  - Peri-procedural anticoagulation

- **Endpoints**
  - Entrance block
  - Exit block
  - Organization/conversion to SR
  - Inducibility

Pulmonary veins are the “cornerstone”

Avoid complications!

“i” is for isolation
Common strategies in the current era

Don’t forget triggers!
Isolation of RCPV

Atria remain in AF
RSPV dissociated potential initially after isolation
Regardless of technique or endpoint, stay cognizant of universal risks

Endocarditis symptoms 2-3d post-op; extensive septic/air emboli +/- hematemesis over next weeks

Which RF catheter to use?

- Multiple demonstrations of irrigated RF superiority in other clinical situations (flutter, VT); limited comparative data in AF

Comparison of Antiarrhythmic Drug Therapy and Radiofrequency Catheter Ablation in Patients With Paroxysmal Atrial Fibrillation
A Randomized Controlled Trial

- Funded by Biosense Webster
- NaviStar ThermoCool used for all procedures (2004-2007) in 19 centers
- 66% of ablation pts v. 16% of AAD pts were “free of treatment failure” at 9 months
One problem with targeting APDs inside PVs...
Many strategies for AF ablation evolved; most studied in 1-2 centers

- **CFAE ablation**
  - CFAEs mapped with CARTO
  - AF terminated w/o DCCV in 95% (concomitant ibutilide in 28%)
  - 76% symptom free at 1-yr with 1 procedure; 91% with 2

- **Stepwise:** PVI + CS/SVC + LA +/- lines (roof, MI, CTI)
Many strategies for AF ablation evolved; most studied in 1-2 centers

- **FIRM ablation**
  Narayan et al. *JACC* 2012; 60(7): 628
  - 92 patients, 107 consecutive ablation procedures, 72% with persistent AF
  - FIRM-guided + conventional, versus conventional alone (WACA, + roof line in persistent AF)
  - 2.1 ± 1 localized rotor or focal impulse sources (in 97% of cases)
  - AF termination or slowing in 86% of FIRM-guided cases, with median time to termination of 2.5 min (versus 20%)
  - 82.4% freedom from AF at median 273 days in FIRM-guided cases (versus 45%)
Many strategies for AF ablation evolved; most studied in 1-2 centers

- **FIRM ablation**
  Narayan et al. *JACC* 2012; 60(7): 628
FIRM ablation

Entire population

Population off AAD’s

Narayan et al. JACC 2012; 60(7): 628
Case Study

AR is a 78 yo woman with HTN, DM, CAD, and chronic kidney disease stage III who presents to her doctor’s office with complaints of fatigue and SOB for 4 weeks.

- Best anticoagulation option prior to 2012 → warfarin

- Best anticoagulation option post 2012 → warfarin or apixaban
Therapy for AF

- Prevent Thromboembolism
- Control ventricular response
- Restore/Maintain sinus rhythm
Thank You for Your Attention