Atrial Fibrillation: New Approaches to an Old Friend

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ASSISTANT PROFESSOR
Disclosures

- None relevant to this presentation
Atrial Fibrillation

- Irregularly irregular rate
- Rapid chaotic atrial electrical activity
- AV node protects the ventricle
AF: Epidemiology

- Single most common sustained cardiac arrhythmia, 1-2% of general population \(^1\)
- Expected to increase to 16 million by 2050 \(^1\)
- Men have 1.5x risk for developing AF after RF adjustment
- 1% of AF occurs in patients <60 yo \(^2\)
- Tall stature and obesity independently associated with AF \(^3\)
- Family history increases risk by 2-3x

AF Is the Leading Cause of Hospitalizations for Arrhythmia

Hospital Admissions in US

- AF
- AFL
- Cardiac arrest
- Conduction disease
- Junctional
- Premature beats
- Sick sinus
- Unspecified
- VF
- VT

N=517,699 (representing 10% of CV admissions).

VF, ventricular fibrillation; VT, ventricular tachycardia.

AF Flavors

- Paroxysmal AF – spontaneously converts to sinus rhythm, or with intervention <7 days
- Persistent AF – Continuous AF >7 days
- Long standing Persistent AF – Continuous AF > 1 year
- Permanent AF – patient and physician have decided to leave patient in AF

- All should be treated the same in regard to stroke risk!
AF Is Associated With Increased Thromboembolic Risk

- Major cause of stroke in elderly\(^1\)
- 5-fold ↑ in risk of stroke\(^1,2\)
- Incidence of all-cause stroke in patients with nonvalvular AF: 5%\(^1\)
- 15% of strokes in US are attributable to AF\(^3\)
- Stroke severity (and mortality) is worse with AF than without AF\(^4\)
- Stroke risk persists even in asymptomatic AF\(^5\)

Reasons We Treat AF

- Symptoms
  - wide spectrum from completely asymptomatic to exquisitely sensitive
  - Palpitations, dyspnea, fatigue

- Risk of stroke
  - Virchow’s Triad
    - Endothelial injury – myocyte hypertrophy, fibrotic changes
    - Stasis - No organized mechanical function, LA dilation
    - Hypercoaguable state – platelet activation, prothrombin
  - Thrombus usually from left atrial appendage

- Rate
  - Chronically elevated heart rate may cause tachycardia cardiomyopathy
Spontaneous Echocardiogram Contrast – “Smoke”
How Effective is Warfarin?

Intention-To-Treat Analysis

- Control
- Warfarin

Risk
- AFASAK: 58%
- SPAF: 67%
- BAATAF: 86%
- CAFA: 42%
- SPINAF: 79%

Reduction
- AFASAK: P < .03
- SPAF: P < .01
- BAATAF: P < .002
- CAFA: P > .2
- SPINAF: P < .002

95% CI
- AFASAK: 7 – 81
- SPAF: 27 – 85
- BAATAF: 51 – 96
- CAFA: 68 – 80
- SPINAF: 52 – 90

TOTAL
- 4.5
- 1.4
- 68%
- P < .001

Total 95% CI: 50 – 79
How Effective is Warfarin?

**Intention-To-Treat Analysis**

- **RRR 68% CI 0.50-0.79 (P<0.01)**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Risk</th>
<th>Reduction</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>58%</td>
<td><em>P&lt;.03</em></td>
<td>7 - 81</td>
</tr>
<tr>
<td>Warfarin</td>
<td>67%</td>
<td><em>P&lt;.01</em></td>
<td>27 - 85</td>
</tr>
<tr>
<td>BAATAF</td>
<td>86%</td>
<td><em>P&lt;.002</em></td>
<td>51 - 96</td>
</tr>
<tr>
<td>CAFA</td>
<td>42%</td>
<td><em>P&gt;.2</em></td>
<td>68 - 80</td>
</tr>
<tr>
<td>SPINAF</td>
<td>79%</td>
<td><em>P&lt;.002</em></td>
<td>52 - 90</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>68%</td>
<td><strong>P&lt;.001</strong></td>
<td>50 - 79</td>
</tr>
</tbody>
</table>

Arch Internal Med 1994; 154: 1449-57
Cumulative Mortality from Any Cause in the Rhythm-Control Group and the Rate-Control Group

Rhythm control
63% in sinus rhythm at 5 yrs

Rate control
35% in sinus rhythm at 5 yrs

Regardless of treatment strategy, majority of strokes occurred in patients with subtherapeutic INR or not taking warfarin.

AF: Anticoagulation

▪ Old paradigm:
  ▪ Lone AF
    ▪ Under age 65
    ▪ Paroxysmal
    ▪ No other medical problems
    ▪ Aspirin is sufficient
  ▪ Everyone else needed warfarin

▪ New Paradigm:
  ▪ Use risk scores to determine need for warfarin
AF: CHADS2 Score

- Congestive heart failure
- Hypertension
- Age > 75 years
- Diabetes Mellitus
- Stroke

- If CHADS2 = 0  low risk of CVA (ASA)
- If CHADS2 = 1, moderate risk of CVA (ASA or warfarin)
- If CHADS2 >=2, higher risk of CVA (warfarin)
**AF: CHADS2 Score**

**Validation of Clinical Classification Schemes for Predicting Stroke: Results From the National Registry of Atrial Fibrillation**

<table>
<thead>
<tr>
<th>CHADS2 Score</th>
<th>No. of Patients (n = 1733)</th>
<th>No. of Strokes (n = 94)</th>
<th>NRAF Crude Stroke Rate per 100 Patient-Years</th>
<th>NRAF Adjusted Stroke Rate, (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>120</td>
<td>2</td>
<td>1.2</td>
<td>1.9 (1.2-3.0)</td>
</tr>
<tr>
<td>1</td>
<td>463</td>
<td>17</td>
<td>2.8</td>
<td>2.8 (2.0-3.8)</td>
</tr>
<tr>
<td>2</td>
<td>523</td>
<td>23</td>
<td>3.6</td>
<td>4.0 (3.1-5.1)</td>
</tr>
<tr>
<td>3</td>
<td>337</td>
<td>25</td>
<td>6.4</td>
<td>5.9 (4.6-7.3)</td>
</tr>
<tr>
<td>4</td>
<td>220</td>
<td>19</td>
<td>8.0</td>
<td>8.5 (6.3-11.1)</td>
</tr>
<tr>
<td>5</td>
<td>65</td>
<td>6</td>
<td>7.7</td>
<td>12.5 (8.2-17.5)</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>2</td>
<td>44.0</td>
<td>18.2 (10.5-27.4)</td>
</tr>
</tbody>
</table>

*CHADS2 score is calculated by adding 1 point for each of the following conditions: recent congestive heart failure, hypertension, age at least 75 years, or diabetes mellitus and adding 2 points for having had a prior stroke or transient ischemic attack. CI indicates confidence interval.

†The adjusted stroke rate is the expected stroke rate per 100 patient-years from the exponential survival model, assuming that aspirin was not taken.
AF: CHADS-VASc Score

- CHF/LV dysfunction 1
- Hypertension 1
- Age > 75 2
- Diabetes 1
- Stroke/TIA 2
- Vascular disease* 1
- Age 65-75 1
- Sex category (female) 1

* Prior MI, peripheral vascular disease, aortic plaque
AF: CHADS2 vs. CHADS-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>
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<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>CHADS-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>
AF: AHA/ACC 2014 AF Guidelines

- CHADS-VASc should be used for risk assessment (class I)
- CHADS-VASc ≥ 2 should be on oral anticoagulant (class I)
- CHADS-VASc 0 Reasonable to omit antithrombotic therapy (class IIa)
- CHADS-VASc 1 Consider no therapy, OAC, or ASA (class IIb)
- Antithrombotic therapy based on shared decision-making, discussion of risks of stroke and bleeding, and patient’s preferences (class I)
AF: CHADS2 vs. CHADS-VASc

Fuster V, et al.. Net clinical benefit of warfarin. 2012. 125; 2285-87
AF: HAS-BLED Score

- Hypertension
- Abnormal renal and liver function
- Stroke
- Bleeding (major prior)
- Labile INRs
- Elderly (>65 years)
- Drugs or alcohol

- Used to assess bleeding risk, if >3 anticoagulate with caution
- HAS-BLED score should not be used alone to dissuade use of anticoagulation
Finding the Right Tool for the Job
AF: Anticoagulation Choices

- **Warfarin**
  - Vast experience, known pitfalls
  - Narrow therapeutic window between ineffective and harmful
  - Dietary limitations
  - Numerous drug-drug interactions
  - Patient perception – “rat poision”

- **Novel Oral Anticoagulants**
  - Dabigatran (direct thrombin inhibitor)
  - Rivaroxaban (Factor Xa inhibitor)
  - Apixaban (Factor Xa inhibitor)
  - Edoxaban? (Factor Xa inhibitor)
AF: NOAC Mechanism of Action

AF: Dabigatran (pradaxa)

- Direct thrombin inhibitor
- Onset within 2 hours
- Approved in 2010 for treatment of non-valvular AF at 150mg BID dose
- GI distress (dyspepsia, heartburn) in some patients
- Pill box not advised
- Approved for DVT/PE if treated parentally for 5-10 days
Dabigatran: RE-LY Trial

- 18,113 patients
  - Atrial fibrillation
  - Another risk factor for stroke
- Randomized to
  - warfarin vs.
  - dabigatran (110 or 150mg BID)
- Primary outcome stroke or systemic embolism
Dabigatran: RE-LY Trial

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

Dabigatran 150mg v. warfarin, p<0.001

Dabigatran: RE-LY Trial

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

Dabigatran 150mg v. warfarin, p<0.001

Dabigatran: RE-LY Trial

Safety Outcomes, According to Treatment Group.

<table>
<thead>
<tr>
<th>Event</th>
<th>Dabigatran, 110 mg</th>
<th>Dabigatran, 150 mg</th>
<th>Warfarin</th>
<th>Dabigatran, 110 mg, vs. Warfarin</th>
<th>Dabigatran, 150 mg, vs. Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of patients</td>
<td>%/yr</td>
<td>no. of patients</td>
<td>%/yr</td>
<td>no. of patients</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>322</td>
<td>2.71</td>
<td>375</td>
<td>3.11</td>
<td>397</td>
</tr>
<tr>
<td>Life threatening</td>
<td>145</td>
<td>1.22</td>
<td>175</td>
<td>1.45</td>
<td>212</td>
</tr>
<tr>
<td>Non–life threatening</td>
<td>198</td>
<td>1.66</td>
<td>226</td>
<td>1.88</td>
<td>208</td>
</tr>
<tr>
<td>Gastrointestinal†</td>
<td>133</td>
<td>1.12</td>
<td>182</td>
<td>1.51</td>
<td>120</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>1566</td>
<td>13.16</td>
<td>1787</td>
<td>14.84</td>
<td>1931</td>
</tr>
<tr>
<td>Major or minor bleeding</td>
<td>1740</td>
<td>14.62</td>
<td>1977</td>
<td>16.42</td>
<td>2142</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>27</td>
<td>0.23</td>
<td>36</td>
<td>0.30</td>
<td>87</td>
</tr>
<tr>
<td>Extracranial bleeding</td>
<td>299</td>
<td>2.51</td>
<td>342</td>
<td>2.84</td>
<td>315</td>
</tr>
<tr>
<td>Net clinical benefit outcome‡</td>
<td>844</td>
<td>7.09</td>
<td>832</td>
<td>6.91</td>
<td>901</td>
</tr>
</tbody>
</table>

* Data are shown for all patients who had at least one event. All analyses were based on the time to the first event. Hemorrhagic stroke was a subcategory of stroke in the efficacy analysis and in the safety analysis is also counted as major, life-threatening bleeding and as part of intracranial bleeding.
† Gastrointestinal bleeding could be life threatening or non–life threatening.
‡ The net clinical benefit outcome was the composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death, or major bleeding.

Rivaroxaban (xarelto)

- Direct factor XA inhibitor
- Approved in 11/2011 for non-valvular atrial fibrillation
- Daily dosing
- Should be taken with a meal
- Rare side effects
- Approved for VTE treatment, VTE prophylaxis in orthopedic surgery
Rivaroxaban: ROCKET-AF Trial

- 14,264 patients
  - Atrial fibrillation
  - CHADS2 score of ≥2
- Randomized to
  - Warfarin v.
  - Rivaroxaban 20mg QD
- Primary outcome stroke or systemic embolism
Rivaroxaban: ROCKET-AF

Cumulative Rates of the Primary End Point (Stroke or Systemic Embolism) in the Per-Protocol Population and in the Intention-to-Treat Population.

P<0.001 for noninferiority

## Rivaroxaban: ROCKET-AF Trial

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rivaroxaban (N=7111)</th>
<th>Warfarin (N=7125)</th>
<th>Hazard Ratio (95% CI)†</th>
<th>P Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Event Rate no./100 patient-yr</td>
<td>Events</td>
<td>Event Rate no./100 patient-yr</td>
</tr>
<tr>
<td>Principal safety end point: major and nonmajor clinically relevant bleeding§</td>
<td>1475 (20.7)</td>
<td>14.9</td>
<td>1449 (20.3)</td>
<td>14.5</td>
</tr>
<tr>
<td>Major bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>395 (5.6)</td>
<td>3.6</td>
<td>386 (5.4)</td>
<td>3.4</td>
</tr>
<tr>
<td>Decrease in hemoglobin ≥2 g/dl</td>
<td>305 (4.3)</td>
<td>2.8</td>
<td>254 (3.6)</td>
<td>2.3</td>
</tr>
<tr>
<td>Transfusion</td>
<td>183 (2.6)</td>
<td>1.6</td>
<td>149 (2.1)</td>
<td>1.3</td>
</tr>
<tr>
<td>Critical bleeding¶</td>
<td>91 (1.3)</td>
<td>0.8</td>
<td>133 (1.9)</td>
<td>1.2</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>27 (0.4)</td>
<td>0.2</td>
<td>55 (0.8)</td>
<td>0.5</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>55 (0.8)</td>
<td>0.5</td>
<td>84 (1.2)</td>
<td>0.7</td>
</tr>
<tr>
<td>Nonmajor clinically relevant bleeding</td>
<td>1185 (16.7)</td>
<td>11.8</td>
<td>1151 (16.2)</td>
<td>11.4</td>
</tr>
</tbody>
</table>

*All analyses of rates of bleeding are based on the first event in the safety population during treatment.
†Hazard ratios are for the rivaroxaban group as compared with the warfarin group and were calculated with the use of Cox proportional-hazards models with the study group as a covariate.
‡Two-sided P values are for superiority in the rivaroxaban group as compared with the warfarin group.
§Minimal bleeding events were not included in the principal safety end point.
¶Bleeding events were considered to be critical if they occurred in intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular (with compartment syndrome), or retroperitoneal sites.

Rivaroxaban: ROCKET-AF Trial

Table 3. Rates of Bleeding Events.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rivaroxaban (N=7111)</th>
<th>Warfarin (N=7125)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events no. (%)</td>
<td>Event Rate no./100 patient-yr</td>
<td>Events no. (%)</td>
<td>Event Rate no./100 patient-yr</td>
</tr>
<tr>
<td>Principal safety end point: major and nonmajor</td>
<td>1475 (20.7)</td>
<td>14.9</td>
<td>1449 (20.3)</td>
<td>14.5</td>
</tr>
</tbody>
</table>

Noninferior to Warfarin for efficacy and safety

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rivaroxaban no. (%)</th>
<th>Warfarin no. (%)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>395 (5.6)</td>
<td>386 (5.4)</td>
<td>1.04 (0.90–1.20)</td>
<td>0.58</td>
</tr>
<tr>
<td>Decrease in hemoglobin ≥2 g/dl</td>
<td>305 (4.3)</td>
<td>254 (3.6)</td>
<td>1.22 (1.03–1.44)</td>
<td>0.02</td>
</tr>
<tr>
<td>Transfusion</td>
<td>183 (2.6)</td>
<td>149 (2.1)</td>
<td>1.25 (1.01–1.55)</td>
<td>0.04</td>
</tr>
<tr>
<td>Critical bleeding¶</td>
<td>91 (1.3)</td>
<td>133 (1.9)</td>
<td>0.69 (0.53–0.91)</td>
<td>0.007</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>27 (0.4)</td>
<td>55 (0.8)</td>
<td>0.50 (0.31–0.79)</td>
<td>0.003</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>55 (0.8)</td>
<td>84 (1.2)</td>
<td>0.67 (0.47–0.93)</td>
<td>0.02</td>
</tr>
<tr>
<td>Nonmajor clinically relevant bleeding</td>
<td>1185 (16.7)</td>
<td>1151 (16.2)</td>
<td>1.04 (0.96–1.13)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

GI Bleeding: 3.2% vs. 2.2%  P<0.001

* Two-sided P values are for superiority in the rivaroxaban group as compared with the warfarin group.
‡ Minimal bleeding events were not included in the principal safety end point.
¶ Bleeding events were considered to be critical if they occurred in intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular (with compartment syndrome), or retroperitoneal sites.

Apixaban (eliquis)

- Direct factor XA inhibitor (same mechanism as rivaroxaban)
- 5mg BID dosing
- If ≥2 risk factors (≥80yo, ≤60kg, Cr≥1.5) reduce to 2.5mg BID
- Rare side effects
- Superior to warfarin and mortality benefit
- Approved for DVT prophylaxis post orthopedic surgery
Apixaban: ARISTOTLE Trial

- 18,201 patients
  - Atrial fibrillation
  - Additional risk factor for stroke
- Randomized to
  - Warfarin v.
  - Apixaban 5 mg BID
- Primary outcome stroke or systemic embolism
Apixaban: ARISTOTLE Trial

Kaplan–Meier Curves for the Primary Efficacy and Safety Outcomes.

A Primary Outcome: Stroke or Systemic Embolism

B Major Bleeding

Apixaban: ARISTOTLE Trial

Kaplan–Meier Curves for the Primary Efficacy and Safety Outcomes.

**A Primary Outcome: Stroke or Systemic Embolism**

- **No. at Risk**
  - Apixaban: 9120, 8726, 8440, 6051, 3464, 1754
  - Warfarin: 9081, 8620, 8301, 5972, 3405, 1768

- **Hazard ratio**: 0.79 (95% CI, 0.66–0.95)
- **P-value**: 0.01
- **21% RRR**

**B Major Bleeding**

- **No. at Risk**
  - Apixaban: 9088, 8103, 7564, 5365, 3048, 1515
  - Warfarin: 9052, 7910, 7335, 5196, 2956, 1491

- **Hazard ratio**: 0.69 (95% CI, 0.60–0.80)
- **P-value**: <0.001
- **31% RRR**

# Apixaban: ARISTOTLE Trial

Table 3. Bleeding Outcomes and Net Clinical Outcomes.\(^*\)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Apixaban Group (N=9088)</th>
<th>Warfarin Group (N=9052)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients Event no. &amp; Rate %/yr</td>
<td>Patients Event no. &amp; Rate %/yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary safety outcome: ISTH major bleeding†</td>
<td>327 2.13</td>
<td>462 3.09</td>
<td>0.69 (0.60–0.80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intracranial</td>
<td>52 0.33</td>
<td>122 0.80</td>
<td>0.42 (0.30–0.58)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other location</td>
<td>275 1.79</td>
<td>340 2.27</td>
<td>0.79 (0.68–0.93)</td>
<td>0.004</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>105 0.76</td>
<td>119 0.86</td>
<td>0.89 (0.70–1.15)</td>
<td>0.37</td>
</tr>
<tr>
<td>Major or clinically relevant nonmajor bleeding</td>
<td>613 4.07</td>
<td>877 6.01</td>
<td>0.68 (0.61–0.75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GUSTO severe bleeding</td>
<td>80 0.52</td>
<td>172 1.13</td>
<td>0.46 (0.35–0.60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GUSTO moderate or severe bleeding</td>
<td>199 1.29</td>
<td>328 2.18</td>
<td>0.60 (0.50–0.71)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TIMI major bleeding</td>
<td>148 0.96</td>
<td>256 1.69</td>
<td>0.57 (0.46–0.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TIMI major or minor bleeding</td>
<td>239 1.55</td>
<td>370 2.46</td>
<td>0.63 (0.54–0.75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>2356 18.1</td>
<td>3060 25.8</td>
<td>0.71 (0.68–0.75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Net clinical outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke, systemic embolism, or major bleeding</td>
<td>521 3.17</td>
<td>666 4.11</td>
<td>0.77 (0.69–0.86)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke, systemic embolism, major bleeding, or death from any cause</td>
<td>1009 6.13</td>
<td>1168 7.20</td>
<td>0.85 (0.78–0.92)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* The bleeding outcomes were assessed in patients who received at least one dose of a study drug and events that occurred from the time the patients received the first dose of the study drug through 2 days after they received the last dose. The net clinical outcome includes all efficacy outcomes through the cutoff date for the efficacy analysis and bleeding outcomes that occurred from the time the patients received the first dose of the study drug through 2 days after they received the last dose. GUSTO denotes Global Use of Strategies to Open Occluded Coronary Arteries, and TIMI Thrombolysis in Myocardial Infarction.

† The comparison of the primary safety outcome of bleeding according to the International Society on Thrombosis and Haemostasis (ISTH) criteria is in the hierarchical sequence preserving a type I error.

Apixaban: ARISTOTLE Trial

Superior to Warfarin for efficacy and safety

Mortality 3.52% vs. 3.94% => 11% RRR (P=0.047)

* The bleeding outcomes were assessed in patients who received at least one dose of a study drug and events that occurred from the time the patients received the first dose of the study drug through 2 days after they received the last dose. The net clinical outcome includes all efficacy outcomes through the cutoff date for the efficacy analysis and bleeding outcomes that occurred from the time the patients received the first dose of the study drug through 2 days after they received the last dose. GUSTO denotes Global Use of Strategies to Open Occluded Coronary Arteries, and TIMI Thrombolysis in Myocardial Infarction.
† The comparison of the primary safety outcome of bleeding according to the International Society on Thrombosis and Haemostasis (ISTH) criteria is in the hierarchical sequence preserving a type I error.

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Summary of Pivotal Trials

- No head to head trials
- Differences in trial design and patient populations limit indirect comparisons

<table>
<thead>
<tr>
<th></th>
<th>DABIGATRAN</th>
<th>RIVAROXABAN</th>
<th>APIXABAN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pivotal study</strong></td>
<td><strong>RE-LY</strong></td>
<td><strong>ROCKET-AF</strong></td>
<td><strong>ARISTOTLE</strong></td>
</tr>
<tr>
<td><strong>TSOAC vs. warfarin (INR 2-3)</strong></td>
<td><strong>Open-label</strong></td>
<td><strong>Double-blind</strong></td>
<td><strong>Double-blind</strong></td>
</tr>
<tr>
<td><strong>Mean CHADS\textsubscript{2} score</strong></td>
<td>2.1</td>
<td>3.5</td>
<td>2.1</td>
</tr>
<tr>
<td><strong>Mean Time in Therapeutic Range (TTR)</strong></td>
<td>64%</td>
<td>55%</td>
<td>62%</td>
</tr>
<tr>
<td><strong>Efficacy: Reduction in all stroke, systemic embolism</strong></td>
<td>Superior</td>
<td>Non-inferior</td>
<td>Superior</td>
</tr>
<tr>
<td><strong>Safety: Major bleeding</strong></td>
<td>Similar</td>
<td>Similar</td>
<td>Superior</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>Favorable trend</td>
<td>Favorable trend</td>
<td>Superior</td>
</tr>
</tbody>
</table>
If you can’t convince them, confuse them
- Harry S. Truman
Who Should Switch from Warfarin to a NOAC?

- Patients with time in therapeutic range (TTR) <55% or who are treated with inferring drugs causing INR changes may benefit.

- Patients who have treatment non-adherence may be more likely to be unprotected than with warfarin.

- Labile INRs not caused by poor patient compliance.
How Important are Labile INRs?

NEJM.2003; 349:1910-26
Can We Predict Who Has Poor TTR?

- Yes, another risk score
- Age is beneficial!
- Score 0-1: Do well
- Score ≥2: Difficult
  
  **Consider NOACs**

### Table 1
The SAMe-TT$_2$R$_2$ score

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>S</td>
<td>Sex (female) 1</td>
</tr>
<tr>
<td>A</td>
<td>Age (less than 60 y) 1</td>
</tr>
<tr>
<td>Me</td>
<td>Medical history$^a$ 1</td>
</tr>
<tr>
<td>T</td>
<td>Treatment (rhythm control strategy) 1</td>
</tr>
<tr>
<td>T</td>
<td>Tobacco use (within 2 y) 2</td>
</tr>
<tr>
<td>R</td>
<td>Race (nonwhite) 2</td>
</tr>
</tbody>
</table>

$^a$ Defined as more than two of the following: hypertension, diabetes, coronary artery disease or MI, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease, and hepatic or renal disease.

Who Should Not Switch to a NOAC?

- Heart valve prosthesis
  - Dabigatran showed harm (RE-ALIGN trial) in bleeding and thrombosis

- Prior GI bleeding
  - Probably related to NOACs local absorption

- Prior acute coronary syndrome?
  - Controversial, warfarin may have benefit rather than harm of NOAC
  - Follow up FDA Registry data showed no increased risk
How to Deal with Surgery?

- Take into account type of surgery and patient characteristics – renal function, age, other medications

- NOACs allow for predictable cessation of anticoagulant effect

- Bridging may still be considered if high thromboembolic risk given black box warning

<table>
<thead>
<tr>
<th>Table 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timing of last anticoagulant intake before elective surgery</td>
</tr>
<tr>
<td>Creatinine Clearance</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>&gt;80 mL/min</td>
</tr>
<tr>
<td>50–80 mL/min</td>
</tr>
<tr>
<td>30–50 mL/min</td>
</tr>
</tbody>
</table>

Patients with Chronic Kidney Disease?

- Degree of renal elimination: DABI > RIVA > APIX

<table>
<thead>
<tr>
<th>DABIGATRAN</th>
<th>RIVAROXABAN</th>
<th>APIXABAN</th>
<th>WARFARIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primarily renal elimination</td>
<td>Significant renal elimination</td>
<td>Minor renal elimination</td>
<td>Minimal renal elimination</td>
</tr>
<tr>
<td>Avoid if CrCl &lt;30 ml/min (Reduced dose available for CrCl 15-30 ml/min but not studied clinically and not recommended)</td>
<td>Avoid if CrCl &lt;30 ml/min (not studied)</td>
<td>Avoid if Scr &gt;2.5 or CrCl &lt;25 ml/min</td>
<td>No adjustment needed</td>
</tr>
<tr>
<td>Avoid if CrCl ≤50 ml/min if on interacting drugs dronedarone or ketoconazole (reduced dose available for CrCl 30-50 ml/min but not studied clinically)</td>
<td>Reduced dose of 15 mg/day available and studied for pts with CrCl 30-50 ml/min</td>
<td>Reduced dose of 2.5 mg BID available and studied if Scr ≥1.5 mg/dL plus ≥1 of the following: ≥80 yrs, wt ≤60 kg</td>
<td></td>
</tr>
</tbody>
</table>
Potential Approach to Anticoagulation Selection

- Renal Dysfunction
  - Warfarin (or apixaban)
  - On Multiple Other Drugs
    - Dabigatran

- Hepatic Dysfunction
  - Dabigatran
  - Poor Compliance
    - Rivaroxaban (or warfarin)

- Upper GI Symptoms
  - Avoid Dabigatran
  - CAD
  - Avoid Dabigatran?
Approach to Novel Anticoagulants

- Usually leave patients on warfarin, unless patient preference or labile INRs
- More difficult to manage around time of EP procedures (pacemaker/ICD, AF ablation)
- Black Box Warning - Rebound hypercoagulant effect?
- No specific antidote
Novel Oral Anticoagulants

- Appear to have an efficacy similar to warfarin
  - With similar to lower bleeding risks
- Much more expensive
  - But when cost of INR monitoring is included, cost difference narrows
  - Some insurance companies will only cover a new anticoagulant if warfarin is contraindicated
- Quick onset and offset, so that no bridging for procedures is required
  - But likely not safe to continue through procedures, as warfarin is for afib ablation, PPM placement, etc.
Novel Oral Anticoagulants

- Distinguishing between the novel anticoagulants is difficult – await head to head trials
- Now we have too many choices?
- Hopefully best choices will become clear as time goes forward
Conclusions

▪ Atrial fibrillation will continue to be a significant problem

▪ CHADS-VASc and HAS-BLED are good starting points to assess risk/benefit of anticoagulation

▪ The novel oral anticoagulants have favorable profiles compared to warfarin and simplify treatment

▪ “One size does not fit all” when it comes to anticoagulation selection
THANK YOU

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