Old and New Anticoagulants

For Stroke Prevention

Benefits and Risks

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Disclosure

Relationships with Industry

Consulting fees from the following companies involved in developing anticoagulant drugs and device-based strategies for thromboembolism prevention:

- Bayer HealthCare
- Biotronik
- Boehringer Ingelheim
- Boston Scientific
- Daiichi Sankyo
- Janssen
- Johnson & Johnson
- Medtronic
- Sanofi-Aventis
Targets for New Anticoagulants

Oral

- TTP889
- Rivaroxaban
- Apixaban
- Edoxaban
- Betrixaban
- Darexaban
- LY517717
- TAK-442
- Ximelagatran
- Dabigatran

Parenteral

- TFPI (tifacogin)
- APC (drotrecogin alfa)
- sTM (ART-123)
- Idra(biota)parinux
- DX-9065a
- Otamixaban

Adapted from Weitz JI, Bates SM. J Thromb Haemost 2005; 3:1843
Turpje AGG. Eur Heart J 2007; 29,155
## “New” Oral Anticoagulants

### Phase III Trials for Stroke Prevention in Patients with AF

<table>
<thead>
<tr>
<th>Trial Acronym</th>
<th>Drug</th>
<th>Dose (mg)</th>
<th>Design</th>
<th>n</th>
<th>Risk Factors (#)</th>
<th>Dose adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY</td>
<td>Dabigatran</td>
<td>150 bid 110 bid</td>
<td>PROBE</td>
<td>18,113</td>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>ROCKET-AF</td>
<td>Rivaroxaban</td>
<td>20 qd 15 qd*</td>
<td>Blinded</td>
<td>14,264</td>
<td>≥ 2</td>
<td>21% at baseline</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>Apixaban</td>
<td>5 bid 2.5 bid*</td>
<td>Blinded</td>
<td>18,206</td>
<td>≥ 1</td>
<td>5% at baseline</td>
</tr>
<tr>
<td>ENGAGE-AF</td>
<td>Edoxaban</td>
<td>60 qd 30 qd*</td>
<td>Blinded</td>
<td>21,105</td>
<td>≥ 2</td>
<td>25% at baseline</td>
</tr>
</tbody>
</table>

* Adjusted based on renal function or other factors associated with reduced drug clearance
Trials of NOACs for AF
Clinical Characteristics and Stroke Risk Factors

<table>
<thead>
<tr>
<th></th>
<th>RE-LY (Dabigatran)</th>
<th>ROCKET-AF (Rivaroxaban)</th>
<th>ARISTOTLE (Apixaban)</th>
<th>ENGAGE AF (Edoxaban)</th>
</tr>
</thead>
<tbody>
<tr>
<td># Randomized</td>
<td>18,113</td>
<td>14,264</td>
<td>18,206</td>
<td>21,110</td>
</tr>
<tr>
<td>Age, years</td>
<td>72 ± 9</td>
<td>73 [65-78]</td>
<td>70 [63-76]</td>
<td>72 [64-78]</td>
</tr>
<tr>
<td>Female, %</td>
<td>37</td>
<td>40</td>
<td>35</td>
<td>38</td>
</tr>
<tr>
<td>Paroxysmal AF</td>
<td>32</td>
<td>18</td>
<td>15</td>
<td>25</td>
</tr>
<tr>
<td>VKA naive</td>
<td>50</td>
<td>38</td>
<td>43</td>
<td>41</td>
</tr>
<tr>
<td>Aspirin use</td>
<td>40</td>
<td>36</td>
<td>31</td>
<td>29</td>
</tr>
</tbody>
</table>

CHADS$_2$

- 0-1
- 2
- 3-6

Relative Risks of Stroke and Systemic Embolism

Meta-Analysis

- Warfarin vs. Placebo/control
- Warfarin vs. low-dose warfarin + ASA
- Warfarin vs. ASA
- VKA vs. ASA + clopidogrel
- Warfarin vs. ximelagatran
- Warfarin vs. dabigatran 110 mg bid
- Warfarin vs. dabigatran 150 mg bid

Camm AJ. European Society of Cardiology, Barcelona, August 30 2009.
Ischemic Stroke and Major Bleeding In Relation to Dabigatran Plasma Concentrations

RE-LY Trial

ROCKET-AF Trial

**Stroke and Systemic Embolism**

<table>
<thead>
<tr>
<th>Days from Randomization</th>
<th>Rivaroxaban</th>
<th>Warfarin</th>
<th>No. at risk:</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td>Rivaroxaban 6958 7004</td>
</tr>
<tr>
<td>0.5</td>
<td></td>
<td></td>
<td>6211</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>1786</td>
</tr>
<tr>
<td>1.5</td>
<td></td>
<td></td>
<td>5468</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>4406</td>
</tr>
<tr>
<td>2.5</td>
<td></td>
<td></td>
<td>3407</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>2472</td>
</tr>
<tr>
<td>3.5</td>
<td></td>
<td></td>
<td>1496</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td>634</td>
</tr>
</tbody>
</table>

Rate (%/y) 1.71 2.16

HR (95% CI) 0.79 (0.66-0.96)

Noninferiority p <0.001

### Rivaroxaban vs Warfarin: Event Rates

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban</th>
<th>Warfarin</th>
<th>HR (95% CI)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>On Treatment</strong></td>
<td>1.7</td>
<td>2.2</td>
<td>0.79</td>
<td>0.015</td>
</tr>
<tr>
<td>N= 14,143</td>
<td></td>
<td></td>
<td>(0.65,0.95)</td>
<td></td>
</tr>
<tr>
<td><strong>ITT</strong></td>
<td>2.1</td>
<td>2.4</td>
<td>0.88</td>
<td>0.117</td>
</tr>
<tr>
<td>N= 14,171</td>
<td></td>
<td></td>
<td>(0.74,1.03)</td>
<td></td>
</tr>
</tbody>
</table>

*Rivaroxaban better* vs *Warfarin better*

* p-values for superiority

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ROCKET-AF Trial

Events During Transition to Open-Label VKA

Patients Completing the Study on Treatment

First dose of study drug

Rivaroxaban

Last dose of study drug

Stop rivaroxaban

Suboptimal Anticoagulation

13 days

Start VKA

Continue warfarin

Double-blind treatment period

Post-treatment observation period

R = Randomization

Study duration

R = Randomization

ARISTOTLE Trial

Primary Outcome: All Stroke or Systemic Embolism

- **Apixaban**: 212 patients, 1.27%/year
- **Warfarin**: 265 patients, 1.60%/year

HR 0.79 (95% CI, 0.66–0.95); Superiority \( p = 0.011 \)

- Non-inferiority \( p < 0.001 \)

21% RRR

Apixaban 327 patients, 2.13%/year
Warfarin 462 patients, 3.09%/year
HR 0.69 (95% CI, 0.60–0.80); p <0.001

Apixaban vs. Aspirin: The AVERROES Trial

Efficacy and Safety Event Rates

Aspirin
Apixaban

Event Rate (% / y)

\( p < 0.001 \)

\( p = 0.57 \)

**ENGAGE AF TIMI-48 Trial**

*Primary Endpoint Stroke + Systemic Embolism*

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**Hazard ratio (97.5% CI)**

- **Edoxaban 60* mg QD vs warfarin**
  - Hazard ratio: 0.79
  - 97.5% CI: (0.50, 1.00)

- **Edoxaban 30* mg QD vs warfarin**
  - Hazard ratio: 1.07
  - 97.5% CI: (0.87, 1.13)

---

**Non-inferiority (mITT, on-treatment)**

- **Edoxaban 60* mg QD vs warfarin**
  - Hazard ratio (97.5% CI): 0.79 (0.50, 1.00)
  - *p* < 0.0001

- **Edoxaban 30* mg QD vs warfarin**
  - Hazard ratio (97.5% CI): 1.07 (0.87, 1.13)
  - *p* = 0.005

---

**Superiority (ITT, Overall)**

- **Edoxaban 60* mg QD vs warfarin**
  - Hazard ratio: 0.87
  - 97.5% CI: (0.50, 1.00)
  - *p* = 0.08

- **Edoxaban 30* mg QD vs warfarin**
  - Hazard ratio: 1.13
  - 97.5% CI: (0.87, 1.13)
  - *p* = 0.10

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ENGAGE AF TIMI-48 Trial
Safety Outcome: Bleeding On Treatment


- **Edoxaban 60 mg**
- **Edoxaban 30 mg**
- **Warfarin TTR 68.4%**

**HR (95% CI)**

- **ISTH Major Bleeding**
  - Edoxaban 60 mg: p < 0.001
  - Edoxaban 30 mg: p < 0.001

- **Fatal Bleeding**
  - Edoxaban 60 mg: p = 0.006
  - Edoxaban 30 mg: p < 0.001

- **ICH**
  - Edoxaban 60 mg: p < 0.001
  - Edoxaban 30 mg: p < 0.001

- **GI Bleeding**
  - Edoxaban 60 mg: p < 0.001
  - Edoxaban 30 mg: p < 0.001

**edoxaban superior**

**edoxaban inferior**
Nonvalvular Atrial Fibrillation
A Moving Target?

Original warfarin trials excluded:

- Rheumatic heart disease (mitral stenosis)
- Prosthetic heart valves (mechanical or biological)
- Valve repair (rare, not considered)
- Thyrotoxicosis
- Self-limited AF due to acute illness or surgery
<table>
<thead>
<tr>
<th>Trial</th>
<th>Excluded Valvular Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPORTIF III &amp; V</td>
<td>Mitral stenosis or previous valvular heart surgery</td>
</tr>
<tr>
<td>RE-LY</td>
<td>Hemodynamically relevant valve disease or prosthetic valve</td>
</tr>
<tr>
<td>ROCKET AF</td>
<td>Mitral stenosis or prosthetic heart valve</td>
</tr>
<tr>
<td>AVERROES</td>
<td>Valvular disease requiring surgery or mechanical prosthetic heart valve</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>Moderate or severe mitral stenosis or prosthetic heart valve requiring anticoagulation</td>
</tr>
<tr>
<td>ENGAGE AF</td>
<td>Moderate or severe mitral stenosis or mechanical heart valve. (Patients with bioprosthetic heart valves or valve repair could be included.)</td>
</tr>
</tbody>
</table>
Newer Oral Anticoagulants for AF

Key Similarities

- All are noninferior to warfarin for prevention of total stroke and systemic embolism
- All reduce the risk of intracerebral hemorrhage
- Outcomes of major bleeding are generally better than with warfarin
- Reductions in mortality are comparable, ~10%/year, mainly related to lower rates of cardiovascular death and fatal bleeding.
## Meta-analysis of NOACs vs. Warfarin in Non-valvular AF

### Secondary Efficacy and Safety Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Pooled NOAC (events)</th>
<th>Pooled warfarin (events)</th>
<th>RR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>665/29292</td>
<td>724/29221</td>
<td>0.92 (0.83-1.02)</td>
<td>0.10</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>130/29292</td>
<td>263/29221</td>
<td>0.49 (0.38-0.64)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>413/29292</td>
<td>432/29221</td>
<td>0.97 (0.78-1.20)</td>
<td>0.77</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>2022/29292</td>
<td>2245/29221</td>
<td>0.90 (0.85-0.95)</td>
<td>0.0003</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial haemorrhage</td>
<td>204/29287</td>
<td>425/29211</td>
<td>0.48 (0.39-0.59)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>751/29287</td>
<td>591/29211</td>
<td>1.25 (1.01-1.55)</td>
<td>0.043</td>
</tr>
</tbody>
</table>

Newer Anticoagulants for AF

*Inferences from the Pivotal Trials*

- Differences in outcomes may be due to variations in study design, sample size, intrinsic risk, concurrent treatment and other factors, rather than the drugs themselves.
- In the doses approved for use in the U.S., factor Xa inhibitors may have less efficacy against ischemic stroke than dabigatran but also less toxicity.
- Factor Xa inhibitors are less dependent on renal elimination and have fewer GI side effects than dabigatran.
Target-Specific Oral Anticoagulants for AF

Areas of Uncertainty Requiring Further Study

- Patients with AF undergoing PCI or CABG
- Cardioversion of AF
- Catheter ablation, Maze or intra-operative cryoablation
- Device-detected AF
- Bioprosthetic heart valves
- Valve repair
- Prior hemorrhagic stroke
Common Concerns about the NOACs

- How to choose between VKA and NOAC – which NOAC to select?
- Lack of monitoring – insecurity about dosing and adherence
- No simple spot-checks – “need-to-know” occasions
- Short half-lives – concern about missed doses
- No antidotes yet – how to manage major bleeding?
- Drug-drug interactions – under- and over-dosing
- Clinical development incomplete – e.g., cardioversion, ablation, PCI
- Contraindications – valvular AF
- Need to monitor renal and hepatic function
- Expense for health care systems and patients

Modified from Camm AJ, American Heart Association Scientific Sessions, Dallas, TX, November 2013
Outcomes of Major Bleeding During Treatment with Dabigatran or Warfarin
1,034 Patients, 1,121 Major Bleeds in 5 Phase III Trials

Reversal of the Anticoagulant Effect of Factor Xa Inhibitors

Dose-Dependent Action of Recombinant Andexanet alfa (PRT064445) On fXa Suppression by Betrixaban, Rivaroxaban or Apixaban

Development of a Specific Dabigatran Antidote
*aDabi-Fab Binding and Reversal of the Anticoagulant Effect*

Millar CM, Lane DA. *Blood* 2013; 121:3543.

### Summary of Phase III NOAC Trial Results

<table>
<thead>
<tr>
<th>Outcomes vs. warfarin</th>
<th>Dabigatran 150 mg bid</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban 60 mg qd</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroke/systemic embolism</strong></td>
<td>Superiority</td>
<td>Non-inferiority</td>
<td>Superiority</td>
<td>Non-inferiority</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Ischemic or unspecified Stroke</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Hemorrhagic stroke</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Disabling or fatal stroke</strong></td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Vascular death</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>All-cause mortality</strong></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Major bleeding</strong></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>ICH</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>GI bleeding</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Treatment discontinuation</strong></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Modified after Savalieva I, Camm AJ. *Clin Cardiol* 2014; 37: 32
Considerations in NOAC Selection for AF

Modified after Savalieva I, Camm AJ. *Clin Cardiol* 2014; 37: 32