Will Oral Anticoagulants Continue to Evolve?

Challenges, Barriers and New Trials In Atrial Fibrillation and Other Conditions

December 14, 2014

Jonathan L. Halperin, M.D.

The Cardiovascular Institute
Mount Sinai Medical Center
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
Target-Specific Oral Anticoagulants

*The “NOACs”*
Main Targets for Therapeutic Anticoagulants

**Oral**
- TTP889
- Rivaroxaban
- Apixaban
- Edoxaban
- Betrixaban
- Darexaban
- LY517717
- TAK-442

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

**Pathways**
- TF/VIIa
  - IX
  - VIIIa
  - IXa
  - X
  - Va
  - AT
  - II (thrombin)
    - Ila
      - Fibrinogen
      - Fibrin

**Modified after**
Target-Specific Oral Anticoagulants
The Pivotal Trials in Atrial Fibrillation
## Target-Specific 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 TIMI 48</td>
<td>Edoxaban</td>
<td>60 qd, 30 or 15 qd*</td>
<td>Blinded</td>
<td>21,105</td>
<td>≥ 2</td>
<td>25% at baseline, &gt;9% after</td>
</tr>
</tbody>
</table>

* Adjusted based on renal function or other factors associated with reduced drug clearance
## Stroke or Systemic Embolism

### Primary Efficacy Events

<table>
<thead>
<tr>
<th>Trial</th>
<th>Event Rate (%/year)</th>
<th>Hazard Ratio</th>
<th>Noninferiority (OT)</th>
<th>Superiority (ITT)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RE-LY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabigatran 150 mg bid</td>
<td>1.11</td>
<td>0.66</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dabigatran 110 mg bid</td>
<td>1.53</td>
<td>0.91</td>
<td>&lt;0.001</td>
<td>0.34</td>
</tr>
<tr>
<td>Warfarin</td>
<td>1.69</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ROCKET AF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban, 20 mg qd</td>
<td>1.7</td>
<td>0.79</td>
<td>&lt;0.001</td>
<td>0.12</td>
</tr>
<tr>
<td>Warfarin</td>
<td>2.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ARISTOTLE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban, 5 mg bid</td>
<td>1.27</td>
<td>0.79</td>
<td>&lt;0.001</td>
<td>0.01</td>
</tr>
<tr>
<td>Warfarin</td>
<td>1.60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ENGAGE-AF TIMI 48</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edoxaban, 60 mg qd</td>
<td>1.18</td>
<td>0.79</td>
<td>&lt;0.001</td>
<td>0.08</td>
</tr>
<tr>
<td>Edoxaban, 30 mg qd</td>
<td>1.61</td>
<td>1.07</td>
<td>0.005</td>
<td>0.10</td>
</tr>
<tr>
<td>Warfarin</td>
<td>1.50</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Indirect Outcome Comparisons

### Pivotal Trials of NOACs for Atrial Fibrillation

<table>
<thead>
<tr>
<th>Trial</th>
<th>RE-LY</th>
<th>ROCKET AF</th>
<th>ARISTOTLE</th>
<th>ENGAGE-AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Dose</td>
<td>Dabigatran 150 mg bid</td>
<td>Rivaroxaban 20 (15) mg qd</td>
<td>Apixaban 5 (2.5) mg bid</td>
<td>Edoxaban 60 (30) mg qd</td>
</tr>
</tbody>
</table>
| 1° efficacy events (%/year) | 1.69 vs 1.11  
  p<0.001 | 2.42 vs 2.12  
  p=0.12 | 1.60 vs 1.27  
  p<0.001 | 1.80 vs 1.57  
  p=0.08 |
| NNT           | 167                       | 303                        |                            |                            |
| Major bleeding (%/year) | 3.57 vs 3.32  
  p=0.31 | 3.45 vs 3.60  
  p=0.58 | 3.09 vs 2.13  
  p<0.001 | 3.43 vs 2.75  
  p<0.0001 |
| ICH (%/year)  | 0.74 vs 0.30  
  p<0.001 | 0.74 vs 0.49  
  p=0.019 | 0.47 vs 0.24  
  p<0.001 | 0.85 vs 0.39  
  p<0.001 |
| Mortality (%/year) | 4.13 vs 3.64  
  p=0.051 | 4.91 vs 4.52  
  p=NS | 3.94 vs 3.52  
  p=0.05 | 4.35 vs 3.99  
  p=0.08 |
| NNT           | 204                       |                            | 238                        | 277                        |
Target-Specific Oral Anticoagulants

Implications and Inferences
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, ~11%/year, mainly related to lower rates of cardiovascular death and fatal bleeding.
Newer Anticoagulants for AF
Inferences from the Pivotal Trials

• Outcome differences seem mainly due to variations in dosing, study design, 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 may have fewer GI side effects than dabigatran.
Target-Specific Oral Anticoagulants

Uncertainties and Concerns
Challenges to Uptake of the NOACs

Common Clinical Concerns

- How to choose between VKA and NOAC?
- Which NOAC to select?
- Need to monitor renal and hepatic function
- Lack of coagulation monitoring – insecurity about dosing, adherence, drug interactions and “need-to-know” situations
- Short half-lives – concern about missed doses
- Incomplete clinical development – e.g., cardioversion, ablation, PCI
- Contraindications – valvular AF
- No antidotes yet – how to manage major bleeding?
- Expense, for health care systems and patients
Challenges to Uptake of the NOACs

Common Clinical Concerns

- How to choose between VKA and NOAC?
- Which NOAC to select?
- Need to monitor renal and hepatic function
- Lack of coagulation monitoring – insecurity about dosing, adherence, drug interactions and “need-to-know” situations
- Short half-lives – concern about missed doses
- Incomplete clinical development – e.g., cardioversion, ablation, PCI
- Contraindications – valvular AF
- No antidotes yet – how to manage major bleeding?
- Expense, for health care systems and patients
Anticoagulation for Patients with Non-valvular AF

Considerations in Selecting a Target-Specific Agent

Specific patient characteristics

- High risk of bleeding
  HAS-BLED ≥ 3

- Previous or high risk of GI bleeding

- High ischemic stroke risk
  low bleeding risk

- Previous stroke
  (secondary prevention)

- CAD, previous MI
  or high-risk for ACS

- Renal impairment

- GI upset / disorders

- Patient preference

Considerations:

- Consider agent / dose with lowest incidence of bleeding

- Consider agent with lowest incidence of GI bleed

- Consider agent with best reduction of ischemic stroke

- Consider agent with best investigated or greatest reduction of 20 stroke

- Consider agent with positive effect in ACS

- Consider agent least dependent on renal excretion

- Consider agent with fewer GI effects

- Consider once-daily formulation

Agents:

- Apixaban
- Edoxaban?
- Rivaroxaban
- Dabigatran
- Rivaroxaban
- Apixaban
- Edoxaban?

Modified after Savalieva I, Camm AJ. Clin Cardiol 2014; 37: 32
Target-Specific Oral Anticoagulants for AF

Areas of Uncertainty Requiring Further Study

• Defining non-valvular AF
• Special subgroups of patients with AF
  ▪ Cardioversion
  ▪ PCI or CABG
  ▪ Catheter ablation
  ▪ Maze or intra-operative cryoablation
  ▪ Device-detected AF
  ▪ Prior hemorrhagic stroke
Target-Specific Oral Anticoagulants for AF

Areas of Uncertainty Requiring Further Study

- Defining non-valvular AF
- Special subgroups of patients with AF
  - Cardioversion
  - PCI or CABG
  - Catheter ablation
  - Maze or intra-operative cryoablation
  - Device-detected AF
  - Prior hemorrhagic stroke
Original warfarin trials excluded:

- Rheumatic heart disease (mitral stenosis)
- Prosthetic heart valves (mechanical or biological)
- Valve repair (rare, not considered)

And also excluded

- Thyrotoxicosis
- Self-limited AF due to acute illness or surgery
## Identifying Patients with Nonvalvular AF

### Valvular Disease Exclusion Criteria in Trials of NOACS

<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 enrolled.</td>
</tr>
</tbody>
</table>
Dabigatran vs. Warfarin in Patients with Mechanical Heart Valves

RE-ALIGN Trial

- AVR or MVR
- <7 days ≥3 months
- Dabigatran dose 150, 220 or 300 mg bid, based on kidney function and blood levels
- 252 patients
- Trial terminated b/o excess thromboembolism and bleeding

Target-Specific Oral Anticoagulants for AF

Areas of Uncertainty Requiring Further Study

- Defining non-valvular AF
- Special subgroups of patients with AF
  - Cardioversion
  - PCI or CABG
  - Catheter ablation
  - Maze or intra-operative cryoablation
  - Device-detected AF
  - Prior hemorrhagic stroke
Target-Specific Oral Anticoagulants for AF
Areas of Uncertainty Requiring Further Study

- Defining non-valvular AF
- Special subgroups of patients with AF
  - Cardioversion
  - PCI or CABG
  - Catheter ablation
  - Maze or intra-operative cryoablation
  - Device-detected AF
  - Prior hemorrhagic stroke
Rivaroxaban For Cardioversion of AF

*X-VERT Trial*

\[ n = 1,504 \text{ patients} \]

Compared with VKA in the pericardioversion period

- Rivaroxaban was associated with a similarly low incidence of primary efficacy outcome events.
- The incidence of major bleeding was also similar between groups.
- Time to cardioversion was similar when an accelerated (TEE-guided) strategy was employed, but shorter with rivaroxaban when a conventional (delayed) strategy was employed.

**Apixaban For Cardioversion of AF**

**EMANATE Trial**

**Clinical Endpoints**
Stroke/SE, Major/CRN Bleeding & Death

**Enrollment**
n=1,500

**Randomization**
30 days post-cardioversion or 90 days after enrollment if cardioversion not performed

**Treatment Period**
1:1

**Usual Care (Heparin/VKA)**
30 + 7 days

**Apixaban**

ClinicalTrials.gov  NCT02100228
## Ongoing and Planned Studies

### Supplementary Studies in Atrial Fibrillation

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardioversion</td>
<td></td>
<td>X-VERT</td>
<td>EMANATE</td>
<td>ENSURE-AF</td>
</tr>
<tr>
<td>Catheter ablation of AF</td>
<td>RE-CIRCUIT</td>
<td>VENTURE-AF OCEAN</td>
<td>AXAFA</td>
<td></td>
</tr>
<tr>
<td>PCI/stent</td>
<td>RE-DUAL PCI</td>
<td>PIONEER AF-PCI</td>
<td>ACS/PCI</td>
<td></td>
</tr>
<tr>
<td>Pacemakers/ICD</td>
<td>BRUISECONTROL2</td>
<td></td>
<td>ARTESIA</td>
<td></td>
</tr>
<tr>
<td>Adherence</td>
<td>NCT02240667</td>
<td></td>
<td>AEGEAN</td>
<td></td>
</tr>
</tbody>
</table>

[http://www.clinicaltrials.gov](http://www.clinicaltrials.gov)
Target-Specific Oral Anticoagulants for AF
Areas of Uncertainty Requiring Further Study

- Defining non-valvular AF
- Special subgroups of patients with AF
  - Cardioversion
  - Percutaneous Coronary Intervention
  - Catheter ablation
  - Maze or intra-operative cryoablation
  - Device-detected AF
  - Prior hemorrhagic stroke
**PIONEER AF-PCI**

**Trial Design**

- **AF**
- **PCI** (with stent)

**Randomization**
up to 72 hours after sheath removal

**PCI**

**Rivaroxaban**, 15 mg daily + clopidogrel or P2Y12 inhibitor

- Rivaroxaban, 2.5 mg b.i.d. + DAPT
- Rivaroxaban 15 mg daily + Low-dose ASA

**VKA** (INR: 2.0 to 3.0)

- VKA (INR: 2.0 to 3.0) + DAPT
- VKA (INR: 2.0 to 3.0) + low-dose ASA

**Intended DAPT duration**
1, 6, or 12 months

**End of treatment**
12 months

**Primary endpoint**
Clinically relevant bleeding

**RE-DUAL PCI**

**Trial Design**

- **Minimum treatment duration**: 6 months
- **AF** (with stent) → PCI

**Randomization**
- 0-72 hours after PCI

- **Dabigatran 150 mg b.i.d. + clopidogrel or ticagrelor**
  - 1 month after BMS or 6 months after DES

- **Dabigatran 110 mg b.i.d. + clopidogrel or ticagrelor**

- **Warfarin (INR: 2.0 to 3.0) + clopidogrel or ticagrelor**
  - 1 month after BMS or 6 months after DES

- **n = 8,520**
  - 2,840 subjects per treatment strategy

**Composite primary endpoint**
- Death, MI, stroke/SE and major bleeding

ClinicalTrials.gov  NCT02164864
Ongoing and Planned Studies
Supplementary Studies in Atrial Fibrillation

<table>
<thead>
<tr>
<th>Practice-based registries</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLORIA-AF</td>
<td>GARFIELD</td>
<td>Planned</td>
<td>PREFER</td>
<td></td>
</tr>
</tbody>
</table>

- Large scope
- Complement data from controlled trials
- Provide insight into epidemiology and practice patterns
- Enrich experience in patients with common comorbidities

http://www.clinicaltrials.gov
## Ongoing and Planned Trials

### Exploring Additional Indications

<table>
<thead>
<tr>
<th>Potential Indication</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute coronary syndrome</td>
<td></td>
<td>GEMINI 1&amp;2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAD with CHF</td>
<td></td>
<td>COMMANDER-HF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAD or CAD</td>
<td></td>
<td>COMPASS VOYAGER</td>
<td></td>
<td>ePAD (Phase II)</td>
</tr>
<tr>
<td>VTE prevention in the medically ill</td>
<td></td>
<td>MARINER</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial venous thrombosis</td>
<td></td>
<td>RASET</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pediatric VTE</td>
<td>NCT01895777</td>
<td>NCT02234843</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NCT02197416</td>
<td>EINSTEIN Junior</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-disabling ischemic stroke or TIA</td>
<td></td>
<td>TRACE</td>
<td>ADANCE</td>
<td>NCT02221102</td>
</tr>
<tr>
<td>2º prevention after embolic stroke of unknown source</td>
<td>RE-SPECT ESUS</td>
<td>NAVIGATE ESUS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[http://www.clinicaltrials.gov](http://www.clinicaltrials.gov)
Target-Specific Oral Anticoagulants

Reversal Strategies
Nonspecific Procoagulant Agents

- 3- or 4-factor prothrombin complex concentrate (40 mg/kg)
- FEIBA (50 IU/kg)
- rFVIIa (90 μg/kg)

- Nonspecific agents cannot immediately counteract the anticoagulant effect of NOACs.
- In normal subjects and animals, PCC and FEIBA seem the most suitable available approaches to reverse dabigatran.
- rFVIIa reduced bleeding time after dabigatran in animals, but in clinical bleeding has been used mainly in conjunction with hemodialysis.
- To manage bleeding on NOACs, FEIBA combines the effects of FVIIa and PCC, but high doses increase thrombin generation, raising the risk of rebound thrombosis.

## Investigational Anticoagulant-Reversal Agents

**Potential Pharmacologic Targets**

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Class</th>
<th>Idarucizumab</th>
<th>Andexanet alfa</th>
<th>PER977</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>IIa inhibitor</td>
<td>✓</td>
<td>O</td>
<td>✓</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Xa inhibitor</td>
<td>O</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Xa inhibitor</td>
<td>O</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Xa inhibitor</td>
<td>O</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Unfractionated heparin</td>
<td>Heparin</td>
<td>O</td>
<td>O</td>
<td>✓</td>
</tr>
<tr>
<td>LMWH</td>
<td>Heparin</td>
<td>O</td>
<td>O</td>
<td>✓</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>AT-III Xa inhibitor</td>
<td>O</td>
<td>?</td>
<td>✓</td>
</tr>
<tr>
<td>Warfarin</td>
<td>VKA</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
</tbody>
</table>

# Trials of Anticoagulation Reversal

## Ongoing or Planned Trials

<table>
<thead>
<tr>
<th>Potential Indication</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulation Reversal</td>
<td>RE-VERSE AD</td>
<td>ANNEXA-R</td>
<td>ANNEXA-A</td>
<td>NCT02207257</td>
</tr>
<tr>
<td></td>
<td>Idarucizumab</td>
<td>Andexanet alfa</td>
<td>Andexanet alfa</td>
<td>Andexanet alfa PER977</td>
</tr>
</tbody>
</table>

Varying stages of accelerated approval as potential breakthrough therapies to reverse anticoagulation:
- Uncontrolled major bleeding
- Prior to urgent surgery or invasive procedures

**Outcomes**
- Laboratory markers of coagulation activity
- Clinical bleeding outcomes

http://www.clinicaltrials.gov
Target-Specific Oral Anticoagulants

Closing Thoughts

• Given the efficacy of warfarin for stroke prevention in AF, NOACs are among the most effective medications for any disease.

• Best evidence favoring NOACs over warfarin relates to avoiding ICH, the main driver of improved survival and net benefit.

• Be wary of:
  • Conditions associated changing renal or hepatic function
  • Off-label situations
  • Early postoperative use
  • Concomitant antiplatelet therapy

• Reversal agents are coming, but we may use them infrequently
Target-Specific Oral Anticoagulants

Future Directions

• Oral anticoagulants will continue to evolve:
  ▪ Additional targets
    ▪ Contact (extrinsic) pathway inhibitors
    ▪ Tissue factor inhibitors
    ▪ Plasmin
    ▪ Combinations
  ▪ Cost considerations – optimizing value
    ▪ Using the right drug in the right dose for each patient
    ▪ Addressing the links between atrial thrombogenesis and aging
    ▪ Potentially initiating low-dose prophylaxis in pre-fibrillators