Novel Oral Anticoagulants Should Replace Warfarin in All Patients with Atrial Fibrillation: Pro

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Declaration of Interest


**Steering Committees:** multiple trials involving antiarrhythmic agents, heart failure drugs and novel anticoagulants.

**DSMBs:** multiple trials of devices and drugs.

**Events Committees:** one trial of novel oral anticoagulants and multiple trials of miscellaneous agents with CV adverse effects.

**Editorial Role:** Editor-in-Chief, European Heart Journal– Case Reports and Clinical Cardiology; Editor, European Textbook of Cardiology, European Heart Journal, Electrophysiology of the Heart, and Evidence Based Cardiology.

**Consultant/Advisor/Speaker:** Astellas, Astra Zeneca, ChanRX, Gilead, Laguna, Incarda, Merck, Menarini, Milestone, Otsuka, Sanofi, Servier, Xention, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Pfizer, Boston Scientific, Biotronik, Medtronic, Sorin, St. Jude Medical, Actelion, GlaxoSmithKline, InfoBionic, Incarda, Johnson and Johnson, Mitsubishi, Novartis, Takeda
Novel Oral Anticoagulants Should Replace Warfarin in All Patients with Atrial Fibrillation

Not just FXals and DTIs

Not now necessarily, but eventually

A gift to my opponent a very high bar, but.....
**NOAC 4-trial Meta-analysis Full Dose**
Pre-specified meta-analysis of all 71,683 patients

<table>
<thead>
<tr>
<th>Trial</th>
<th>Stroke and Systemic Embolism</th>
<th>p</th>
<th>Major Bleeding</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY</td>
<td><img src="#" alt="Graph" /></td>
<td>0.0001</td>
<td><img src="#" alt="Graph" /></td>
<td>0.34</td>
</tr>
<tr>
<td>ROCKET-AF</td>
<td><img src="#" alt="Graph" /></td>
<td>0.12</td>
<td><img src="#" alt="Graph" /></td>
<td>0.72</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td><img src="#" alt="Graph" /></td>
<td>0.012</td>
<td><img src="#" alt="Graph" /></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ENGAGE TIMI 48*</td>
<td><img src="#" alt="Graph" /></td>
<td>0.10</td>
<td><img src="#" alt="Graph" /></td>
<td>0.0002</td>
</tr>
<tr>
<td>Combined</td>
<td>≠0.81 (Favours DOAC)</td>
<td>&lt;0.0001</td>
<td>0.86 (Favours DOAC)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

*Favours DOAC*
Efficacy vs Safety
NOAC 4-trial Meta-analysis Full Dose

<table>
<thead>
<tr>
<th>Result</th>
<th>Pooled DOAC Events/Total</th>
<th>Pooled Warfarin Events/Total</th>
<th>Risk Ratio</th>
<th>95% CIs</th>
<th>p</th>
<th>Hazard Ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
<td></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</td>
<td>0.83-1.02</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>130/29292</td>
<td>263/29221</td>
<td>0.49</td>
<td>0.38-0.64</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>413/29292</td>
<td>432/29221</td>
<td>0.97</td>
<td>0.78-1.20</td>
<td>0.97</td>
<td></td>
</tr>
<tr>
<td>All Cause mortality</td>
<td>2022/29292</td>
<td>2245/29221</td>
<td>0.90</td>
<td>0.851-0.95</td>
<td>0.0003</td>
<td></td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intra-cranial hemorrhage</td>
<td>204/29287</td>
<td>425/29211</td>
<td>0.48</td>
<td>0.39-0.59</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>751/29287</td>
<td>591/29211</td>
<td>1.25</td>
<td>1.01-1.55</td>
<td>0.043</td>
<td></td>
</tr>
</tbody>
</table>

Dabigatran: Favourable Benefit-Fisk Profile

FDA study of >134 000 Medicare patients

Dabigatran was associated with a lower risk of ischaemic stroke, intracranial haemorrhage and death than warfarin

<table>
<thead>
<tr>
<th>Event</th>
<th>Incidence rate per 1000 person-years</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dabigatran etexilate</td>
<td>Warfarin</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>11.3</td>
<td>13.9</td>
</tr>
<tr>
<td>Intracranial haemorrhage</td>
<td>3.3</td>
<td>9.6</td>
</tr>
<tr>
<td>Major GI bleeding</td>
<td>34.2</td>
<td>26.5</td>
</tr>
<tr>
<td>Acute MI</td>
<td>15.7</td>
<td>16.9</td>
</tr>
<tr>
<td>Mortality</td>
<td>32.6</td>
<td>37.8</td>
</tr>
</tbody>
</table>

Comparison of matched new-user cohorts treated with dabigatran etexilate 150 mg or 75 mg* or warfarin for non-valvular AF based on 2010–2012 Medicare data  *Primary findings are based on analysis of both doses (no stratification by dose)
Warfarin Drug Interactions

A total of 873 drugs (5865 brand and generic names) are known to interact with warfarin.

- 214 major drug interactions (1010 brand and generic names)
- 454 moderate drug interactions (3475 brand and generic names)
- 205 minor drug interactions (1380 brand and generic names)

Show all medications in the database that may interact with warfarin.
## Results of Cost-effectiveness Model

### Atrial Fibrillation

### Estimated costs and outcomes

<table>
<thead>
<tr>
<th></th>
<th>Warfarin (INR 2–3): mean (95% CI)</th>
<th>Apixaban (5 mg bd): mean (95% CI)</th>
<th>Dabigatran (150 mg bd): mean (95% CI)</th>
<th>Edoxaban (60 mg od): mean (95% CI)</th>
<th>Rivaroxaban (20 mg od): mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expected total costs (£)</td>
<td>24,418 (12,189 to 50,365)</td>
<td>23,340 (12,842 to 45,753)</td>
<td>23,064 (12,674 to 46,075)</td>
<td>23,985 (13,098 to 46,319)</td>
<td>24,841 (13,198 to 47,603)</td>
</tr>
<tr>
<td>Expected QALYs</td>
<td>5.166 (3.629 to 6.541)</td>
<td>5.488 (3.841 to 6.795)</td>
<td>5.416 (3.817 to 6.701)</td>
<td>5.405 (3.819 to 6.678)</td>
<td>5.451 (3.824 to 6.797)</td>
</tr>
<tr>
<td>Expected incremental total costs (£)</td>
<td>(− to −)</td>
<td>−1078 (−7626 to 2568)</td>
<td>−1354 (−8049 to 2273)</td>
<td>−433.4 (−6430 to 3619)</td>
<td>422.5 (−4730 to 5104)</td>
</tr>
<tr>
<td>Incremental expected QALYs</td>
<td>(− to −)</td>
<td>0.3227 (−0.0148 to 0.814)</td>
<td>0.2505 (−0.0803 to 0.702)</td>
<td>0.2389 (−0.112 to 0.684)</td>
<td>0.2851 (−0.0681 to 0.809)</td>
</tr>
<tr>
<td>Incremental expected net benefit (£20,000)</td>
<td>(− to −)</td>
<td>7533 (489.9 to 18,228)</td>
<td>6365 (−167.7 to 17,039)</td>
<td>5212 (−893.8 to 14,826)</td>
<td>5279 (−1097 to 15,180)</td>
</tr>
</tbody>
</table>

NOACs: Cost Effectiveness Acceptability Curves Network Meta-analysis

José A López-López et al. BMJ 2017;359:bmj.j5058
INVICTUS Programme

**INVestigation of Rheumatic aTrial Fibrillation Treatment Using Vitamin K Antagonists, Rivaroxaban or Aspirin Studies**

- **INVICTUS registry (17,000 patients)**
  - Registry of patients with RVHD
  - Continuation and expansion of the 3000 patient REMEDY registry

- **INVICTUS non-inferiority randomized clinical trial (4500 patients)**
  - Rivaroxaban 20 mg (15 mg) vs vitamin K antagonist (VKA)
  - Patients with RVHD and AF (mitral stenosis or CHA2DS2-VASc ≥2) [NCT02832544]

- **INVICTUS superiority randomized clinical trial (2000 patients)**
  - Rivaroxaban 15 mg vs Aspirin
  - Patients with RVHD and AF but unsuitable for VKA therapy
  - OR patients with RVHD in sinus rhythm at high risk of stroke [NCT02832531]

RE-ALIGN - ph2 dose-finding trial of dabigatran in pts with mechanical valves, 150-330 mg bid, adjusted based on renal function and results of Hemoclot

Trial terminated early after enrolment of 252 pts

Heart Valves, Dabigatran and Warfarin
Attenuating Mechanical Heart Valve-Induced Thrombin Generation

- Thrombin generated via contact pathway overwhelms safe dabigatran concentration (50 ng/ml)
- Dabigatran concentration of 260 ng/ml needed
- ? Need to give 3m anticoagulation for bioprostheses
NOACs and Reversal Agents

**RE-VERSE AD**

Unbound dabigatran (ng/mL)

- **Idarucizumab 5g**

Time post-idarucizumab

- Baseline
- 10–30 min
- 1 h
- 2 h
- 4 h
- 12 h
- 24 h

**ANNEXA-4**

Anti-FXa activity (ng/mL)

- Baseline
- End of bolus
- End of infusion
- 4 h
- 8 h
- 12 h

**Pollack et al. N Engl J Med 2017**

**Connolly et al. N Engl J Med 2016**
When oral anticoagulation is initiated in a patient with AF who is eligible for a NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), a NOAC is recommended in preference to a Vitamin K antagonist.

AF patients already on treatment with a vitamin K antagonist may be considered for NOAC treatment if TTR is not well controlled despite good adherence, or if patient preference without contra-indications to NOAC (e.g. prosthetic valve).
In summary

- NOACs do not require anticoagulation status monitoring (but can be measured)
- NOACs are associated with less strokes and far less intra-cranial haemorrhage
- NOACs are associated with a better quality of life
- NOACs reduce mortality when compared to warfarin
- NOACs have no food-drug interactions and few drug-drug interactions
- NOACs are cost-effective and in many situations cheaper than warfarin
- NOACs are not now recommended in moderate/severe mitral stenosis, but ....
- NOACs are not now recommended for metallic valves, but new NOACs will be
- NOACs can be easily reversed
- NOACs are recommended over warfarin in ESC AF guidelines
- NOACs are preferred by physicians – warfarin will disappear
Evolution in Baseline Treatment for Patients Enrolled in GARFIELD-AF


Cohorts 1–5, N=51,270
In view of all of this, I think that we should all agree that:

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