What You Should “NOAC” About the New Anticoagulants

Dr Calum Young
Cardiologist
Overview

- The Burden of AF
- What’s Wrong With Warfarin?
- The Era of NOACs
- NOACs in New Zealand
- Clinical Trials with NOACs
- Potential issues NOACs- including the Media
- The Future
The Burden of AF

• Overall prevalence in population is at least 1%, but rises with age (>10% of 80 year olds)

• Common incidental finding

• Management:
  – Symptom control (rate versus rhythm control)
  – Risk reduction
    • Stroke
    • Rate-related cardiomyopathy
The Burden of AF

• Stroke Risk:
  – NOT defined by:
    • Pattern of AF (paroxysmal versus persistent)
    • Left atrial size
The Burden of AF

• Stroke Risk:
  – Is defined by \((\text{CHADS}_2\text{-VASC}_2)\):
    • Congestive heart failure
    • Hypertension
    • Age (2 points if 75+ years)
    • Diabetes
    • Stroke/ TIA history (2 points)
    • Vascular disease
    • Sex
The Burden of AF
The Burden of AF

• Stroke Risk:
  – Balance anticoagulation risk with bleeding risk (HAS-BLED)
    • Hypertension
    • Abnormal renal and liver function
    • Stroke history
    • Bleeding predisposition
    • Labile INRs
    • Elderly (>65 years)
    • Drugs/ alcohol (include aspirin, NSAIDs)
The Burden of AF

• Stroke Risk:
  – Balance anticoagulation risk with bleeding risk (HAS-BLED)
    • Falls risk is generally considered now to have a minimal impact on decision to commence oral anticoagulation
What’s Wrong With Warfarin?

• INR must be kept between strict boundaries (usually 2.0-3.0)
  – Risk of bleeds versus risk of stroke

• Regular blood tests
  – Rural patients, travellers, needle phobics, poor veins (although options now for finger-prick testing)

• Medication and dietary interactions

• Image problem: “rat poison”
What’s Wrong With Warfarin?

• But...
  – Warfarin has been round for years
  – Warfarin is cheap (INR testing not necessarily so)
  – Can be “reversed” with Vitamin K (orally or IV)
The Era of NOACs
Currently Available Anticoagulants

Classification Based on Route of Administration and Mode of Action

Anticoagulants

- Parenteral
  - Indirect: Thrombin inhibitors
    - UFH
    - LMWH
    - Fondaparinux
    - M118
  - Direct: Factor Xa inhibitors
    - Hirudin
    - Bivalirudin
    - Argatroban
    - Otamixaban

- Oral
  - Indirect: Thrombin inhibitors
  - Direct: Factor Xa inhibitors
    - VKA
    - Dabigatran
    - Rivaroxaban
    - Apixaban
    - Edoxaban (Japan)

LMWH = low-molecular-weight heparin; UFH = unfractionated heparin; VKA = vitamin K antagonist

Pharmacodynamic Properties of New Oral Anticoagulants

<table>
<thead>
<tr>
<th>Measure</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>3%-7%</td>
<td>66% without food</td>
<td>50%</td>
<td>62%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Almost 100% with food</td>
<td></td>
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<tr>
<td>Clearance nonrenal/renal of absorbed dose</td>
<td>20%/80%</td>
<td>65%/35%</td>
<td>73%/27%</td>
<td>50%/50%</td>
</tr>
<tr>
<td>Half-life</td>
<td>12-17 hours</td>
<td>5-9 hours (young)</td>
<td>12 hours</td>
<td>9-11 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11-13 hours (elderly)</td>
<td></td>
<td></td>
</tr>
</tbody>
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*Investigational; not approved by the US Food and Drug Administration or European Medicines Agency

NOACs in NZ

• Dabigatran (Pradaxa) available since 2011 in New Zealand
  – Some criticism (eg from Haematologists) that introduction was hasty, and little consultation with them (or Cardiologists)
  – Fully funded
  – Licensed for:
    • Non-valvular AF stroke prevention
    • Post-operative DVT/ PE prophylaxis (75mg daily)
    • And now, PE treatment
NOACs in NZ

• Dabigatran:
  ▪ AF:
    • Dose 150mg BD, unless
      • Age >75 or 80 years
      • Impaired renal function, CrCl 30-50
  ▪ Post-operative DVT/ PE prophylaxis
    ▪ 220mg (or 150mg) once daily
  ▪ PE treatment
    ▪ 150mg BD
NOACs in NZ

• Re dabigatran and P-glycoprotein inhibitors:
  – Do **NOT** need to adjust dose in presence of amiodarone use (but can elevate dabigatran levels 14-60%, nor with verapamil (21% dabigatran level increase)
  – Avoid concomitant use with ketoconazole (150% dabigatran level increase)
  – No clinical concerns with quinidine, clarithromycin
NOACs in NZ

• CARM received 345 reports of adverse reactions to dabigatran in the first three months
  – A quarter involved prescriber error
• Up to a third of patients experience transient, or ongoing, dyspepsia (likely related to the tartaric acid in the dabigatran formulation)
NOACs in NZ

• In March 2013, CARM reported three NZ cases of blood clots in mechanical valve patients using dabigatran (off label)

• RE-ALIGN study (published NEJM, September 2013) was terminated early after studying 252 mechanical valve patients randomised to warfarin or dabigatran - due to excess risk with dabigatran
NOACs in NZ

- Patients with **mechanical** heart valves (or severe underlying native valve issues—especially mitral stenosis) should **NOT** be treated with NOACs
  - Warfarin is the only suitable agent in this group of patients

  - Patients with **bioprosthetic** valves and AF **can** be treated with NOACs
Figure 1. Kaplan–Meier Analysis of Event-free Survival.

Panel A shows event-free survival from the first thromboembolic event (i.e., stroke, systemic embolism, transient ischemic attack, or myocardial infarction) or death (P=0.24). Panel B shows event-free survival from the first bleeding event (P=0.01). In each panel, the vertical line indicates the start of the RE-ALIGN extension trial (RE-ALIGN-EX) and the P value was calculated with the use of the Wald chi-square test.
NOACs in NZ

• Rivaroxaban (Xarelto) now funded via an early access programme in New Zealand via dedicated pharmacies
  • Bay Pharmacy at Tauranga Hospital
  • 252 The Strand, Whakatane
  • Total Health Pharmacy, Riverslea Mall, Edgecumbe
  – 20mg once daily (10mg if CrCl 30-49) for non-valvular AF stroke prevention
  – Also licensed for treatment of PE/ DVT
NOACs in NZ

• **Apixaban (Eliquis)** now funded via an early access programme in New Zealand via private Cardiologists only
  – Patient must remain a private patient
The Trials

- **RE-LY**, 2009: dabigatran
- **ROCKET-AF**, 2011: rivaroxaban
- **ARISTOTLE**, 2011: apixaban
- **ENGAGE-AF**, 2013: edoxaban
The Trials

• Aspirin is now **not** recommended for stroke prophylaxis in AF
  – Nothing (CHADS$_2$VASC$_2$ 0-1), vs
  – Formal OAC Therapy
RE-LY Trial (2009)
Table 1. Baseline Characteristics of the Study Participants, According to Treatment Group.‡

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dabigatran, 110 mg</th>
<th>Dabigatran, 150 mg</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>71.4±8.6</td>
<td>71.5±8.8</td>
<td>71.6±8.6</td>
</tr>
<tr>
<td>Weight — kg</td>
<td>82.9±19.9</td>
<td>82.5±19.4</td>
<td>82.7±19.7</td>
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<tr>
<td>Blood pressure — mm Hg</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Systolic</td>
<td>130.8±17.5</td>
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<td>Diastolic</td>
<td>77.0±10.6</td>
<td>77.0±10.6</td>
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<tr>
<td>Male sex — no./total no. (%)</td>
<td>3865/6015 (64.3)</td>
<td>3840/6076 (63.2)</td>
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<td>Type of atrial fibrillation — no./total no. (%)</td>
<td></td>
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<tr>
<td>Persistent</td>
<td>1950/6011 (32.4)</td>
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<tr>
<td>Paroxysmal</td>
<td>1929/6011 (32.1)</td>
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<tr>
<td>CHADS$_2$ score†</td>
<td>2.1±1.1</td>
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<td>1958/6014 (32.6)</td>
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<td>2 — no./total no. (%)</td>
<td>2088/6014 (34.7)</td>
<td>2137/6076 (35.2)</td>
<td>2230/6022 (37.0)</td>
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<td>3—6 — no./total no. (%)</td>
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<td>Previous stroke or transient ischemic attack — no./total no. (%)</td>
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<td>Heart failure — no./total no. (%)</td>
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‡ Statins are defined here as 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors.
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§ Long-term therapy with a vitamin K antagonist (VKA) denotes a total lifetime use of a VKA of 61 or more days.
### Table 2. Efficacy Outcomes, According to Treatment Group.

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<tr>
<th>Event</th>
<th>Dabigatran, 110 mg (N=6015)</th>
<th>Dabigatran, 150 mg (N=6076)</th>
<th>Warfarin (N=6022)</th>
<th>Dabigatran, 110 mg, vs. Warfarin</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
<th>Dabigatran, 150 mg, vs. Warfarin</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
<th>Dabigatran, 150 mg vs. 110 mg</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or systemic embolism*</td>
<td>182 (1.53)</td>
<td>134 (1.11)</td>
<td>199 (1.69)</td>
<td>0.91 (0.74–1.11)</td>
<td>&lt;0.001 for noninferiority, 0.34</td>
<td></td>
<td>0.66 (0.53–0.82)</td>
<td>&lt;0.001 for noninferiority, &lt;0.001</td>
<td></td>
<td>0.73 (0.58–0.91)</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>171 (1.44)</td>
<td>122 (1.01)</td>
<td>185 (1.57)</td>
<td>0.92 (0.74–1.13)</td>
<td>0.41</td>
<td></td>
<td>0.70 (0.56–0.89)</td>
<td>0.001</td>
<td></td>
<td>0.85 (0.69–0.98)</td>
<td>0.002</td>
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<tr>
<td>Hemorrhagic</td>
<td>14 (0.12)</td>
<td>12 (0.10)</td>
<td>45 (0.38)</td>
<td>0.31 (0.17–0.56)</td>
<td>&lt;0.001</td>
<td></td>
<td>0.26 (0.14–0.49)</td>
<td>&lt;0.001</td>
<td></td>
<td>0.89 (0.54–0.98)</td>
<td>0.67</td>
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</tr>
<tr>
<td>Ischemic or unspecified</td>
<td>159 (1.34)</td>
<td>111 (0.92)</td>
<td>142 (1.20)</td>
<td>1.11 (0.89–1.40)</td>
<td><strong>0.35</strong></td>
<td></td>
<td>0.76 (0.60–0.98)</td>
<td>0.03</td>
<td></td>
<td>0.69 (0.54–0.88)</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Nondisabling stroke</td>
<td>60 (0.50)</td>
<td>44 (0.37)</td>
<td>69 (0.58)</td>
<td>0.86 (0.61–1.22)</td>
<td>0.40</td>
<td></td>
<td>0.62 (0.43–0.91)</td>
<td>0.01</td>
<td></td>
<td>0.72 (0.49–1.07)</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>Disabling or fatal stroke</td>
<td>112 (0.94)</td>
<td>80 (0.66)</td>
<td>118 (1.00)</td>
<td>0.94 (0.73–1.22)</td>
<td>0.65</td>
<td></td>
<td>0.66 (0.50–0.88)</td>
<td>0.005</td>
<td></td>
<td>0.70 (0.53–0.94)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>86 (0.72)</td>
<td>89 (0.74)</td>
<td>63 (0.53)</td>
<td>1.35 (0.98–1.87)</td>
<td>0.07</td>
<td></td>
<td>1.38 (1.00–1.91)</td>
<td>0.048</td>
<td></td>
<td>1.02 (0.76–1.38)</td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>14 (0.12)</td>
<td>18 (0.15)</td>
<td>11 (0.09)</td>
<td>1.26 (0.57–2.78)</td>
<td>0.56</td>
<td></td>
<td>1.61 (0.76–3.42)</td>
<td>0.21</td>
<td></td>
<td>1.27 (0.63–2.56)</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>Hospitalization</td>
<td>2311 (19.4)</td>
<td>2430 (20.2)</td>
<td>2458 (20.8)</td>
<td>0.92 (0.87–0.97)</td>
<td>0.003</td>
<td></td>
<td>0.97 (0.92–1.03)</td>
<td>0.34</td>
<td></td>
<td>1.06 (1.00–1.12)</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Death from vascular causes</td>
<td>289 (2.43)</td>
<td>274 (2.28)</td>
<td>317 (2.69)</td>
<td>0.90 (0.77–1.06)</td>
<td>0.21</td>
<td></td>
<td>0.85 (0.72–0.99)</td>
<td>0.04</td>
<td></td>
<td>0.94 (0.79–1.11)</td>
<td>0.44</td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>446 (3.75)</td>
<td>438 (3.64)</td>
<td>487 (4.13)</td>
<td>0.91 (0.80–1.03)</td>
<td>0.13</td>
<td></td>
<td>0.88 (0.77–1.00)</td>
<td>0.051</td>
<td></td>
<td>0.97 (0.85–1.11)</td>
<td>0.66</td>
<td></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. P values are for superiority, unless otherwise indicated. The modified Rankin scale (on which scores can range from 0 [no neurologic disability] to 5 [severe disability], with 6 indicating a fatal stroke) was used to categorize stroke: nondisabling stroke was defined by a score of 0 to 2, and disabling or fatal stroke, a score of 3 to 6.
Cumulative Hazard Rates for the Primary Outcome of Stroke or Systemic Embolism, According to Treatment Group

### Table 3. 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>
<th>Dabigatran, 150 mg vs. 110 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of patients</td>
<td>%/yr</td>
<td>no. of patients</td>
<td>%/yr</td>
<td>Relative Risk (95% CI)</td>
<td>Relative Risk (95% CI)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>322</td>
<td>2.71</td>
<td>375</td>
<td>3.11</td>
<td>0.80 (0.69-0.93)</td>
<td>0.93 (0.81-1.07)</td>
</tr>
<tr>
<td>Life threatening</td>
<td>145</td>
<td>1.22</td>
<td>175</td>
<td>1.45</td>
<td>0.68 (0.55-0.83)</td>
<td>0.81 (0.66-0.99)</td>
</tr>
<tr>
<td>Non-life threatening</td>
<td>198</td>
<td>1.66</td>
<td>226</td>
<td>1.88</td>
<td>0.94 (0.78-1.15)</td>
<td>1.07 (0.89-1.29)</td>
</tr>
<tr>
<td>Gastrointestinal†</td>
<td>133</td>
<td>1.12</td>
<td>182</td>
<td>1.51</td>
<td>1.10 (0.86-1.41)</td>
<td>1.50 (1.19-1.89)</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>1566</td>
<td>13.16</td>
<td>1787</td>
<td>14.84</td>
<td>0.79 (0.74-0.84)</td>
<td>0.91 (0.85-0.97)</td>
</tr>
<tr>
<td>Major or minor bleeding</td>
<td>1740</td>
<td>14.62</td>
<td>1977</td>
<td>16.42</td>
<td>0.78 (0.74-0.83)</td>
<td>0.91 (0.86-0.97)</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>27</td>
<td>0.23</td>
<td>36</td>
<td>0.30</td>
<td>0.31 (0.20-0.47)</td>
<td>0.40 (0.27-0.60)</td>
</tr>
<tr>
<td>Extradural bleeding</td>
<td>299</td>
<td>2.51</td>
<td>342</td>
<td>2.84</td>
<td>0.94 (0.80-1.10)</td>
<td>1.07 (0.92-1.25)</td>
</tr>
<tr>
<td>Net clinical benefit outcome</td>
<td>844</td>
<td>7.09</td>
<td>832</td>
<td>6.91</td>
<td>0.92 (0.84-1.02)</td>
<td>0.91 (0.82-1.00)</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.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Dabigatran, 110 mg (N=6015)</th>
<th>Dabigatran, 150 mg (N=6076)</th>
<th>Warfarin (N=6022)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study-drug discontinuation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinued at 1 yr †</td>
<td>862 (15)</td>
<td>935 (16)</td>
<td>608 (10)</td>
</tr>
<tr>
<td>Discontinued at 2 yr †</td>
<td>1161 (21)</td>
<td>1211 (21)</td>
<td>902 (17)</td>
</tr>
<tr>
<td><strong>Reason for discontinuation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient’s decision</td>
<td>440 (7.3)</td>
<td>474 (7.8)</td>
<td>375 (6.2)</td>
</tr>
<tr>
<td>Outcome event</td>
<td>192 (3.2)</td>
<td>164 (2.7)</td>
<td>130 (2.2)</td>
</tr>
<tr>
<td>Serious adverse event §</td>
<td>163 (2.7)</td>
<td>166 (2.7)</td>
<td>105 (1.7)</td>
</tr>
<tr>
<td>Gastrointestinal symptoms §</td>
<td>134 (2.2)</td>
<td>130 (2.1)</td>
<td>38 (0.6)</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>58 (1.0)</td>
<td>80 (1.3)</td>
<td>54 (0.9)</td>
</tr>
<tr>
<td><strong>Adverse events ‡</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspepsia ‡</td>
<td>707 (11.8)</td>
<td>688 (11.3)</td>
<td>348 (5.8)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>486 (8.1)</td>
<td>506 (8.3)</td>
<td>568 (9.4)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>557 (9.3)</td>
<td>580 (9.5)</td>
<td>586 (9.7)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>473 (7.9)</td>
<td>478 (7.9)</td>
<td>463 (7.8)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>399 (6.6)</td>
<td>401 (6.6)</td>
<td>372 (6.2)</td>
</tr>
<tr>
<td>Cough</td>
<td>344 (5.7)</td>
<td>348 (5.7)</td>
<td>364 (6.0)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>312 (5.2)</td>
<td>377 (6.2)</td>
<td>357 (5.9)</td>
</tr>
<tr>
<td>Back pain</td>
<td>316 (5.3)</td>
<td>314 (5.2)</td>
<td>337 (5.6)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>270 (4.5)</td>
<td>335 (5.5)</td>
<td>346 (5.7)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>337 (5.6)</td>
<td>330 (5.4)</td>
<td>336 (5.6)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>377 (6.3)</td>
<td>397 (6.5)</td>
<td>346 (5.7)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>330 (5.5)</td>
<td>357 (5.9)</td>
<td>349 (5.8)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>273 (4.5)</td>
<td>289 (4.8)</td>
<td>335 (5.6)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>288 (4.8)</td>
<td>285 (4.7)</td>
<td>313 (5.2)</td>
</tr>
<tr>
<td><strong>Liver function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT or AST &gt;3x ULN</td>
<td>124 (2.1)</td>
<td>117 (1.9)</td>
<td>132 (2.2)</td>
</tr>
<tr>
<td>ALT or AST &gt;3x ULN with concurrent bilirubin &gt;2x ULN</td>
<td>13 (0.2)</td>
<td>13 (0.2)</td>
<td>21 (0.3)</td>
</tr>
<tr>
<td><strong>Hepatobiliary disorder</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>33 (0.5)</td>
<td>34 (0.6)</td>
<td>33 (0.5)</td>
</tr>
<tr>
<td>Non-serious adverse event</td>
<td>101 (1.7)</td>
<td>109 (1.8)</td>
<td>112 (1.9)</td>
</tr>
</tbody>
</table>

* ALT denotes alanine aminotransferase, AST aspartate aminotransferase, and ULN upper limit of the normal range.
† Rates of discontinuation at 1 and 2 years were higher with dabigatran than with warfarin (P<0.001). The rates are based on Kaplan-Meier estimates.
‡ Gastrointestinal disorders included pain, vomiting, and diarrhea.
§ The adverse events listed are those that were reported in more than 5% of patients in any of the three treatment groups.
¶ Dyspepsia was defined to include abdominal pain, flatulence, bloating, anorexia, and discomfort in the antrum or duodenum.
** Hepatobiliary disorders were classified as serious adverse events if they consisted of clinical or biochemical liver dysfunction requiring hospitalization, most frequently cholelithiasis or cholecystitis. Hepatobiliary disorders classified as adverse events were most frequently cholelithiasis, cholecystitis, abnormal hepatic function, and jaundice.
Other NOAC Trials
Cumulative Rates of the Primary End Point (Stroke or Systemic Embolism) in the Per-Protocol Population and in the Intention-to-Treat Population.


ROCKET-AF, 2011
Kaplan–Meier Curves for the Primary Efficacy and Safety Outcomes.


ARISTOTLE, 2011

A Primary Outcome: Stroke or Systemic Embolism

Patients with Event (%)

Warfarin
Apixaban

Hazard ratio, 0.79 (95% CI, 0.66–0.95)
P = 0.01

Months
No. at Risk
Apixaban 9120 8726 8440 6051 3464 1754
Warfarin 9081 8620 8301 5972 3405 1768

B Major Bleeding

Patients with Event (%)

Warfarin
Apixaban

Hazard ratio, 0.69 (95% CI, 0.60–0.80)
P < 0.001

Months
No. at Risk
Apixaban 9084 8103 7564 5365 3048 1515
Warfarin 9052 7910 7335 5196 2956 1491
Kaplan–Meier Curves for the Primary Efficacy and Principal Safety End Points.


ENGAGE-AF, 2013
Other Advantages for NOACs

• Quick spontaneous offset of action
  – No prolonged time off agent required prior to elective surgery, and therefore less likelihood of requiring bridging therapy with heparin/ LMWH
  – Is a definite rebound effect for strokes when stopping oral anti-coagulants

• Prompt onset of action on re-commencement
  – Avoidance of post-operative heparin/ LMWH
Switching to NOACs

• If patient is on warfarin, wait until INR is <2.0 before commencing NOAC
• Bridging therapy with heparin/ LMWH should not generally be required
The Media and NOACs
driving. The vehicle was gone when the deputy arrived.

A deputy responded to a report of a vehicle stopping at mail boxes. It was the mailman.

A deputy responded to take a report of property damage.
Injured by Pradaxa®?

Pradaxa® has been linked to serious, life threatening side effects, including internal bleeding and heart attack.

Learn more - schedule a free case review with a Pradaxa® lawyer.
Are we being told the whole truth about the new 'wonder' stroke drug? Worrying side-effects. Missing emails. And a very troubling question about the alternative to warfarin

By SPECIAL REPORT BY BY JEROME BURNE

PUBLISHED: 00:11 GMT, 20 May 2014 | UPDATED: 07:22 GMT, 20 May 2014
Management of Bleeding

• Supportive care:
  – Fluid resuscitation
  – Red blood cell transfusions
  – Maintenance of renal function
  – Identification of bleeding source
  – Surgical intervention
## Reversal of Warfarin and the VKAs: Time to Effect

<table>
<thead>
<tr>
<th>Product</th>
<th>Time to Effect (After Administration)</th>
<th>Duration of Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral vitamin K</td>
<td>24 hours</td>
<td>Days</td>
</tr>
<tr>
<td>Intravenous vitamin K</td>
<td>8-12 hours</td>
<td>Days</td>
</tr>
<tr>
<td>FFP</td>
<td>Immediate</td>
<td>12-24 hours</td>
</tr>
<tr>
<td>PCCs</td>
<td>Immediate</td>
<td>12-24 hours</td>
</tr>
<tr>
<td>Recombinant factor VIIa</td>
<td>Immediate</td>
<td>2-6 hours</td>
</tr>
</tbody>
</table>

Dabigatran associated bleeding

- Initiate standard resuscitation measures
  - Check coagulation screen including activated partial thromboplastin time (aPTT), thrombin time (TT) and fibrinogen assay. Indicate time of last dabigatran dose when requesting test.
  - Check full blood count, renal function and electrolytes (including calcium).

There is no specific reversal agent for dabigatran currently and its anticoagulant effect will not be reversed by administration of vitamin K or plasma infusion.

STOP dabigatran therapy

Mild bleeding
- Local haemostatic measures
  - Mechanical compression
  - Tranexamic acid orally/topically, 15mg/kg four times a day
- Delay next dose of dabigatran or discontinue treatment as appropriate

Moderate to Severe bleeding
- Consult Haematology service
- Local measures
  - Mechanical compression
  - Consider surgical intervention or wound packing
- Fluid replacement
  - Maintain good urine output as dabigatran excreted renally
- Blood product transfusion
  - Consider platelets if levels less than 70-80 X 10^9/L or patient on anti-platelet agent
  - Administration of anti-fibrinolytic agent
    - Tranexamic acid IV (15-30mg/kg) +/- continuous infusion (1mg/kg/hr)
- Oral charcoal application if dabigatran ingestion <2 hours ago
- Consider Prothrombinex-VF 25-50 iu/kg. Repeat if necessary with Haematology guidance

Life threatening bleeding
- Implement measures for Moderate to Severe bleeding and consider:
  - Recombinant factor VIIa (Novoseven) (100mcg/kg by iv bolus): Repeat if necessary with Haematology guidance
  - Haemodialysis especially if renal failure present

---

*Moderate to Severe bleeding* – reduction in Hb ≥ 20g/L, transfusion of ≥ 2 units of red cells or symptomatic bleeding in critical area or organ (for example, intraocular, intracranial, intraspinal, intramuscular with compartment syndrome, retroperitoneal, intraarticular or pericardial bleeding).

*Life-threatening bleeding* – symptomatic intracranial bleed, reduction in Hb ≥ 50g/L, transfusion of ≥ 4 units of red cells, hypotension requiring inotropic agents or bleeding requiring surgical intervention.

*The potential use of Prothrombinex-VF and recombinant factor VIIa (Novoseven) is based on preclinical data.*
Issues with “Pro-Coagulants”

• TRALI
  – Transfusion-Related Acute Lung Injury
  – A severe reaction particularly to Fresh Frozen Plasma (FFP)
  – Immune associations

• TACO
  – Transfusion-Associated Circulatory Overload
Thirty-day mortality rate after a major bleeding event.

Transfusions After Major Bleeding: Dabigatran vs Warfarin

<table>
<thead>
<tr>
<th></th>
<th>D 110 mg</th>
<th>D 150 mg</th>
<th>Warfarin</th>
<th>P Value D 110 vs Warfarin</th>
<th>P Value D 150 vs Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>All 5 trials—first major bleed, N</td>
<td>217</td>
<td>318</td>
<td>376</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood transfusion, n (%)</td>
<td>124 (57) ↑</td>
<td>189 (59) ↑</td>
<td>148 (39)</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Plasma transfusion, n (%)</td>
<td>29 (13) ↓</td>
<td>68 (21) ↓</td>
<td>105 (28)</td>
<td>&lt; .001</td>
<td>.048</td>
</tr>
<tr>
<td>Vitamin K, n (%)</td>
<td>15 (7)</td>
<td>26 (8)</td>
<td>115 (31)</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>RE-LY—first major bleed, N</td>
<td>217</td>
<td>281</td>
<td>305</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood transfusion, n (%)</td>
<td>124 (57) ↑</td>
<td>172 (61) ↑</td>
<td>123 (40)</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Plasma transfusion, n (%)</td>
<td>29 (13) ↓</td>
<td>61 (22) ↓</td>
<td>88 (29)</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Vitamin K, n (%)</td>
<td>15 (7)</td>
<td>23 (8)</td>
<td>93 (30)</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

Blood transfusions were more frequent with both dabigatran doses, but plasma transfusions were less frequent compared with warfarin.

Effect of the Anti-Dabigatran Antibody Fragment (Fab) on the Reversal of Anticoagulation in Healthy Adults

![Diluted Thrombin Time Graph]

- Prolongation of clotting times induced by dabigatran was reversed to baseline at the end of the 5-minute infusion of anti-dabigatran Fab.
- Reversal of dabigatran was complete and sustained in all subjects administered 4 g Fab and in 7 of 9 subjects administered 2 g Fab.

“Normal upper reference limit” refers to (mean+2*SD) of 86 predose measurements from a total of 51 subjects.

Laboratory Monitoring of NOACs

- aPTT
- TT
- DTI
- Specific Factor Xa assays

- INR levels are NOT reliable for NOAC monitoring
Laboratory Monitoring of NOACs

- Regulatory authorities do not recommend routine plasma measurement of NOAC activity
- Plasma levels may vary between individuals
Alcohol and escalators don’t mix.

Hold onto the handrails and always take care on the escalators.
Thienopyridine Anti-Platelet Agents

• Generally these are used as an adjunct to aspirin after cardiac events (MI) or coronary intervention (especially PCI/stenting)

• The most common agent is the thienopyridine, ADP-receptor blocker clopidogrel
  – It’s predecessor, ticlopidine, was associated with higher rates of thrombocytopenia
Thienopyridine Anti-Platelet Agents

• Clopidogrel:
  – Generally given for at least a month post coronary stenting
    • Up to 12 months, particularly if drug-eluting stent
  – Also given often for 3 months after a medically-treated MI, and for 1-3 months post bypass surgery (CABG)
Thienopyridine Anti-Platelet Agents

• Clopidogrel:
  – Issues have included:
    • Clopidogrel resistance
      – Should we measure this??
    • Theoretical interactions with PPIs
Thienopyridine Anti-Platelet Agents

- Clopidogrel:
  - Can be considered in mono-therapy use if aspirin intolerant
  - But, is aspirin-desensitisation an option?
Thienopyridine Anti-Platelet Agents

• Ticagrelor
  – Different binding site on ADP receptor, with reversible block and rapid onset/offset (BD regimen required)
  – Studied in the PLATO trial
    • Compared to clopidogrel, with a lower mortality rate for ticagrelor (9.8 vs 11.7%, p<0.001)
      – Lower vascular risk and similar bleeding rates
Thienopyridine Anti-Platelet Agents

• Ticagrelor
  • But, ticagrelor had higher discontinuation rates (7.4 vs 6.0%, p<0.001): driven by dyspnoea (adenosine-related)
Thienopyridine Anti-Platelet Agents

• Ticagrelor
  – Funded in NZ for the non-thrombolysed MI
Thienopyridine Anti-Platelet Agents

• Prasugrel
  – what niche???
  – Neutral compared to clopidogrel in the TRILOGY-ACS trial
  – Lower repeat MI but higher bleeding than clopidogrel in the TRITON-TIMI 38 Study
### Prasugrel

#### INITIAL APPLICATION - coronary angioplasty and bare metal stent
Applications from any relevant practitioner. Approvals valid for 6 months.

**Prerequisites (tick box where appropriate)**

- The patient has undergone coronary angioplasty in the previous 4 weeks and is clopidogrel-allergic*  

#### INITIAL APPLICATION - drug eluting stent
Applications from any relevant practitioner. Approvals valid for 12 months.

**Prerequisites (tick box where appropriate)**

- The patient has had a drug-eluting cardiac stent inserted in the previous 4 weeks and is clopidogrel-allergic*  

#### INITIAL APPLICATION - stent thrombosis
Applications from any relevant practitioner. Approvals valid without further renewal unless notified.

**Prerequisites (tick box where appropriate)**

- The patient has experienced cardiac stent thrombosis whilst on clopidogrel  

#### RENEWAL - coronary angioplasty and bare metal stent
Current approval Number (if known):

Applications from any relevant practitioner. Approvals valid for 6 months.

**Prerequisites (tick box where appropriate)**

- The patient has undergone coronary angioplasty or had a bare metal cardiac stent inserted in the previous 4 weeks and is clopidogrel-allergic*  

#### RENEWAL - drug eluting stent
Current approval Number (if known):

Applications from any relevant practitioner. Approvals valid for 12 months.

**Prerequisites (tick box where appropriate)**

- Had a drug-eluting cardiac stent inserted in the previous 4 weeks and is clopidogrel-allergic*  

* Indicates a condition that may require additional considerations or documentation.
Other Anti-Platelet Agents

• Is there still a role for dipyridamole?
The Quiz...
Question One:

Which patient with atrial fibrillation would be the best potential candidate for dabigatran?

a. 78 year old male with a mechanical mitral valve replacement
b. 38 year old female with severe mitral stenosis
c. 82 year old male with a bioprosthetic mitral valve replacement
d. 72 year old female with a creatinine clearance of 18
e. 42 year old male with mechanical aortic valve replacement
Question Two:

• What statement is true?
  
a. Apixaban is available for selected public Cardiology patients via an early access programme
  
b. Rivaroxaban is given once daily
  
c. Edoxaban is widely available overseas but not yet in New Zealand
  
d. Overseas regulatory authorities have recommended avoiding commencing new patients on dabigatran pending new safety data
  
e. Warfarin is safer than the new anticoagulant agents because it can be reversed by Vitamin K
Question Two:

- What statement is true?
  a. Apixaban is available for selected public Cardiology patients via an early access programme
  b. Rivaroxaban is given once daily
  c. Edoxaban is widely available overseas but not yet in New Zealand
  d. Overseas regulatory authorities have recommended avoiding commencing new patients on dabigatran pending new safety data
  e. Warfarin is safer than the new anticoagulant agents because it can be reversed by Vitamin K
Question Three:

• What statement is true?

  a. An INR level gives a good indication of plasma dabigatran levels
  b. Vitamin K can help reverse the effects of dabigatran
  c. Prior to elective surgery, dabigatran should be withheld for a week prior to the operation date
  d. When restarting dabigatran after surgery, subcutaneous low-molecular weight heparin should be given as “bridging” therapy for 3 days
  e. The half-life of dabigatran is 12-17 hours
Question Four:

• What factor is least important when selecting appropriate patients (and dose) for NOACs?
  a. Age
  b. Patient weight
  c. Estimated risk of falls
  d. Renal function
  e. History of prior bleeding episodes
Question Five:

• What statement is true?
  a. Apixaban is a direct thrombin inhibitor
  b. Patients on dabigatran can choose to open the capsules and take the contents in a glass of water if that is easier for them
  c. Rivaroxaban cannot be packaged in blister packaging
  d. An “antidote” for dabigatran under development is a Fab-binding agent, and may be available as soon as 2015
  e. You can switch a patient from warfarin to dabigatran as soon as the INR is less than 3.0
Question Six:

- What statement is true?
  a. All thienopyridines bind to the same ADP receptor
  b. Ticagrelor has a more prolonged action than the other thienopyridines
  c. Prasugrel is available on Special Authority in NZ for clopidogrel-allergic patients post coronary angioplasty
  d. Prasugrel has a much lower bleeding risk than clopidogrel
  e. Shorter courses of dual anti-platelet therapy can be used in patients with drug-eluting stents
Quiz Answers
Question One:

Which patient with atrial fibrillation would be the best potential candidate for dabigatran?

a. 78 year old male with a mechanical mitral valve replacement
b. 38 year old female with severe mitral stenosis
c. 82 year old male with a bioprosthetic mitral valve replacement
d. 72 year old female with a creatinine clearance of 18
e. 42 year old male with mechanical aortic valve replacement
Question Two:

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Summary

• Current studies indicate that NOACs have a net benefit over warfarin
  – Lower strokes
  – Lower bleeding risk

• The lack of reversal agent for NOACs should be part of the routine patient discussion, but the issue is not necessarily straightforward
  – Supportive therapies etc
Summary

• Currently fully-funded agents are:
  – Warfarin
  – Dabigatran

• Early-access funding for:
  – Rivaroxaban
  – Apixaban (private patients only)

• There are a few options for anti-platelet therapy with specific side effect profiles