RESULTS: Efficacy & Safety – median follow-up of 1.8 years (ITT)

<table>
<thead>
<tr>
<th>Clinical Endpoints</th>
<th>Apixaban</th>
<th>Warfarin</th>
<th>HR (95% CI)</th>
<th>NNT</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>StROKE or systemic embolism</strong></td>
<td>2.32% (n=212)</td>
<td>1.27%/y</td>
<td>2.92% (n=265)</td>
<td>1.60%/y</td>
<td>0.79 (0.66-0.96)</td>
</tr>
</tbody>
</table>

**Efficacy**

- **Apixaban** vs **warfarin** for 1st stroke:
  - Stroke/hemorrhagic stroke rates lower with apixaban
  - All-cause mortality lower with apixaban

**SAFETY**

- Warfarin rates of major bleed, intracranial hemorrhage were higher than apixaban
- Higher major or more pts in apixaban group (11%, vs 9% in warfarin group)
- Slightly more pts in NOSADES in warfarin group (9.5% vs 6.2% in apixaban group)
- Higher rate of warfarin in warfarin group

**Other**

- NOSADES to follow up
  - >31% pts (74%) had missing data
  - Lower dose group

<table>
<thead>
<tr>
<th><strong>Adverse Events based on N=9036 in rivaroxaban arm and N=9529 in warfarin arm</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleed</td>
</tr>
</tbody>
</table>

**Incidence**

- Higher rate of disSite
  - >31% pts (74%) had missing data
  - Lower dose group

**Net clinical outcomes**

- Higher rate of major bleed, interaction significant for DM & renal failure
- Greater reduction for bleeding in pts who did not have DM (p=0.003) and among pts with moderate or severe renal impairment (p=0.002)

**Strengths, Limitations, & Uncertainties**

**Strengths**

- Important clinical endpoints
- Both arms blinded
- Low-moderate high risk for stroke

**Limitations**

- Warfarin was within therapeutic range 66% of the study period
- Study period: 2009-2010
- Short study

**Uncertainties**

- Drug not yet studied in pts with CrCl<25mL/min, Scr>221umol/L or liver disease?
- Drug interactions?
- Cost of drug?
Although touted in the guidelines as the only alternative to warfarin, it may be the weakest amongst the players. There has been criticism that this was an open label design. Tolerance is an issue with the higher discontinuation rates than warfarin driven by dyspepsia. The tartaric acid in the formulation is likely driving the increased dyspepsia rates. Also to take note is the high GI bleed discontinuance rate.

Pros vs warfarin
Non-inferior & superior to warfarin for stroke/systemic embolism
Less all-cause mortality/hemorrhagic stroke
Less major/intracranial/other/any bleeding than warfarin
No INR monitoring required
Less clinically significant drug interactions

Cons vs warfarin
Higher drug cost? ($290 recently available in Canada)
No antidote with apixaban
No long term (greater than 2yr) follow up
New drug; lacks “real life” evidence and postmarketing surveillance

Additional references:

RXFILES TRIAL SUMMARY
MARGARET JIN, PHARM.D – SEPT 2011 – WWW.RXFILES.CA

Apixaban in Atrial Fibrillation Pros & Cons:
Not apixaban if prosthetic heart valve, renal dx (CrCl < 25 ml/min), or significant liver dx

Pros vs warfarin
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Rocket-AF, Aristotle & RE-LY: Comparison Tables of Baseline Characteristics

Baseline | Age (mean) | Male | HT | DM | Prior MI | Time in TTR (mean) | CHADS2 (mean) | Trial design | n | Follow up
--- | --- | --- | --- | --- | --- | --- | --- | --- | --- | ---
Dabigatran 110mg bid | 71.5 | 63.3 | 78.9% | 23.2% | 20% | 16.5% | 64% (mean) | 2.1 | RCT Open blinded assessment | 18k | 2 yr
Dabigatran 150mg bid | 71.5 | 63.3 | 78.9% | 23.2% | 20% | 16.5% | 64% (mean) | 2.2 | RCT Open blinded assessment | 18k | 2 yr
Rivaroxaban 20mg od | 73 | 60% | 90.5% | 39.5% | 55% | 17.5% | 55% (mean) | 3.4 | RCT DB DD | 14k | 1.94 yr
Apixaban 5mg bid | 70 | 65% | 87.5% | 25% | 19.4% | 14.2% | 62% (mean) | 2.1 | RCT DB DD | 18k | 1.8 yr

Results

Rocket-AF, Aristotle & RE-LY: Comparison Table of Results

<table>
<thead>
<tr>
<th>Results</th>
<th>Stroke or systemic embolism</th>
<th>Ischemic stroke</th>
<th>Hemorrhagic stroke</th>
<th>All cause death</th>
<th>MI/ACS</th>
<th>Major bleed</th>
<th>Intracranial bleed</th>
<th>GI bleed</th>
<th>Discontinuance rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran 110 vs warf</td>
<td>NS</td>
<td>3.0 vs 3.3%</td>
<td>2.6 vs 2.4%</td>
<td>0.2 vs 0.7%</td>
<td>0.3</td>
<td>7.4 vs 8.1%</td>
<td>1.4 vs 1.0%</td>
<td>5.4 vs 6.6%</td>
<td>RR 0.81</td>
</tr>
<tr>
<td>Dabigatran 150 vs warf</td>
<td>2.2 vs 3.3%</td>
<td>1.8 vs 2.4%</td>
<td>RR 0.77</td>
<td>0.2 vs 0.7%</td>
<td>0.2</td>
<td>7.2 vs 8.1%</td>
<td>1.5 vs 1.0%</td>
<td>RR 1.40</td>
<td>NSA 6.2 vs 6.6%</td>
</tr>
<tr>
<td>Rivaroxaban vs warf</td>
<td>NSA 3.8 vs 3.3%</td>
<td>RR 0.88</td>
<td>2.1 vs 2.3%</td>
<td>0.4 vs 0.7%</td>
<td>0.4</td>
<td>2.9 vs 3.5</td>
<td>1.4 vs 1.8</td>
<td>NSA 5.6 vs 5.4%</td>
<td>0.8 vs 1.2%</td>
</tr>
<tr>
<td>Apixaban vs warf</td>
<td>NSA 2.3 vs 2.9%</td>
<td>RR 0.80</td>
<td>1.8 vs 1.9%</td>
<td>0.4 vs 0.9%</td>
<td>0.5</td>
<td>6.6 vs 7.4</td>
<td>1.6 vs 1.1</td>
<td>NSA 3.6 vs 3.5%</td>
<td>0.6 vs 1.3%</td>
</tr>
</tbody>
</table>

Rocket-AF, Aristotle & RE-LY: Comparison Table of NNT & NNH

<table>
<thead>
<tr>
<th>NNT</th>
<th>Stroke or systemic embolism</th>
<th>Ischemic stroke</th>
<th>Hemorrhagic stroke</th>
<th>All cause death</th>
<th>MI/ACS</th>
<th>Major bleed</th>
<th>Dyspepsia</th>
<th>GI bleed</th>
<th>Antidote</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran 110 vs warf</td>
<td>192</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>77</td>
<td>17</td>
<td>11.8 vs 5.8%</td>
<td>?</td>
</tr>
<tr>
<td>Dabigatran 150 vs warf</td>
<td>88</td>
<td>132</td>
<td>182</td>
<td>239-284?</td>
<td>18</td>
<td>11.3 vs 5.8%</td>
<td>100</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban vs warf</td>
<td>135p</td>
<td>333</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Octaplex</td>
</tr>
<tr>
<td>Apixaban vs warf</td>
<td>167</td>
<td>238</td>
<td>132</td>
<td>67</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Octaplex</td>
</tr>
</tbody>
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Concluding comments:

Dabigatran (RELY)
Although touted in the guidelines as the only alternative to warfarin, it may be the weakest amongst the players. There has been criticism that this was an open label design. Tolerance is an issue with the higher discontinuation rates than warfarin driven by dyspepsia. The tartaric acid in the formulation is likely driving the increased dyspepsia rates. Also to take note is the high GI bleeding events with a NNT of 100. Although not statistically significant after re-analysis, the increasing trend for MIs is worrisome. On the plus side the 150mg dosage has the best NNT for the stroke and systemic embolism, hemorrhagic stroke and the only statistically significant NNT for ischemic stroke. The 110mg dosage may be appropriate for those at high risk for major bleeding. It’s available in Canada and around $110/month, but there is no antidote yet discovered for dabigatran.

Rivaroxaban (ROCKET-AF)
The trial design was superior to RELY in that it was double blinded with sham INR for both comparator and control groups. Their patient population was also sicker with CHADS2 score mean of 3.4 compared to 2.1-2.2 from RELY. However, a criticism has been that the time within TTR (INR2-3) for the warfarin group was only 55%, which is lower than RELY and ROCKET-AF. This is understandable because sicker patients are more difficult to dose to TTR with warfarin. Also rivaroxaban was shown to be non-inferior to warfarin for the intention to treat analysis and was only superior in the per protocol group. As far as efficacy for the
Apixaban (ARISTOLE)

This drug has potentially the most promise because all cause mortality was reduced for the Apixaban group compared to warfarin, which is already a very efficacious drug. This endpoint trumps the other two trials. On the safety side there is 30% less major bleeding (a combination of less intra-cranial and a decreasing trend for GI bleeds). Overall, lots of green and no red letters for Apixaban. Octaplex is a likely antidote because it is a Xa inhibitor like rivaroxaban but recently available in Canada at over $150/month.

References: