ARISTOTLE: Apixaban vs Warfarin in patients with Atrial Fibrillation

**BOTTOM LINE**

In atrial fibrillation (AF) patients with an ↑ risk of stroke (mean CHADS<sub>2</sub> score 2.1):

- Apixaban 5mg po BID was superior to warfarin for ↓ stroke or systemic embolism (NNT=167/1.8 years)
- Apixaban, compared to warfarin, had:
  - ↓ stroke (NNT=175/1.8yr), hemorrhagic stroke (NNT=238/1.8yr) & mortality (NNT=132/1.8yr)
  - ↓ bleeding major (NNT=67/1.8yr), intracranial (NNT=128/1.8yr), other & any bleeding & ↓ discontinuation rates (NNT=45/1.8yr)
- Net clinical benefit stroke, systemic embolism, major bleeding or death from any cause favours apixaban over warfarin (NNT=56/1.8 years)
- At time of publication, apixaban is not approved by Health Canada for stroke prevention in AF patients. $150-290/month.

**BACKGROUND**

- Vitamin K antagonists (VKA) are used to ↓ the risk of stroke in AF patients; however, these agents require frequent monitoring, interact with drugs/food, & require several days of therapy to become therapeutic/discontinuation before clearing the body.
- New oral anticoagulants (apixaban ELIQUIES, dabigatran PRADAX<sup>2,3</sup> & rivaroxaban XARELTO<sup>4,5</sup>) are alternatives to VKA, such as warfarin.
- Apixaban ELIQUIES is a new direct oral factor Xa inhibitor.
- AVERROES: apixaban 5mg bid was superior to ASA 81.324mg/d in AF patients. Stroke/systemic embolism: HR 0.45 (95% CI 0.32-0.62), p<0.001, NNT=45. Major bleeding & intracranial hemorrhage: NS. Study stopped early for benefit, mean follow-up = 1.1 yrs.

**TRIAL BACKGROUND**

**DESIGN:** randomized, multi-centre 39 countries, non-inferiority with pre-designed superiority<sup>1</sup>, major bleeding & mortality, double-blinded, double-dummy intention-to-treat controlled trial with concealed allocation. Funded by Bristol-Myers Squibb & Pfizer.

**INTERVENTION:** apixaban 2.5mg po twice daily in patients who had ≥2 of the following: age ≥80 years, body weight ≤60kg, or Scr ≥133umol/L

**INCLUSION:** permanent or persistent AF or flutter ECG at enrolment, or AF or flutter ECG or as an episode ≥1 minute on rhythm strip/ Holter monitor/ Intracardiac recording on 2 separate occasions at least 2 weeks apart in 12 months before enrolment; age ≥ 18 yrs; ≥ 1 of the following stroke risk factors: age ≥75 years, prior stroke/TIA/systemic embolus, symptomatic HF within 3 months or LVEF ≤40%, DM or HTN requiring pharmacological treatment; women contraception required if childbearing.

**EXCLUSION:** AF/atrial flutter due to reversible causes eg, thyrotoxicosis, pericarditis; planned ablation procedure<sup>6</sup> AF or atrial flutter; ↑ bleeding risk eg, previous intracranial hemorrhage; conditions other than AF that require chronic anticoagulation eg, prosthetic mechanical heart valves; required ASA ≥165 mg/d; treatment with both ASA + thienopyridine clopidogrel, ticlopidine<sup>7</sup> recent stroke within 7 days; infective endocarditis active;<sup>8</sup> mitral stenosis moderate/severe;<sup>8</sup> uncontrolled HTN SBP>180mmHg or DBP>100mmHg; major surgery planned; hemoglobin <90g/L; platelet ≤100,000/mm<sup>3</sup>; ↑ liver enzymes ALT>2xULN or total bilirubin>1.5xULN; renal insufficiency Scr>221umol/L or CrCl<25mL/min; active alcohol/drug abuse/psychosocial reasons that make study participation impractical; inability to comply with INR monitoring; life expectancy ≤ 1 year; or unapproved investigation drug or device in past 30 days.

**POPULATION** at baseline: n=18,201 non-valvular AF pts at risk of stroke.

- AF ≈85% persistent/permanent, ≈15% paroxysmal; CHADS<sub>2</sub>mean = 2.1, CHADS<sub>2</sub> score 34% ≥1, ~36% ≥2, 30% ≥3
- Median age 70yrs, age ≥75yr 31%; ≥65% ; median weight 82kg; median systolic blood pressure 130mmHg
- History of stroke/TIA/systemic embolism 19%, HF 35%, HTN 87%, DM 25%, MI ~14%, bleeding ~17%, VKA use >30 days 57%
- Renal function: CrCl >80mL/min 41%, CrCl >50-80mL/min ~42%, CrCl >30-50mL/min 15%, CrCl ≤30mL/min 1.5%
- Baseline medications: ACE-I 70%, ASA 31%, amiodarone 11%, β-blocker 63%, CCB 30%, clopidogrel 1.9%, digoxin 32%, gastric antacid drugs 18%, NSAIDS 8%, statins 45%

**RESULTS**

**TABLE: Efficacy & Safety Superiority Data**

<table>
<thead>
<tr>
<th>TABLE: Efficacy &amp; Safety Superiority Data</th>
<th>APIXABAN (n=9120)</th>
<th>WARFARIN (n=9081)</th>
<th>HAZARD RATIO (95% CI)</th>
<th>NNT/1.8yrs</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRIMARY ENDPOINT</strong></td>
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<tr>
<td>Stroke or Systemic Embolism</td>
<td>2.32% (n=212)</td>
<td>2.94% (n=265)</td>
<td>1.60% /y</td>
<td>0.79 (0.66-0.95)</td>
<td>167</td>
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<tr>
<td><strong>SECONDARY ENDPOINTS: EFFICACY</strong></td>
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<tr>
<td>Stroke</td>
<td>2.18% (n=199)</td>
<td>2.75% (n=250)</td>
<td>1.51% /y</td>
<td>0.79 (0.65-0.95)</td>
<td>175</td>
</tr>
<tr>
<td>Ischemic/Non-specified stroke</td>
<td>1.78% (n=162)</td>
<td>1.93% (n=175)</td>
<td>1.05% /y</td>
<td>NS</td>
<td>-</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.44% (n=40)</td>
<td>0.86% (n=78)</td>
<td>0.47% /y</td>
<td>0.51 (0.35-0.75)</td>
<td>238</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>0.16% (n=15)</td>
<td>0.19% (n=17)</td>
<td>0.10% /y</td>
<td>NS</td>
<td>-</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>0.99% (n=90)</td>
<td>1.12% (n=102)</td>
<td>0.61% /y</td>
<td>NS</td>
<td>-</td>
</tr>
<tr>
<td>All Cause Mortality</td>
<td>6.61% (n=603)</td>
<td>7.37% (n=669)</td>
<td>3.94% /y</td>
<td>0.89 (0.8-0.998)</td>
<td>0.047</td>
</tr>
<tr>
<td><strong>ADVERSE EVENTS BASED ON N=9088 IN APIXABAN ARM &amp; N=9592 IN WARFARIN ARM</strong></td>
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<tr>
<td>Major Bleed*</td>
<td>3.6% (n=327)</td>
<td>5.1% (n=462)</td>
<td>3.09% /y</td>
<td>0.69 (0.6-0.8)</td>
<td>67</td>
</tr>
<tr>
<td>Intracranial</td>
<td>0.57% (n=52)</td>
<td>1.35% (n=122)</td>
<td>0.80% /y</td>
<td>0.42 (0.3-0.58)</td>
<td>128</td>
</tr>
<tr>
<td>Other location</td>
<td>3.03% (n=275)</td>
<td>3.76% (n=340)</td>
<td>2.27% /y</td>
<td>0.79 (0.68-0.93)</td>
<td>137</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>1.16% (n=105)</td>
<td>1.31% (n=119)</td>
<td>0.86% /y</td>
<td>NS</td>
<td>-</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>25.92% (n=2356)</td>
<td>31.38% (n=3060)</td>
<td>25.8% /y</td>
<td>0.71 (0.68-0.75)</td>
<td>13</td>
</tr>
</tbody>
</table>

**TABLE: Efficacy & Safety Superiority Data**

**APRILABAN VS WARFARIN:**

- ↓ stroke or systemic embolism & + stroke, hemorrhagic strokes & mortality
- ↓ major bleed, intracranial, other & any bleeding
- ↓ net clinical outcomes & discontinuation rates

**OTHER COMMENTS:**

- Lower apixaban dose 2.5mg BID: n=428 (4.7%).
- Lost to follow-up: 69 patients.
- Missing data: 380 pts (2.1%).
- Warfarin TTR: median 66%, mean 62.2%
**TABLE: Efficacy & Safety continued**

<table>
<thead>
<tr>
<th>NET CLINICAL OUTCOMES</th>
<th>APIXABAN (n=9120)</th>
<th>WARFARIN (n=9081)</th>
<th>HAZARD RATIO (95% CI)</th>
<th>NNT/1.8YRS</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke, systemic embolism, or major bleed</td>
<td>5.73% (n=521) (3.17%/yr)</td>
<td>7.36% (n=666) (4.11%/yr)</td>
<td>0.77 (0.69-0.86)</td>
<td>61</td>
<td>□ for major bleeding in pts who did not have DM (p=0.003) &amp; pts with moderate or severe renal impairment (≥55mL/min) (p=0.03)</td>
</tr>
<tr>
<td>Stroke, systemic embolism, major bleed, or death from any cause</td>
<td>11.1% (n=1009) (6.13%/yr)</td>
<td>12.9% (n=1168) (7.20%/yr)</td>
<td>0.85 (0.78-0.92)</td>
<td>56</td>
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</tr>
<tr>
<td>Discontinuation rate</td>
<td>25.3% (3.6%/death)</td>
<td>27.5% (3.8%/death)</td>
<td>p=0.001</td>
<td>45</td>
<td></td>
</tr>
</tbody>
</table>

*Major Bleeding: Hemoglobin ≤20g/L, transfused ≥2 units, fatal bleeding or 1 critical site intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, retroperitoneal

**STRENGTHS, LIMITATIONS, & UNCERTAINTIES**

**STRENGTHS:**
- Important clinical endpoints (e.g. stroke & bleed)
- Both study arms were blinded
- Included patients with low-moderate-high risk of stroke
- Warfarin was within therapeutic range 66% of the study period

**LIMITATIONS:**
- ~31% of patients were on concomitant aspirin therapy
- Used intention-to-treat without per-protocol analysis (per-protocol is generally recommended in non-inferiority trials), but did include modified intention-to-treat for bleeding.

**UNCERTAINTIES:**
- Drug not yet studied in patients with CrCl <25mL/min, Scr >221μmol/L or liver disease?
- Drug interactions?
- No antidote for reversing bleeding with apixaban
- Lack long-term data & real-world experience with apixaban
- Risk of bleeding in patients with AF & ACS: ARISTOTLE ▼ bleeding in AF pts, APPRAISE ▲ bleeding post-ACS. – APPRAISE apixaban 5mg po bid added to antiplatelet therapy in high risk patients after ACS. Rate of major bleeding events (HR=2.48 95% CI 1.72-3.58, NNH=63) with NS in recurrent ischemic events vs placebo; study stopped early because of harm; follow-up median=241 days.

**RxFiles RELATED LINKS**
- **Canadian Family Physician RxFiles: Article Oral anticoagulation in atrial fibrillation** [http://www.cfp.ca/content/58/8/850.full](http://www.cfp.ca/content/58/8/850.full)

**ADDITIONAL REFERENCES**

**ACCF/AHA/HRS Atrial Fibrillation 2011 Focused Update.** Circulation 2011; http://circ.ahajournals.org/cgi/reprint/CIR.0b013e3181fa9e41


**Beasley RN, Leger EF, Temple R. Anticoagulant options. Why the FDA approved warfarin patients with atrial fibrillation (using the 2006 guidelines): A report of the American College of Cardiology Foundation/Canadian Heart Association Task Force on Practice Guidelines.** Circulation 2010; DOI: 10.1161/CIR.0b013e3181fa3f34


ARISTOTLE REFERENCES:


(ROCKET-AF)


8 Zee BC. Planned equivalence or noninferiority trials versus unplanned noninferiority claims: are they equal?. J Clin Oncol. 2006 Mar 1;24(7):1026-8. [http://jco.ascopubs.org/cgi/reprint/24/7/1026.pdf]