ARISTOTLE: Apixaban vs Warfarin in patients with Atrial Fibrillation [1]

Apixaban for Reduction In STroke and Other ThromboemboLic Events in Atrial Fibrillation

BOTTOM LINE

In atrial fibrillation (AF) patients with an ↑ risk of stroke (mean $CHADS_2$ 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 ELIQUIS, dabigatran PRADAX[2,3] & rivaroxaban XARELTO[4,5]) are alternatives to VKA, such as warfarin.
- **Apixaban** ELIQUIS 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. [6]

TRIAL BACKGROUND [7]

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

INTERVENTION: apixaban 5mg* po *twice* daily versus dose-adjusted warfarin (INR 2-3 measured ≤1 month)
*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 AF or atrial flutter; ↑ bleeding risk eg, previous intracranial hemorrhage; conditions other than AF that require chronic anticoagulation eg, prosthetic mechanical heart valve; required ASA >165 mg/d; treatment with both ASA + thienopyridine clopidogrel, ticlopidine; **recent stroke within 7 days**; infective endocarditis active; mitral stenosis moderate/severe; **uncontrolled HTN SBP>180 mmHg or DBP > 100 mmHg**; major surgery planned; **hemoglobin <90g/L**; **platelet ≤100,000/mm^3**; ↑ **liver enzymes ALT/AST>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; $CHADS_2$ mean = 2.1, $CHADS_2$ 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

follow-up: median 1.8 years

TABLE: EFFICACY & SAFETY SUPERIORITY DATA

CLINICAL ENDPOINTS	APIXABAN (n=9120)	WARFARIN (n=9081)	HAZARD RATIO (95% CI)	NNT/ 1.8YRS	COMMENTS
PRIMARY ENDPOINT					
Stroke or Systemic Embolism	2.32% {n=212} 1.27%/yr	2.92% {n=265} 1.60%/yr	0.79 (0.66-0.95)	167	**APIXABAN VS WARFARIN:**
SECONDARY ENDPOINTS: EFFICACY					- ↓ stroke or systemic embolism
Stroke	**2.18% {n=199} (1.19%/yr)**	**2.75% {n=250} (1.51%/yr)**	**0.79 (0.65-0.95)**	**175**	- ↓ stroke, hemorrhagic strokes & mortality
Ischemic/Non-specified stroke	1.78% {n=162} (0.97%/yr)	1.93% {n=175} (1.05%/yr)	NS	-	- ↓ major bleed, intracranial, other & any bleeding
Hemorrhagic stroke	**0.44% {n=40} (0.24%/yr)**	**0.86% {n=78} (0.47%/yr)**	**0.51 (0.35-0.75)**	**238**	- ↓ net clinical outcomes & discontinuation rates
Systemic embolism	0.16% {n=15} (0.09%/yr)	0.19% {n=17} (0.10%/yr)	NS	-	
Myocardial Infarction	0.99% {n=90} (0.53%/yr)	1.12% {n=102} (0.61%/yr)	NS	-	
All Cause Mortality	**6.61% {n=603} (3.52%/yr)**	**7.37% {n=669} (3.94%/yr)**	**0.89 (0.8-0.998) (p=0.047)**	**132**	**OTHER COMMENTS:**
ADVERSE EVENTS BASED ON N=9088 IN APIXABAN ARM & N=9052 IN WARFARIN ARM					- Lower apixaban dose 2.5mg BID: n=428 (4.7%).
Major Bleed*	3.6% {n=327} (2.13%/yr)	5.1% {n=462} (3.09%/yr)	**0.69 (0.6-0.8)**	**67**	- Lost to follow-up: 69 patients.
Intracranial	0.57% {n=52} (0.33%/yr)	1.35% {n=122} (0.80%/yr)	0.42 (0.3-0.58)	128	- Missing data: 380 pts (2.1%).
Other location	3.03% {n=275} (1.79%/yr)	3.76% {n=340} (2.27%/yr)	0.79 (0.68-0.93)	137	- Warfarin TTR: median 66%, mean 62.2%
Gastrointestinal	1.16% {n=105} (0.76%/yr)	1.31% {n=119} (0.86%/yr)	NS	-	
Any bleeding	25.92% {n=2356} (18.1%/yr)	33.8% {n=3060} (25.8%/yr)	0.71 (0.68-0.75)	13	

TABLE: EFFICACY & SAFETY continued

CLINICAL ENDPOINTS	APIXABAN (n=9120)	WARFARIN (n=9081)	HAZARD RATIO (95% CI)	NNT/ 1.8YRS	COMMENTS
NET CLINICAL OUTCOMES					**SUB-GROUP ANALYSES:** - ↓ for major bleeding in pts who did not have DM (p=0.003) & pts with moderate or severe renal impairment {≤50mL/min} (p=0.03)
Stroke, systemic embolism, or major bleed	5.73% {n=521} (3.17%/yr)	7.36% {n=666} (4.11%/yr)	0.77 (0.69-0.86)	61	
Stroke, systemic embolism, major bleeding, or death from any cause	11.1% {n=1009} (6.13%/yr)	12.9% {n=1168} (7.20%/yr)	0.85 (0.78-0.92)	56	
Discontinuation rate	25.3% {3.6%=death)	27.5% {3.8%=death}	p=0.001	45	

***Major Bleeding:** Hemoglobin ↓≥20g/L, transfused ≥2units, 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 ACTIVE-W 63.8%, RELY 64%, ROCKET 55%

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)[8], but did include modified intention-to-treat for bleeding.

UNCERTAINITIES:
- Drug not yet studied in patients with CrCl <25mL/min, Scr >221umol/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.[9]

RxFILES RELATED LINKS

- Atrial Fibrillation Treatment Overview http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht-Atrial-Fibrillation.pdf
- Oral Antiplatelet & Antithrombotic Agents Comparison Chart http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht-AntiThrombotics.pdf
- Canadian Family Physician RxFiles: Article Oral anticoagulation in atrial fibrillation http://www.cfp.ca/content/58/8/850.full
- RELY (dabigatran PRADAX vs warfarin in AF) Trial Summary http://www.rxfiles.ca/rxfiles/uploads/documents/RE-LY-Trial-Dabigatran.pdf
- ROCKET-AF (rivaroxaban XARELTO vs warfarin in AF) Trial Summary http://www.rxfiles.ca/rxfiles/uploads/documents/ROCKET-AF-Rivaroxaban.pdf
- ACTIVE-A (ASA ± clopidogrel PLAVIX in AF) & ACTIVE-W (ASA + clopidogrel PLAVIX vs warfarin in AF) Trial Summary http://www.rxfiles.ca/rxfiles/uploads/documents/ACTIVE-A-Trial-Summary.pdf
- RACE-II (lenient vs strict rate control in AF) Trial Summary http://www.rxfiles.ca/rxfiles/uploads/documents/RACE-II-trial.pdf
- PALLAS (dronedarone MULTAQ in permanent AF) Trial Summary http://www.rxfiles.ca/rxfiles/uploads/documents/PALLAS-trial%20summary.pdf

✘=non-formulary ⊗= not covered by NIHB ♂= male **ACE-I**=angiotensin converting enzyme inhibitor **ACS**=acute coronary syndrome **AF**=atrial fibrillation **ALT**=alanine aminotransferase **AST**=aspartate aminotransferase **ASA**=acetylsalicylic acid **β -blocker**=beta blocker **CCB**=calcium channel blocker **CHADS$_2$**=congestive heart failure, hypertension, age >75 years, diabetes mellitus, stroke or transient ischemic attack **CI**=confidence interval **CrCl**=creatinine clearance **DBP**=diastolic blood pressure **DM**=diabetes mellitus **ECG**=electrocardiogram **HF**=heart failure **HR**=hazard ratio **HTN**=hypertension **INR**=international normalized ratio **LVEF**=left ventricular ejection fraction **MI**=myocardial infarction **NNT**=number needed to treat **NNH**=number needed to harm **NS**=not statistically significant **NSAIDs**=nonsteroidal anti-inflammatory drugs **pts**=patients **SCr**=serum creatinine **SBP**=systolic blood pressure **TIA**=transient ischemic attack **TTR**=time in therapeutic range **ULN**=upper limit of normal **VKA**=vitamin K antagonist **yrs**=years

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