

# ARISTOTLE: Apixaban vs Warfarin in patients with Atrial Fibrillation (AF)<sup>1</sup>

Apixaban for Reduction In Stroke and Other Thromboembolic Events in Atrial Fibrillation

## Bottomline

- Apixaban superior to warfarin without need for INR monitoring, but with higher drug cost. *Cost Comparison (/month): Warfarin + monitoring \$35 vs Apixaban 5mg po bid (\$290 recently available in Canada).*
- In AF: Apixaban reduced stroke or systemic embolism compared to warfarin (NNT=167 in 1.8 years)
- In AF: Apixaban reduced all-cause mortality compared to warfarin (NNT=132 in 1.8 years)
- In AF: Apixaban had less major bleeding compared to warfarin (NNT=67 in 1.8 years)
- In AF: Net clinical outcomes of stroke, systemic embolism, major bleeding, or death from any cause favours apixaban vs warfarin (NNT=56 in 1.8 years)

## Background

- Apixaban (Eliquis®), a factor Xa inhibitor, T<sub>1/2</sub>=8-15h, 25-30% unchanged via renal elimination, metabolized mainly by CYP 3A4 & 1A1/2
- TKR: apixaban 2.5mg bid non-inferior to enoxaparin SC<sup>40mg OD or 30mg BID</sup> for major VTE with lower bleeding rates.<sup>3=meta-analysis</sup>
- THR: apixaban 2.5mg bid reduced VTE more than enoxaparin SC<sup>40mg OD</sup> (NNT=41 in 32-38 days) with similar bleeding rates.<sup>4=ADVANCE-3</sup>
- ACS: apixaban 5mg 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 b/c of harm; f/U<sub>median</sub>=241 days<sup>5=APPRAISE-2</sup>
- AF: apixaban 5mg bid was superior to ASA<sup>81-324mg/d</sup> for stroke/systemic embolism (HR=0.45, 95% CI 0.32-0.62, p<0.001, NNT=45) with similar major bleeding/intracranial haemorrhage; study stopped early for benefit, f/U<sub>mean</sub>= 1.1 years<sup>6=AVERROES</sup>
- Highlights of apixaban: more predictable anticoagulation (no required INR monitoring), oral administration, BID dosing, possibly fewer drug/food interactions<sup>than warfarin</sup> (DIs=CYP P450 3A4 inhibitors<sup>strong</sup> = grapefruit, keto/itra/vori/posa-conazole, rifampicin), quick onset of action.
- Limitations of apixaban: lack reversibility (no antidote), awaiting long-term efficacy & safety data, & ↑cost?

## Trial Background

- Randomized, multi-centre 39 countries, non-inferiority & superiority, double-blinded, double-dummy controlled trial (Funded by Bristol-Myers Squibb & Pfizer); allocation concealed; apixaban 5mg or 2.5mg<sup>2</sup> of age≥80, wt≤60kg, Scr≤133umol/L twice daily vs dose-adjusted warfarin (INR 2-3<sup>measured monthly</sup>) to reduce stroke or systemic embolism
- INCLUSION:** Age ≥ 18 yrs; permanent/persistent AF or atrial flutter<sup>ECG at enrolment</sup>, or AF or atrial flutter<sup>ECG or as an episode ≥ 1 minute on rhythm strip/Holter monitor/intracardiac recording on 2 separate occasions at least 2 wks apart in 12 months before enrolment</sup>, ≥ 1 of the following: age≥75 yrs, prior stroke/TIA/systemic embolus, symptomatic HF<sup>within 3 months</sup> or LVEF≤40%, DM or HTN<sup>requiring pharmacological tx</sup>, women<sup>contraception required if childbearing</sup>
- EXCLUSION:** Active alcohol/drug abuse/psychosocial<sup>reasons that make study participation impractical</sup>, AF/atrial flutter due to reversible causes<sup>eg. thyrotoxicosis, pericarditis</sup>, ↑bleeding risk<sup>eg. previous intracranial hemorrhage</sup>, conditions<sup>other than AF</sup> that require chronic anticoagulation<sup>eg. prosthetic mechanical heart valve</sup>, Hb<90g/L; inability to comply with INR monitoring; infective endocarditis<sup>active</sup>; life expectancy ≤ 1yr; ↑liver enzymes<sup>ALT/AST>2xULN or total bilirubin≥1.5xULN</sup>; major surgery<sup>planned</sup>; mitral stenosis<sup>moderate/severe</sup>; planned ablation procedure<sup>AF or atrial flutter</sup>; platelet ≤100,000/mm<sup>3</sup>; recent stroke<sup>within 7 days</sup>; renal insufficiency<sup>Scr>221umol/L or CrCl<25mL/min</sup>; required ASA > 165 mg/d; tx with both aspirin+thienopyridine<sup>clopidogrel, ticlopidine</sup>; uncontrolled HTN<sup>(SBP>180 mmHg or DBP> 100 mmHg)</sup>; or unapproved investigation drug or device in past 30 d
- POPULATION at Baseline** (n=18,201 over 1.8 years): Age<sub>median</sub>=70; ~65%♂; wt<sub>median</sub>=82 kg; SBP<sub>median</sub>=130 mmHg; AF: ~85% persistent/permanent, ~15% paroxysmal; CHADS<sub>2</sub> mean = 2.1, CHADS<sub>2</sub> score 34%≤1, ~36%=2, 30%≥3; 19% hx of stroke/TIA/systemic embolism; 35% HF; 87% HTN; 25% DM; ~14% hx of MI; 31%; age≥75yr; ~17%; hx of bleeding; renal function: CrCl>80mL/min<sup>41%</sup>, CrCl>50-80mL/min<sup>42%</sup>, CrCl>30-50mL/min<sup>15%</sup>, CrCl≤30mL/min<sup>15%</sup>
- Previous med: VKA<sup>57%</sup>; Baseline meds: ACEI<sup>70%</sup>, ASA<sup>31%</sup>, amiodarone<sup>1%</sup>, BB<sup>63%</sup>, CCB<sup>30%</sup>, clopidogrel<sup>1.9%</sup>, digoxin<sup>32%</sup>, gastric antacid drugs<sup>18%</sup>, NSAIDs<sup>8%</sup>, statins<sup>5%</sup>

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

Clinical Endpoints	Apixaban	Warfarin	HR (95% CI)	NNT	Comments
	(n=9120)	(n=9081)			
1 <sup>o</sup> 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	Efficacy of apixaban: ⇒non-inferior/superior to warfarin for 1 <sup>o</sup> ⇒Stroke/hemorrhagic stroke rates lower with apixaban
<b>2<sup>o</sup> Efficacy Endpoints</b>					
Stroke	2.18% {n=199} (1.19%/yr)	2.75% {n=250} (1.51%/yr)	0.79 (0.65-0.95) (p=0.01)	175	⇒All-cause mortality lower with apixaban
Ischemic/uncertain type of stroke	1.78% {n=162} (0.97%/yr)	1.93% {n=175} (1.05%/yr)	NS (p=0.42)	-	
Hemorrhagic stroke	0.44% {n=40} (0.24%/yr)	0.86% {n=78} (0.47%/yr)	0.51 (0.35-0.75) (p<0.001)	238	⇒Warfarin rates of major bleed, intracranial/other/any bleed were higher than apixaban
Systemic embolism	0.16% {n=15} (0.09%/yr)	0.19% {n=17} (0.10%/yr)	NS (p=70)	-	
MI	0.99% {n=90} (0.53%/yr)	1.12% {n=102} (0.61%/yr)	NS (p=0.37)	-	⇒Slightly more pts on ASA in apixaban group (31.3%) vs. 30.5% in warfarin group
All Cause Mortality	6.61% {n=603} (3.52%/yr)	7.37% {n=669} (3.94%/yr)	0.89 (0.80-0.998) (p=0.047)	132	⇒Slightly more pts on NSAIDs in warfarin group (8.5%) vs. 8.2% in apixaban group ⇒Higher d/c rate in warfarin group
<b>Adverse Events based on N=9088 in rivaroxaban arm &amp; N=9052 in warfarin arm</b>					
Major bleed	3.60% {n=327} (2.13%/yr)	5.10% {n=462} (3.09%/yr)	0.69 (0.60-0.80) (p<0.001)	67	⇒Higher d/c rate in warfarin group Other: ⇒69 pts lost to follow up ⇒380 pts (4.7%) had missing data
Intracranial	0.57% {n=52} (0.33%/yr)	1.35% {n=122} (0.80%/yr)	0.42 (0.30-0.58) (p<0.001)	128	⇒Lower dose of apixaban 2.5mg BID in 4.7% (n=428) pts
Other location	3.02% {n=275} (1.79%/yr)	3.76% {n=340} (2.27%/yr)	0.79 (0.68-0.93) (p=0.04)	135	⇒Warfarin group: INR values within 2.0-3.0: 66.0% <sub>median</sub> & 62.2% <sub>mean</sub> of the time
Gastrointestinal	1.15% {n=105} (0.76%/yr)	1.31% {n=119} (0.86%/yr)	NS (p=0.37)	-	
Any bleeding	25.92% {n=2356} (18.1%/yr)	33.80% {n=3060} (25.8%/yr)	0.71 (0.68-0.75) (p<0.001)	13	
<b>Net clinical outcomes</b>					
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) (p<0.001)	61	⇒No significant interactions for 1 <sup>o</sup> ⇒For major bleeding, interaction significant for DM & renal function
Stroke, systemic embolism, major bleeding, or death from any cause	11.10% {n=1009} (6.13%/yr)	12.90% {n=1168} (7.20%/yr)	0.85 (0.78-0.92) (p<0.001)	56	⇒Greater reduction for bleeding in pts who did not have DM (p=0.003) and among pts with moderate or severe renal impairment (≤50mL/min) (p=0.03)
Discontinuation rate	25.3% {3.6%=death}	27.5% {3.8%=death}	p=0.001	45	

ACEI=angiotensin converting enzyme inhibitor ACS=acute coronary syndrome AF=atrial fibrillation ALT=alanine aminotransferase AST=aspartate aminotransferase ASA=acetylsalicylic acid BB=beta blocker CCB=calcium channel blocker CI=confidence interval CKD=chronic kidney disease CNS=central nervous system CrCl=creatinine clearance CYP=cytochrome DBP=diastolic blood pressure d/c=discontinuation DIs=drug interactions DM=diabetes mellitus dx=disease EDS=exceptional drug status ECG=electrocardiogram fu=follow-up GI=gastrointestinal HF=heart failure Hgb=hemoglobin HR=hazard ratio HTN=hypertension Hx=history INR=international normalized ratio ITT=intention-to-treat IV=intravenous LV=left ventricle LVEF=left ventricular ejection fraction MI=myocardial infarction NNT=number needed to treat NNH=number needed to harm NS=not significant NSAIDs=nonsteroidal anti-inflammatory drugs PE=pulmonary embolism PP=per-protocol pts=patients SBP=systolic blood pressure SC=subcutaneous THR=total hip replacement T<sub>1/2</sub>=elimination half-life TIA=transient ischemic attack TKR=total knee replacement tx=treatment ULN=upper limit of normal VKA=vitamin K antagonist VTE=venous thromboembolism yrs=years

## 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 <sup>ACTIVE-W 63.8%, RE-LY 64% ROCKET-AF 55%</sup> • Short study
- Used ITT analysis, PP analysis is generally recommended in non-inferior studies • ~ 31% were on concomitant aspirin tx
- Uncertainties:** • Drug not yet studied in pts with CrCl<25mL/min, Scr>221umol/L or liver disease? • Drug interactions? • Cost of drug?

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

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

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Additional references:

**Rocket-AF, Aristotle & RE-LY: Comparison Tables of Baseline Characteristics**

Baseline	Age median	Male	HT	DM	Prior TIA/S	Prior MI	Time <sub>3pent</sub> INR 2-3	CHADS <sub>2</sub> (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								2.2			
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

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

Results	Stroke or systemic embolism	Ischemic stroke	Hemorrhagic stroke	All cause death	MI/ACS	Major bleed	Intra-cranial bleed	GI bleed	Discontinuance rate
Dabigatran 110 vs warf	NSS 3.0vs3.3%	NSS 2.6vs2.4%	0.2vs0.7% RR 0.31	NSS 7.4vs8.1%	NSS 1.4vs1.0%	5.4vs6.6% RR 0.81	0.4vs1.4% RR 0.31	NSS 2.2vs2.0%	20.7vs16.6%
Dabigatran 150 vs warf	2.2vs3.3% RR 0.67	1.8vs2.4% RR 0.77	0.2vs0.7% RR 0.26	NSS 7.2vs8.1%	1.5vs1.0% RR 1.40?	NSS 6.2vs6.6%	0.6vs1.4% RR 0.41	3.0vs2.0% RR 1.5	21.2vs16.6%
Rivaroxaban vs warf	3.8vs4.3% RR 0.88 <sub>pp</sub>	NSS 2.1vs2.3%	0.4vs0.7% RR 0.58	NSS 2.9vs3.5%	NSS 1.4vs1.8%	NSS 5.6vs5.4%	0.8vs1.2% RR 0.66	NSS 3.2vs2.2%	23.9vs22.4%
Apixaban vs warf	2.3vs2.9% RR 0.80	NSS 1.8vs1.9%	0.4vs0.9% RR 0.51	6.6vs7.4 RR 0.90	NSS 1.0vs1.1%	3.6vs5.1% RR 0.70	0.6vs1.3% RR 0.42	NSS 1.2vs1.3%	25.3vs27.5%

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

NNT NNH	Stroke or systemic embolism	Ischemic stroke	Hemorrhagic stroke	All cause death	MI/ACS	Major bleed	Dyspepsia	GI bleed	Antidote
Dabigatran 110 vs warf			192			77	17 11.8vs5.8%		?
Dabigatran 150 vs warf	88	132	182		239-284?		18 11.3vs5.8%	100	?
Rivaroxaban vs warf	135 <sub>pp</sub>		333						Octaplex
Apixaban vs warf	167		238	132		67			Octaplex?

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 NNH 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

primary endpoint, I would rank it second to last before dabigatran 110mg dosage. Octaplex is an antidote for rivaroxaban and it is available in Canada but it is about \$100/month).

### 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.

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