

# ROCKET-AF: Rivaroxaban vs Warfarin in patients with Atrial Fibrillation (AF)<sup>1, 2</sup>

Rivaroxaban once daily oral direct factor Xa inhibition compared with vitamin K antagonist for prevention of stroke and embolism trial in AF

## Bottomline

- Rivaroxaban non-inferior to warfarin without need for INR monitoring, but with higher drug cost. *Cost Comparison (/month): Warfarin+monitoring (~\$35) vs Rivaroxaban 20mg po daily \$100.*
- In AF: Rivaroxaban significantly reduced risk of hemorrhagic stroke & systemic embolism compared to warfarin
- In AF: Warfarin had more intracranial/fatal/critical bleeding compared to rivaroxaban
- In AF: Rivaroxaban had more transfusions, Hgb ↓ ≥20g/L, GI bleed, epistaxis & hematuria compared to warfarin

## Background

- Rivaroxaban (**Xarelto**®), a factor Xa inhibitor, is EDS on Sask formulary for post-orthopedic surgery VTE prophylaxis was superior to enox 40mg daily in RECORD- trials I<sub>TKA</sub>, II<sub>THA</sub>, & III<sub>TKA</sub> (but not superior to enox 30mg BID in RECORD-IV<sub>TKA</sub>). **Approved** by Health Canada for A. Fib Jan/12.
- Highlights of Rivaroxaban: more predictable anticoagulation (no required INR monitoring), oral administration, OD dosing, possibly fewer drug/food interactions <sup>than warfarin</sup> (DIs=CYP P450 3A4 inhibitors<sup>strong</sup> & P-glycoprotein = carbamazepine, keto/itra/vori/posa-conazole, phenytoin, ritonavir), quick onset of action.
- Limitations of Rivaroxaban: lack reversibility (no antidote <sup>? Octaplex may help</sup>), awaiting long-term efficacy & safety data, & ↑cost.

## Trial Background<sup>3</sup>

- Randomized, multi-centre <sup>45 countries</sup>, non-inferiority & superiority, double-blinded, double-dummy controlled trial (Funded by Johnson & Johnson); allocation concealed; **rivaroxaban 20mg or 15mg** CrCl=30-49 mL/min **once daily vs dose-adjusted warfarin** (INR 2-3<sup>measured ≤4 weeks</sup>) **to reduce stroke or systemic embolism**
- INCLUSION:** Age ≥ 18 yrs, persistent/paroxysmal AF on ≥ 2 episodes<sup>1</sup> documented on EKG within 30 days of enrolment, risk of future stroke (hx of stroke/TIA or systemic embolism) **OR** ≥ 2 of the following: HF or LVEF≤35%, HTN (on BP meds <sup>6 months before</sup> or SBP>140 mmHg or DBP >90 mmHg), age≥75 yr, or DM
- EXCLUSION: Cardiac-related conditions** AF due to reversible disorders, active endocarditis, mitral stenosis, presence of atrial myxoma or LV thrombus, planned cardioversion, prosthetic heart valve, BP ≥ 180/100;
- Hemorrhage risk-related criteria** active internal bleeding, hx of major surgical procedure or trauma within 30 days, GI bleed within 6 months, hx of intracranial/intraocular/spinal/traumatic intraarticular bleeding, chronic hemorrhagic disorder, known intracranial neoplasm, arteriovenous malformation, or aneurysm, planned invasive procedure with potential for uncontrolled bleeding, including major surgery; any **stroke within 14 days; TIA within 3 days;** indication for anticoagulant therapy for a condition other than AF (eg, VTE); tx with ASA>100mg/d, ASA/thienopyridine or IV antiplatelets within 5 days; fibrinolytics within 10 days; anticipated need for long-term tx with NSAID; systemic treatment with a strong inhibitor/inducer of CYP P450 3A4 within 4 days or planned treatment during the study; anemia <sup>Hgb<100g/L</sup>; pregnancy/breastfeeding; HIV; **CrCl<30mL/min**; liver disease or ALT>3x ULN
- POPULATION-Baseline** (n=14,264 in 1.9 years): Age<sub>median</sub>=73; 60.3%♂; BMI<sub>median</sub>≅28 kg/m<sup>2</sup>; BP<sub>median</sub>=130/80mmHg; AF: ~81% persistent, ~17.6% paroxysmal, 1.4% newly diagnosed/onset; CHADS<sub>2</sub>mean = **3.5**, CHADS<sub>2</sub> score ~13% = 2, 43% = 3, 29% = 4, 13% = 5, 2% = 6; 55% hx stroke/TIA; 63% HF; 91% HTN; 40% DM; 17% hx MI; CrCl<sub>median</sub>=67 mL/min { **<21% CrCL 30-49mL/min** <sup>N=2950 (n=1474=apixaban 15mg/d), age=79, 45%♂, BMI=25kg/m<sup>2</sup>, CHADS<sub>2</sub>=3.7, 50% hx of stroke/TIA, 32% DM<sub>1</sub>}; Previous med: ASA<sup>36%</sup>, VKA<sup>62%</sup>; Baseline meds: ~65% BB, 60% diuretics, 55% ACEI, 43% statins, 39% digitalis glycosides, 38% ASA</sup>

## Results: Efficacy & Safety –median duration of tx exposure=590 days (PP), median follow-up of 707 days (ITT)

Clinical Endpoints	Rivaroxaban		Warfarin		HR (95% CI)		NNT/NNH		Comments
	Per-protocol (n=6958)	ITT (n=7081)	Per-protocol (n=7004)	ITT (n=7090)	Per-protocol	ITT	PP	ITT	
<b>1<sup>st</sup> Stroke &amp; systemic embolism</b>	2.70% {n=188} 1.7%/yr	3.80% {n=269} 2.1%/yr	3.44% {n=241} 2.2%/yr	4.32% {n=306} 2.4%/yr	0.79 (0.66-0.96)	0.88 (0.75-1.03) <b>Superior (p=0.12)</b>	135	-	<b>Efficacy of rivaroxaban:</b> => non-inferior to warfarin for 1 <sup>st</sup> => <b>NOT superior</b> for 1 <sup>st</sup> <b>Safety:</b> => Warfarin rates of life-threatening, intracranial/critical/fatal/GI bleeding were higher than rivaroxaban => More transfusions/↓Hgb with rivaroxaban => More epistaxis & hematuria with rivaroxaban <b>Other:</b> => 32 pts lost to follow up => 93 pts excluded (50 rivaroxaban & 43 warfarin) from all efficacy analyses before unblinding because of violations in Good Clinical Practice => Concurrent ASA: more in warfarin (36.2%) vs. rivaroxaban (34.9%) => Warfarin group: INR values within 2.0-3.0 55% of the time => Renal: No dose adjustment post-baseline for changing CrCl; pts with CrCl<30mL/min were required to d/c rivaroxaban <b>Sub-group analyses:</b> => No significant interactions identified/reported => CrCl 30-49mL/min pts had more rates of stroke & major bleeding compared to CrCl≥50mL/min pts => Rivaroxaban 15mg/d results consistent with overall trial in comparison with warfarin
<b>2<sup>nd</sup> Efficacy Endpoints based on N=7061 in rivaroxaban arm and N=7082 in warfarin arm (violating site not used)</b>									
Stroke	2.61% {n=184} (1.65%/yr)	3.12% {n=221} (1.96%/yr)	3.12% {n=221} (1.96%/yr)	3.12% {n=221} (1.96%/yr)	NS (p=0.092)		-	-	
Hemorrhagic stroke	0.41% {n=29} (0.26%/yr)	0.71% {n=50} (0.44%/yr)	0.71% {n=50} (0.44%/yr)	0.71% {n=50} (0.44%/yr)	0.59 (0.37-0.93) (p=0.024)		333	-	
Non-CNS systemic embolism	0.07% {n=5} (0.04%/yr)	0.31% {n=22} (0.19%/yr)	0.31% {n=22} (0.19%/yr)	0.31% {n=22} (0.19%/yr)	0.23 (0.09, 0.61) (p=0.003)		417	-	
MI	1.43% {n=101} (0.91%/yr)	1.78% {n=126} (1.12%/yr)	1.78% {n=126} (1.12%/yr)	1.78% {n=126} (1.12%/yr)	NS (p=0.121)		-	-	
All Cause Mortality	2.95% {n=208} (1.87%/yr)	3.53% {n=250} (2.21%/yr)	3.53% {n=250} (2.21%/yr)	3.53% {n=250} (2.21%/yr)	NS (p=0.073)		-	-	
<b>Adverse Events based on N=7111 in rivaroxaban arm &amp; N=7125 in warfarin arm</b>									
Major bleed Hgb ↓≥20g/L, transfused ≥2units, or symptomatic bleeding critical area or organ	5.6% {n=395} (3.6%/yr)	5.4% {n=386} (3.4%/yr)	5.4% {n=386} (3.4%/yr)	5.4% {n=386} (3.4%/yr)	NS (p=0.58)		-	-	
Hgb ↓≥20g/L	4.3% {n=305} (2.8%/yr)	3.6% {n=254} (2.3%/yr)	3.6% {n=254} (2.3%/yr)	3.6% {n=254} (2.3%/yr)	1.22 (1.03-1.44) (p=0.02)		77	-	
Transfusion	2.6% {n=183} (1.6%/yr)	2.1% {n=149} (1.3%/yr)	2.1% {n=149} (1.3%/yr)	2.1% {n=149} (1.3%/yr)	1.25 (1.01-1.55) (p=0.04)		200	-	
Critical bleeding	1.3% {n=91} (0.8%/yr)	1.9% {n=133} (1.2%/yr)	1.9% {n=133} (1.2%/yr)	1.9% {n=133} (1.2%/yr)	0.69 (0.53-0.91) (p=0.007)		167	-	
Fatal bleeding	0.4% {n=27} (0.2%/yr)	0.8% {n=55} (0.5%/yr)	0.8% {n=55} (0.5%/yr)	0.8% {n=55} (0.5%/yr)	0.50 (0.31-0.79) (p=0.003)		250	-	
Intracranial bleed	0.8% {n=55} (0.5%/yr)	1.2% {n=84} (0.7%/yr)	1.2% {n=84} (0.7%/yr)	1.2% {n=84} (0.7%/yr)	0.67 (0.47-0.93) (p=0.02)		250	-	
GI bleed <sup>upper, lower, rectal</sup>	3.2% {n=224}	2.2% {n=154}	2.2% {n=154}	2.2% {n=154}	P<0.05		100	-	
Epistaxis	10.1% {n=721}	8.6% {n=609}	8.6% {n=609}	8.6% {n=609}	P<0.05		67	-	
Hematuria	4.2% {n=296}	3.4% {n=340}	3.4% {n=340}	3.4% {n=340}	P<0.05		83	-	
Discontinuation rate	23.7%	22.2%	22.2%	22.2%	-		-	-	

ACEI=angiotensin converting enzyme inhibitor AF=atrial fibrillation ALT=alanine aminotransferase ASA=acetylsalicylic acid BB=beta blocker BMI=body mass index CAD=coronary heart disease CI=confidence interval CKD=chronic kidney disease CNS=central nervous system CrCl=creatinine clearance CYP=cytochrome DBP=diastolic blood pressure d/c=discontinue Dis=drug interactions DM=diabetes dx=disease EDS=exceptional drug status EKG=electrocardiogram enox=enoxaparin GI=gastrointestinal Hgb=hemoglobin HIV=human immunodeficiency virus 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 NSAID=nonsteroidal anti-inflammatory drug PE=pulmonary embolism PP=per-protocol pts=patients SBP=systolic blood pressure THR=total hip replacement TIA=transient ischemic attack TKR=total knee replacement tx=treatment ULN=upper limit of normal VKA=vitamin K antagonist VTE=venous thromboembolism

## Strengths, Limitations, & Uncertainties

**Strengths:** ♦ Important clinical endpoints ♦ Both arms blinded ♦ Moderate-high risk for stroke ♦ Used both PP & ITT analysis ♦ Similar d/c rates

**Limitations:** ♦ Warfarin within therapeutic range **only 55%** of the study period <sup>ACTIVE-W 63.8%, RE-LY 64% ARISTOTLE 66%</sup> ♦ Short study

♦ ~ 35% of pts in each arm of the trial were on concomitant aspirin tx ♦ 1 site violated Good Clinical Practice

**Uncertainties:** ♦ Drug not yet studied in pts with CrCl<30 mL/min or liver disease? ♦ Drug interactions? ♦ stroke after rivaroxaban stopped <sup>28days later</sup>

**Rivaroxaban in Atrial Fibrillation Pros & Cons:** Not rivaroxaban if prosthetic heart valve, renal dx <sup>CrCl<30mL/min</sup> or significant liver dx

Pros vs warfarin	Cons vs warfarin
Non-inferior to warfarin for stroke/systemic embolism	Higher drug <b>cost (\$100/month)</b>
Less intracranial/fatal/critical bleeding than warfarin	No antidote with rivaroxaban <sup>? Octaplex may help</sup>
No INR monitoring required	More transfusions, drop in Hgb, epistaxis & hematuria with rivaroxaban
Less clinically significant drug interactions	No long term (greater than 2yr) follow up
	New drug; lacks “real life” data and postmarketing surveillance

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

Baseline	Age median	Male	HT	DM	Prior TIA/S	Prior MI	Time <sub>spent</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	Hemor-rhagic 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	Hemor-rhagic 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 is the cheapest (\$110/month) of the three 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 the most expensive (\$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 it is not available in Canada yet and we don't have a price.

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