PIONEER AF-PCI: Rivaroxaban XARELTO + P2Y12 Inhibitor clopidogrel ~94% or Rivaroxaban + DAPT vs. Warfarin + DAPT in Patients with Atrial Fibrillation & PCI [1]

OPen-Label, Randomized, Controlled, Multicenter Study ExplorIng TwO TreatmeNt StratEgiEs of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention

BOTTOM LINE

In **PIONEER AF-PCI**, patients with AF & PCI who received rivaroxaban 15mg daily + $P2Y_{12}$ inhibitor, or rivaroxaban 2.5mg BID + DAPT:

- Had a lower risk of **clinically significant bleeding** compared to warfarin INR 2-3, mean TTR 65% + DAPT (NNT=11-12)
  - Clinically significant bleeding (major TIMI bleeding, minor TIMI bleeding or bleeding requiring medical attention) was driven by bleeding requiring medical attention (NNT=16-19). Differences in major & minor bleeding were NS.
- Experienced **no difference in major cardiovascular events** (composite of death from CV causes, MI, or stroke) or stent thrombosis compared to warfarin + DAPT → not powered for this outcome, clinical efficacy remains uncertain.
- **PIONEER AF-PCI** does not address the ideal duration of triple therapy, as duration was not randomized & was at the discretion of the clinician (i.e. 1, 6 or 12 months).
- At time of publication, rivaroxaban 2.5mg tablets are not available in Canada. The 10mg, 15mg & 20mg tablets are not scored.

TERMINOLOGY

- **$P2Y_{12}$ inhibitors:** clopidogrel PLAVIX ☎ ▼ ($26/month), ticagrelor BRILINTA ☎ ▼ ($109/month), prasugrel EFFIENT ☎ ⊗ ($100/month)
- **DAPT (dual antiplatelet therapy):** $P2Y_{12}$ inhibitor + ASA (75-100 mg)
- **Dual therapy:** an oral anticoagulant (OAC) + an antiplatelet (e.g. warfarin or rivaroxaban, + ASA)
  - rivaroxaban XARELTO ☎ ✆ ($104/month), warfarin COUMADIN ($15/month)
- **TT (triple therapy)**: an oral anticoagulant + DAPT (e.g. warfarin or rivaroxaban, + clopidogrel + ASA)

BACKGROUND see Table 2 page 3 for a summary of the below trials

- Approximately 5-8% of patients who undergo PCI have AF;[1] unfortunately, there is limited evidence to guide therapy.
- Triple therapy is often used for these patients as DAPT was *inferior* to an OAC for the prevention of AF associated stroke,[ACTIVE-W] but was *superior* to an OAC for the prevention of thrombosis related to coronary stent insertion.[STARS]
- Most of the limited evidence with triple therapy has been with warfarin observational studies, small open-label RCTs.[WOEST, ISAR-TRIPLE]
- The CCS 2016 AF Guidelines suggest using a DOAC in preference to warfarin in patients with non-valvular AF & CAD (conditional recommendation, low-quality evidence), based on an extrapolation of the DOAC vs warfarin AF landmark trials.[ARISTOTLE, RELY, ROCKET-AF]
  - A small percentage (4.5%) of patients from the **RELY** trial (dabigatran) were inadvertently put on triple therapy. For the other two landmark studies,[ARISTOTLE, ROCKET-AF] patients were excluded if they were on clopidogrel.
- Three of the DOACs (apixaban, dabigatran & rivaroxaban) have been studied in triple therapy regimens for secondary ACS prevention; however, the percentage of patients who had concomitant AF was not published.[APPRAISE, ATLAS, REDEEM]
  - Apixaban:[APPRAISE] no benefit, trial stopped early due to increased risk of harm (bleeding)
  - Dabigatran:[REDEEM] no benefit, increased risk of harm (bleeding)
  - Rivaroxaban:[ALTAS] 2.5mg BID x 2yrs ↓ thrombotic events (NNT=63) but ↑ bleed risk (NNH=83); dose is not available
- The **WOEST** study found that dual therapy (warfarin + clopidogrel) x 1yr post coronary stent insertion ↓ bleed risk (NNT=4) versus triple therapy. However, the study was underpowered to assess ischemic endpoints & was small n=573 (69% had AF, ~27% ACS).
- The **PIONEER-AF-PCI** trial is the largest RCT n=2124 to date comparing triple therapy with warfarin vs a DOAC (i.e. rivaroxaban). It also compared dual therapy with rivaroxaban to triple therapy with warfarin.

TRIAL BACKGROUND[1,2,3,4]

DESIGN: randomized, open-label, international 26 countries, multicentre, ITT/mITT trial with concealed allocation. Modified ITT used for all patients who underwent randomization & ≥1 dose of study drug during the tx period. ITT based on data obtained through follow-up. Recruitment: May 2013 to July 2015. Funded by Janssen Scientific Affairs and Bayer Pharmaceuticals (rivaroxaban).

INTERVENTION: patients were randomized to treatment arm, but not to DAPT duration (see Figure on page 2)

- **Group 1 (dual):** rivaroxaban 15mg daily (10 mg daily if CrCl 30-50mL/min) + single antiplatelet tx with $P2Y_{12}$ inhibitor x 12 months
- **Group 2 (TT)**: rivaroxaban 2.5mg BID + DAPT x 1, 6 or 12 months. Step-down: rivaroxaban 15mg + ASA 75-100mg daily until 12 months post-stent.
- **Group 3 (TT)**: warfarin (INR 2-3) + DAPT x 1, 6 or 12 mos. Step-down: warfarin + ASA 75-100mg daily until 12 months post-stent.

INCLUSION: ≥ 18 years of age with **non-valvular AF** (paroxysmal, persistent, or permanent) who had just undergone PCI with stent placement. AF occurred within 1yr before screening, or if >1yr & had been receiving OAC x 3 months immediately preceding PCI.

EXCLUSION: Major exclusion criteria included any condition that contraindicated anticoagulant therapy or would confer an unacceptable risk of bleeding such as: history of stroke or TIA, clinically significant GI bleed within 12 months before randomization, CrCl < 30 mL/min, anemia of an unknown cause with a Hgb < 10g/dL or any condition known to increase the risk of bleeding; current or history of alcohol abuse within the last 6 months; stent thrombosis or stent within a stent in previous year.

POPULATION at baseline: n=2124 patients with AF & recent PCI. No significant differences between groups.

- ♂ (74.4%), mean age 70±9 years, ≥65 years of age (73.7%), ≥75 years of age (34.3%), North America <10%
- Type of index event: stable angina ~48%, unstable angina ~22%, NSTEMI ~18%, ~STEMI 12%; elective PCI 61.5%, urgent PCI 38.5%
- Type of AF: paroxysmal 44.2%, permanent 35%, persistent 20.8%
- Type of stent: DES 66.2%, BMS 31.9%, both DES/BMS 1.9%
- CHA_2DS_2-VASc: score 0-1 (9.5%), score 2-4 (54.7%), score 5-7 (35.9%)
- HAS-BLED: score ≤2 (29.8%), score 3-4 (65.8%), score ≥5 (4.5%)
- Type of $P2Y_{12}$ inhibitor: clopidogrel 94.4%, ticagrelor 4.3%, prasugrel 1.3%
- Proton pump inhibitor: 38%
- CrCl (Cockcroft-Gault): mean 78.8±31mL/min, 30-59mL/min 27.9%, < 30mL/min 0.85%

RESULTS[1,2,3,4]

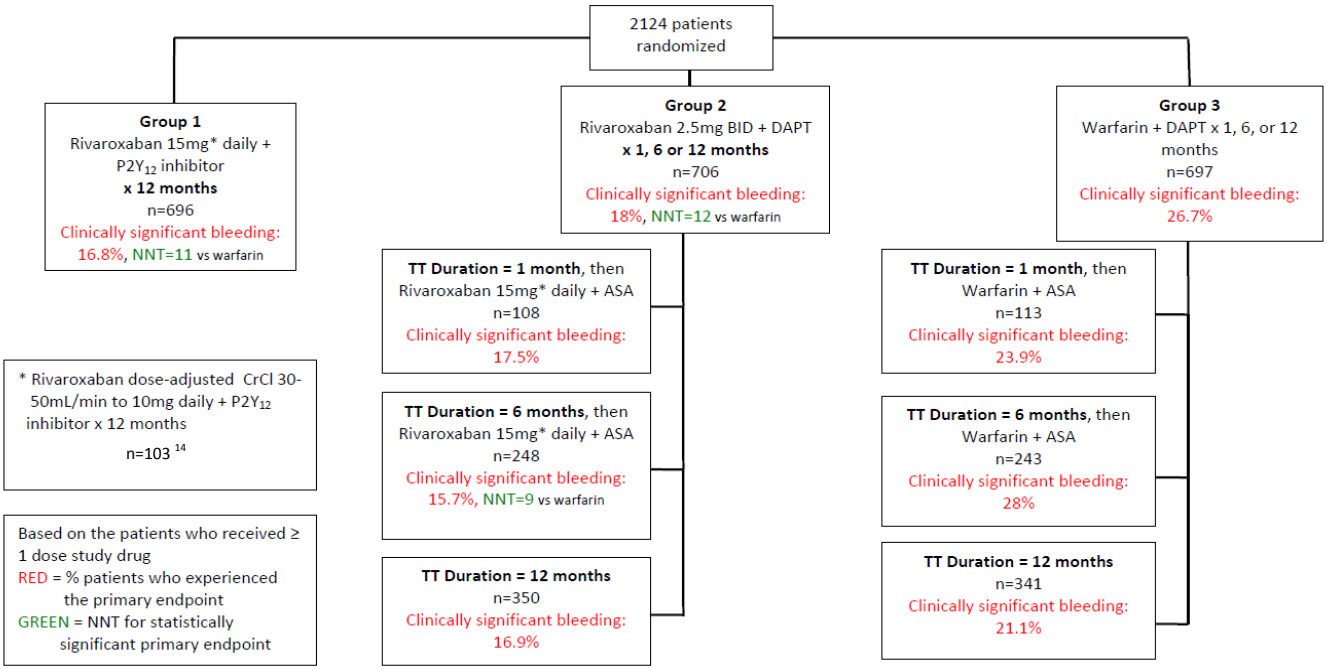
follow-up: 12 months

TABLE 1: SAFETY & EFFICACY

CLINICAL ENDPOINTS	RIVA 15MG DAILY + P2Y12 INHIBITOR N=696	RIVA 2.5MG BID + DAPT N=706	WARFARIN + DAPT N=697	HR (95% CI) VS. WARFARIN + DAPT		NNT/1YR		COMMENTS
				RIVA15 + CLOP75	RIVA2.5 + DAPT	RIVA15 + CLOP75	RIVA2.5 + DAPT	
PRIMARY ENDPOINT								**DAPT Duration (groups 2 & 3):** 1 month: 15.8%; 6 months: 34.9%; 12 months: 49.3% Duration chosen based on type of stent placed and local guidelines (non-randomized) The primary endpoint was similar across duration strata, although only those treated for 6 months had a SS result (HR 0.51, 95% CI (0.34-0.75), p< 0.001), NNT=24 TTR = 65% overall, 60.7%±25.7% in North America (excludes first 14 days of therapy; differences across regions were NS)
Clinically significant bleeding*	16.8% (n=109)	18% (n=117)	26.7% (n=167)	0.59 (0.47-0.76) p<0.001	0.63 (0.50-0.80) p<0.001	11	12	
SECONARY ENDPOINTS								
SAFETY	n=696	n=706	n=697					
Major bleeding[#]	14 (2%)	12 (1.7%)	20 (2.9%)	NS	NS	-		
Fatal bleeds	2 (0.3%)	2 (0.3%)	6 (0.9%)	NS	NS	-		
Minor bleeding[¶]	7 (1%)	7 (1%)	13 (1.9%)	NS	NS	-		
Bleeding requiring medical attention[Δ]	93 (13.4%)	102 (14.4%)	139 (19.9%)	0.61 (0.47-0.80) p<0.001	0.67 (0.52-0.86) p=0.002	16	19	
Early discontinuation^	146 (21%)	149 (21.1%)	205 (29.4%)	p<0.001	p<0.001	12	12	
EFFICACY	n=694	n=704	n=695					
Cardiovascular event (CV death, MI, stroke)	41 (5.9%)	36 (5.1%)	36 (5.2%)	NS	NS	-		
CV death	15 (2.2%)	14 (2.0%)	11 (1.6%)	NS	NS	-		
Myocardial infarction	19 (2.7%)	17 (2.4%)	21 (3.0%)	NS	NS	-		
Stroke	8 (1.2%)	10 (1.4%)	7 (1.0%)	NS	NS	-		
Stent thrombosis	5 (0.7%)	6 (0.9%)	4 (0.6%)	NS	NS	-		
Major adverse CV event or stent thrombosis	41(5.9%)	36 (5.1%)	36 (5.2%)	NS	NS	-		

*Composite endpoint of major and minor bleeding according to TIMI criteria or bleeding requiring medical attention
[#]Defined as intracranial hemorrhage or clinically overt signs of hemorrhage associated with a drop in Hgb ≥ 5 g/dL
[¶]Defined as any clinically overt sign of hemorrhage associated with a fall in Hgb of 3-<5 g/dL
[Δ]Defined as a bleeding event that requires medical tx, surgical tx or laboratory evaluation and does not meet the criteria of major or minor bleeding. Examples of tx: CT or MRI, nasal packing, endoscopy.
^Most common discontinuation reason was due to an adverse effect

Figure: Treatment arms with durations of therapy & primary endpoint results



STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS:

- Important safety endpoint – clinically significant bleeding; medical attention considers patient QOL and health care costs
- Blinded adjudication for efficacy endpoints
- Largest triple therapy study to date, no patients were lost to follow up

LIMITATIONS:

- This study was not powered to evaluate thrombotic events (e.g. stent thrombosis, ischemic stroke).
- Open label design → possible reporting bias. Patients not randomized to triple therapy duration.
- ~10% of patients with CHA_2DS_2VASC scores < 2 were randomized to the study despite some suggestions (CHADS ≤ 1, no anticoagulation or DAPT alone)
- Limited information about other medications taken during the study (NSAIDs, corticosteroids, SSRIs, herbal products)
- Location of bleeds (e.g. gastrointestinal, intracranial) were not reported
- Type of OAC prior to PCI not published

UNCERTAINITIES:

- Clinical efficacy of low-dose rivaroxaban in AF with PCI needs to be established. A post-hoc analysis found that both rivaroxaban groups decreased the primary composite endpoint (all-cause death and rehospitalisation) (NNT=22 and 14 for groups 1 and 2 respectively) compared to standard TT, but when all-cause death was examined alone, it was NS.[4]

continued on next page

UNCERTAINITIES: continued from previous page

- Bleeding events requiring medical attention was defined as any bleeding event that requires medical treatment, surgical treatment or laboratory evaluation, and did not meet criteria for major or minor bleeding. However, details on this endpoint were not provided (e.g. what percentage of events fell under each category – i.e. medical treatment, surgical treatment or laboratory evaluation).
- Some patients may have been clopidogrel non-responders. Without ASA, these individuals in the dual treatment arm are at greater risk of thrombosis.
- Generation of the DES was not provided
- Frequency of INR testing (completed based on local standards), & bleeding events with a reduced INR target (e.g. INR 2-2.5)
- Excluded patients with alcohol abuse in the previous 6 months, but did not exclude patients who drink ≥ 8 drinks/week→ anticoagulation effects (from HASBLED score criteria)
- Safety of other DOACs with DAPT → an increased risk of bleeding has been associated with apixaban 5mg BID and dabigatran 150mg BID when combined with DAPT (**APPRAISE-2** and **REDEEM**)[12,13]

Table 2: Trial Summary Table

	Evidence	Intervention/Endpoints	Results
Rivaroxaban Efficacy	**ROCKET-AF** (n=14,264)	Rivaroxaban **20mg daily** vs. warfarin for prevention of stroke and embolism in AF	Rivaroxaban was non-inferior to warfarin (NNT^{PP}=135) but increased GI bleeds (NNH=100)[8] 38% of patients were also taking ASA <100mg 17% had previous history of MI, but unsure if any patients had prior PCI
	ATLAS-2 (n=15,526)	Rivaroxaban **2.5mg BID or rivaroxaban 5mg BID** vs. placebo for prevention of composite endpoint (CV death, MI or stroke) in patients with ACS	Rivaroxaban regimens significantly reduced composite endpoint (NNT=82 both regimens) Increased risk of bleeding: rivaroxaban 2.5mg NNH= 112 and rivaroxaban 5mg NNH=82 Unknown how many patients had AF Rivaroxaban 2.5mg & 5mg doses not commercially available
TT Trial – efficacy and safety	**WOEST study** (n=573)	Compared bleeding rates of clopidogrel + warfarin (**INR 2-3)** vs. warfarin + DAPT x 12 months	Clopidogrel + warfarin decreased the risk of bleeding vs. warfarin + DAPT (NNT=4). No differences in secondary endpoints (death, MI, stroke, revascularization, or stent thrombosis)→study was underpowered 69% of patients had AF, 27.5% had ACS and 20% were non-ACS with elective PCI
Duration	**ISAR-TRIPLE** (n=606)	6 week and 6 month tx durations with TT (INR 2-2.5) post PCI Primary composite endpoint of death, MI, stent thrombosis, stroke or TIMI bleeding at 9 months	No differences in primary endpoint between tx durations 83.9% of patients had AF or flutter, 2/3 patients had stable ACS and the majority had new DES.[11] INR values were within therapeutic range in 66.2% of patients
	CCS' 2016 AF Guidelines	Conditionally recommend TT for 3-6 months in patients with AF and PCI for NSTEACS/STEMI at risk of stroke (age ≥ 65 or $CHADS_2$ ≥ 1) (low-quality evidence)[5].	

RxFILES RELATED LINKS

1. RxFiles Dual Antiplatelet & Triple Therapy Chart: http://www.rxfiles.ca/rxfiles/uploads/documents/DAPT%20and%20Triple%20Therapy%20Newsletter%20and%20Chart.pdf
2. RxFiles ACTIVE-W Trial Summary: http://www.rxfiles.ca/rxfiles/uploads/documents/ACTIVE-A-Trial-Summary.pdf
3. RxFiles Rocket-AF Trial Summary: http://www.rxfiles.ca/rxfiles/uploads/documents/ROCKET-AF-Rivaroxaban.pdf

☎=EDS in SK ✆=NIHB prior approval ⊗=not covered by NIHB ▼=covered by NIHB ♂=male **ACS**=acute coronary syndrome **ASA**=acetylsalicylic acid **BMS**=bare-metal stent **CABG**=coronary artery bypass graft **CI**=confidence interval **CrCl**=creatinine clearance CV=cardiovascular **DAPT**=dual antiplatelet therapy **DES**=drug-eluting stent **DOAC**=direct oral anticoagulant **EDS**=exception drug **G_1DES**=1st generation DES **GI**=gastrointestinal **Hgb**=hemoglobin **HR**=hazard ratio status **INR**=international normalized **ITT**=intention to treat **MI**=myocardial infarction **NNT**=number needed to treat **NNH**=number needed to harm **NS**=non-statistically significant **NSAID**=nonsteroidal anti-inflammatory drug **NSTEMI**=non-ST elevated MI **P2Y12 inhibitor**=platelet receptor inhibitor **PP**=per-protocol **PCI**=percutaneous coronary intervention **QOL**=quality of life **STEMI**=ST elevated MI **TT**=triple therapy **TTR** =time in therapeutic range **tx**=treatment

ACKNOWLEDGEMENTS: Contributors & Reviews: Dr. Colin Pearce (Interventional Cardiologist, SHR), Loren Regier, & Brent Jensen. **Prepared By**: Andrea Tang, Lynette Kosar

REFERENCES

1. Gibson CM, Mehran R, Bode C, et al; Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI (**PIONEER AF-PCI**). N Eng J Med. 2016 Nov 16; online access only.
2. Gibson CM, Mehran R, Bode C, et al; Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI (**PIONEER AF-PCI**) - Protocol. N Eng J Med. 2016 Nov 16; online access only.
3. Gibson CM, Mehran R, Bode C, et al; Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI (**PIONEER AF-PCI**) - Supplementary Appendix. N Eng J Med. 2016 Nov 16; online access only.
4. Gibson CM, Mehran R, Bode C, et al; An open-label, randomized, controlled, multicenter study exploring two treatment strategies of rivaroxaban and a dose-adjusted oral vitamin k antagonist treatment strategy in subjects with atrial fibrillation who undergo percutaneous coronary intervention (PIONEER AF-PCI). American Heart Journal. 2014 Dec 17;169(4):472-8.
5. Macle L, Carins J, Leblanc K, et al; 2016 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation. Can J of Cardiology. 2016 Jul 28;32:1170-85.
6. Kosar L, Koziol K, Martens A, Shmyr D. Making Goldilocks Happy – Not too short, not too long, but JUST RIGHT. RxFiles Newsletter. 2016 Mar. Available online: http://rxfiles.ca/rxfiles/uploads/documents/DAPT%20and%20Triple%20Therapy%20Newsletter%20and%20Chart.pdf.
7. Bareham J, Regier L, Jensen B, Kielly J. ACTIVE W: Clopidogrel + ASA vs. oral anticoagulation (VKA) for Atrial Fibrillation. RxFiles Trial Summary. 2009 Sept. Available online: http://www.rxfiles.ca/rxfiles/uploads/documents/ACTIVE-A-Trial-Summary.pdf.
8. Jin M, Kosar L. ROCKET-AF: Rivaroxaban vs. Warfarin in patients with Atrial Fibrillation. RxFiles Trial Summary. 2012 Dec. Available online: http://www.rxfiles.ca/rxfiles/uploads/documents/ROCKET-AF-Rivaroxaban.pdf.
9. Mega JL, Braunwald E, Wiviott SD, et al; Rivaroxaban in Patients with a Recent Acute Coronary Syndrome (**ATLAS ACS 2-TIMI 51**). N Eng J Med. 2012;366:9-19.
10. Dewilde WJM, Oirbans T, Verheugt FWA, et al; Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial (**WOEST**). Lancet. 2013 Mar 30;381:1107-15.
11. Fiedler KA, Maeng M, Mehilli J, et al; Duration of Triple Therapy in Patients Requiring Oral Anticoagulation After Drug-Eluting Stent Implantation (**ISAR-TRIPLE**). Journal of the American College of Cardiology. 2015 Apr 28;65(16):1619-29.
12. Alexander JH, Lopes RD, James S, et al; Apixaban with Antiplatelet Therapy after Acute Coronary Syndrome (**APPRAISE-2**). N Eng J Med. 2011;365:699-708.
13. Oldgren J, Budaj A, Granger C, et al; Dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial (**REDEEM**). European Heart Journal. 2011;32:2781-9.
14. Bayer. Data on file. PIONEER AF-PCI Clinical Study Report.