PIONEER AF-PCI: Rivaroxaban XARELTO + P2Y₁₂ Inhibitor clopidogrel ~94% or Rivaroxaban + DAPT vs.

Warfarin + DAPT in Patients with Atrial Fibrillation & PCI

OOpen-Label, Randomized, Controlled, Multicenter Study Exploring TwO TreatmeNT StrategEies 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 + P2Y₁₂ 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

- P2Y₁₂ inhibitors: clopidogrel ($26/month), ticagrelor ($109/month), prasugrel ($100/month)
- DAPT (dual antiplatelet therapy): P2Y₁₂ 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; unfortunately, there is limited evidence to guide therapy.
- Triple therapy is often used for these patients as DAPT was prevention; however, the percentage of patients who had concomitant AF was not published.
- Three of the DOACs (apixaban, dabigatran & rivaroxaban) have been studied in triple therapy regimens for secondary ACS; however, the percentage of patients who had concomitant AF was not published.

TRIAL BACKGROUND

- Group 1 (dual): rivaroxaban 15mg daily (10 mg daily if CrCl 30-50mL/min) + single antiplatelet tx with P2Y₁₂ 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.

- female (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%, persistent 35%, persistent 20.8%
- Type of stent: DES 66.2%, BMS 31.9%, both DES/BMS 1.9%
- CHADS₂-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 P2Y₁₂ inhibitor: clopidogrel 94.4%, ticagrelor 4.3%, prasugrel 1.3%
- Proton pump inhibitor: 38%
- CrCl (Cockcroft-Gault): mean 78.±31mL/min, 30-59mL/min 27.9%, < 30mL/min 0.85%
RESULTS 1,2,3,4

follow-up: 12 months

TABLE 1: SAFETY & EFFICACY

<table>
<thead>
<tr>
<th>CLINICAL ENDPOINTS</th>
<th>RIVA 15MG DAILY + P2Y12 INHIBITOR N=696</th>
<th>RIVA 2.5MG BID + DAPT N=706</th>
<th>WARFARIN + DAPT N=697</th>
<th>HR (95% CI) VS. WARFARIN + DAPT</th>
<th>NNT/1YR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIMARY ENDPOINT</td>
<td></td>
<td></td>
<td></td>
<td>RIVA15 + CLOP75</td>
<td>RIVA2.5 + DAPT</td>
</tr>
<tr>
<td>Clinical significantly bleeding*</td>
<td>16.8% (n=109)</td>
<td>18% (n=117)</td>
<td>26.7% (n=167)</td>
<td>0.59 (0.47-0.76)</td>
<td>0.63 (0.50-0.80)</td>
</tr>
<tr>
<td>SAFETY</td>
<td>n=696</td>
<td>n=706</td>
<td>n=697</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleedinga</td>
<td>14 (2%)</td>
<td>12 (1.7%)</td>
<td>20 (2.9%)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>2 (0.3%)</td>
<td>2 (0.3%)</td>
<td>6 (0.9%)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Minor bleedinga</td>
<td>7 (1%)</td>
<td>7 (1%)</td>
<td>13 (1.9%)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Bleeding requiring medical attentiona</td>
<td>93 (13.4%)</td>
<td>102 (14.4%)</td>
<td>139 (19.9%)</td>
<td>0.61 (0.47-0.80)</td>
<td>0.67 (0.52-0.86)</td>
</tr>
<tr>
<td>Early discontinuationa</td>
<td>146 (21%)</td>
<td>149 (21.1%)</td>
<td>205 (29.4%)</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>EFFICACY</td>
<td>n=694</td>
<td>n=704</td>
<td>n=695</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular event (CV death, MI, stroke)</td>
<td>41 (5.9%)</td>
<td>36 (5.1%)</td>
<td>36 (5.2%)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>CV death</td>
<td>15 (2.2%)</td>
<td>14 (2.0%)</td>
<td>11 (1.6%)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>19 (2.7%)</td>
<td>17 (2.4%)</td>
<td>21 (3.0%)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Stroke</td>
<td>8 (1.2%)</td>
<td>10 (1.4%)</td>
<td>7 (1.0%)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>5 (0.7%)</td>
<td>6 (0.9%)</td>
<td>4 (0.6%)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Major adverse CV event or stent thrombosis</td>
<td>41(5.9%)</td>
<td>36 (5.1%)</td>
<td>36 (5.2%)</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Composite endpoint of major and minor bleeding according to TIMI criteria or bleeding requiring medical attention
aDefined as intracranial hemorrhage or clinically overt signs of hemorrhage associated with a drop in Hgb ≥ 5 g/dL
bDefined as any clinically overt sign of hemorrhage associated with a fall in Hgb of 3−<5 g/dL
cDefined 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.
dMost 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 CHA2DS2VASC scores < 2 were randomized to the study despite some suggestions (CHA2DS ≤ 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

UNCERTAINTIES: continued on next page

- 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.
### Table 2: Trial Summary Table

<table>
<thead>
<tr>
<th>Evidence</th>
<th>Intervention/Endpoints</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rivaroxaban Efficacy</strong></td>
<td>Rivaroxaban 20mg daily vs. warfarin for prevention of stroke and embolism in AF</td>
<td>Rivaroxaban was non-inferior to warfarin (NNT=135) but increased GI bleeds (NNH=100). 38% of patients were also taking ASA &lt;100mg/17% had previous history of MI, but unsure if any patients had prior PCI</td>
</tr>
<tr>
<td><strong>ATLAS-2</strong> (n=15,526)</td>
<td>Rivaroxaban 2.5mg BID or rivaroxaban 5mg BID vs. placebo for prevention of composite endpoint (CV death, MI or stroke) in patients with ACS</td>
<td>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 &amp; 5mg doses not commercially available</td>
</tr>
<tr>
<td><strong>TT Trial – efficacy and safety</strong></td>
<td>Compared bleeding rates of cilopidogrel + warfarin (INR 2-3) vs. warfarin + DAPT x 12 months</td>
<td>Cilopidogrel + 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</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>6 week and 6 month tx durations with TT (INR 2-2.5) post PCI</td>
<td>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. INR values were within therapeutic range in 66.2% of patients</td>
</tr>
<tr>
<td><strong>CCS’ 2016 AF Guidelines</strong></td>
<td>Conditionally recommend TT for 3-6 months in patients with AF and PCI for NSTEACS/STEMI at risk of stroke (age ≥ 65 or CHADS2 ≥ 1) (low-quality evidence)</td>
<td></td>
</tr>
</tbody>
</table>

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

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