TRITON-TIMI 38: Prasugrel **EFFIENT** vs Clopidogrel **PLAVIX** in Patients with ACS

**BOTTOM LINE**
- In patients without a history of stroke/TIA, prasugrel may benefit those with a high risk of thrombosis & a low risk of bleeding.
- In **TRITON-TIMI 38**, patients with moderate to high-risk ACS **76% NSTEACS undergoing PCI** treated with a P2Y12 inhibitor × 14.5 months:
  - Prasugrel ↘ risk of CV death, nonfatal MI, & nonfatal stroke (NNT=46), which was primarily driven by nonfatal MI (NNT=44)
    - No difference in mortality (CV or all-cause) or stroke
  - Prasugrel also ↘ risk of urgent target-vessel revascularization (NTT=84) & stent-thrombosis (NTT=77) significant for DES & BMS subgroups
  - But prasugrel ↑ risk of bleeding: major non-CABG TIMI (NNT=167), life-threatening (NNT=200) & fatal bleeding (NNT=334)
- Post hoc analysis of subgroups with net clinical harm or no net benefit:
  - **History of stroke/TIA resulted in net harm**: CV death, MI, stroke & major bleeding non-CABG related (including ↑ risk of intracranial bleeding) NNT=15
  - Age ≥75, weight <60 kg & history of stroke/TIA: no net benefit
- Based on **TRITON-TIMI 38** results, the **2012 Canadian Cardiovascular Society Antiplatelet Guidelines** recommend the following:
  - **NSTEACS + PCI**: Prasugrel 10mg daily (or ticagrelor) preferred over clopidogrel 75mg daily × 12 months in addition to ASA 81mg daily in P2Y12 inhibitor naive patients after coronary anatomy has been defined & PCI planned.
    - Avoid prasugrel in patients with previous stroke/TIA or in patients who are not treated with PCI. Except in patients with a high probability of underdoign PCI, avoid prasugrel before coronary anatomy has been defined.
  - **STEMI + PCI**: Prasugrel 10mg daily (or ticagrelor) preferred over clopidogrel 75mg daily × 12 months in addition to ASA 81mg daily after primary PCI.
    - Avoid prasugrel in patients with a previous stroke/TIA and use a 5mg dose if required in patients ≥75 years old or weigh <60kg.
- At time of publication, prasugrel **EFFIENT** $100/month vs clopidogrel **PLAVIX** $26/month.

**BACKGROUND**
- DAPT with ASA + P2Y12 inhibitor is recommended after ACS with PCI to prevent thrombotic complications.
- Benefits of DAPT with ASA + clopidogrel have been established for patients with ACS and those undergoing PCI, however, some patients have recurrent CV events while receiving this standard therapy.
- Prasugrel inhibits ADP induced platelet aggregation more rapidly, more consistently, and to a greater extent than standard doses of clopidogrel (in healthy volunteers and patients with CAD, including those undergoing PCI).3
- Of note, subsequent to the **TRITON-TIMI 38** study, the **TRILOGY** trial compared prasugrel to clopidogrel in NSTEACS without revascularization. There was no difference in efficacy or safety outcomes between the two groups, and it therefore not recommended in patients who are not undergoing PCI.4

**TRIAL BACKGROUND**
- **INTERVENTION**: prasugrel 60 mg LD followed by 10 mg daily vs clopidogrel 300 mg LD followed by 75 mg daily, + ASA x 14.5 months
- **INCLUSION**: ≥18 years old with ACS & planned PCI
  - NSTEACS: ischemic symptoms lasting ≥10 minutes & occurring within 72hr before randomization, a TIMI risk score of ≥3, & either ST-segment deviation of ≥1 mm or elevated levels of cardiac biomarker of necrosis
  - STEMI: ischemic symptoms onset within 12hr of randomization if undergoing primary PCI or 12hr to 14 days after symptom onset if primary PCI was not planned
- **EXCLUSION**: Any thienopyridine use within 5 days of randomization, cardiogenic shock, recent fibrinolytic, bleeding diathesis, pathologic intracranial findings, anemia, thrombocytopenia, pregnant

**POPULATION**
- n=13,608, NSTEACS (74%, n=10,074) & STEMI (26% n=3,534)
  - Median age 61yr (IQR 53-69yr), 13% ≥75yr, ~25% female 25% prasugrel vs 27% clopidogrel, p=0.02, median BMI 28kg/m², 92.5% Caucasian, ~32% from North America
  - 99% had PCI at time of randomization (1% had CABG), ~95% received ≥1 stent (47% at least 1 DES, 48% BMS)
  - Index hospitalization: ~99% ASA, ~92% statin, ~88% beta blocker, ~75% ACEI or ARB 76% prasugrel vs 75% clopidogrel, p=0.03, ~18% CCB
  - 64% HTN, 56% hypercholesterolemia, 38% tobacco use, 23% DM, 18% previous MI, 7.5% previous CABG, 11.5% CrCl<60 mL/min

**RESULTS**

**TABLE 1: EFFICACY**

<table>
<thead>
<tr>
<th>PRIMARY ENDPOINTS</th>
<th>PRASUGREL 60 MG LD THEN 10 MG DAILY</th>
<th>CLOPIDOGREL 300 MG LD THEN 75 MG DAILY</th>
<th>HR (95% CI)</th>
<th>P VALUE</th>
<th>NNT/NNH 14.5 MONTHS</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, nonfatal MI, nonfatal stroke</td>
<td>643 (9.9%)</td>
<td>781 (12.1%)</td>
<td>0.81 (0.73-0.90)</td>
<td>&lt;0.001</td>
<td>46</td>
<td>Primary outcome driven by nonfatal MI</td>
</tr>
<tr>
<td>SECONARY ENDPOINTS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from CV causes</td>
<td>133 (2.1%)</td>
<td>150 (2.4%)</td>
<td>0.89 (0.70-1.12)</td>
<td>NS</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>475 (7.3%)</td>
<td>620 (9.5%)</td>
<td>0.76 (0.67-0.85)</td>
<td>&lt;0.001</td>
<td>44</td>
<td>Primary outcome driven by nonfatal MI</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>61 (1.0%)</td>
<td>60 (1.0%)</td>
<td>1.02 (0.71-1.45)</td>
<td>NS</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>68 (1.1%)</td>
<td>142 (2.4%)</td>
<td>0.48 (0.36-0.64)</td>
<td>&lt;0.001</td>
<td>72</td>
<td>Primary outcome driven by nonfatal MI</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>188 (3.0%)</td>
<td>197 (3.2%)</td>
<td>0.95 (0.78-1.16)</td>
<td>NS</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Urgent target-vessel revascularization</td>
<td>156 (2.5%)</td>
<td>233 (3.7%)</td>
<td>0.66 (0.54-0.81)</td>
<td>&lt;0.001</td>
<td>84</td>
<td>Primary outcome driven by nonfatal MI</td>
</tr>
</tbody>
</table>

**median follow up: 14.5 months**
TABLE 2: SAFETY & NET CLINIC BENEFIT

<table>
<thead>
<tr>
<th>SAFETY ENDPOINTS (TIMI Bleeding Criteria)</th>
<th>PRASUGREL 60 MG FOLLOWED BY 10 MG DAILY n=6741</th>
<th>CLOPIDOGREL 300 MG FOLLOWED BY 75 MG DAILY n=6716</th>
<th>HR (95% CI)</th>
<th>P VALUE</th>
<th>NNT/NNH 14.5 MONTHS</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-CABG related major bleed (primary safety endpoint)</td>
<td>146 (2.4%)</td>
<td>111 (1.8%)</td>
<td>1.32 (1.03-1.68)</td>
<td>0.03</td>
<td>167</td>
<td>Safety endpoints included patients who received ≥1 doses of the study drug</td>
</tr>
<tr>
<td>CABG-related major bleed</td>
<td>24 (13.4%)</td>
<td>6 (3.2%)</td>
<td>OR=4.73 (1.90-11.82)</td>
<td>&lt;0.001</td>
<td>10</td>
<td>Discontinuation of study drug due to adverse events not related to bleeding was NS</td>
</tr>
<tr>
<td>Bleeding requiring transfusion</td>
<td>244 (4.0%)</td>
<td>182 (3.0%)</td>
<td>1.31 (1.11-1.63)</td>
<td>&lt;0.001</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Life threatening bleed</td>
<td>85 (1.4%)</td>
<td>56 (0.9%)</td>
<td>1.52 (1.08-2.13)</td>
<td>0.01</td>
<td>200</td>
<td></td>
</tr>
<tr>
<td>Fatal bleed</td>
<td>21 (0.4%)</td>
<td>5 (0.1%)</td>
<td>4.19 (1.58-11.11)</td>
<td>0.002</td>
<td>334</td>
<td></td>
</tr>
<tr>
<td>Intracranial bleed</td>
<td>19 (0.3%)</td>
<td>17 (0.3%)</td>
<td>1.12 (0.58-2.15)</td>
<td>NS</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Discontinuation due to bleeding</td>
<td>2.5%</td>
<td>1.4%</td>
<td>-</td>
<td>&lt;0.001</td>
<td>91</td>
<td></td>
</tr>
</tbody>
</table>

SUBGROUP ANALYSES: NET CLINIC BENEFIT

<table>
<thead>
<tr>
<th>Safety endpoints</th>
<th>Primary Endpoint: CV death, nonfatal MI, nonfatal stroke</th>
<th>HR (95% CI)</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-CABG related TIMI major bleeding</td>
<td>47/262 (19.1%)</td>
<td>35/256 (14.4%)</td>
<td>1.37 (0.89-2.13)</td>
</tr>
<tr>
<td>Death from any cause, nonfatal MI, nonfatal stroke, or non-CABG-related nonfatal TIMI major bleed</td>
<td>14/257 (5%)</td>
<td>6/252 (2.4%)</td>
<td>1.46 (0.74-2.91)</td>
</tr>
<tr>
<td>Death from any cause, nonfatal MI, nonfatal stroke, or non-CABG-related nonfatal TIMI major bleed</td>
<td>57/262 (23%)</td>
<td>39/256 (16%)</td>
<td>1.54 (1.02-2.32)</td>
</tr>
</tbody>
</table>

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS:
- First major study comparing prasugrel to clopidogrel in patients representative of the full spectrum of ACS undergoing PCI.
- Important clinical endpoints (e.g. cardiovascular death, MI, bleeding) with blinded adjudication of outcomes.
- Study population size met requirements for 90% power.
- Only 0.1 % of patients lost to follow up

LIMITATIONS:
- Primary endpoint a composite with only one component (MI) driving the results.
- Baseline use of PPI was not stated.

UNCERTAINTIES:
- Higher rate of colon cancer identified in prasugrel group but cannot rule out either causative effect or chance.
- DAPT study identified more cancer related deaths in patients with extended thienopyridine therapy than standard, which may have been influenced by a higher number of patients with known cancer before enrollment in the intervention group.6
- The loading dose for clopidogrel was 300mg, versus 600mg.
- Stent thrombosis, as defined by the Academic Research Consortium, was reported as definite/probable (unclear what % was definite).
- Unclear if allocation was concealed
ACKNOWLEDGEMENTS: Prepared By: Karolina Koziol, Lynette Kosar, Brent Jensen, Loren Regier

DISCLAIMER: The content of this newsletter represents the research, experience and opinions of the authors and not those of the Board or Administration of Saskatoon Health Region (SHR). Neither the authors nor Saskatoon Health Region nor any other party who has been involved in the preparation or publication of this work warrants or represents that the information contained herein is accurate or complete, and they are not responsible for any errors or omissions or for the result obtained from the use of such information. Any use of the newsletter will imply acknowledgment of this disclaimer and release any responsibility of SHR, its employees, servants or agents. Readers are encouraged to confirm the information contained herein with other sources. Additional information and references online at www.RxFiles.ca Copyright 2016 – RxFiles, Saskatoon Health Region (SHR)

References: