PLATO: Ticagrelor BRILLINTA vs Clopidogrel PLAVIX in Acute Coronary Syndrome

PLATelet inhibition and patient Outcomes trial

BOTTOM LINE
- Patients with a high risk of thrombosis & low risk of bleeding may benefit from ticagrelor. Caution in those with a history of COPD, asthma, HF, gout & severe renal impairment due to increased risk of dyspnea & elevated uric acid & creatinine.

- In PLATO, ACS patients ~50% NSTEACS who received ticagrelor + ASA, versus clopidogrel + ASA, for a median of 9 months had:
  - ↓ risk composite of death from vascular causes, MI, stroke (NNT=53)
  - ↓ risk of non-CABG related major bleeding (NNH=167) & fatal bleeding, non-intracranial NNH=500, intracranial NNH=1112
  - ↑ risk of dyspnea (NNH=17), & premature discontinuation of therapy (NNH=53)

- Based on the PLATO results, the 2012 Canadian Cardiovascular Society Antiplatelet Guidelines recommend the following: Ticagrelor + ASA 81mg daily is preferred over clopidogrel + ASA 81mg daily x 12 months for:
  - STEMI with primary PCI
  - NSTEACS (medical management or revascularization)

- At time of publication, ticagrelor BRILLINTA $108/month vs clopidogrel PLAVIX $26/month.

BACKGROUND
- Dual antiplatelet therapy (DAPT, i.e. ASA + clopidogrel/prasugrel/ticagrelor) is recommended after ACS (STEMI or NSTEACS) to reduce the risk of thrombosis.
  - Prior to PLATO, clopidogrel PLAVIX & prasugrel EFFIENT demonstrated a reduction in a composite endpoint of CV mortality, MI or stroke (always driven by a reduction in MI) with an associated increased risk in major bleeding.
    - Clopidogrel, however, has inter-individual genetic variability that may result in poor antiplatelet response in some patients, irreversable antiplatelet effect, and a slower onset.
    - Prasugrel reduced CV mortality, MI or stroke more than clopidogrel, but it also increased the risk of major bleeding (including life-threatening and fatal bleeds). Prasugrel also resulted in net harm in those with a history of stroke/TIA and no net benefit was found in those ≥75yrs and ≤60kg.

- Compared to clopidogrel and prasugrel, ticagrelor is not a pro-drug and is a reversible P2Y12 inhibitor, resulting in more favourable pharmacokinetic effects such as rapid onset, offset, and lower inter-individual response.

TRIAL BACKGROUND

- INCLUSION: ≥18yrs, hospitalized for ACS with onset during previous 24 hours
  - NSTEACS: ≥2 had to be met: a) ST segment changes indicating ischemia, b) positive biomarker, c) ≥1 risk factor: ≥60yrs, prior MI or CABG, CAD ≥50% stenosis in ≥2 vessels, prior ischemic stroke/TIA, carotid stenosis, cerebral revascularization, DM, PAD, CKD
  - STEMI: both ST-segment elevation ≥0.1mV & planned primary PCI

- EXCLUSION: Pregnant, CI to clopidogrel, use of fibrinolytic therapy <24 hrs before randomization, need for OAC, ↑ risk of bradycardia, strong CYP3A inhibitor/inducer, dialysis, clinically important thrombocytopenia or anemia

- POPULATION: at baseline: n=18,624, NSTEACS (~60% NSTEACS 42.7%, UA 16.7%, n=11,067) & STEMI (37.7%, n=7026)
  - Mean age 62yrs, ~15% ≥75yrs, 28% female, ~92% Caucasian, ~2% from Canada; median body weight 80 kg, BMI 27 kg/m²
  - ~65% HTN, ~46% dyslipidemia, ~36% smoker, ~25% DM, ~15% dyspnea, ~6% COPD, 5.5% HF, ~4% CKD, ~3% asthma, ~3% gout

- ~20% prior MI, ~13% prior PCI, ~6% prior CABG
- ~89% statin, ~89% beta blocker, ~75% ACEI, ~12% ARB, ~45% on PPI
- During the trial, 64% PCI (42% BMS, 18% DES), 10% CABG
- Clopidogrel LD: 60% received 300mg, 20% received 600mg
  - 46% of ticagrelor arm also received open-label clopidogrel LD prior to randomization (in addition to ticagrelor LD).
- ASA dose: overall, 97.5% 75-100 mg daily. 9.7% from North America; ~50% of the US sites: median ASA dose of 60mg.

RESULTS

TABLE 1: EFFICACY (ITT ANALYSIS)

<table>
<thead>
<tr>
<th>CLINICAL ENDPOINTS</th>
<th>TICAGRELOR 90 MG BID</th>
<th>CLOPIDOGREL 75 MG DAILY</th>
<th>HR (95% CI)</th>
<th>ARR</th>
<th>NNT / 9 MONTHS</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIMARY EFFICACY ENDPOINT</td>
<td>Death from vascular causes, MI or stroke</td>
<td>9.8%</td>
<td>11.7%</td>
<td>0.84 (0.77-0.92)</td>
<td>1.9%</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>MI</td>
<td>5.8%</td>
<td>6.9%</td>
<td>0.84 (0.75-0.95)</td>
<td>1.1%</td>
<td>91</td>
</tr>
<tr>
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<td>Stroke</td>
<td>1.5%</td>
<td>1.3%</td>
<td>1.17 (0.91-1.52)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Death from any cause</td>
<td>4.5%</td>
<td>5.9%</td>
<td>0.78 (0.69-0.89)</td>
<td>1.4%</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>Death from any cause, MI, or stroke</td>
<td>10.2%</td>
<td>12.3%</td>
<td>0.84 (0.77-0.92)</td>
<td>2.1%</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>Death from vascular causes, MI, stroke in subgroup with planned invasive tx</td>
<td>8.9%</td>
<td>10.6%</td>
<td>0.84 (0.75-0.94)</td>
<td>1.7%</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td>Death from vascular causes, MI, stroke, severe recurrent ischemia, recurrent ischemia, TIA or arterial thrombotic event</td>
<td>14.6%</td>
<td>16.7%</td>
<td>0.88 (0.81-0.95)</td>
<td>2.1%</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>Stent thrombosis (definite)</td>
<td>1.3%</td>
<td>1.9%</td>
<td>0.67 (0.5-0.91)</td>
<td>0.6%</td>
<td>167</td>
</tr>
</tbody>
</table>
TABLE 2: ADVERSE EVENTS AND LAB ABNORMALITIES

<table>
<thead>
<tr>
<th>OUTCOME OR ENDPOINT</th>
<th>TICAGRELOR 90 MG BID n=9235</th>
<th>CLOPIDOGREL 75 MG DAILY n=9186</th>
<th>HR (95% CI)</th>
<th>ARI</th>
<th>NNH / 9 MONTHS</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal non-intracranial bleeding</td>
<td>0.1%</td>
<td>0.3%</td>
<td>RR 0.33</td>
<td>0.2%</td>
<td>500</td>
<td>NS differences in the following:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- major bleeding (trial or TIMI criteria)</td>
</tr>
<tr>
<td>Fatal intracranial bleeding</td>
<td>0.1%</td>
<td>0.1%</td>
<td>RR 10</td>
<td>0.09%</td>
<td>1112</td>
<td>- bleeding requiring transfusion</td>
</tr>
<tr>
<td>Non-CABG major bleeding (trial criteria)</td>
<td>4.5%</td>
<td>3.8%</td>
<td>1.19 (1.02-1.38)</td>
<td>0.7%</td>
<td>143</td>
<td>- life-threatening or fatal bleeding (study criteria)</td>
</tr>
<tr>
<td>Non-CABG major bleeding (TIMI criteria)</td>
<td>2.8%</td>
<td>2.2%</td>
<td>1.25 (1.03-1.53)</td>
<td>0.6%</td>
<td>167</td>
<td>- intracranial bleeding</td>
</tr>
<tr>
<td>Major or minor bleeding (trial criteria)</td>
<td>16.1%</td>
<td>14.6%</td>
<td>1.11 (1.03-1.2)</td>
<td>1.5%</td>
<td>67</td>
<td>- major or minor bleeding (TIMI criteria)</td>
</tr>
<tr>
<td>Any dyspnea</td>
<td>13.8%</td>
<td>7.8%</td>
<td>1.84 (1.68-2.02)</td>
<td>6%</td>
<td>17</td>
<td>- CABG related (procedural)</td>
</tr>
<tr>
<td>Dyspnea requiring discontinuation</td>
<td>0.9%</td>
<td>0.1%</td>
<td>6.12 (3.41-11.01)</td>
<td>0.8%</td>
<td>125</td>
<td>- bradycardia/ventricular pauses at 30 days</td>
</tr>
<tr>
<td>Ventricular Pauses ≥3 sec in first week</td>
<td>5.8%</td>
<td>3.6%</td>
<td>RR 1.61</td>
<td>2.2%</td>
<td>46</td>
<td>Clinical significance of elevated SCr &amp; uric acid cannot be determined as study only reported % ↑ without indicating what the baseline mean was.</td>
</tr>
<tr>
<td>Premature discontinuation</td>
<td>23.4%</td>
<td>21.5%</td>
<td>RR 1.09</td>
<td>1.9%</td>
<td>53</td>
<td>- 1 month after end of tx, % ↑ for Scr &amp; uric acid was NS.</td>
</tr>
<tr>
<td>Premature discontinuation due to AE</td>
<td>7.4%</td>
<td>6%</td>
<td>RR 1.23</td>
<td>1.4%</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Premature discontinuation due to unwillingness to continue</td>
<td>10.1%</td>
<td>9.2%</td>
<td>RR 1.03</td>
<td>0.9%</td>
<td>112</td>
<td></td>
</tr>
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<th>LAB ABNORMALITIES</th>
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</thead>
<tbody>
<tr>
<td>↑ serum uric acid: baseline to 1 month</td>
<td>14% +/- 46%</td>
<td>7% +/- 44%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>↑ serum uric acid: baseline to 12 months</td>
<td>15% +/- 52%</td>
<td>7% +/- 31%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>↑ in SCr: baseline to 1 month</td>
<td>10% +/- 22%</td>
<td>8% +/- 21%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>↑ in SCr: baseline to 12 months</td>
<td>11% +/- 22%</td>
<td>9% +/- 22%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS:
- Clinically meaningful endpoints (death from vascular causes, MI, stroke).
- ITT analysis of efficacy outcomes
- Only 5 patients lost to follow up (0.03%)

LIMITATIONS:
- Only 2.2% (n=401) of patients were from Canada.1,3
- The independent data & safety monitoring board had access to unblinded data.
- 46% of patients randomized to ticagrelor received both clopidogrel and ticagrelor loading dose.
- Variability existed in clopidogrel loading dose (300 to 600 mg).
- >20% discontinued treatment prematurely
- Potential lack of ticagrelor efficacy in North Americans (n=1814, US n=1413, Canada n=401), lower weight patients, and those not taking lipid lowering therapies at randomization. Subgroup analysis of geographic location showed significantly higher proportion of Americans received median ASA dose ≥300 mg vs rest of world (53.6% vs 1.7%). As such, ASA <100 mg/day is the recommended dose when combined with ticagrelor.
- Of the 64% who underwent PCI, only 18% received DES. DES have largely replaced BMS in current practice.

UNCERTAINTIES:
- Safety of ticagrelor in patients with pulmonary diseases (dyspnea), bradycardia/heart block (ventricular pauses), renal dysfunction (elevation in SCr), & gout (elevation in uric acid). There was a low percentage of patients with a history of COPD, asthma, CHF, gout, & CKD included in the study.
- Unclear if allocation was concealed.

RxFILES RELATED LINKS
- Duration of DAPT & Triple Therapy RxFiles Chart
- DAPT RxFiles Trial Summary: http://www.rxfiles.ca/rxfiles/uploads/documents/DAPT-Trial-12vs30months.pdf

©not covered by NIHB = Exceptional Drug Status in SK ACEI=angiotensin converting enzyme inhibitor ACS=acute coronary syndrome AE=adverse event ARB=angiotensin II receptor blocker ARB=absolute risk increase ARRI=absolute risk reduction ASA=acetylsalicylic acid BID=twice daily BMI=body mass index BMS=bare metal stent CABG=coronary artery bypass grafting CAD=coronary artery disease CI=confidence interval/Clinically important CKS=coronary artery disease C/O=cardiovascular CYP3A=cytochrome P450 3A, DAPT=dual antiplatelet therapy DES=drug-eluting stent DM=diabetes mellitus HR=heart failure HR=risk ratio HR=relative HR=relative risk IC=insulin resistant PCI=percutaneous coronary intervention IQR=interquartile range ITT=intention to treat LDL=low-density lipoprotein LDLH=low-density lipoprotein HDL=high-density lipoprotein MI=myocardial infarction NNH=number needed to treat NNH=number needed to treat NHL=negative statistically significant NS=nonsignificant NSTEACS=non-ST-elevated ACS NSTE=non-ST-elevated MI OAC=oral anticoagulant PAD=peripheral artery disease PPI=proton pump inhibitor P2Y=relative risk P2Y receptor blocker PAD=peripheral artery disease LVEF=left ventricular ejection fraction ser=seconds STEMI=ST-elevated myocardial infarction TIMI=thrombolysis in MI tx=treatment URI=unstable angina US=United States yr=year

ACKNOWLEDGEMENTS: Prepared By: Danielle Shmyr, Lynnette Kosar, Brent Jensen, Loren Regier

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