PLATO: Ticagrelor **BRILINTA** 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, HFrEF, gout & severe renal impairment due to increased risk of dyspnea & elevated serum 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) & intracranial fatal bleeding
  - ↑ risk of dyspnea (NNH=17), and premature discontinuation of therapy (NNT=53).
- Based on the **PLATO** results, the **2012 Canadian Cardiovascular Society Antithrombotic Guidelines** recommend the following: 2
  - 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 **$108/month vs clopidogrel $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 risk in major bleeding.
  - Clopidogrel, however, has inter-individual genetic variability that may result in poor antiplatelet response in some patients, irreversible 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**

- **DESIGN**: randomized, double-blind, double dummy, international 43 countries, multicentre 862 sites, Controlled trial. ITT & superiority for efficacy outcomes. Enrolment: October 2006 to July 2008. Funded by AstraZeneca (ticagrelor).
- **INTERVENTION**: ticagrelor 180 mg LD followed by 90 mg BID vs clopidogrel 300-600mg LD followed by 75 mg daily, + ASA x 12 months (median 9 months). After coronary stenting, protocol allowed for ASA 325 mg for ≤6 months.
- **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, clonidine, 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, 18% ARB, ~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 75-100 mg daily.

**RESULTS**

**TABLE 1: EFFICACY (ITT ANALYSIS)**

<table>
<thead>
<tr>
<th>Clinical Endpoints</th>
<th>Ticagrelor 90 mg BID (n=9333)</th>
<th>Clopidogrel 75 mg daily (n=9291)</th>
<th>HR (95% CI)</th>
<th>ARR</th>
<th>NNT / 9 MONTHS</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRIMARY EFFICACY ENDPOINT</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<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>
<td></td>
</tr>
<tr>
<td><strong>SECONDARY EFFICACY ENDPOINTS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from vascular causes</td>
<td>4%</td>
<td>5.1%</td>
<td>0.79 (0.69-0.91)</td>
<td>1.1%</td>
<td>91</td>
<td></td>
</tr>
<tr>
<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>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>1.5%</td>
<td>1.3%</td>
<td>1.17 (0.91-1.52)</td>
<td>NS</td>
<td>-</td>
<td></td>
</tr>
<tr>
<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>
<td></td>
</tr>
<tr>
<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>
<td></td>
</tr>
<tr>
<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>59</td>
<td></td>
</tr>
<tr>
<td>Death from vascular causes, MI, stroke, severe recurrent ischemia, recurrent ischemia, TIA or arterial thrombotic</td>
<td>14.6%</td>
<td>16.7%</td>
<td>0.88 (0.81-0.95)</td>
<td>2.1%</td>
<td>48</td>
<td></td>
</tr>
<tr>
<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>
<td></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 OR ARR</th>
<th>NNH OR NNT / 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>Fatal intracranial bleeding</td>
<td>0.1%</td>
<td>0.01%</td>
<td>RR 10</td>
<td>0.09%</td>
<td>1112</td>
<td>- major bleeding (trial or TIMI criteria)</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>- bleeding requiring transfusion</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>- life-threatening or fatal bleeding (study criteria)</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>77</td>
<td>- intracranial bleeding</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>- major or minor bleeding (TIMI criteria)</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>- CABG related (procedural)</td>
</tr>
<tr>
<td>Ventricular Paus 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>- bradycardia</td>
</tr>
<tr>
<td>Premature discontinuation</td>
<td>23.4%</td>
<td>21.5%</td>
<td>RR 1.10</td>
<td>1.9%</td>
<td>53</td>
<td>- ventricular pauses ≥3 sec at 30 days</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>• 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 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>- 1 month after end of tx, % ↑ for Scr &amp; uric acid was NS.</td>
</tr>
</tbody>
</table>

† serum uric acid: baseline to 1 month                    | 14% +/- 46%                 | 7% +/- 44%                      | -           | -           | -                     | -        |
† serum uric acid: baseline to 12 months                  | 15% +/- 52%                 | 7% +/- 31%                      | -           | -           | -                     | -        |
↑ in Scr: baseline to 1 month                             | 10% +/- 22%                 | 8% +/- 21%                      | -           | -           | -                     | -        |
↑ in Scr: baseline to 12 months                           | 11% +/- 22%                 | 9% +/- 22%                      | -           | -           | -                     | -        |

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS:
• Clinically meaningful endpoints (death from vascular causes, MI, stroke).
• ITT analysis of efficacy outcomes
• Only 5 patients lost to follow (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.3
• 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 NIHBB = Exceptional Drug Status in SK ACCE = angiotensin converting enzyme inhibitor ACS = acute coronary syndrome AE = adverse event ARB = angiotensin II receptor blocker AR = 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/conditionalized CIK = coronary artery disease COPD = chronic obstructive pulmonary disease CV = cardiovascular CYP3A4 = cytochrome P450 3A4 DAPT = dual antiplatelet therapy DES = drug-eluting stent DM = diabetes mellitus HF = heart failure HR = hazard ratio INR = hour HTN = hypertension ITT = intention to treat LD = loading dose MII = myocardial infarction NNT = number needed to treat NSTEACS = non ST-elevated ACS NSTE = non ST-elevated MI OAC = oral anticoagulant PAD = peripheral artery disease PCI = percutaneous coronary intervention pBH = statistically significant for interaction PPI = proton pump inhibitor RR = relative risk Scr = serum creatinine sec = seconds STEMI = ST-elevated myocardial infarction TIMI = transient ischemic attack TIMI = thrombolysis in MI tx = treatment UA = unstable angina US = United States yr = year

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References:


