

PLATO: Ticagrelor ^{BRILINTA} vs Clopidogrel ^{PLAVIX} in Acute Coronary Syndrome ¹

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 serum uric acid & creatinine.
- In **PLATO**, ACS patients ~60% NSTEMIs 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)
 - Individual components of the composite: vascular death (NNT=91), MI (NNT=91), stroke (NS)
 - ↑ risk of non-CABG related major bleeding (NNH=167) & intracranial fatal bleeding, NNH=112; but a ↓ in non-intracranial fatal bleeding NNT=500. There was an ↑ 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:²
 - Ticagrelor + ASA 81mg daily is preferred over clopidogrel + ASA 81mg daily x 12 months for:
 - STEMI with primary PCI Strong Recommendation, Moderate-Quality Evidence
 - NSTEMIs (medical management or revascularization) Strong Recommendation, High-Quality Evidence
- At time of publication, ticagrelor ^{BRILINTA} ☹️ ⓧ \$108/month vs clopidogrel ^{PLAVIX}, ☹️ ⓧ \$26/month.

BACKGROUND ^{1,2,3,4,5,6,7,8,9}

- Dual antiplatelet therapy (DAPT, i.e. ASA + clopidogrel/prasugrel/ticagrelor) is recommended after ACS (STEMI or NSTEMIs) 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. CURE, PCI-CURE, CLARITY, PCI-CLARITY, TRITON-TIMI
 - 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. TRITON-TIMI
- 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 ^{1,4}

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

- **NSTEMIs:** ≥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, NSTEMIs (~60% NSTEMI 42.7%, UA 16.7%, n=11,067) & STEMI (37.7%, n=7026)

- Mean age 62yrs, ~15% ≥75yr, 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 ≥300mg daily.³

RESULTS

follow-up: median 277 days (9.2 months)

TABLE 1: EFFICACY (ITT ANALYSIS)

CLINICAL ENDPOINTS	TICAGRELOR 90 MG BID n=9333	CLOPIDOGREL 75 MG DAILY n=9291	HR (95% CI)	ARR	NNT / 9 MONTHS	COMMENTS	
PRIMARY EFFICACY ENDPOINT							
Death from vascular causes, MI or stroke	9.8%	11.7%	0.84 (0.77-0.92)	1.9%	53	• No difference in stroke, except ↑ risk of stroke of unknown cause (NNH=1250). • Difference between groups seen at 30 days and persisted throughout study. • The difference between ticagrelor & clopidogrel was NS in the following: - North American patients (p _{int} =0.045) - patients weighing less than median weight for their gender (males <82kg & females <71kg, p _{int} =0.04) - those not taking lipid lowering drugs at randomization (p _{int} =0.04)	
SECONDARY EFFICACY ENDPOINTS							
Death from vascular causes	4%	5.1%	0.79 (0.69-0.91)	1.1%	91		
MI	5.8%	6.9%	0.84 (0.75-0.95)	1.1%	91		
Stroke	1.5%	1.3%	1.17 (0.91-1.52)	NS	-		
Death from any cause	4.5%	5.9%	0.78 (0.69-0.89)	1.4%	72		
Death from any cause, MI, or stroke	10.2%	12.3%	0.84 (0.77-0.92)	2.1%	48		
Death from vascular causes, MI, stroke in subgroup with planned invasive tx	8.9%	10.6%	0.84 (0.75-0.94)	1.7%	59		
Death from vascular causes, MI, stroke, severe recurrent ischemia, recurrent ischemia, TIA or arterial thrombotic	14.6%	16.7%	0.88 (0.81-0.95)	2.1%	48		
Stent thrombosis (definite)	1.3%	1.9%	0.67 (0.5-0.91)	0.6%	167		

TABLE 2: ADVERSE EVENTS AND LAB ABNORMALTIES

OUTCOME OR ENDPOINT	TICAGRELOR 90 MG BID n=9235	CLOPIDOGREL 75 MG DAILY n=9186	HR (95% CI)	ARI OR ARR	NNH OR NNT / 9 MONTHS	COMMENTS
Fatal non-intracranial bleeding	0.1%	0.3%	RR 0.33	0.2%	500	<ul style="list-style-type: none"> • NS differences in the following: <ul style="list-style-type: none"> - major bleeding (trial or TIMI criteria) - bleeding requiring transfusion - life-threatening or fatal bleeding (study criteria) - intracranial bleeding - major or minor bleeding (TIMI criteria) - CABG related (procedural) - bradycardia - ventricular pauses ≥3 sec at 30 days • Clinical significance of elevated SCr & uric acid cannot be determined as study only reported % ↑ without indicating what the baseline mean was. <ul style="list-style-type: none"> - 1 month after end of tx, % ↑ for SCr & uric acid was NS.
Fatal intracranial bleeding	0.1%	0.01%	RR 10	0.09%	1112	
Non-CABG major bleeding (trial criteria)	4.5%	3.8%	1.19 (1.02-1.38)	0.7%	143	
Non-CABG major bleeding (TIMI criteria)	2.8%	2.2%	1.25 (1.03-1.53)	0.6%	167	
Major or minor bleeding (trial criteria)	16.1%	14.6%	1.11 (1.03-1.2)	1.5%	67	
Any dyspnea	13.8%	7.8%	1.84 (1.68-2.02)	6%	17	
Dyspnea requiring discontinuation	0.9%	0.1%	6.12 (3.41-11.01)	0.8%	125	
Ventricular Pauses ≥3 sec in first week	5.8%	3.6%	RR 1.61	2.2%	46	
Premature discontinuation	23.4%	21.5%	RR 1.09	1.9%	53	
Premature discontinuation due to AE	7.4%	6%	RR 1.23	1.4%	72	
Premature discontinuation due to unwillingness to continue	10.1%	9.2%	RR 1.03	0.9%	112	
↑ 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 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.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>
- **PCI-CLARITY** RxFiles Trial Summary: <http://www.rxfiles.ca/rxfiles/uploads/documents/PCI-CLARITY%20Trial%20Summary.pdf>
- **PCI-CURE** RxFiles Trial Summary: <http://www.rxfiles.ca/rxfiles/uploads/documents/PCI-CURE%20Trial%20Summary.pdf>
- **TRITON-TIMI** RxFiles Trial Summary: <http://www.rxfiles.ca/rxfiles/uploads/documents/TRITON-TIMI%2038%20Trial%20Summary.pdf>

⊗=not covered by NIHBS ⊖=Exceptional Drug Status in SK ACEI=angiotensin converting enzyme inhibitor ACS=acute coronary syndrome AE=adverse event ARB=angiotensin II receptor blocker ARI=absolute risk increase ARR=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/contraindicated CKD=coronary artery disease COPD=chronic obstructive pulmonary disease CV=cardiovascular CYP3A=cytochrome P450 3A DAPT=dual antiplatelet therapy DES=drug-eluting stent DM=diabetes mellitus HF=heart failure HR=hazard ratio hr=hour HTN=hypertension ITT=intention to treat LD=loading dose MI=myocardial infarction NNT=number needed to treat NNH=number needed to harm NS=non-statistically significant NSTEACS=non ST-elevated ACS NSTEMI=non ST-elevated MI OAC=oral anticoagulant PAD=peripheral artery disease PCI=percutaneous coronary intervention p_{int}=statistically significant for the interaction PPI=proton pump inhibitor RR=relative risk SCr=serum creatinine sec=seconds STEMI=ST-elevated myocardial infarction TIA=transient ischemic attack TIMI=thrombolysis in MI tx=treatment UA=unstable angina US=United States yr=year

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

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