

PEGASUS-TIMI 54: Ticagrelor ^{BRILINTA} versus Placebo in Patients with Prior MI ¹

Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin—Thrombolysis in Myocardial Infarction 54

BOTTOM LINE

- Patients are treated with dual antiplatelet therapy (DAPT, e.g. ASA + clopidogrel, ticagrelor or prasugrel) for 1 year after ACS. Stable patients (i.e. >1 year after ACS) may benefit from continued DAPT with a low dose of ticagrelor (60 mg BID) + ASA beyond 12 months. Caution in patients with an ↑risk of bleeding, or a history of COPD, asthma, or HF due to ↑risk of dyspnea.
- In **PEGASUS-TIMI 54**, patients with history of MI (1-3 years prior) treated with **ticagrelor 60 mg BID + ASA** versus ASA alone for a median of 33 months had: 94% were on clopidogrel x 1 year after their index MI
 - ↓ risk of the composite endpoint (cardiovascular death, MI, stroke) (NNT=79/3 years)
 - individual components of the composite: CV death (NS), MI (NNT=139/3 years), stroke (NNT=213/3 years)
 - ↑risk of major bleeding (NNH=81/3 years), & ↑risk of bleeding resulting in discontinuation of study drug (NNH=22/3 years)
 - ↑risk of dyspnea (NNH=11/3 years), & ↑risk of dyspnea resulting in discontinuation of study drug (NNH=27/3 years)
 - Benefit was **only seen in patients who had uninterrupted P2Y₁₂ inhibitor therapy** or restarted therapy within ≤30 days²
- As of summer 2016, Health Canada approved ticagrelor 60mg BID for patients with a history of MI & a high risk of developing an atherothrombotic event. Cost per month is ~\$110/month, and currently not listed on the Saskatchewan Drug Plan.

BACKGROUND

- Patients with a MI are at heightened risk for ischemic events & therefore DAPT (ASA + clopidogrel, prasugrel, or ticagrelor) is recommended for 1 year post MI to reduce this risk.^{3, CCS'12}
- Prior to **PEGASUS**, the **CHARISMA** trial looked at long-term DAPT median follow-up 28 months with clopidogrel + ASA versus ASA alone in patients at high risk of atherothrombotic events established cardiovascular disease or multiple risk factors.⁴ Overall, DAPT did not provide a benefit over ASA alone.⁴ However, in a **post-hoc analysis** of those with a history of MI, the risk of CV death, MI or stroke was lower with DAPT (NNT=59) underpowered.⁵
- After the release of **PEGASUS**, a meta-analysis was conducted which included 6 RCTs that evaluated extended DAPT in patients with a history of MI.⁶ **CHARISMA MI, PRODIGY, ARTIC-Interruption, DAPT, DES-LATE, PEGASUS** The authors concluded that extended DAPT mean 31 months compared to ASA alone, ↓ the risk of major adverse cardiovascular events (NNT=91) but ↑ the risk of major bleeding (NNH=132).⁶
- The 2016 ACC/AHA Guidelines on the Duration of DAPT in Patients with CAD state it may be reasonable to continue DAPT beyond 12 months in ACS patients. The committee categorized the statement as IIb,A (i.e. weak recommendation based on high quality evidence), and did not suggest how long therapy should continue for.⁷

TRIAL BACKGROUND ^{1,8,9}

DESIGN: randomized, double-blind, international 31 countries, multicentre 1161 sites, placebo controlled trial with concealed allocation. ITT for primary efficacy endpoints. Enrolment from October 2010 to May 2013. Funded by AstraZeneca (ticagrelor).

INTERVENTION: ticagrelor (60 mg BID or 90 mg BID) vs placebo, + ASA 75-150 mg daily for a median follow up of 33 months.

INCLUSION: spontaneous MI 1-3 years prior to enrolment, ≥50 years old, plus ≥1 additional high-risk feature: ≥65 years age, DM requiring medication, 2nd prior spontaneous MI, multivessel CAD, or non-end stage chronic renal dysfunction CrCl≤60 mL/min.

EXCLUSION: Planned course of P2Y₁₂ receptor antagonist, dipyridamole, cilostazol, potent CYP3A inducer/inhibitor/substrate, or anticoagulant use; known bleeding disorder; increased risk of bleeding including history of intracranial bleed, intracranial vascular abnormality or CNS tumor, intracranial or spinal cord surgery 5 years prior, GI bleed 6 months prior, major surgery 30 days prior; severe liver disease; pregnancy/lactation; dialysis; history of ischemic stroke; planned revascularization; CABG 5 years prior; risk of bradycardic events unless have pacemaker

POPULATION at baseline: n=21,162, median time from qualifying MI to randomization 1.7 years (IQR 1.2-2.3)

- Mean age 65 yrs, ~24% female, ~87% Caucasian, 18% from North America, median body weight ~82 kg
- 77.5% HTN, ~77% hypercholesterolemia, ~17% smoker, ~32% DM, 5.4% PAD, ~23% eGFR <60 mL/min
- ~54% STEMI, ~41% NSTEMI, 83% PCI history (41% BMS, 39% DES 52% new-DES, 27% G₁DES, 21% unknown),⁹ 16.5% >1 previous MI, ~59% multi-vessel CAD
- Baseline medications: 99.9% ASA, ~93% statin, ~83% beta-blocker, 80.5% ACEI or ARB; 94% were on clopidogrel post-MI x 1 year¹⁰

RESULTS ^{1,9,10}

follow-up: median 33 months (2.75 years)

TABLE 1: EFFICACY (ITT ANALYSIS)

CLINICAL ENDPOINTS	TICAGRELOR		PLACEBO n=7067	HR (95% CI)		ARR		NNT/3YRS		COMMENTS	
	90 MG BID n=7050	60 MG BID n=7045		90 MG VS PLACEBO	60 MG VS PLACEBO	90MG	60MG	90MG	60MG		
PRIMARY ENDPOINT											
CV death, MI or stroke	7.85%	7.77%	9.04%	0.85 (0.75-0.96)	0.84(0.74-0.95)	1.19%	1.27%	84	79	ARC Definite Stent Thrombosis (ST): ⁹ - rare (0.7% with placebo) - ticagrelor 90mg BID ↓ the risk of ST, but 60mg BID did not (NS)	
PRIMARY ENDPOINT (CV death, MI or stroke) IN RELATION TO TIME FROM P2Y₁₂ INHIBITOR WITHDRAWAL¹⁰											
≤ 30 days (n=7181)	7.4%	8.0%	9.9%	0.70 (0.57-0.87)	0.75(0.61-0.92)	2.5%	1.9%	40	53		
> 30 days to ≤ 1 year (n=6501)	8.1%	7.2%	8.7%	0.90 (0.72-1.12)	0.82(0.65-1.02)	NS		-	-		
> 1 year (n=5079)	6.3%	6.9%	6.9%	0.96 (0.73-1.26)	1.05(0.81-1.38)	NS		-	-		
SECONDARY ENDPOINTS											
Death from CHD, MI or stroke	6.99%	7.09%	8.33%	0.82 (0.72-0.93)	0.83(0.73-0.94)	1.34%	1.24%	75	81	For every 10,000 patients treated/year: ticagrelor - 60 mg BID would prevent 42 primary endpoint events but cause 31 major bleeds - 90 mg BID would prevent 40 primary endpoint events but cause 41 major bleeds	
CV death or MI	6.79%	6.77%	7.81%	0.85 (0.75-0.97)	0.85(0.74-0.96)	1.02%	1.04%	98	97		
Death from CHD or MI	5.59%	5.75%	6.68%	0.81 (0.71-0.94)	0.84(0.73-0.96)	1.09%	0.93%	92	108		
CV death	2.94%	2.86%	3.39%	0.87 (0.71-1.06)	0.83(0.68-1.01)	NS		-	-		
Death from CHD	1.53%	1.72%	2.08%	0.73 (0.56-0.95)	0.80(0.62-1.04)	0.55%	NS	182	-		
Death from any cause	5.15%	4.69%	5.16%	1.00 (0.86-1.16)	0.89(0.76-1.04)	NS		-	-		
MI	4.4%	4.53%	5.25%	0.81 (0.69-0.95)	0.84(0.72-0.98)	0.85%	0.72%	118	139		
Any stroke	1.61%	1.47%	1.94%	0.82 (0.63-1.07)	0.75(0.57-0.98)	NS	0.47%	-	213		
Ischemic stroke	1.41%	1.28%	1.65%	0.85 (0.64-1.14)	0.76(0.56-1.02)	NS		-	-		

TABLE 2: SAFETY

CLINICAL ENDPOINTS	TICAGRELOR		PLACEBO n=6996	HR (95% CI)		ARI		NNH/3YRS		COMMENTS
	90 MG BID n=6988	60 MG BID n=6958		90 MG VS PLACEBO	60 MG VS PLACEBO	90MG	60MG	90MG	60MG	
TIMI major bleeding	2.6%	2.3%	1.06%	2.69 (1.96-3.70)	2.32(1.68-3.21)	1.54%	1.24%	65	81	NS differences in: - Fatal bleeding or nonfatal intracranial hemorrhage - Intracranial hemorrhage - Hemorrhagic stroke - Renal events - Bradyarrhythmia
TIMI minor bleeding	1.31%	1.18%	0.36%	4.15 (2.47-7.00)	3.31(1.94-5.63)	0.95%	0.82%	106	122	
Bleeding requiring transfusion	2.43%	2.09%	0.72%	3.75 (2.59-5.42)	3.08(2.12-4.48)	1.71%	1.37%	59	73	
Bleeding leading to study-drug discontinuation	7.81%	6.15%	1.5%	5.79 (4.60-7.29)	4.40 (3.48-5.57)	6.31%	4.65%	16	22	
Dyspnea	18.93%	15.84%	6.38%	3.55 (3.16-3.98)	2.81(2.50-3.17)	12.6%	9.46%	8	11	
Dyspnea event leading to study-drug discontinuation	6.5%	4.55%	0.79%	8.89 (6.65-11.88)	6.06 (4.50-8.15)	5.71%	3.76%	18	27	
Dyspnea - serious adverse event	0.41%	0.45%	0.15%	2.68 (1.24-5.83)	2.70(1.25-5.84)	0.26%	0.3%	385	334	
Gout	2.28%	1.97%	1.51%	1.77 (1.32-2.37)	1.48(1.10-2.00)	0.77%	0.46%	130	218	
Discontinuation Rate	32%	28.7%	21.4%	-	-	10.6%	7.3%	10	14	

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS:

- Clinically meaningful endpoints (CV death, MI, stroke).
- ITT analysis for efficacy outcomes.
- Only 10 patients were lost to follow-up (0.05%).¹¹ (Supplement)
- **PEGASUS** reported adverse events with gout & renal events (although, not defined), whereas **PLATO** reported elevations in serum creatinine & serum uric acid levels.¹³
- The investigators published additional data on efficacy of ticagrelor based on presence & type of stent,⁹ efficacy in relation to P2Y12 inhibitor withdrawal,¹⁰ and platelet inhibition between the two ticagrelor regimens.¹²
- 60 mg BID of ticagrelor showed high levels of peak and trough platelet inhibition, and similar mean levels of platelet inhibition to 90 mg BID.¹²

LIMITATIONS:

- Ticagrelor was used in <1% of patients prior to randomization (~94% were on clopidogrel).¹⁰
- Patients at risk of bradycardia were excluded from the trial. Ticagrelor has been shown to cause more ventricular pauses than clopidogrel,¹³ and therefore may not be appropriate for individuals with bradycardia but safety data is lacking.
- There was not a direct comparison of the two ticagrelor regimens.
- ~27% of all patients discontinued treatment prematurely.
- The PK/PD study of ticagrelor 60 mg was not large enough to allow assessment of relationship between platelet function results and clinical outcomes. As well, no Asian or low body weight (<60 kg) patients were assessed for PK/PD.¹²
- Safety profile of long term ticagrelor was not studied in patients with heightened risk of bleeding (recent bleeds, prior stroke, or need for anticoagulant therapy).
- Number of gastrointestinal bleeds and baseline proton-pump inhibitor use was not reported.

UNCERTAINTIES:

- Further analysis is needed to help clarify the profile of post-MI patients most likely to benefit from continued DAPT.
- Ideal length of extended DAPT therapy beyond 1 year remains unknown.
- Safety of ticagrelor in patients with pulmonary diseases (dyspnea), HF and gout unknown. The number of patients at baseline with gout, HF or pulmonary disease was not reported in **PEGASUS**. In **PLATO**, only 6% had COPD, 5.5% had HF, ~3% had asthma & ~3% had gout.¹³
- Number of patients from Canada was not reported (18% from North America).
- Protocol allowed for a modified study-drug option (blinded, double-dummy ticagrelor or clopidogrel) if a patient had an indication for P2Y₁₂ receptor blockade during the study. The number of patients who received the modified study-drug option was not reported.
- Should patients with a BMS receive extended DAPT? 41% of stented patients in **PEGASUS** had a BMS. Endothelialization with a BMS is complete within 3 to 6 months (less risk for stent thrombosis), but the risk of thrombosis due to disease progression still exists. However, the **DAPT** study (DAPT with clopidogrel or prasugrel for 12 vs 30 months) failed to show a benefit with extended DAPT in patients with a BMS, although the study was underpowered.¹⁴
- Ticagrelor 60mg BID reduced the risk of stroke (NNT=213) in post-MI patients, but ticagrelor 90mg BID failed to show a benefit, compared to ASA, in patients with a recent stroke or transient ischemic attack in the **SOCRATES** trial.¹⁵

ACEI=angiotensin converting enzyme inhibitor ACS=acute coronary syndrome ARB=angiotensin II receptor blocker ARC=Academic Research Consortium ARI=absolute risk increase ARR=absolute risk reduction ASA=acetylsalicylic acid BID=twice daily BMS=bare metal stent CABG=coronary artery bypass grafting CAD=coronary artery disease CHD=coronary heart disease CI=contraindication CNS=central nervous system COPD=chronic obstructive pulmonary disease CrCl=creatinine clearance CV=cardiovascular CYP3A=cytochrome P450 3A DAPT=dual antiplatelet therapy DES=drug-eluting stent DM=diabetes mellitus eGFR=estimated glomerular filtration rate G₁DES=first generation drug-eluting stent GI=gastrointestinal HF=heart failure HR=hazard ratio HTN=hypertension IQR=interquartile range ITT=intention to treat MI=myocardial infarction new-DES=newer generation drug-eluting stent NNT=number needed to treat NNH=number needed to harm NS=non-statistically significant NSTEMI=non ST-elevated myocardial infarction PAD=peripheral artery disease PCI=percutaneous coronary intervention PD=pharmacodynamic PK=pharmacokinetic RCT=randomized controlled trial STEMI=ST-elevated myocardial infarction TIMI=thrombolysis in MI US=United States yr=year

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- Q&A Does Clopidogrel + ASA Impact Mortality (http://www.rxfiles.ca/rxfiles/uploads/documents/QandA_Clopidogrel_and_Mortality.pdf)

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