TRITON-TIMI 38: Prasugrel EFFIENT vs Clopidogrel PLAVIX in Patients with ACS [1]

TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel - Thrombolysis In Myocardial Infarction

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 (74% NSTEACS) **undergoing PCI** treated with a $P2Y_{12}$ inhibitor **x 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 (NNT=84) & stent-thrombosis (NNT=77) significant for DES & BMS subgroups
  - But prasugrel ↑ risk of bleeding: major non-CABG TIMI (NNH = 167), life-threatening (NNH = 200) & fatal bleeding (NNH = 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) NNH=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: [2]
  - **NSTEACS + PCI:** Prasugrel 10mg daily (or ticagrelor) preferred over clopidogrel 75mg daily x 12 months in addition to ASA 81mg daily in $P2Y_{12}$ inhibitor naive patients after coronary anatomy has been defined & PCI planned. Strong Recommendation, High-Quality Evidence
    - 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 underdoing PCI, avoid prasugrel before coronary anatomy has been defined. Strong Recommendation, Moderate-Quality Evidence
  - **STEMI + PCI:** Prasugrel 10mg daily (or ticagrelor) preferred over clopidogrel 75mg daily x 12 months in addition to ASA 81mg daily after primary PCI. Strong Recommendation, Moderate Quality Evidence
    - Avoid prasugrel in patients with a previous stroke/TIA and use a 5mg dose if required in patients ≥75 years old or weigh <60kg. Strong Recommendation, Low-Quality Evidence Note: the 5mg dose has not been studied & the 10mg tablet is not scored.
- At time of publication, prasugrel EFFIENT ☎ ⊗ $100/month vs clopidogrel PLAVIX, g ☎ $26/month.

BACKGROUND

- DAPT with ASA + $P2Y_{12}$ 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; CLARITY, PCI-CLARITY, CURE, PCI-CURE 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 [1,5]

DESIGN: randomized, double-blind, double-dummy, parallel-group, international 30 countries, multicentre 707 sites trial. Superiority & ITT analysis for efficacy outcomes. Enrolment: November 2004 to January 2007. Fund by: Eli Lilly (prasugrel), Daiichi Sankyo.

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/m^2, 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

median follow up: 14.5 months

TABLE 1: EFFICACY

CLINICAL EFFICACY ENDPOINTS	PRASUGREL 60 MG LD THEN 10 MG DAILY ITT analysis: n=6813	CLOPIDOGREL 300 MG LD THEN 75 MG DAILY ITT analysis: n=6795	HR (95% CI)	P VALUE	NNT/NNH 14.5 MONTHS	COMMENTS
PRIMARY ENDPOINT						
CV death, nonfatal MI, nonfatal stroke	643 (9.9%)	781 (12.1%)	0.81 (0.73-0.90)	<0.001	46	• Primary outcome driven by nonfatal MI • Despite ↓ risk in MI & ST, mortality was NS • Statistically significant difference in primary endpoint was evident at 3 days and persisted throughout follow up
SECONARY ENDPOINTS						
Death from CV causes	133 (2.1%)	150 (2.4%)	0.89 (0.70-1.12)	NS	-	
Nonfatal MI	475 (7.3%)	620 (9.5%)	0.76 (0.67-0.85)	< 0.001	44	
Nonfatal stroke	61 (1.0%)	60 (1.0%)	1.02 (0.71-1.45)	NS	-	
Stent thrombosis	68 (1.1%)	142 (2.4%)	0.48 (0.36-0.64)	< 0.001	77	
Death from any cause	188 (3.0%)	197 (3.2%)	0.95 (0.78-1.16)	NS	-	
Urgent target-vessel revascularization	156 (2.5 %)	233 (3.7%)	0.66 (0.54-0.81)	< 0.001	84	

RESULTS continued — median follow up: 14.5 months

TABLE 2: SAFETY & NET CLINIC BENEFIT

	Safety Endpoints	Prasugrel 60 mg followed by 10 mg daily n=6741	Clopidogrel 300 mg followed by 75 mg daily n=6716	HR (95% CI)	P value	NNT/NNH 14.5 months	Comments
SAFETY ENDPOINTS (TIMI Bleeding Criteria)							• Safety endpoints included patients who received ≥1 doses of the study drug • Discontinuation of study drug due to adverse events not related to bleeding was NS
	Non-CABG related major bleed (primary safety endpoint)	146 (2.4%)	111 (1.8%)	1.32 (1.03-1.68)	0.03	167	
	CABG-related major bleed	24 (13.4%)	6 (3.2%)	OR=4.73 (1.90-11.82)	< 0.001	10	
	Bleeding requiring transfusion	244 (4.0%)	182 (3.0%)	1.31 (1.11-1.63)	<0.001	100	
	Life threatening bleed	85 (1.4%)	56 (0.9%)	1.52 (1.08-2.13)	0.01	200	
	Fatal bleed	21 (0.4%)	5 (0.1%)	4.19 (1.58-11.11)	0.002	334	
	Intracranial bleed	19 (0.3%)	17 (0.3%)	1.12 (0.58-2.15)	NS	-	
	Discontinuation due to bleeding	2.5%	1.4%	-	<0.001	91	
SUBGROUP ANALYSES: NET CLINIC BENEFIT							**Net Clinical Benefit** p-values for interaction: • history of stroke/TIA vs no history of stroke/TIA • ≥75yrs, <60kg, history of stroke/TIA vs <75yrs, ≥60kg, no history of stroke/TIA
History of Stroke or TIA	Primary Endpoint: CV death, nonfatal MI, nonfatal stroke	47/262 (19.1%)	35/256 (14.4%)	1.37 (0.89-2.13)	NS p=0.02	-	
History of Stroke or TIA	Non-CABG related TIMI major bleeding	14/257 (5%)	6/252 (2.9%)	2.46 (0.94-6.42)	NS p=0.06	-	
History of Stroke or TIA	Death from any cause, nonfatal MI, nonfatal stroke, or non-CABG-related nonfatal TIMI major bleed	57/262 (23%)	39/256 (16%)	1.54 (1.02-2.32)	0.04 p=0.006	15	
≥75yrs, <60kg, Hx Stroke/TIA	Primary Endpoint: CV death, nonfatal MI, nonfatal stroke	198/1320 (16.1%)	199/1347 (16%)	1.02 (0.84-1.24)	NS p=0.008	-	
≥75yrs, <60kg, Hx Stroke/TIA	Non-CABG related TIMI major bleeding	52/1305 (4.3%)	38/1328 (3.3%)	1.42 (0.93-2.15)	NS	-	
≥75yrs, <60kg, Hx Stroke/TIA	Death from any cause, nonfatal MI, nonfatal stroke, or non-CABG-related nonfatal TIMI major bleed	249/1320 (20.2%)	239/1347 (19%)	1.07 (0.9-1.28)	NS p=0.006	-	

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 adjucation 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.

UNCERTAINITIES:

- Higher rate of colonic 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

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
- **PLATO** RxFiles Trial Summary: http://www.rxfiles.ca/rxfiles/uploads/documents/PLATO%20Trial%20Summary.pdf

⊗=not covered by NIHB ☎=Exceptional Drug Status in SK **ACEI**=angiotensin converting enzyme inhibitor **ACS**=acute coronary syndrome **ADP**=adenosine diphosphate **ARB**=angiotensin II receptor blocker **ASA**=acetylsalicylic acid **BMI**=body mass index **BMS**=bare metal stent **CABG**=coronary artery bypass grafting **CAD**=coronary artery disease **CCB**=calcium channel blocker **CI**=confidence interval **CrCl**=creatinine clearance **CV**=cardiovascular **DAPT**=dual antiplatelet therapy **DES**=drug-eluting stent **DM**=diabetes mellitus **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-elevation ACS **OR**=odds ratio **PCI**=percutaneous coronary intervention **PPI**=proton pump inhibitor **ST**=stent thrombosis **STEMI**=ST-elevated myocardial infarction **TIA**=transient ischemic attack **TIMI**=thrombolysis in MI **yr**=year

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