PCI-CLARITY: Effect of clopidogrel [PLAVIX] pre-treatment before PCI in patients with STEMI treated with fibrinolytics [1]

CLopidogrel as Adjunctive ReperfusIon TherapY PCI Subgroup

BOTTOM LINE

In **PCI-CLARITY**, patients with STEMI treated with fibrinolytics and DAPT (ASA + clopidogrel), vs ASA alone, before PCI had:

- ↓ risk of CV death, recurrent MI or stroke for 30 days after PCI (NNT=39); individual components did not reach significance
- no difference in major or minor bleeding risk (NS)

BACKGROUND

- The **CLARITY TIMI 28** study assessed the efficacy & safety of adding DAPT (ASA + clopidogrel) vs ASA alone to fibrinolytic therapy in individuals with STEMI.[2]
- The **PCI-CLARITY** study was a prospectively designed sub-study of the **CLARITY TIMI 28** trial for individuals who underwent PCI.[1]
- At the time of publication, DAPT before and after PCI was not standard of practice; however, these are considered landmark trials which helped shape our current approach.[3,4,5]
- Current clinical practice guidelines recommend DAPT with ASA and a P2Y12 inhibitor (clopidogrel, prasugrel or ticagrelor) for 12 months after **STEMI with PCI**, followed by ASA indefinitely. CCS'12 (3), ESC'14 (4), ACCF/AHA'13 (5)
- Note: prasugrel [EFFIENT] & ticagrelor [BRILINTA] were not on the market when the study was conducted.

TRIAL BACKGROUND [1,2,6]

DESIGN (**CLARITY**): randomized, double-blind, placebo controlled, international 23 countries, multicentre 319 sites trial with concealed allocation. Funded by Sanofi-Aventis & Bristol-Myers-Squibb (clopidogrel), & the National Heart, Lung and Blood Institute. Enrolment: February 2003 to October 2004.

- **PCI-CLARITY**: PCI was performed at the discretion of the local investigator. ITT for efficacy & per protocol for safety outcomes.

INTERVENTION: in addition to a fibrinolytic (± heparin) & ASA (150-325mg on the first day, then 75-162mg daily thereafter):

- **Pre-PCI:** randomized, double-blind clopidogrel 300mg LD then 75mg daily or placebo until angiography (**CLARITY**)
- **Post-PCI:** all stented patients (95%) received open-label clopidogrel 300mg LD (~75%) then 75mg daily (~90%) (**PCI-CLARITY**)

INCLUSION: CLARITY: age 18 to 75 years, onset of ischemic discomfort ≤12 hr before randomization (lasting more than 20 minutes), ST elevation at least 0.1 mV in at least 2 contiguous limb leads or at lease 0.2 mV in at least 2 contiguous precordial leads, or left bundle branch block, planned treatment with fibrinolytic, anticoagulant (if receiving a fibrin-specific lytic) and aspirin

- **PCI-CLARITY**: Met enrolment criteria for **CLARITY** and underwent PCI during index hospitalization.

EXCLUSION: CLARITY: treatment with clopidogrel within 7 days prior to enrolment, or clopidogrel or glycoprotein IIb/IIIa inhibitor before angiography was planned, CI to fibrinolytics, cardiogenic shock, intention of angiography within 48 hours in absence of new clinical indication, undergone prior CABG, ≤67 kg who received >4000 unit bolus of heparin or >67 kg who received > 5000 unit bolus of heparin or received greater than standard doses of LMWH. Excluded after randomization if did not get fibrinolytic drug, underwent CABG, received medical therapy, or did not have PCI on index hospitalization.

POPULATION at baseline: n=1,863 of 3,491 (53.4% from **CLARITY**)

- Mean age ~57 yrs 28% between 65-75 yr, ~82% ♂, 93% Caucasian, # of patients from North America not reported
- 50.8% smoker, 41% HTN, 40% hyperlipidemia, anterior MI 38.9%, 15.4% DM, prior MI 8.3%, prior PCI 5.5%
- **Fibrinolytic**: median 2.35 hr from symptom onset to fibrinolytic, 79% fibrin-specific 98.5% received heparin, 21% non-fibrin-specific
- **PCI:** median 3 days from randomization to PCI 3.2 days clopidogrel vs. 2.9 days placebo, p=0.003; infarct related artery patency: 84% before PCI 86.9% clopidogrel vs. 80.8% placebo, p<0.001, 98.7% after PCI; ~32% glycoprotein IIb/IIIa; 95% coronary artery stenting; open-label clopidogrel: 77.6% LD at time of PCI, 89.6% MD given after PCI

RESULTS

follow-up: 30 days

TABLE: EFFICACY ENDPOINTS (SAFETY ENDPOINTS DISCUSSED IN COMMENTS)

CLINICAL ENDPOINTS	CLOPIDOGREL LD 300-600MG THEN 75 MG DAILY n=933	PLACEBO n=930	ARR	OR 95% CI	NNT	COMMENTS
PRIMARY ENDPOINT from PCI to 30 days after randomization						• None of individual components for the primary composite endpoint reached statistical significance. • ~ 2/3 of all MIs occurred before PCI. • Kaplan Meier curve separated after the first day of therapy, and continued to diverge over time. • LD: all patients received clopidogrel 300mg at study entry. ~75% received another 300mg at time of PCI. **SAFETY ENDPOINTS:** • TIMI major bleeding, TIMI minor bleeding or combined major and minor TIMI bleeding: NS
CV death, recurrent MI, stroke	3.6%	6.2%	2.6%	0.54 (0.35-0.85)	39 / 30 days	
SECONARY ENDPOINTS from PCI to 30 days after randomization						
CV death or MI	3.3%	5.4%	2.1%	0.58 (0.36-0.94)	48 / 30 days	
CV death	1.4%	2.6%	NS	0.49 (0.24-1.03)	-	
Recurrent MI	1.9%	3.1%	NS	0.60 (0.33-1.11)	-	
Stroke	0.4%	1.2%	NS	0.35 (0.11-1.11)	-	
SECONDARY ENDPOINTS before PCI						
Recurrent MI, stroke	4%	6.2%	2.2%	0.62 (0.4-0.95)	46 / 3 days	
MI	4%	6.1%	2.1%	0.6 (0.38-0.95)	47 / 3 days	
Stroke	0	0.1%	NS	-	-	
SECONDARY ENDPOINTS from randomization to 30 days (mean 33 days)						
CV death, recurrent MI, stroke	7.5%	12%	4.5%	0.59 (0.43-0.81)	23 / 33 days	
CV death or MI	7.2%	11.1%	3.9%	0.62 (0.45-0.86)	26 / 33 days	
CV death	1.4%	2.6%	NS	0.49 (0.24-1.03)	-	
Recurrent MI	5.9%	8.9%	3%	0.64 (0.44-0.92)	34 / 33 days	
Stroke	0.4%	1.3%	NS	0.32 (0.1-1.01)	-	

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS:

- Important clinical endpoints (e.g. cardiovascular death, MI) with blinded adjucation of outcomes.
- All patients enrolled in the study were accounted for (1 lost to follow up on treatment arm after 10 d included in primary analysis).
- Used a propensity score to minimize potential selection bias due to non-randomized PCI.

LIMITATIONS:

- Short follow up period of only 30 days (followed up with a telephone call and then confirmed using medical records).
- Power calculated for **CLARITY** and not for **PCI-CLARITY**.
- Narrow population studied (only STEMI treated with fibrinolytics e.g. tenecteplace ~47%, streptokinase ~30%).
- Patients >75 years old were excluded from the trial.
- Did not report PPI use or stent thrombosis

UNCERTAINITIES:

- Optimal length of DAPT after PCI.
- How much of the benefit was due to the pre-PCI loading dose, versus 30 days of open-label clopidogrel.

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-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
- **TRITON-TIMI** RxFiles Trial Summary: http://www.rxfiles.ca/rxfiles/uploads/documents/TRITON-TIMI%2038%20Trial%20Summary.pdf

✗ =non-formulary in SK ⊗=not covered by NIHB ☎=Exceptional Drug Status in SK ♂=male **ACC**=American College of Cardiology, **AE**=adverse effects, **AHA**=American Heart Association **ARI**=absolute risk increase **ARR**=absolute risk reduction **ASA**=acetylsalicylic acid **CABG**=coronary artery bypass grafting **CCS**=Canadian Cardiovascular Society **CLARITY**=Clopidogrel as Adjunctive Reperfusion Therapy **CV**=cardiovascular **d**=day **DAPT**=Dual Anti-platelet Therapy **DI**=drug interaction **ECG**=electrocardiogram **Hg**=hemoglobin **hr**=hour **ITT**=intention to treat **LD**=loading dose **LMWH**=low molecular weight heparin **MD**=maintenance dose **MI**=myocardial infarction **NNH**=number needed to harm **NNT**=number needed to treat **NS**=non-statistically significant **OD**=once daily **PCI**=percutaneous coronary intervention **PCI-CLARITY**=Percutaneous Coronary Intervention-Clopidogrel as Adjunctive Reperfusion Therapy **PPI**=proton pump inhibitor **STEMI**=ST elevation myocardial infarction **TIMI**=Thrombolysis in Myocardial Infarction **yr**= year

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