PCI-CURE: Effects of pre-treatment with clopidogrel PLAVIX & acetylsalicylic acid ASPIRIN followed by long-term therapy in patients undergoing PCI [1]

Clopidogrel in Unstable angina to prevent Recurrent Events PCI Subgroup

BOTTOM LINE

In **PCI-CURE**, patients with NSTEACS treated with DAPT (clopidogrel + ASA), vs ASA alone, before PCI had:

- ↓ risk of CV death, MI, & urgent revascularization **within 30 days of PCI** (NNT=53), which was driven by a ↓ risk of MI (NNT=59)
- ↓ risk of CV death, MI, & any revascularization **after PCI to end of follow-up** (mean 8 months) (NNT=30), which was also driven by a ↓ risk of MI (NNT=53)
- these benefits were not associated with an ↑in the risk of major bleeding, although there were more minor bleeds (NNH=72)

BACKGROUND

- The **CURE** study assessed early & long-term use of DAPT (ASA + clopidogrel) versus ASA alone in individuals with NSTEACS.[2]
- The **PCI-CURE** study was a prospectively designed sub-study of the **CURE** trial for individuals who underwent PCI.[1]
- At the time of the 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 & a $P2Y_{12}$ inhibitor (clopidogrel, prasugrel or ticagrelor) for 12 months after **NSTEACS with PCI**, followed by ASA indefinitely. CCS'12 (3), ESC'15 (4), AHA/ACC'14 (5)
- Note: prasugrel EFFIENT & ticagrelor BRILINTA were not on the market when the study was conducted.

TRIAL BACKGROUND [1,2,6]

DESIGN (**CURE**): randomized, double-blind, placebo controlled, international 28 countries, multicentre 482 sites, ITT trial with concealed allocation. Funded by Sanofi & Bristol-Myers-Squibb (clopidogrel), Heart & Stroke Foundation of Canada, & Canadian Institutes of Health Research. Enrolment: December 1998 to September 2000.

- **PCI-CURE**: PCI was performed after randomization at the discretion of the local investigator. The trial also included a per protocol analysis which excluded those who received open-label clopidogrel prior to PCI.

INTERVENTION:

- **Pre PCI:** randomized, double-blind clopidogrel 300mg LD then 75mg daily or placebo, + ASA 75-325mg daily (**CURE**)
- **Post PCI x 2-4 weeks:** all stented patients (82%) received open-label clopidogrel 75mg + ASA 75-325mg daily
- **Post PCI months 2 to 12 (mean 8 months):** randomized, double-blind clopidogrel 75 mg daily or placebo, + ASA 75-325 mg daily

INCLUSION: **CURE**: hospitalized within 24 hours after the onset of ACS symptoms with no ST elevation > 1mm on ECG, **plus** other ECG evidence of new ischemia or cardiac enzymes 2x ULN. **PCI-CURE**: Met enrolment criteria for **CURE** and underwent PCI.

EXCLUSION: CI to antithrombotic or antiplatelet therapy, high risk of bleeding, NYHA class IV, ongoing long-term need for anticoagulants, PCI or CABG 3 months prior, received a glycoprotein IIb/IIIa inhibitor within 3 days of randomization

POPULATION at baseline: n=2,658 of 12,562 (~21% from **CURE**)

- Mean age 61 years, 70% ♂; 21.4% from North America.[7] **CURE**: ~75% UA & ~25% NSTEMI.
- ~30% smokers, ~27% previous MI, 19% DM, 13.6% previous PCI, 12.5% previous CABG
- 42.8% ST depression, 4.8% ST elevation, **~82% stent use** drug-eluting stents were not available at the time
- **Randomization to PCI (median):** 10 days for all patients, 6 days during initial hospital stay, 49 days after initial hospital stay
- **Open-label clopidogrel:** ~25% before PCI, 83.5% overall (median 30 days [IQR 19-33])

RESULTS

follow-up: mean 8 months post-PCI (3-12 months)

TABLE: EFFICACY & SAFETY

CLINICAL ENDPOINTS	CLOPIDOGREL 300 MG X1 THEN, 75 MG OD n=1313	PLACEBO n=1345	ARR/ARI	RR (95% CI)	NNT/NNH	COMMENTS
PRIMARY ENDPOINT WITHIN 30 days of PCI (ITT Analysis)						• Composite outcome driven by reduction in MI. • All-cause mortality was not reported. • Kaplan Meier curve for primary outcome separated on day 2 after randomization, and continued to diverge throughout the trial. • All other safety endpoints were NS (e.g. trial defined major/life-threatening bleeding). • Trial defined minor bleed: any other bleeding that led to interruption of study medication. • Pre-protocol analysis excluded those who received open-label clopidogrel pre-PCI.
CV death, MI, urgent target vessel revascularization	4.5%	6.4%	1.9%	0.70 (0.50-0.97)	53 / 30 days	
SECONARY ENDPOINTS WITHIN 30 days of PCI						
CV death, MI	2.9%	4.4%	1.5%	0.66 (0.44-0.99)	67 / 30 days	
CV death	1.1%	1%	NS	1.10 (0.52-2.35)	-	
MI	2.1%	3.8%	1.7%	0.56 (0.35-0.89)	59 / 30 days	
Q-wave MI (i.e. STEMI)	0.8%	2.4%	1.6%	0.35 (0.18-0.70)	63 / 30 days	
Urgent Revascularization	1.9%	2.8%	NS	0.67 (0.41-1.11)	-	
Per-protocol analysis of composite: CV death, MI, urgent target revascularization	4.2%	7.2%	3%	0.58 (0.40-0.85)	34 / 30 days	
SECONDARY ENDPOINTS at other timeframes						
CV death, MI (overall - before & after PCI)	8.8%	12.6%	3.8%	0.69 (0.54-0.87)	27 / 8 months	
MI or refractory ischemia (before PCI)	12.1%	15.3%	3.2%	0.76 (0.62-0.93)	32 / 10 days	
MI (before PCI)	3.6%	5.1%	1.5%	0.68 (0.47-0.99)	67 / 10 days	
SECONDARY ENDPOINTS AFTER PCI TO END OF FOLLOW-UP						
CV death, MI	6%	8%	NS	0.75(0.56-1.00)	-	
CV death, MI, any revascularization	18.3%	21.7%	3.4%	0.83 (0.70-0.99)	30 / 8 months	
CV death	2.4%	2.3%	NS	1.07 0.65-1.75)	-	
MI	4.5%	6.4%	1.9%	0.71 (0.51—0.99)	53 / 8 months	
Q-wave MI (i.e. STEMI)	1.5%	3.5%	2%	0.43 (0.26-0.73)	50 / 8 months	
Any revascularization	14.2%	17.1%	NS	0.82 (0.68-1.00)	-	
SAFETY ENDPOINTS AFTER PCI TO END OF FOLLOW-UP						
Minor bleeding (trial defined)	3.5%	2.1%	1.4%	1.68 (1.06-2.68)	72 / 8 months	

ASA DOSE [7]

- The dose of ASA ranged from 75-325mg daily. The prescribed dose was at the discretion of the treating physician.
- In a subsequent publication,[7] patients from PCI-CURE were stratified into three ASA dose groups: high dose (≥200mg, median dose 325mg, n=1064), moderate dose (101-199mg, median dose 150mg, n=538) and low (≤100mg, median dose 100mg, n=1056).
- The dose of ASA did not impact ischemic events (e.g. CV death, MI, stroke), but high dose ASA increased the risk of major bleed compared to low dose ASA (NNH=35/8 months) when combined with clopidogrel.

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS:

- Important clinical endpoints (e.g. cardiovascular death, MI, bleeding) with blinded adjucation of outcomes.
- ITT analysis for efficacy, with a per-protocol analysis which excluded those who received open-label clopidogrel pre-PCI.
- Propensity score developed to minimize potential selection bias due to non-randomized PCI; score was also validated during study.
- No patients were lost to follow up.

LIMITATIONS:

- Patients recruited later in the study may have only been followed for 3 months.
- Power calculated for **CURE** not **PCI-CURE**.
- All-cause mortality was not reported.
- Patients excluded if they received a glycoprotein IIb/IIIa inhibitor within 3 days of randomization which may be part of clinical practice.
- Did not report PPI use or stent thrombosis.

UNCERTAINITIES:

- Optimal length of DAPT post-PCI.
- If the benefit pertains to patients who received PCI on initial hospitalization or in subsequent hospitalizations equally.
- Use of clopidogrel at presentation may delay CABG (clinical implications unclear).
- Guidelines recommend DAPT x 12 months based on this study, mean duration only 8 months (% patients who got 12 months therapy unknown).

Note: there was a statically significant difference in major bleeding in the **CURE** study, with a NNH=100. Gastrointestinal bleed was the most common type of major bleed.

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
- **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

♂=male **ACC**=American College of Cardiology **AHA**=American Heart Association **ARI**=absolute risk increase **ARR**=absolute risk reduction **ASA**=acetylsalicylic acid **CABG**=coronary artery bypass graft **CCS**=Canadian Cardiovascular Society **CI**=contraindication **CURE**=Clopidogrel in Unstable Angina to Prevent Recurrent Events **CV**=cardiovascular **DAPT**= dual antiplatelet therapy **DM**=diabetes mellitus **ECG**=electrocardiogram **IQR**=interquartile range **ITT**=intention to treat **LD**=loading dose **MI**=myocardial infarction **NNH**=number needed to harm **NNT**=number needed to treat **NS**=non-statistically significant **NSTEACS**=non ST-elevation acute coronary syndrome **NYHA**=New Year Heart Association **OD**=once daily **PCI**= percutaneous coronary intervention **PCI-CURE**= Percutaneous Coronary Intervention- Clopidogrel in Unstable Angina to Prevent Recurrent Events **PPI**=proton pump inhibitor **STEMI**=ST-elevated MI **ULN**=upper limit of normal

ACKNOWLEDGEMENTS: Prepared By: A. Martens, L.Kosar, B. Jensen, L. Regier

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7. Jolly SS, Pogue J, Haladyn K, et al. Effects of aspirin dose on ischaemic events and bleeding after percutaneous coronary intervention: insights from the **PCI-CURE** study. Eur Heart J. 2009 Apr;30(8):900-7. doi: 10.1093/eurheartj/ehn417.