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Clinical Question: *In patients undergoing PCI, does dual anti-platelet therapy with clopidogrel and ASA lead to better outcomes than ASA alone?*

Case:

Admit to Senior Medicine 8/28/2008

Impression: CAD

45 y/o M with PMHx of poorly controlled DMII, HTN, recent stroke, now admitted for atypical chest pain. Negative troponins, EKG shows e/o old IWMI, TTE without WMAs. Stress testing revealed e/o multivessel CAD, post-stress EF 37%. Left-heart cath (9/4) confirms multi-vessel disease—90% distal LCx, 30% proximal RCA, distal LAD 70%. Pt. now s/p DES to mid-LAD dissection and BMS to distal-LAD lesion. Pt started on ASA 325mg daily and Plavix 75mg daily. Of note, pt does not carry insurance, with Medicaid application pending.

Search Strategy:

Database: MEDLINE <1950 to September Week 2 2008>

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1. exp PCI/ [Therapy] (5201)
2. *clopidogrel/ (3456)
3. *aspirin/ (42281)
4. 1 and 3 and 2 (198)
5. limit 4 to [randomized control trial and English language and “all adult (19 plus years)”] (35)

In PICO terminology, my search was broken down into P—patients undergoing PCI, I—clopidogreal, C—aspirin, O—mortality, cardiovascular events

Journal Article:

Steinhubl SR. Berger PB. Mann JT 3rd. Fry ET. DeLago A. Wilmer C. Topol EJ. CREDO Investigators. Clopidogrel for the Reduction of Events During Observation. **Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial** [Clinical Trial. Journal Article. Multicenter Study. Randomized Controlled Trial. Research Support, Non-U.S. Gov't] JAMA. 288(19):2411-20, 2002 Nov 20.

Article Summary:

CONTEXT: Following percutaneous coronary intervention (PCI), short-term clopidogrel therapy in addition to aspirin leads to greater protection from thrombotic complications than aspirin alone. However, the optimal duration of combination oral antiplatelet therapy is unknown. Also, although current clinical data suggest a benefit for beginning therapy with a clopidogrel loading dose prior to PCI, the practical application of this therapy has not been prospectively studied. OBJECTIVES: To evaluate the benefit of long-term (12-month) treatment with clopidogrel after PCI and to determine the benefit of initiating clopidogrel with a preprocedure loading dose, both in addition to aspirin therapy. DESIGN, SETTING, AND PARTICIPANTS: The Clopidogrel for the Reduction of Events During Observation (CREDO) trial, a randomized, double-blind, placebo-controlled trial conducted among 2116 patients who were to undergo elective PCI or were deemed at high likelihood of undergoing PCI, enrolled at 99 centers in North America from June 1999 through April 2001. INTERVENTIONS: Patients were randomly assigned to receive a 300-mg clopidogrel loading dose (n = 1053) or placebo (n = 1063) 3 to 24 hours before PCI. Thereafter, all patients received clopidogrel, 75 mg/d, through day 28. From day 29 through 12 months, patients in the loading-dose group received clopidogrel, 75 mg/d, and those in the control group received placebo. Both groups received aspirin throughout the study. MAIN OUTCOME MEASURES: One-year incidence of the composite of death, myocardial infarction (MI), or stroke in the intent-to-treat population; 28-day incidence of the composite of death, MI, or urgent target vessel revascularization in the per-protocol population. RESULTS: At 1 year, long-term clopidogrel therapy was associated with a 26.9% relative reduction in the combined risk of death, MI, or stroke (95% confidence interval [CI], 3.9%-44.4%; P =.02; absolute reduction, 3%). Clopidogrel pretreatment did not significantly reduce the combined risk of death, MI, or urgent target vessel revascularization at 28 days (reduction, 18.5%; 95% CI, -14.2% to 41.8%; P =.23). However, in a prespecified subgroup analysis, patients who received clopidogrel at least 6 hours before PCI experienced a relative risk reduction of 38.6% (95% CI, -1.6% to 62.9%; P =.051) for this end point compared with no reduction with treatment less than 6 hours before PCI. Risk of major bleeding at 1 year increased, but not significantly (8.8% with clopidogrel vs 6.7% with placebo; P =.07). CONCLUSIONS: Following PCI, long-term (1-year) clopidogrel therapy significantly reduced the risk of adverse ischemic events. A loading dose of clopidogrel given at least 3 hours before the procedure did not reduce events at 28 days, but subgroup analyses suggest that longer intervals between the loading dose and PCI may reduce events.

PMID: 12435254 [PubMed - indexed for MEDLINE]

Group	Criteria or definition	N
Population screened	Participating US and Canadian sites. Planned PCI or coronary angiogram.	17898
Inclusion Criteria	1) symptomatic CAD with e/o ischemia (angina sx, positive stress, dynamic EKG changes) 2) referred for PCI or angiography with high likelihood of PCI 3) at least 21 y/o 4) provided informed consent	2116
Exclusion Criteria	1) contraindications to antithrombotic tx 2) >50% stenosis of LM 3) failed PCI within last 2 weeks, persistent ST elevation within last 24 hrs, prior administration of clopidogrel, ASA, or GpIIb-IIIa	15782
Treatment Group	Clopidogrel 300mg loading dose + Clopidogrel 75mg daily x 1year +ASA 81-325mg daily	1053
No treatment group	Placebo + ASA 81-325mg daily x 1 year	1063

Primary endpoints: 1) composite of death, MI, and stroke in the intent-to-treat population at 1 year

2) composite of death, MI, and urgent target vessel revascularization at 28 days

all randomized patients who underwent PCI

Secondary endpoints: 1) individual components of composite endpoint

2) incidence of major or minor bleeding events

Study Appraisal

- Are the results of the trial valid?

Randomized?	Yes	Blinding?	Yes
All patients accounted for at the end?	No	Equal treatment of groups?	Yes
Intention-to-treat?	Yes and no	Did randomization work?	Yes

- Are the results of the trial important?

Endpoint	Result	Significance	RRR	NNT
Primary outcome at 28 days	Death: 0 vs 4 MI: 52 vs 60 Urgent revascularization: 9 vs 12 Total: 61 vs 76	P=0.23	18.5% risk reduction for clopidogrel vs. placebo	6
Primary outcome at 28 days (pre-loading >3h and <6h prior to PCI)		P=0.60	13.4% RR for clopidogrel vs placebo	8
Primary outcome at 28 days (pre-loading <12h and >6h prior to PCI)		P=0.051	38.6% RR for clopidogrel vs placebo	3
Primary outcome at 1-year	89 vs 122	P=0.02	26.9% RR	4
Primary outcome from day 29 to 1-year		P=0.04	37.4%	3

- Can I apply these results to my patient?

1. This trial could be used to apply to my 45 year old patient who fit the inclusion criteria of the study.

2. I would pre-load him with 300mg PO Plavix at least 6h before his PCI as well as ASA 325mg. I would continue him on Plavix 75mg PO daily with ASA 81mg PO daily thereafter for 1 year. This decreases his risk for death, MI, or stroke without significantly increasing his risk of major bleeding.

- Study limitations

1. Study may have actually underestimated the long-term benefit of plavix because almost 10% of each study arm was lost to follow-up.

2. Since pt's were not randomized after the first 28 days of therapy, it is not completely possible to separate the pre-treatment effect from the long-term effect of plavix.

3. Study funded and, in part, designed by Bristol-Meyer-Squibb (manufacturer of Plavix)

4. Cannot assess whether treatment with Plavix beyond 1 year would continue to reduce risk…