

# Clopidogrel after percutaneous coronary intervention was effective

Steinhubl SR, Berger PB, Mann JT 3d, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA*. 2002;288:2411-20.

## QUESTIONS

In patients having percutaneous coronary intervention (PCI), is clopidogrel effective at 1 year? Is a loading dose of clopidogrel before PCI effective?

## DESIGN

Randomized (allocation concealed\*), blinded (clinicians, patients, outcome assessors, {data collectors, and data analysts}†),\* placebo-controlled trial with 1-year follow-up (Clopidogrel for the Reduction of Events During Observation [CREDO]).

## SETTING

United States and Canada.

## PATIENTS

2116 patients who were  $\geq 21$  years of age (mean age 61.7 y, 71% men), had symptomatic coronary artery disease with objective evidence of ischemia, and were considered likely candidates for PCI with either stent placement (with or without conventional balloon angioplasty) or another type of revascularization device. Exclusion criteria included  $> 50\%$  stenosis of the left main coronary artery; failed coronary intervention in the previous 2 weeks; and persistent ST elevation within 24 hours before the study began. Follow-up was 86% at 28 days and 100% for the intention-to-treat analysis at 1 year.

## INTERVENTION

Patients were allocated to a loading dose of clopidogrel, 300 mg ( $n = 1053$ ), or placebo ( $n = 1063$ ) at 3 to 24 hours before PCI. All patients received aspirin, 325 mg. After PCI, both groups received clopidogrel, 75 mg/d, and aspirin, 325 mg/d, for 28 days. After day 28, the clopidogrel group continued to receive clopidogrel, 75 mg/d, and the placebo group reverted to placebo. Both groups received standard therapy including aspirin, 81 to 325 mg/d, for 12 months.

## MAIN OUTCOME MEASURES

Composite of death, myocardial infarction (MI), and stroke at 1 year; composite of death, MI, or urgent target vessel revascularization at 28 days; and adverse events.

## MAIN RESULTS

Clopidogrel and placebo did not differ for the 28-day composite endpoint (Table). At

1 year, clopidogrel reduced the composite endpoint of death, MI, and stroke (Table). Major and minor bleeding rates did not differ significantly between groups.

## CONCLUSIONS

In patients having percutaneous coronary intervention (PCI), a loading dose of clopidogrel before PCI did not reduce the composite endpoint of death, myocardial infarction (MI), or target vessel revascularization. Clopidogrel after PCI reduced the composite endpoint of death, MI, and stroke at 1 year.

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\*See Glossary.

†Information provided by author.

### A loading dose of clopidogrel vs placebo before percutaneous intervention followed by clopidogrel to day 28, then clopidogrel vs placebo from day 29 to day 365†

Outcomes	Clopidogrel	Placebo	RRR (95% CI)	NNT (CI)
Composite endpoint at day 28 <sup>§</sup>	6.8%	8.3%	18.5% (-14 to 42)	Not significant
Composite endpoint at day 365 <sup>  </sup>	8.5%	11.5%	27% (3.9 to 44)	33 (20 to 233)

‡Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

§Death, myocardial infarction, and target vessel revascularization in the per-protocol population.

||Death, myocardial infarction, and stroke in the intention-to-treat population.

## COMMENTARY

As a central mediator in the development and progression of coronary artery disease and ischemic complications of acute coronary syndromes and PCI, platelets may be the link between thrombosis and inflammation (1). Platelet inhibitory therapies have therefore emerged as essential for treating acute and chronic vascular diseases (2).

With  $> 800\,000$  PCI procedures done annually in North America, reducing the risk for coronary thrombosis after a PCI-induced plaque rupture is a public health imperative. The CREDO investigators have shown the benefits of treating with clopidogrel before PCI and continuing treatment up to a year afterward. Despite their caution in interpreting the trial's 28-day results—which is appropriate given the lack of statistical significance—their hypothesis that pretreatment  $\geq 6$  hours before PCI is valuable concurs with recent data. How to apply this finding to practice, however, is a clinical conundrum. When coronary anatomy is known and PCI highly indicated, the data support clopidogrel loading followed by daily dosing. When cardiac catheterization has *not* been done and coronary anatomy is unknown, concern exists about the increased risk for bleeding in patients having bypass surgery who have received clopidogrel (3). Quantifying this risk requires study in a clinical practice environment where patients routinely have early cardiac catheterization and anatomy-driven revascularization.

It is impressive to note the 1-year benefit in CREDO when approximately 40% of patients discontinued treatment. Details on the timing of the discontinuations would be helpful to guide clinical decision-making, as would information on the degree of benefit beyond 30 days for patients with 1-vessel compared with multivessel disease.

Which patients might benefit the most and for how long are important considerations in caring for patients without prescription drug insurance—adding clopidogrel to other effective therapies, such as aspirin,  $\beta$ -blockers, statins, and angiotensin-converting enzyme inhibitors, may become financially problematic. Critical research is needed to determine which drugs or technologies add clinically important benefit to the standard of care and to gain insight into the magnitude of the benefit for specific groups.

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## References

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