Impact of pretreatment with clopidogrel on initial patency and outcome in patients treated with primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: a systematic review

Vlaar PJ, Svilaas T, Damman K, De Smet BJ, Tijssen JG, Hilleges HL, Zijlstra F

CRD summary
The review concluded that pre-treatment with clopidogrel before primary percutaneous coronary intervention for ST-segment elevation myocardial infarction significantly improved initial coronary artery patency and reduced mortality and combined death/reinfarction. The limitations of the evidence, including uncertain trial quality and a lack of direct comparisons, imply that the authors' conclusions should be interpreted with caution.

Authors' objectives
To evaluate the safety and effectiveness of pre-treatment with clopidogrel before primary percutaneous coronary intervention for ST-segment elevation myocardial infarction.

Searching
MEDLINE and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched over the past 20 years (from 1988 to 2008) for publications in English, French and German; search terms were reported. Bibliographies of each retrieved article were hand-searched.

Study selection
Randomised controlled trials (RCTs) that enrolled unselected patients with ST-segment elevation myocardial infarction (STEMI) undergoing percutaneous coronary intervention were eligible for inclusion. Eligible trials had to evaluate pre-treatment or no pre-treatment with clopidogrel before percutaneous coronary intervention. There were no inclusion criteria with respect to type of infarction or angiographic characteristics. Included trials had to report pre-percutaneous coronary intervention angiographic and clinical characteristics, symptom duration less than 24 hours, and information with regard to pre-treatment. Pre-treatment with clopidogrel was defined as any thienopyridine given before the initial coronary angiogram. Pilot trials were excluded, along with trials of patients undergoing rescue thienopyridine, and trials where angiographic data were not assessed by a core laboratory or two blinded investigators. Additionally trials where optional pre-treatment with clopidogrel, pre-treatment with glycoprotein IIb/IIIa inhibitor, or fibrinolysis was reported for patient subgroups were also excluded.

The primary outcome was initial coronary artery patency before primary percutaneous coronary intervention (defined as thrombolysis in myocardial infarction grade 2/3 flow on the initial coronary angiogram). Secondary outcomes were short-term mortality (both cardiac and non-cardiac deaths), death/reinfarction, and in-hospital major bleeding (in-hospital need for blood transfusion).

Most of the included trials, where patients received a loading dose of clopidogrel before percutaneous coronary intervention, used a dose of 300mg; the remaining study used 600mg. One 300mg clopidogrel dose trial additionally used 500mg ticlopidine. The timing of pre-treatment varied (details were provided). All the patients not pre-treated received clopidogrel after percutaneous coronary intervention. None of the included trials directly compared pre-treatment with clopidogrel with no pre-treatment with clopidogrel before percutaneous coronary intervention; their design compared the use of different techniques, stents, drugs or the timings of administration of other drugs, or placebo. All included patients received aspirin and heparin; most trials used an unfractionated heparin loading dose of 5,000 or 10,000U (or 60 or 70U/kg). Included patients' symptom duration ranged from less than six 6 to less than 24 hours; time from symptoms to admission ranged from a median 1.4 to 2.7 hours and a mean 1.7 to 6.9 hours (where reported); the time from symptoms to percutaneous coronary intervention ranged from a mean of 3.0 to 5.6 hours (where reported).

Two independent reviewers performed the study selection.
Assessment of study quality
The authors did not state that they assessed trial validity.

Data extraction
The number of events for each outcome was extracted in order to calculate percentages for each treatment group separately with 95% confidence intervals (CIs). Authors were contacted for incomplete or unclear data.

Two independent reviewers performed the extraction.

Methods of synthesis
Weighted logistic regression was used to pool the results for individual trials giving odds ratios (OR) and 95% confidence intervals. Multivariate-weighted logistic regression was then performed to account for baseline differences between treatment groups; jackknife estimation was used to find the robustness of the treatment effect. Propensity scores were also calculated based on matching of all demographic variables. Adjustments were made for age, gender, history of diabetes and hypertension, heparin dose (high or low), symptom duration, smoking and year of publication.

Results of the review
Twenty-six RCTs were included in the review (n=8,429 patients, range 27 to 2,082), comprising 38 treatment groups, of which 13 included pre-treatment with clopidogrel (in six RCTs). Short-term follow-up ranged from in-hospital to 42 days after percutaneous coronary intervention.

Initial coronary artery patency was significantly higher in the groups pre-treated with clopidogrel (34.3%, 95% CI 32.9 to 35.8; 13 groups) than in control groups (25.8%, 95% CI 24.5 to 27.1; 25 groups), with an unadjusted odds ratio of 1.53 (95% CI 1.39 to 1.68); the effect was also significant after multivariate analysis (OR 1.51, 95% CI 1.31 to 1.74).

Mortality was significantly lower in the groups pre-treated with clopidogrel (2.4%, 95% CI 2.0 to 3.0; 11 groups) than in the control groups (4.6%, 95% CI 3.9 to 5.3; 22 groups), with an unadjusted odds ratio of 0.52 (95% CI 0.41 to 0.67). The effect was also significant after multivariate analysis (OR 0.57, 95% CI 0.38 to 0.85).

Combined death/reinfarction was also significantly lower in the groups pre-treated with clopidogrel (3.3%, 95% CI 2.8 to 3.9; 11 groups) than in the untreated groups (6.3%, 95% CI 5.6 to 7.2; 22 groups), with an unadjusted odds ratio of 0.50 (95% CI 0.40 to 0.62). The effect was also significant after multivariate analysis (OR 0.54, 95% CI 0.38 to 0.75).

A pooled analysis was not possible for major bleeding since few trials reported this outcome.

Forest plots for odds ratios were not presented.

Authors’ conclusions
Initial patency and clinical outcome were improved in treatment groups that received pre-treatment with clopidogrel. These results in patients undergoing primary percutaneous coronary intervention were in line with the experience of pre-treatment with clopidogrel in elective patients, non-ST-elevation coronary syndromes, and thrombolytic studies.

CRD commentary
The review addressed a well-defined question in terms of participants, interventions, and relevant outcomes, but eligible study designs were less clearly described. Relevant databases were searched in several languages, but unpublished studies were not considered, so some relevant studies may have been missed. Publication bias was not assessed. Efforts were made to reduce error and bias in study selection and data extraction processes.

Trial quality was not assessed and very little relevant information was reported. Some relevant trial details were reported, but no details were provided of the age or gender of the participants or loss to follow-up. The authors commented that both the interventions and included groups of patients were heterogeneous and that no direct comparisons were made between no pre-treatment versus pre-treatment with clopidogrel. Therefore, it was not clear whether the pooled analysis was appropriate. Efforts were made to adjust for baseline differences between patient groups.
In view of some potential limitations arising from the review process, evidence limitations, and uncertainties about the quality of included trials, the authors' conclusions should be interpreted with caution.

Implications of the review for practice and research

**Practice:** The authors stated that the evidence suggests that it was appropriate to give a loading dose of clopidogrel to patients as early as possible after electrocardiogram confirmation of ST-elevation myocardial infarction.

**Research:** The authors implied that a pooled analysis of individual patient data and a meta-analysis of RCTs, which directly compare pre-treatment with clopidogrel with no pre-treatment before percutaneous coronary intervention in STEMI patients, were required. Using a higher loading dose of 600mg clopidogrel before primary percutaneous coronary intervention and the relative merits of prasugrel versus clopidogrel were being investigated.

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