**Meta-analysis appraising high clopidogrel loading in patients undergoing percutaneous coronary intervention**


**CRD summary**
The authors concluded that a higher clopidogrel loading dose regimen is superior to a standard (300 mg) loading regimen in patients undergoing percutaneous coronary intervention, and that the benefits are greater in patients at higher risk. This was a well-conducted review and the conclusions are likely to be reliable.

**Authors' objectives**
To compare high and standard clopidogrel loading regimens in patients undergoing percutaneous coronary intervention (PCI).

**Searching**
BioMed Central, the Cochrane CENTRAL Register, ClinicalTrials.gov and PubMed were searched to 2006. Additional studies were sought by checking the references of retrieved articles and by contacting primary investigators. There were no language restrictions. Unpublished studies (where data were unavailable from the principal investigator) and ongoing studies were not sought.

**Study selection**
Studies of patients with coronary artery disease who were scheduled for catheterisation and/or PCI were eligible for inclusion. The mean age of the participants ranged from 61 to 66 years. In all of the studies, the majority of participants were men (range: 59 to 82%).

Studies comparing high (>300 mg) and standard (300 mg) clopidogrel loading doses were eligible for inclusion. High loading doses ranged from 450 to 900 mg.

The primary outcome was the rate of cardiac death or nonfatal myocardial infarction within 1 month. The secondary outcomes included other ischaemic and bleeding adverse events, including urgent vessel revascularisation and stent thrombosis. The majority of included studies evaluated platelet function as the primary end point.

Randomised controlled trials (RCTs) and non-randomised controlled trials were eligible for inclusion. Studies with incomplete follow-up (<80%) were excluded from the review.

Two reviewers independently selected articles, with any discrepancies resolved through consensus.

**Assessment of study quality**
The quality of the included studies was assessed using criteria of the Cochrane Collaboration: randomisation, allocation concealment, evaluations of selection, performance, attrition and detection bias, and adjustment for confounders.

Two reviewers independently assessed quality, with any discrepancies resolved through consensus.

**Data extraction**
Where possible, myocardial infarction was abstracted as an increase in creatine kinase-MB mass greater than three times the upper limit of normal in at least two samples, and more than 3 hours apart. Authors were contacted for data where necessary.

Two independent reviewers extracted the data using pre-specified forms, with any discrepancies resolved through consensus.
Methods of synthesis
The pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using the Peto fixed-effect method. The authors assessed heterogeneity using the $I^2$ statistic and by using a l’Abbe plot and weighted least-squares meta-regression. Sensitivity analyses were conducted by pooling the data as relative risks, assessing the results using a random-effects method, and by sequentially excluding studies. Small study and publication biases were appraised by inspection of funnel plots and Egger's and Peter's tests.

Results of the review
Ten studies, with a total of 1,567 participants, were included in the review: 7 RCTs and 3 non-randomised controlled trials.

Seven studies used random allocation, of which three used concealed allocation. Only one study was categorised as low risk for selection, performance, attrition and detection bias; a further 4 studies were categorised as low to medium risk. Three studies adjusted for confounders.

Participants who received a high clopidogrel loading dose regimen had a significantly lower risk for cardiac death or nonfatal myocardial infarction within 1 month compared with those who received a standard clopidogrel loading dose regimen (OR 0.54, 95% CI: 0.32, 0.90, p=0.02). There was no statistical heterogeneity between the studies. There was no significant differences in major or minor bleeding between the treatment groups (p=0.55 and p=0.98, respectively), or differences in revascularisation (p=0.48) and stent thrombosis (p=0.51).

Similar results were observed when only high-quality RCTs were included in the analysis (OR 0.42, 95% CI: 0.23, 0.75, p=0.003). This resulted in a number-needed-to-treat of 33 (95% CI: 20, 200).

Meta-regression analysis did not demonstrate any significant interactions between high and standard clopidogrel loading doses and sample size, diabetes mellitus, acute coronary syndromes, aspirin dose, glycoprotein IIb/IIIa inhibitor use, unfractionated heparin use, or drug-eluting stent use. A significant interaction was found between the superiority of a high loading dose and the control event rate ($\beta=-0.147$, p=0.031).

Sensitivity analyses confirmed the direction and magnitude of significance of the overall results. There was no evidence of small study bias.

Authors' conclusions
A high clopidogrel loading dose for coronary heart disease is clinically and statistically superior to standard loading. These benefits are greater in patients at higher risk.

CRD commentary
The research question and inclusion criteria for the review were clear. The authors searched a number of databases but did not seek unpublished studies, which might have introduced publication bias. They did, however, conduct tests to assess small study bias. Language bias was minimised by searching without language restrictions. Appropriate methods were used to reduce the risk of bias and error during the review process. Validity was also appropriately assessed and incorporated into the analyses. This was a well-conducted review and the conclusions are likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that a higher clopidogrel loading dose regimen is superior to a standard (300 mg) loading dose regimen in preventing coronary ischaemic events.

Research: The authors stated that future studies should use a 600-mg loading dose as the reference treatment for comparing novel oral antiplatelet drugs with clopidogrel.

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