Benefits of clopidogrel in patients undergoing coronary stenting significantly depend on loading dose: evidence from a meta-regression


CRD summary
This review concluded that clopidogrel given with an initial loading dose is associated with a reduced risk of death or heart attack compared with ticlopidine in patients undergoing coronary stenting. The review had methodological limitations and relied mainly on short-term studies with small numbers of events, hence the conclusions should be treated with caution.

Authors' objectives
To assess the effectiveness of clopidogrel versus ticlopidine in patients undergoing coronary stenting, with specific emphasis on the role of front-loaded clopidogrel treatment.

Searching
The authors searched PubMed (to March 2006) and the reference lists of relevant articles. The search terms were reported and no language restrictions were imposed. Experts in the field were contacted for other relevant trials.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with analysis by intention-to-treat and at least 90% follow-up were eligible for the review.

Specific interventions included in the review
Studies that compared clopidogrel and ticlopidine in addition to aspirin were eligible for the review. In the included studies clopidogrel was given at a dose of 75 mg/day, with or without a larger initial loading dose (150 to 600 mg). Ticlopidine was given at a dose of 250 mg twice daily, with or without a 500-mg loading dose. Doses of aspirin ranged from 100 mg daily to 300 mg twice daily. Treatment duration ranged from 2 weeks to 6 months and follow-up from 1 to 28 months.

Participants included in the review
Studies of in-patients undergoing coronary stent implantation were eligible for the review. Details of the participants in the included studies were not reported.

Outcomes assessed in the review
Inclusion criteria for the outcomes were not explicitly stated, but the primary outcome of the review was a composite of death or nonfatal myocardial infarction (MI). Death, MI, target vessel revascularisation and the occurrence of significant blood dyscrasia (neutropenia or thrombocytopenia) were also assessed.

How were decisions on the relevance of primary studies made?
Two independent reviewers screened studies for relevance.

Assessment of study quality
The authors stated that validity was assessed using the criteria of the Cochrane Collaboration, but no results were reported. It appears that two independent reviewers performed the assessment, with any disagreements resolved by consensus.
Data extraction
Two independent reviewers extracted the data, with any disagreements resolved by consensus. Data on the numbers of events in each group were used to calculate the odds ratio (OR) and its 95% confidence interval (CI) for each outcome.

Methods of synthesis
How were the studies combined?
The studies were combined by meta-analysis using a DerSimonian and Laird random-effects model. Publication bias was assessed by inspection of funnel plots and by the Egger's and Peter's tests.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared and I-squared statistics. The effect of clopidogrel loading on the clopidogrel versus ticlopidine comparison was tested by a weighted least-squares random-effects meta-regression, with weighting by the inverse of the variance. A subgroup analysis of ticlopidine loading versus no loading was also performed.

Results of the review
Seven RCTs with 3,402 participants were included (3,382 participants included in the analyses).

Across all studies, clopidogrel and ticlopidine groups did not differ significantly for the composite primary outcome (pooled OR 0.90, 95% CI: 0.44, 1.84, p=0.77). Significant heterogeneity was present (I-squared 58.5%; p=0.02). The studies in which clopidogrel loading was used (based on six RCTs) showed a significant advantage of clopidogrel (pooled OR 0.60, 95% CI: 0.36, 0.99, p=0.05), without significant statistical heterogeneity. The two comparisons in which clopidogrel was not front-loaded showed a significant advantage of ticlopidine (pooled OR 2.31, 95% CI: 1.33, 4.0, p=0.003); again, statistical heterogeneity was not significant. The results for death and MI separately were similar to those for the primary outcome.

There were no significant differences between clopidogrel and ticlopidine for target vessel revascularisation or blood dyscrasia.

Meta-regression analysis found a significant interaction between loading dose of clopidogrel and its effectiveness relative to ticlopidine (p=0.012).

There was no evidence of publication bias from the funnel plot or statistical tests.

Authors' conclusions
Clopidogrel given with an initial loading dose is associated with a reduced risk of death or MI compared with ticlopidine in patients undergoing coronary stenting.

CRD commentary
The research question and inclusion criteria for the review were clear. The authors searched a limited range of sources so it is possible that relevant studies could have been missed. Language bias was minimised by searching without language restrictions and the risk of publication bias was assessed. Appropriate methods were used to reduce the risk of bias and error during the review process. Validity was assessed using standard methods, but the results were not reported; this makes it difficult to comment on the reliability of the included studies and the synthesis derived from them.

Limited details of the included studies were presented; a lack of information about study participants makes it difficult to assess the generalisability of the results of the review. The studies were combined by meta-analysis and differences investigated by subgroup analysis and meta-regression. The methods used seem appropriate. However, as the authors noted, most of the studies had short follow-up and small numbers of events; furthermore, meta-regression results are normally considered as hypothesis generating rather than definitive. In view of this and the methodological limitations
of the review, the authors' conclusions should be treated with caution.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that additional randomised evidence is needed to determine the safety and efficacy of high-dose (300 mg or more) clopidogrel loading regimens.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.