Increased mortality after coronary stenting in patients treated with clopidogrel without loading dose: evidence from a meta-analysis


CRD summary
This review compared clopidogrel with ticlopidine, in addition to aspirin, for the prevention of complications in patients undergoing implantation of coronary stent devices. The results indicated that clopidogrel with a loading regimen was as good as or better than ticlopidine, whereas without a loading regimen it was worse. However, with only five studies included in the review, these findings may not be definitive.

Authors' objectives
To compare the efficacy of clopidogrel (especially front-loaded clopidogrel treatment) with ticlopidine after coronary stenting.

Searching
MEDLINE (1986 to October 2003), BioMed Central, Current Contents, LILACS and the meta Register of Controlled Trials were searched; the search terms were reported. Another publication was referred to for the MEDLINE search strategy (see Other Publications of Related Interest). No language restrictions were applied. In addition, relevant reviews were sought, references quoted in the included papers were checked, and experts were contacted for other relevant trials.

Study selection
Study designs of evaluations included in the review
Only randomised controlled trials (RCTs) that used an intention-to-treat analysis were eligible for inclusion. Studies that used equivocal treatment allocation processes, had severe imbalances in baseline characteristics between study groups, or had less than 80% follow-up, were excluded.

Specific interventions included in the review
Studies in which clopidogrel was compared with ticlopidine, in addition to aspirin, in patients undergoing coronary stent implantation were eligible for inclusion. The specific dosage and initial administration regimen of the drugs were defined as either a single dose (i.e. single 75-mg tablet for clopidogrel) or loading dose (e.g. 300 mg clopidogrel). Three included studies used a loading dose, one used a single dose and one compared both.

Participants included in the review
Studies of patients undergoing coronary stent implantation were eligible for inclusion. The mean age of the participants in the included studies ranged from 59 to 65 years.

Outcomes assessed in the review
Inclusion criteria for the outcomes were not stated. The primary outcome of interest was all-cause mortality. The secondary outcomes were: combined rate of death or nonfatal myocardial infarction (MI), MI, stroke, repeat revascularisation or clinical restenosis, major bleeding, and severe haematologic adverse events. All were assessed by intention-to-treat analysis, with the longest follow-up reported for each trial and outcome.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Validity was assessed according to a modified Jadad scale, with one point awarded for each of the following criteria:
statement of objectives; explicit inclusion and exclusion criteria; description of the interventions; objective follow-up; description of adverse event assessment; power analysis; description of statistical methods; multicentre design; discussion of withdrawals; and details on long-term medical treatment after revascularisation. The degree of blinding was also assessed (0 to 2 points). The authors did not state how the papers were assessed for validity, or many reviewers performed the validity assessment.

Data extraction
Two reviewers extracted the data independently of each other, without blinding. Any disagreements were resolved by consensus. An a priori decision was made to add a value of 0.25 per group where the event rate was zero, and to perform even splitting of non-paired control groups in case of randomisation to more than two groups.

Methods of synthesis
How were the studies combined?
The binary outcomes were pooled using the Mantel-Haenszel fixed-effect model to produce pooled relative risks (RRs) with 95% confidence intervals (CIs). Funnel plots were generated to assess publication bias.

How were differences between studies investigated?
Studies were stratified a priori by single dose or loading dose, with the Breslow-Day chi-squared test used for trend. The studies were also subgrouped according to higher versus lower median quality score and the calculations were repeated using a random-effects model. Between-study heterogeneity was assessed using the Cochran Q test (considered statistically significant at P<0.1) and the I-squared test.

Results of the review
Five RCTs (n=2,962) were included.

The overall pooled RR showed no significant difference for all-cause mortality between clopidogrel and ticlopidine, with a non significant trend towards increased mortality in the clopidogrel group (RR 1.64, 95% CI: 0.94, 2.86; heterogeneity P=0.12, I-squared 66%). The combined risk of death or MI was not statistically significantly different between clopidogrel and ticlopidine (RR 1.31, 95% CI: 0.91, 1.91; heterogeneity P=0.22, I-squared 32%).

Subgroup analysis.
Clopidogrel with loading was associated with non-significantly lower mortality than ticlopidine (RR 0.68, 95% CI: 0.29, 1.63; heterogeneity P=0.64, I-squared 0%), whereas clopidogrel without loading was associated with an increased risk of death (RR 2.9, 95% CI 1.45, 6.1; heterogeneity P=0.53, I-squared not applicable). Clopidogrel without loading was also associated with a higher combined risk of death or MI (RR 1.89, 95% CI: 1.15, 3.1; heterogeneity P=0.38, I-squared 0%), whereas clopidogrel with loading showed no statistically significantly difference between clopidogrel and ticlopidine (RR 0.83, 95% CI: 0.47, 1.45; heterogeneity P=0.67, I-squared 0%).

Further analysis indicated no statistically significant differences between clopidogrel and ticlopidine in rates of MI, repeat revascularisation, stroke, major bleeding, or severe haematologic adverse effects. The use of a random-effects model and stratification according to validity score did not change the results.

The funnel plots were symmetrical.

Trend analysis with the Breslow-Day chi-squared test indicated a significant association between clopidogrel loading and risk of death (P=0.0028), as well as death or MI (P=0.026).

Authors’ conclusions
Clopidogrel treatment, including a 300-mg loading regimen, was equivalent or possibly superior to ticlopidine therapy. However, clopidogrel therapy without a loading dose may be associated with significantly more major cardiovascular events than ticlopidine.
CRD commentary
This review addressed a clear question using predefined inclusion criteria for the interventions and study designs; inclusion criteria for the trial participants and outcomes were less clear. The literature search was comprehensive with no language restrictions, and some effort seemed to have been made to search for unpublished studies. Symmetrical funnel plots indicated that it was unlikely that relevant studies were missed, although as only five studies were included the funnel plots were of limited use. A validity assessment was undertaken and, although the results were not reported in detail, validity scores were used in a sensitivity analysis. Some details of the review process (such as how many reviewers selected the studies and assessed validity) were missing, so it is possible that bias may have occurred in the process.

The meta-analysis seemed appropriate and well-conducted, with the review authors discussing the assumptions they made in the analysis to enable transparency in the interpretation of the results. The authors' conclusions follow from the evidence presented in the review, but it should be remembered that the comparison of ticlopidine and clopidogrel without a loading dose was based on only two studies (and the whole review on only five studies). Therefore, the evidence base was somewhat limited.

Implications of the review for practice and research
Practice: The authors stated that great caution should be exercised when extrapolating the results of the present review on adverse effects (which were sparse in the included studies) into clinical practice.

Research: The authors stated that more RCTs are required to estimate the safety and efficacy of novel, very high-dose loading regimens. Further research into aspirin or clopidogrel individual resistance, the interaction between clopidogrel and statins, and the implantation of heparin-coated stents is also needed, as well as an economic comparison of clopidogrel versus ticlopidine.

Bibliographic details

PubMedID
15194981

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Coronary Disease /drug therapy /mortality /surgery; Humans; Platelet Aggregation Inhibitors /administration & dosage; Randomized Controlled Trials as Topic; Stents; Ticlopidine /administration & dosage /analogs & derivatives

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Record Status
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.