Stroke prevention by cilostazol in patients with atherothrombosis: meta-analysis of placebo-controlled randomized trials


CRD summary
The authors concluded that cilostazol significantly reduced the risk of cerebrovascular events, with no associated increase in risk of bleeding for patients with atherothrombosis. This study was generally well conducted and the authors’ conclusions appear to reflect the findings, but issues with the statistical analysis should be considered when interpreting these conclusions.

Authors’ objectives
To evaluate the effects of cilostazol on ischaemic and haemorrhagic events in adults with vascular risk factors.

Searching
MEDLINE and EMBASE were searched up to August 2007. Cochrane Central Register of Controlled Trials (CENTRAL) was also searched. Articles in any language were included in the search and the search terms were reported.

Study selection
Randomised controlled trials (RCTs) were eligible for inclusion if they lasted a minimum of 12 weeks and compared oral cilostazol with placebo, in adults with vascular risk factors and at least one cardiac event, cardiovascular disease, or peripheral arterial disease. Trials where antithrombotic medication was also taken were eligible for inclusion. Trials had to report one of these outcomes: cardiac events (myocardial infarction, unstable angina, sudden cardiac death, or coronary intervention); cerebrovascular events (stroke, transient ischaemic attack, or carotid intervention); or adverse haemorrhagic events (bleeding events that were fatal, life threatening, or required hospitalisation).

Included trials evaluated cilostazol in 50mg, 100mg, or 150mg twice daily doses compared with placebo in patients with peripheral arterial disease, intermittent claudication, coronary stenting, or cerebrovascular events. The duration of trials ranged from 12 to 144 weeks. Antithrombotic medication of aspirin, clopidogrel, or both was also taken in four trials. The percentage of male patients ranged from 60.3 to 88.9 and the mean age ranged from 60 to 67.6 years. Where stated, most of the patients had hypertension. Other reported comorbidities were diabetes (12.1% to 38.8% of patients), stroke (3% to 17% in non-stroke trials), and coronary vascular disease (7.5% to 29.3%).

Several reviewers selected the trials for review, with disagreements resolved by consensus.

Assessment of study quality
The quality of the included trials was evaluated using the Jadad Scale, a three-item checklist assessing randomisation, blinding, and withdrawals or dropouts to give a maximum score of five. Several reviewers assessed the quality of the included trials and disagreements were resolved by consensus.

Data extraction
The number of vascular events, cardiac events, cerebrovascular events, and adverse events were extracted to calculate relative risks, with 95% confidence intervals. Where trials had more than one intervention group at different doses of cilostazol, these groups were combined into one intervention group.

Data were extracted by several reviewers and disagreements were resolved by consensus.

Methods of synthesis
The trials were combined for meta-analysis using a fixed-effect model. Pooled relative risks were calculated using the
asymptotic variance method. Statistical heterogeneity was assessed. Where no events were detected in either the control or the intervention group, the trial was excluded from the analysis. Publication bias was assessed using funnel plots, the fail-safe N, and Rosenthal's file drawer test.

Results of the review
Twelve double-blind placebo-controlled RCTs were eligible for the review (n=5,674 patients). One trial (n=189) had no vascular events in either group for any of the outcomes and was not included in the analysis. All trials had a Jadad score of five.

Cilostazol significantly reduced the risk of all vascular events (RR 0.86 95% CI 0.74 to 0.99; 11 RCTs, n=5,485) and cerebrovascular events (RR 0.58 95% CI 0.43 to 0.78; four RCTs, n=3,708) compared with placebo. The incidence of cardiac events and serious bleeding complications did not significantly differ between the cilostazol and placebo groups. There was no evidence of significant statistical heterogeneity for any of the outcomes. There was a very small probability of publication bias.

Authors' conclusions
Cilostazol significantly reduced the risk of cerebrovascular events, with no associated increase in risk of bleeding for patients with atherothrombosis.

CRD commentary
The review addressed a clear question with well-defined inclusion criteria. Three relevant databases were searched for articles in any language, minimising the risk of language bias. No attempts to identify unpublished data were reported, but publication bias was assessed and only a very small risk was found. Appropriate steps were taken throughout the review to minimise the risk of reviewer error and bias. A suitable validity assessment was carried out and all the included trials were of high quality. It was unclear what was used as placebo. Excluding trials with no events in one arm might have biased the results. The results were weighted mainly on three large trials and the remaining smaller trials had wide confidence intervals. Statistical heterogeneity was assessed and ruled out, but there was clinical heterogeneity between trials which might affect the generalisability of the findings. For these reasons, the suitability of the analyses is unclear.

This was a generally well-conducted study and the authors' conclusions appear to reflect the findings, but the issues mentioned above should be considered when interpreting them.

Several authors received honoraria and fees from four pharmaceutical companies, including Otsuka, the manufacturer of cilostazol.

Implications of the review for practice and research
Practice: The authors did not state any recommendations for practice.

Research: The authors did not state any recommendations for research.

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Bibliographic details

PubMedID
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.