Systematic review and meta-analysis of randomized clinical trials appraising the impact of cilostazol after percutaneous coronary intervention


CRD summary
The review concluded that cilostazol appeared effective and safe in reducing the risk of restenosis and repeat revascularisation after percutaneous coronary intervention, but that available evidence was limited by small study effects. Although there was limited reporting on some aspects of the review, the authors' conclusions were suitably cautious in reflecting the evidence available and appear likely to be reliable.

Authors' objectives
To compare the risks and benefits of cilostazol with control therapy following percutaneous coronary intervention (PCI).

Searching
BioMed Central, Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, EMBASE and PubMed were searched to November 2007. There were no language restrictions. References of included studies and relevant reviews were searched.

Study selection
Randomised trials that compared cilostazol with a control treatment in patients who had a PCI and were followed up for at least a month were eligible for inclusion. Studies with a lack of outcome data beyond hospitalisation were excluded. Primary outcomes were midterm risk of binary angiographic restenosis and rate of repeat revascularisation at the longest available follow-up. Secondary outcomes were rates of major adverse cardiac events (death, myocardial infarction and repeat revascularisation), stent thrombosis and bleeding.

Most included studies were of patients who received bare metal stents. Some patients received percutaneous transluminal coronary angioplasty, drug-eluting stents or directional coronary atherectomy. All studies except one used 200mg of cilostazol; one study used 100mg cilostazol. Most studies also used aspirin. In some studies cilostazol was combined with clopidogrel, warfarin or probucol. Comparator treatments varied, but were mostly comprised of ticlopidine (or clopidogrel) plus aspirin.

The authors did not state how many reviewers selected studies for inclusion.

Assessment of study quality
Study quality was assessed according to the Cochrane Collaboration methods of appraisal of risk of selection, performance, adjudication and attrition bias. Studies were rated as having a high or low overall risk of bias (it was unclear how this was done).

The authors did not state how many reviewers assessed study quality.

Data extraction
Two reviewers independently extracted data to enable calculation of relative risks (RR) and odds ratios, with 95% confidence intervals (CI). Disagreements were resolved by consensus.

Methods of synthesis
Meta-analyses were performed to calculate pooled relative risks using a random effects model. Statistical heterogeneity was assessed using $\chi^2$ and $I^2$. Sensitivity and subgroup analyses (mostly related to treatments and statistical methodology) were prespecified by the authors. Publication bias was assessed using funnel plots and Egger's & Peters' test.
Results of the review
Twenty-three studies (n=5,428, range 35 to 705 participants) were included. Thirteen studies had a low risk of bias and 10 studies had a high risk of bias. Median follow-up was six months (range one to 36 months).

Cilostazol was associated with statistically significant reductions in risk of binary angiographic restenosis (RR 0.60, 95% CI 0.49 to 0.73, I²=53%; 21 studies) and repeat revascularisation (RR 0.69, 95% CI: 0.55 to 0.86, I²=40%;15 studies). There was evidence of publication bias in both analyses (both p<0.001). There were no significant increases in risk of stent thrombosis or bleeding (23 studies). There was a trend for fewer major adverse events following treatment with cilostazol (RR 0.75, 95% CI 0.56 to 1.00).

Subgroup and sensitivity analyses (which included analyses for only studies with a low risk of bias) yielded similar results.

Authors' conclusions
Cilostazol appeared effective and safe in reducing risks of restenosis and repeat revascularisation after PCI, but available evidence was limited by small study effects.

CRD commentary
The review addressed a clear question supported by appropriate inclusion criteria. Attempts to identify relevant studies in any language were undertaken by searching electronic databases and checking references. No specific attempt was made to identify unpublished studies; analyses suggested there was evidence that the review was subject to publication bias. Suitable methods were employed to reduce risks of reviewer error and bias during data extraction; there were no details of whether such methods were used during study selection and quality assessment. Sufficient study details were provided. Appropriate methods were used to pool the data using meta-analyses. Study quality was assessed and the results were used in a sensitivity analysis. No detailed results for the quality assessment and the methods by which ratings were assigned were presented, which made it difficult to fully evaluate the risk of bias.

The authors' conclusions were suitably cautious in reflecting the evidence available and appear likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that cilostazol treatment can be envisaged on top of aspirin and thienopyridines in selected patients where drug-eluting stents were contraindicated or there was a need for further neointimal hyperplasia inhibition. The authors discouraged the adoption of an antithrombotic regimen based on aspirin and cilostazol only after PCI, because it appeared to increase the hazard of stent thrombosis.

Research: The authors stated a need for larger randomised trials.

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