A meta-analysis of randomized controlled trials appraising the efficacy and safety of cilostazol after coronary artery stent implantation


CRD summary
This review concluded that cilostazol added to aspirin and thienopyridine seemed effective in reducing the risk of restenosis and repeat revascularisation after percutaneous coronary interventions. Most of the studies were subject to a high risk of bias. Despite this the review was well-conducted and results of the included studies were consistent; the overall conclusion is likely to be reliable.

Authors' objectives
To evaluate the impact of cilostazol on angiographic and clinical outcomes in patients who underwent percutaneous coronary intervention (PCI) with stents and treated with aspirin and thienopyridine.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched without language restrictions from 2001 to March 2012; search terms were reported. Reference lists of included studies and meta-analyses were searched.

Study selection
Randomised controlled trials (RCTs) that compared antiplatelet therapy using aspirin and a thienopyridine with and without cilostazol in patients who underwent stent implantation were eligible for inclusion. Studies had to report angiographic or clinical outcomes beyond platelet function; the primary outcomes were in-segment late loss and angiographic restenosis.

Across the trial arms, mean ages ranged from 57 to 68 years, 58% to 76% of participants were male, 46% to 69% had hypertension, 20% to 100% had diabetes, where reported 34% to 100% had acute coronary syndrome and mean left ventricular ejection fraction ranged from 55% to 62%. Most studies used various drug-eluting stents. Most of the included studies were conducted in high-risk populations. Most studies were conducted in Asian countries.

Two independent reviewers selected studies for the review; disagreements were resolved by consensus.

Assessment of study quality
Two independent reviewers assessed study quality in terms of randomisation, allocation concealment, completeness data and blinding of outcome assessors.

Data extraction
Two independent reviewers extracted data to calculate odds ratios (OR) for binary outcomes and mean differences for continuous outcomes, with 95% confidence intervals (CI).

Methods of synthesis
Pooled odds ratios and weighted mean differences (WMD), with 95% CI, were calculated using a fixed-effect model where heterogeneity was absent and random-effects where heterogeneity was present. Heterogeneity was investigated using the Cochran Q and I² statistics. Subgroup analyses were used to investigate the impact of stent type. Sensitivity analyses were conducted to assess the impact of individual trials. Potential for publication bias was assessed using the Duval and Tweedie trim and fill method and Egger’s regression.

Results of the review
Eleven RCTs were included in the review. Follow-up ranged from one to 12 months. Four studies had a low risk of selection bias, three had a low risk of performance bias, three had a low risk of attrition bias, two had a low risk of detection bias and four were considered to have adequately adjusted for potential confounders.
Adding cilostazol to dual therapy with aspirin and a thienopyridine reduced in-segment late loss (WMD 0.14, 95% CI 0.08 to 0.20; $I^2$=54%), angiographic restenosis (OR 0.58, 95% CI 0.48 to 0.71; $I^2$=0%), target lesion revascularisation (OR 0.56, 95% CI 0.41 to 0.77; seven studies; $I^2$=16%) and major adverse cardiovascular events (OR 0.72, 95% CI 0.60 to 0.86; 10 studies; $I^2$=14%). There was no impact on mortality (seven studies), stent thrombosis (seven studies) and major bleeding (seven studies).

There was no strong evidence for publication bias. Results for bare-metal and drug-eluting stents individually were reported.

**Authors' conclusions**
Cilostazol in addition to dual antiplatelet therapy appeared to be effective in reducing the risk of restenosis and repeat revascularisation after PCI without any significant benefits for mortality or stent thrombosis.

**CRD commentary**
The review addressed a clear review question supported by reproducible inclusion criteria. Relevant sources were searched without language restrictions. There seemed to be no specific attempt to locate unpublished studies. Each stage of the review process was conducted in duplicate, which reduced the risk of error and bias. Appropriate criteria were used to assess study quality and the results were reported in full. Most of the studies had a period of follow-up of six months or less, which the authors acknowledged as a limitation of the evidence. Appropriate methods of synthesis were used.

This was generally a well-conducted review but most of the included studies were subject to a high risk of bias and the reliability of the results of the primary studies, and therefore the pooled results, was uncertain. Despite this, the results of the included studies were consistent for most outcomes and the overall conclusion is likely to be reliable.

**Implications of the review for practice and research**
**Practice:** The authors stated that the benefit of triple therapy could be more pronounced in patients with long coronary lesions and in diabetic patients who were at higher risk of restenosis. They went on to state that the lack of any study demonstrating the superiority of dual antiplatelet therapy suggested that cilostazol-based triple therapy should be the optimal antiplatelet regimen in high-risk patients undergoing stent-based PCI.

**Research:** The authors did not report implications for research.

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