Addition of cilostazol to aspirin and a thienopyridine for prevention of restenosis after coronary artery stenting: a meta-analysis

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CRD summary
This review concluded that adding cilostazol to dual antiplatelet therapy (aspirin and thienopyridine) reduced angiographic restenosis at six months after coronary artery stenting, without affecting major adverse cardiac events or bleeding. Overall, the review appeared adequately conducted and the conclusions likely to be reliable.

Authors' objectives
To evaluate the effect of adding cilostazol to dual antiplatelet therapy (aspirin and thienopyridine) on rates of restenosis after coronary artery stenting.

Searching
MEDLINE and EMBASE (both from inception to January 2009), CINAHL (from inception to October 2008), and the Cochrane Database of Systematic Reviews (dates not specified) were searched. Search terms were reported. Only studies published in English were included. Reference lists of included papers and reviews were searched for further relevant papers.

Study selection
To be eligible for inclusion, studies had to use a randomised controlled parallel group design and compare triple versus dual antiplatelet therapy. Eligible trials were also required to report data on angiographic restenosis.

In included trials, aspirin doses ranged from 100 to 200mg/day (where reported), clopidogrel doses were 75mg/day for one or six months, and cilostazol doses were 100mg twice daily for six months. One trial used ticlopidine (250mg/day) instead of clopidogrel. In included trials, either bare-metal stents or drug-eluting stents were used. The mean age of participants ranged from 57 to 63 years; the proportion with diabetes ranged from 23 to 100%; participants who smoked ranged from 24 to 61%; the proportion men ranged from 59 to 76%; participants with hypertension ranged from 28 to 66%.

The primary endpoint was the incidence of angiographic restenosis at six months (defined as 50% or more narrowing of the reference lumen diameter). Secondary endpoints included coronary artery minimal luminal diameter, and in-stent and in-segment late loss. Rates of target vessel revascularization, major adverse cardiac events, and bleeding were also extracted.

The authors did not state how reviewers selected studies for the review.

Assessment of study quality
Trials were assessed using the Jadad scale, and assigned a score of between zero and a maximum of 5.

The number of reviewers involved in this stage of the process was not stated.

Data extraction
Data were extracted in order to calculate mean differences and odds ratios.

The authors did not state how many reviewers performed the validity assessment.

Methods of synthesis
Odds ratios (ORs) for continuous data, and mean differences (MDs) for dichotomous data, with 95% confidence intervals (CIs), were pooled using a fixed-effect model. The $X^2$ test was used, with a threshold of $p<0.10$ interpreted as indicating the presence of heterogeneity.

Two a priori subgroup analyses were planned, comparing the effect of stent type (drug-eluting versus bare-metal), and
duration of thienopyridine therapy (one versus six months) on outcome.

Two sensitivity analyses were conducted, assessing the effects of excluding trials with a Jadad score of less than 3 out of 5, and of using a random-effects rather than fixed-effect model.

A funnel plot was used to assess the potential for publication bias.

**Results of the review**

Five RCTs were included in the review (n=1,597 patients in text, 1,591 patients in table 1; range 59 to 500 patients). One trial scored 4 points on the Jadad scale, two RCTs scored 3, and two RCTs scored 2.

**Primary endpoint:** The pooled odds ratio for stenosis at six months was 0.50 (95% CI 0.38 to 0.66), favouring triple over dual therapy; heterogeneity was not significant (I²=0%).

**Secondary endpoints:** Coronary artery minimal luminal diameter favoured triple over dual therapy (mean difference 0.18mm, 95% CI 0.1 to 0.27). In-segment and in-stent late loss were reported and significantly lower in patients receiving triple therapy (three RCTs comprising 90% of the patients). Bleeding rates were not statistically significantly different between double and triple therapy groups (three RCTs).

**Subgroup analyses:** No significant difference in outcome was identified related to the type of stent used or the duration of thienopyridine therapy.

**Sensitivity analyses:** The results did not differ substantially when trials with Jadad scores of 2 or less were excluded, or for a random-effects rather than fixed-effect model.

The funnel plot was reported to be asymmetrical, raising the possibility of publication bias.

**Authors’ conclusions**
The addition of cilostazol to standard dual antiplatelet therapy reduced angiographic restenosis and increased minimal luminal diameter at six months after coronary artery stenting, without affecting major adverse cardiac events or bleeding.

**CRD commentary**
The review question was clear. Study selection criteria appeared to be clear and appropriate. The search appeared comprehensive for the databases searched, although the restriction to studies published in English increased the risk of language bias. The lack of a search for unpublished studies increased the risk of publication bias. The number of reviewers involved and how the review stages were conducted were not reported, raising the possibility of reviewer error and bias.

A quality assessment was conducted using a standard tool and used in the sensitivity analyses. Details of which studies satisfied which study quality criteria were not reported, reducing review transparency and repeatability. Sufficient primary trial details were reported. The methods of syntheses, including subgroup comparisons and sensitivity analyses, appeared appropriate (although the results for assessment of heterogeneity were only presented for the primary outcome).

Overall, the review appeared adequately conducted, the results clear, and the conclusions likely to be reliable or understated given the evidence presented.

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

**Practice:** The reviewers stated that more data are needed before this regimen can be routinely used in patients undergoing PCI.

**Research:** The reviewers stated that, to gauge the possible risks associated with triple antiplatelet therapy, additional studies powered to assess the effect of this regimen on bleeding must be completed. Additionally, studies that include patients with myocardial infarction and provide information on the peri-PCI anti-coagulation regimen would be of value, as would trials that focus on clinical end points like target-vessel revascularization and major adverse cardiac
events.

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