Comparative safety and efficacy of a sirolimus-eluting versus paclitaxel-eluting stent: a meta-analysis

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CRD summary
This review compared sirolimus-eluting stents to paclitaxel-eluting stents used with percutaneous coronary intervention. The authors concluded that compared to paclitaxel-eluting stents, sirolimus-eluting stents reduced the need for revascularisation. There were no differences in mortality, myocardial infarction or stent thrombosis. Follow-up was six to 12 months. Some methods of the review were not well reported, but the conclusions appear reasonable.

Authors' objectives
To compare the effects of paclitaxel-eluting stents with sirolimus-eluting stents in people with coronary artery disease.

Searching
MEDLINE, EMBASE, ISI Web of Knowledge, Current Contents, International Pharmaceutical Abstracts and Cochrane Central Register of Controlled Trials were searched from 1990 to November 2006. The search terms were reported. Abstracts from relevant scientific meetings (2005 and 2006), relevant identified reviews and editorials, and internet sources were checked. Relevant manufacturers were contacted.

Study selection
Randomised controlled trials (RCTs) that compared sirolimus-eluting stents to paclitaxel-eluting stents in people who underwent percutaneous coronary intervention (PCI), and that reported at least one relevant outcome, with a follow-up of 6 months or more, were eligible for inclusion. The outcomes of interest were death, myocardial infarction, angiographic stent thrombosis, target lesion revascularisation (TLR) and target vessel revascularisation (TVR). Target lesion revascularisation was defined as repeat revascularisation (percutaneous coronary intervention or coronary artery bypass graft) in the index lesion. Target vessel revascularisation was defined as repeat revascularisation on the same vessel proximal or distal to the index lesion. Restenosis was defined as a diameter stenosis of 50% or more on follow up angiography. Clinical target vessel revascularisation and target lesion revascularisation were assessed separately.

Mean age of participants, where given, ranged from 55 to 68 years. The proportion of men ranged from 61% and 83%. Indications for percutaneous coronary intervention ranged from stable coronary disease to acute ST elevation myocardial infarction. One study was on people with diabetes, in the other studies between 15% and 40% of participants had diabetes. Where given, mean lesion lengths ranged from 11.5mm to 34.5mm and vessel diameter ranged from 2.4mm to 3.2mm. Clinical follow up ranged from six to 12 months and angiographic follow up from six to eight months.

The authors stated neither how the papers were selected for the review nor how many reviewers performed the selection.

Assessment of study quality
Study quality was assessed by evaluating aspects of study design (allocation concealment, intention to treat analysis, blinding of outcome measures).

The authors did not state how the validity assessment was performed.

Data extraction
Numbers and percentages of outcome events were extracted. Odds ratios were calculated for relevant outcomes in the individual studies. Where no events occurred in one or both groups within a particular study it was excluded from pooling of data for that outcome for the main analyses; adjusted data were included in subsidiary analyses.

All analyses were performed on an intention to treat basis.
Date were extracted independently by two reviewers. Disagreements were resolved by consensus. Where necessary, authors of studies were contacted for missing information.

**Methods of synthesis**

Pooled odds ratios with 95% confidence intervals (CI) were calculated using both a fixed-effect and random-effects models. Pooled risk differences were calculated for target vessel revascularisation. Projected numbers needed to treat to prevent one target vessel revascularisation were calculated using a hypothetical risk of restenosis.

In order to assess the effect of any potentially missed studies, the reviewers calculated the number of additional studies that would have been needed to nullify results for target vessel revascularisation between the two treatments. They used Orwin's and Rosenberg's methods.

Heterogeneity was assessed using the Cochran Q test. To assess the effects of individual studies analyses were repeated, removing one study at a time.

**Results of the review**

Twelve RCTs (7,455 participants) were included.

Results for fixed-effect and random-effects analyses were similar. Fixed effect were reported. There was no evidence of heterogeneity for any of the analyses (p>0.10).

Pooled incidence of death was 1.7% with sirolimus-eluting stents and 1.9% with paclitaxel-eluting stents (12 trials). There was no difference in mortality between sirolimus-eluting stents and paclitaxel-eluting stents (odds ratio 0.88, 95% CI: 0.61 to 1.25, p=0.46; nine trials). When studies with no events in one or both study arms were included, using continuity correction, results were similar (odds ratio 0.89, 95% CI: 0.63 to 1.28).

Pooled incidence of myocardial infarction was 3.5% with sirolimus-eluting stents and 3.8% with paclitaxel-eluting stents (10 trials). There was no difference in the risk of myocardial infarction (odds ratio 0.92, 95% CI: 0.71 to 1.19, p=0.51; nine trials).

There was no difference in the incidence of stent thrombosis: 0.93% with sirolimus-eluting stents and 1.01% with paclitaxel-eluting stents (odds ratio 0.75, 95% CI: 0.40 to 1.40, p=0.37; four trials). When all 11 studies were included using continuity correction, results were similar (odds ratio 0.90, 95% CI: 0.52 to 1.69; p=0.35).

Sirolimus-eluting stents reduced angiographic restenosis compared to paclitaxel-eluting stents (odds ratio 0.64, 95% CI: 0.52 to 0.78, p<0.001; eight trials). Removing one trial significantly altered results, but not the direction of effect (odds ratio 0.50, 95% CI: 0.38 to 0.65)

Compared to paclitaxel-eluting stents, sirolimus-eluting stents reduced target lesion revascularisation (4.50% versus 6.63%; odds ratio 0.67, 95% CI: 0.53 to 0.84, p=0.001; nine trials) and target vessel revascularisation (5.66% versus 7.70%; odds ratio 0.72, 95% CI: 0.59 to 0.88, p=0.002; eight trials). When results were restricted to people who underwent target lesion revascularisation or target vessel revascularisation for clinical reasons the results were similar (see paper for details).

Removing individual studies from analyses did not significantly change findings for all outcomes other than for angiographic stenosis (see above).

The absolute risk difference for target vessel revascularisation between sirolimus-eluting stents and paclitaxel-eluting stents was 0.02 (95% CI: 0.033 to 0.008; 12 studies). The paper included a graph that showed numbers needed to treat according to expected risk of target vessel revascularisation.

The classic fail-safe test indicated that 23 studies that showed no effect between paclitaxel-eluting stents and sirolimus-eluting stents would be required to nullify the results of analysis. Orwin's fail-safe suggested that four studies with a mean odds ratio of 2 in favour of paclitaxel-eluting stents would be needed to change the direction of effect between
treatments.

**Authors' conclusions**
Sirolimus-eluting stents were more effective than paclitaxel-eluting stents at reducing the need for target lesion revascularisation or target vessel revascularisation. There was no evidence of any difference in the incidence of death, myocardial infarction or stent thrombosis.

**CRD commentary**
The aims and inclusion criteria for this review were clearly stated. The search covered a number of sources, including looking for unpublished studies. This is likely to have minimised the possibility of publication bias. There was no mention of any language restrictions which, if used, could have introduced language bias into the review. The method of study selection was not described, but data extraction was performed in a way that should have minimised the introduction of reviewer bias or error. Quality was assessed, but the results of quality assessment were not reported. Appropriate statistical methods were used to pool data and to investigate differences between studies. As the authors commented, the timescale of follow-up may have been too short to pick up some effects of the interventions. Although some methods of the review were not reported, the authors conclusions appear reasonable.

**Implications of the review for practice and research**
**Practice**: The authors stated that as the absolute clinical advantage of sirolimus-eluting stents over paclitaxel-eluting stents was strongly related to the baseline risk of restenosis, patients at high risk were likely to benefit from sirolimus-eluting stent use.

**Research**: The authors did not state any implications for further research.

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