Drug eluting stents: an updated meta-analysis of randomised controlled trials
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CRD summary
This review assessed the effects of sirolimus and paclitaxel drug-eluting stents (DES) for coronary disease. The authors concluded that DES were very effective in reducing restenosis and major cardiac events. Based on less reliable indirect comparisons, sirolimus appeared more effective than paclitaxel. Overall, given the lack of an assessment of study validity and the significant variation between studies, these conclusions may not be reliable.

Authors' objectives
To assess the effects of drug-eluting stents (DES) in the treatment of coronary artery disease.

Searching
MEDLINE (January 1966 to September 2005) and the Cochrane Controlled Trials Register were searched; the search terms were reported. Meeting abstracts from the American Heart Association, the American College of Cardiology, the European Society of Cardiology and Transcatheter Cardiovascular Therapeutics (January 2000 to September 2005) were screened. The authors also searched online sources (theheart.org and tctmd websites) and checked the reference lists of identified studies.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with at least 6 months' follow-up were eligible for inclusion.

Specific interventions included in the review
Studies that compared paclitaxel or sirolimus (or analogues of either drug) DES with bare metal stents (BMS) were eligible for inclusion. The included studies assessed sirolimus and its analogues everolimus and biolimus, and the paclitaxel analogues 7-hexanoyltoxol, slow/moderate release polymer-based paclitaxel and non-polymer-based paclitaxel.

Participants included in the review
Individuals undergoing percutaneous coronary angioplasty with stent implantation were eligible for inclusion. The mean ages of participants in the included studies ranged from 60 to 66.5 years. Some participants had diabetes and/or a previous myocardial infarction (MI). Where reported, lesion lengths ranged from 9.6 to 20.6 mm and reference diameters from 2.2 to 3.0 mm.

Outcomes assessed in the review
The primary outcomes of interest were angiographic binary restenosis of more than 50% of luminal diameter and major adverse cardiac events (MACE), which was a combined outcome of death, MI and revascularisation. Deaths, Q-wave and non-Q-wave-MI and stent thrombosis rates were also reported. Definitions of percutaneous revascularisation and restenosis were reported.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Two reviewers independently extracted the data. Any disagreements were resolved by consensus. Where outcomes were reported as percentages, absolute numbers of events were calculated. The odds ratio (OR) and 95% confidence interval (CI) were calculated for each outcome.

**Methods of synthesis**

**How were the studies combined?**

Where there was no evidence of heterogeneity, the pooled OR and 95% CI were calculated using a fixed-effect method. If heterogeneity was present, a random-effects model was used. Publication bias was assessed using funnel plots and by calculating the number of neutral trials needed to induce a non significant effect.

**How were differences between studies investigated?**

The chi-squared test was used to assess heterogeneity. Subgroup analyses were performed according to drug used (sirolimus and analogues; paclitaxel and analogues), and including only commercially available DES. The relationship between the baseline risk of the population and the effects was assessed using the Walter weighted regression method. Sensitivity analyses were carried out by removing the 3 largest trials.

**Results of the review**

Nineteen RCTs (8,987 participants: 4,574 with DES and 4,413 with BMS) were included.

Rates of restenosis were significantly lower in the DES groups compared with the BMS groups: 10.5% in the DES group (19 studies) versus 31.7% with BMS (OR 0.25, 95% CI: 0.22, 0.29, p<0.001), 7.6% in the sirolimus subgroup (9 studies) versus 36.8% with BMS (OR 0.14, 95% CI: 0.11, 0.17, p<0.01), and 12.4% in the paclitaxel subgroup (10 studies) versus 28.4% with BMS (OR 0.35, 95% CI: 0.30, 0.41, p<0.001).

Rates of MACE were significantly lower in the DES groups compared with the BMS groups: 19.9% in the DES group (19 studies) versus 10.1% with BMS (OR 0.46, 95% CI: 0.41, 0.52, p<0.001), 7.4% in the sirolimus subgroup (9 studies) versus 21.9% with BMS (OR 0.28, 95% CI: 0.22, 0.35, p<0.001), and 12% in the paclitaxel subgroup (10 studies) versus 18.3% with BMS (OR 0.62, 95% CI: 0.53, 0.73, p<0.001).

However, no significant differences were observed between DES groups and BMS groups with respect to the individual outcomes of mortality, Q-wave MI and non-Q-wave MI events.

No significant differences were observed between DES groups and BMS groups with regard to stent thrombosis.

In the sensitivity analyses, the removal of three of the largest studies did not alter the overall effect on MACE or binary restenosis.

In the effect model, the effectiveness of sirolimus stents improved with increasing baseline risk in the control groups; the effectiveness of the paclitaxel stents remained constant regardless of baseline risk.

Tests for publication bias suggested that 10 negative studies would be needed to affect the meta-analysis results for MACE or binary restenosis.

**Authors' conclusions**

There was a very significant overall benefit with DES on restenosis and MACE. There was significant heterogeneity between results for sirolimus and paclitaxel, suggesting a higher efficiency of sirolimus-eluting stents.

**CRD commentary**

The aims and inclusion criteria of this review were clearly defined. A number of relevant sources were searched but there was no mention of any language restrictions. Tests were conducted to assess publication bias. The methods of study selection were not described, although those for the data extraction were appropriate for minimising the introduction of bias or error. There was no mention of any quality assessment of the included studies, so it was
difficult to assess the reliability of the data.

Some of the comparisons made within the review relied on indirect comparisons between studies; the results of these comparisons are considered to be less robust than those from direct comparisons. The statistical and clinical heterogeneity between studies also raises concerns about the reliability of the indirect comparisons and the appropriateness of pooling the data. Thus, the authors’ conclusions may not be reliable, in particular with regard to differences between the two DES types. However, the authors commented that another review on this topic came to similar conclusions using direct comparisons (see Other Publications of Related Interest no.1). Overall, given the analyses presented and the lack of an assessment of study validity, the authors’ conclusions seem overstated and may not be reliable.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that studies with longer term follow-up and in high-risk populations are needed to assess the effects on stent thrombosis.

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