Efficacy of drug eluting stents in patients with and without diabetes mellitus: indirect comparison of controlled trials

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CRD summary
This well-conducted review assessed the effects of sirolimus and paclitaxel drug-eluting stents (DES) for coronary disease. The authors concluded that DES are effective in reducing restenosis and revascularisation in patients with and without diabetes; sirolimus appeared more effective than paclitaxel in non-diabetics, whereas both had similar effects in diabetics. Given the reliance on indirect evidence the findings should be interpreted with some caution.

Authors' objectives
To assess whether polymer-based coronary stents eluting sirolimus or paclitaxel stents are as effective in people with and without diabetes.

Searching
MEDLINE, EMBASE and the Cochrane Controlled Trials Register were searched from inception to April 2004 for studies in any language. Reference lists of relevant studies or reviews, book chapters, conference abstracts, specialist journals and proceedings of relevant U.S. Food and Drug Administration advisory panels were checked.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with at least 4 months' follow-up were eligible for inclusion. In the included studies, the mean follow-up periods ranged from 6 to 9 months for angiographic outcomes and 8 to 24 months for clinical outcomes.

Specific interventions included in the review
Studies that compared commercially available polymer-based drug-eluting stents (DES) (eluting sirolimus or paclitaxel) with bare metal stents (BMS) were eligible for inclusion.

Participants included in the review
Studies of people with stable or unstable angina and signs of myocardial ischaemia, with a new target lesion in a native coronary artery, were eligible for inclusion. One study was on people with diabetes, whereas in the other studies those with diabetes represented a subgroup of participants. Overall, 25% of the included participants had diabetes, between 28% and 42% had a previous myocardial infarction (MI), and others had hypertension, dyslipidaemia or were smokers. All of the included studies excluded people with a recent MI, a stenosis of at least 50% in the left main coronary artery, or those with heart failure. The majority of the participants were males over the age of 60 years.

Outcomes assessed in the review
The outcomes of interest were in-stent restenosis (50% or greater confirmed by angiography or ultrasound), in-segment restenosis (50% or greater confirmed by angiography or ultrasound), target lesion revascularisation (coronary artery bypass graft, repeat percutaneous coronary intervention at or adjacent to stent site) and major adverse cardiac events (Q-wave and non Q-wave MI, revascularisation or death).

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed papers for inclusion. Any discrepancies were resolved through discussion with a third reviewer.

Assessment of study quality
Two reviewers independently assessed studies for quality. Any disagreements were resolved through discussion with a third reviewer. Factors considered were adequacy of allocation concealment to treatment groups and blinding of the care providers and research staff assessing outcomes.

**Data extraction**
Two reviewers independently extracted the data. Any disagreements were resolved through discussion with a third reviewer. Authors from the included studies were contacted and asked to check the extracted data and, where necessary, provide additional data.

Incidence rates were calculated in individual studies by dividing the number of events by the number of person-years at follow-up. Incidence rate ratios (IRRs) were calculated by dividing the incidence in the DES group by the incidence in the BMS group. Studies with no outcome event in either group were excluded. Where studies had events in only one group, 0.5 was added to all cells in the analysis.

**Methods of synthesis**

How were the studies combined?
Pooled IRRs with 95% confidence intervals (CIs) were calculated separately for all participants and for those with or without diabetes using crude and adjusted indirect fixed-effect meta-analyses. A random-effects meta-regression model was used to calculate the ratio of IRRs (RIRR) between the two DES types. Numbers-needed-to-treat to prevent one event were calculated, along with 95% CIs. Funnel plots were used to assess publication bias.

How were differences between studies investigated?
I-squared statistics, together with standard tests, were used to assess heterogeneity. Sensitivity analyses were carried out using a random-effects model. In addition, the data were reanalysed to correct for angiographic-driven revascularisation.

**Results of the review**

Ten RCTs (4,513 participants: 1,146 with diabetes and 3,367 without) were included; 6 studies were of sirolimus DES and 4 studies were of paclitaxel DES. In two of the included studies randomisation was stratified according to diabetic status.

The trials were of a high methodological quality.

Compared with BMS, DES were associated with substantial reductions in the risk of restenosis. This reduction was greater with sirolimus- than with paclitaxel-eluting stents (in-stent restenosis, RIRR 0.35, 95% CI: 0.21, 0.57; in-segment restenosis, RIRR 0.68, 95% CI: 0.45, 1.01).

Sirolimus-eluting stents were statistically superior to paclitaxel-eluting in patients without diabetes with regard to in-stent restenosis (RIRR 0.21, 95% CI: 0.10, 0.48, p<0.001), in-segment restenosis (RIRR 0.47, 95% CI: 0.24, 0.92, p=0.027), target lesion revascularisation (RIRR 0.54, 95% CI: 0.30, 0.99, p=0.045) and major adverse events (RIRR 0.46, 95% CI: 0.26, 0.83, p=0.010). No significant differences between the two different DES were identified for any of the end points in patients with diabetes. A significant difference between patients with and without diabetes was identified using meta-regression (tests for interaction: p=0.036 and p=0.016 for in-stent restenosis and in-segment restenosis, respectively).

**Authors' conclusions**
DEs result in substantial reductions in restenosis and revascularisation rates in people with or without diabetes. Indirect comparisons showed that sirolimus-eluting stents appear more effective than paclitaxel-eluting stents in people without diabetes, but their efficacy seems comparable in people with diabetes.
CRD commentary
The aims and inclusion criteria for this review were clearly stated. The search covered a range of both published and unpublished sources. Methods used for the study selection, quality assessment and data extraction processes were appropriate for minimising the introduction of errors or bias. Study quality was assessed appropriately and details of the included studies were described.

The authors discussed the limitations of the review with regard to the use of indirect comparisons. They noted that the included studies recruited similar populations, but that the results obtained from indirect comparisons should be interpreted with some caution as they are not as robust as results from trials that directly compare treatments. This was a well-conducted review, however, as the reviewers acknowledged, the findings should be interpreted with caution given the limitations of the studies and the indirect analyses.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that a collaborative individual patient data meta-analysis should be performed to assess the effects of the two different DES systems in people with or without diabetes and, more generally, between people in higher or lower risk groups.

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