Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents

CRD summary
This well-conducted review using individual patient data compared the long-term effects of sirolimus-eluting stents and bare metal stents. The authors found no difference in overall long-term survival or survival free of myocardial infarction between the two stents. The need for re-intervention was reduced with sirolimus-eluting stents, but the risk of thrombosis was no less. These conclusions are likely to be reliable.

Authors' objectives
To assess the long-term effects of treatment with sirolimus-eluting stents (SES) compared with bare metal stents (BMS).

Searching
PubMed, the National Institutes of Health clinical trials registry (ClinicalTrials.gov) and the Cochrane CENTRAL Register were searched for primary studies. Further studies were sought via named cardiology trials information websites, from conference proceedings of specified cardiology meetings, and from reviews and editorials published within the previous year. All searches were conducted from January 2002 to September 2006.

Study selection
Study designs of evaluations included in the review
The review included individual patient data (IPD) from randomised controlled trials (RCTs) with a mean follow-up period of at least 1 year. The length of follow-up in the included studies ranged from 12.1 to 58.9 months.

Specific interventions included in the review
Studies comparing SES with BMS were eligible for inclusion. All studies also included thienopyridine therapy for between 2 and 12 months.

Participants included in the review
Studies of patients with coronary artery disease were eligible for inclusion. Some of the included studies selected patients with diabetes; 28% of patients in the review had diabetes. Some studies selected patients with acute myocardial infarction. The mean age of the participants in the studies ranged from 59.3 to 66.6 years.

Outcomes assessed in the review
No inclusion criteria were specified for the outcomes. The primary outcome of interest for the review was death from any cause. Secondary outcomes were the composite of death or myocardial infarction, and the composite of death, myocardial infarction or re-intervention (major adverse cardiac events), and the occurrence of stent thrombosis. The reviewers accepted the authors' definition of stent thrombosis.

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
All data were checked for consistency, both logical checking and checking against the original publications. Queries were resolved and final database entries were verified by study investigators. In addition, individual studies were evaluated on allocation concealment, intention-to-treat analysis and blinding of the outcome assessment. The authors did not state explicitly how judgements of validity were made, in terms of who made the decisions or the criteria used.
Data extraction
An electronic form was sent to all principal investigators or sponsors of the studies requesting IPD. The data requested included date of randomisation, treatment allocation, diabetes status, events of interest and date of last follow-up. In eight of the included studies, data for patients undergoing target-lesion revascularisation were censored for analyses of stent thrombosis.

Methods of synthesis
How were the studies combined?
Survival analyses were performed stratified by study, using the Mantel-Cox test. The log rank test was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). The HRs were then pooled using a random-effects model, weighting each study by the inverse variance of its log HR. In addition, Kaplan-Meier survival curves were constructed across all studies for each event of interest.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the Cochran test and the I-squared statistic. Sensitivity analyses were performed to investigate the influence of individual studies on the pooled result by consecutively removing each study in turn. Random-effects meta-regression analysis was used to investigate the influence on treatment effect of four covariates of interest: blinding within the study, length of follow-up, duration of dual antiplatelet therapy and presence of myocardial infarction. Interaction between treatment effect and the presence of diabetes was assessed using the Mantel-Cox model. The subgroup of diabetic patients was also analysed separately.

Results of the review
The review included IPD from 14 RCTs (4,958 participants).

Death: there was no statistically significant difference in the risk of death between patients treated with SES and patients treated with BMS; the HR for death was 1.03 (95% CI: 0.80, 1.30, p=0.80). There was no evidence of statistical heterogeneity across the trials and the exclusion of each trial in turn from the analysis had no significant effect on the HR. There was no significant influence of the four pre-specified covariates on the treatment effect.

Death or myocardial infarction: there was no statistically significant difference between SES and BMS for the composite outcome of death and myocardial infarction; the HR was 0.97 (95% CI: 0.81, 1.16, p=0.76). There was no evidence of statistical heterogeneity across the trials.

Death or myocardial infarction or re-intervention: there was a significant reduction in the risk of the composite outcome of death, myocardial infarction and re-intervention in the SES group compared with the BMS group; the HR was 0.43 (95% CI: 0.34, 0.54, p<0.001). There was significant heterogeneity among the trials (p=0.001).

Patients with diabetes: no significant interaction between treatment and diabetes was seen for any of the three end points. Among patients with diabetes, there was no significant difference in the risk of death between the SES and BMS groups; the HR was 1.27 (95% CI: 0.83, 1.95, p=0.26).

Stent thrombosis: there was no significant difference in the risk of stent thrombosis between the SES group and the BMS group; the HR was 1.09 (95% CI: 0.64, 1.86, p=0.75). After the 1st year, the risk of stent thrombosis was significantly higher over the following 4 years in the SES group compared with the BMS group (0.6% versus 0.05%, p=0.02).

Authors' conclusions
There was no significant difference between SES and BMS in overall long-term survival or survival free of myocardial infarction, but SES did reduce the need for re-intervention in comparison with BMS. SES are associated with a risk of thrombosis at least as high as that seen with BMS.
CRD commentary
The review question and inclusion criteria were clear, and the search for relevant studies was extensive. IPD were retrieved from all eligible studies, and the authors involved study investigators in checking the consistency of the patient data used in the analyses. However, no details of the methods used to select studies were reported. The quality of the included studies was assessed using established criteria, and the potential influence of the level of blinding in the included studies on treatment effect was investigated. Appropriate statistical methods were used to handle the IPD, and the investigation of potential sources of heterogeneity between the included studies was thorough. This was a well-conducted review and the conclusions are likely to 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 data on the long-term outcomes of patients with diabetes treated with SES should be collected.

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