Safety and efficacy of drug-eluting and bare metal stents: comprehensive meta-analysis of randomized trials and observational studies


CRD summary
The authors concluded that the use of drug-eluting stents compared with bare metal stents did not appear to produce adverse safety outcomes, had comparable efficacy for mortality and myocardial infarction, and was associated with reductions in target-vessel revascularisation. Due to methodological limitations in the review, including unclear study quality, the reliability of this conclusion is unclear.

Authors’ objectives
To evaluate the safety and effectiveness of drug-eluting stents (DES) versus bare metal stents (BMS).

Searching
MEDLINE, the Cochrane Library, ClinicalTrials.gov, Clinical Trial Results, TCTMD, Cardiosource, EuroIntervention journal, and abstracts and presentations from major cardiovascular meetings were searched through to February 2008 for relevant articles; search terms were reported.

Study selection
Studies with at least 100 patients comparing the commercially available CYPHER (Cordis, Miami Lakes, Florida) or TAXUS (Boston Scientific, Natick, Massachusetts) DES versus BMS were eligible for inclusion in the review. Studies had to include mortality data and have a follow-up at least one year after implantation. The primary outcomes of interest were all-cause mortality, myocardial infarction, and target-vessel revascularisation.

Studies of landmark data, or analyses that censored patients at a specified time point after implantation, unless data were presented cumulatively, were excluded. Other excluded studies were those without reported outcomes at a fixed time point (and with the same follow-up duration for both stent types), and those with a control group from another included study. The included patients were described to be at various levels of risk, with a broad range of lesions. Elderly patients and those with diabetes were included.

Two independent reviewers selected studies for inclusion and disagreements were resolved with the involvement of a third reviewer.

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

Data extraction
Data were extracted or calculated to enable the presentation of relative risks (RRs) or hazard ratios (HRs) and 95% confidence intervals (CIs).

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
Summary estimates were pooled in a meta-analysis, using both fixed-effect (weighted by the inverse of the variance) and random-effects (DerSimonian and Laird) models. A single time point estimate was used for each study end point, assuming a constant hazard of DES versus BMS over the follow-up period. Statistical heterogeneity was assessed using the χ² and I² statistics, and this was explored further in bivariate meta-regression. The influence of each study was examined by excluding one at a time. Publication bias was explored using funnel plots and the Begg-Mazumdar test.

Randomised controlled trials (RCTs) and observational studies were analysed separately. For RCTs, grouping was...
conducted according to US Food and Drug Administration labeling (instructions for use). Off-label was defined as trials including only myocardial infarction patients or using non-approved indications (chronic total occlusions, bifurcation lesions, or other complex lesions). Other sensitivity analyses for RCTs involved follow-up periods of two or more, three or more, and four or more years. For observational studies, separate analyses were conducted for studies with at least 1,000 patients, those using adjusted and unadjusted estimates or derived using propensity score matching, and those with a follow-up of two or more, or three or more years. Observational studies were also analysed by enrolment type: sequential (consecutive time periods of BMS followed by DES) or concurrent (simultaneous BMS and DES) use.

Results of the review
Twenty-two RCTs (n=9,470 patients) and 33 observational studies (n=179,772) were included. There was a discrepancy between the table and the text in the reporting of the observational studies.

Mortality (21 RCTs and 31 observational studies): The analysis of RCTs showed no statistically significant differences in HR for DES compared with BMS and heterogeneity was not observed. The pooled analysis of observational studies showed a statistically significant reduction in mortality of 22% favouring DES (HR 0.78, 95% CI 0.71 to 0.86) using the random-effects model and an 18% reduction in the fixed-effect model (HR 0.81, 95% CI 0.78 to 0.85). Heterogeneity was significantly high (I²=71%). The reduction in mortality was consistent in sensitivity analysis with studies of at least 1,000 patients, and those with follow-up extending to two or more and three or more years. Results were also statistically significant for adjusted analyses, propensity-matched analyses, and for concurrent and sequential enrolment analyses. Publication bias was not present in any analysis; and meta-regression suggested no significant variation in the number of enrolled patients, number of DES patients, and percentage of those with diabetes.

Myocardial infarction (20 RCTs and 25 observational studies): The analysis of RCTs showed no statistically significant differences in HR for DES compared with BMS, and heterogeneity was minimal. There was some evidence of publication bias. The analysis of observational studies showed a statistically significant reduction in myocardial infarction of 13% favouring DES (HR 0.87, 95% CI 0.78 to 0.97) in the random-effects model. A significantly high level of heterogeneity was observed (I²=60.3%). The benefits of DES were consistent in sensitivity analysis with studies of at least 1,000 patients. Results were also statistically significant for unadjusted analyses and those involving sequential enrolment. Publication bias was not present, and meta-regression suggested no significant variation in the number of enrolled patients, number of DES patients, and percentage of those with diabetes.

Target-vessel revascularisation (16 RCTs and 18 observational studies): The analysis of RCTs showed a statistically significant reduction in revascularisation of 55% favouring DES (HR 0.45, 95% CI 0.37 to 0.54, random-effects model), with a high level of heterogeneity (I²=53.2%). This result was consistent in studies with a follow-up of two or more, three or more, and four or more years. In studies of off-label DES use, the hazard ratio remained statistically significant (HR 0.38, 95% CI 0.27 to 0.52). The analysis of observational studies showed a statistically significant reduction of 46% favouring DES (HR 0.54, 95% CI 0.48 to 0.61, random-effects model), with high heterogeneity (I²=69.7%). This reduction was consistent in all other sensitivity analyses. There was no evidence of publication bias.

No individual study influenced the results for any outcome.

Authors' conclusions
The use of DES compared with BMS did not appear to produce adverse safety outcomes, had comparable efficacy for mortality and myocardial infarction, and was associated with significant reductions in target-vessel revascularisation.

CRD commentary
The review question was clear and it was supported by detailed inclusion criteria for intervention and outcomes, but these were less clear for study design and participants. The broad range of design and participants appeared to be appropriate for the objective. The search strategy provided access to published and unpublished material, which minimised the risk of publication bias. There was no reported assessment of study quality, and this was a substantial limitation to the reliability of the review. The process of study selection was carried out with sufficient attempts to minimise error and bias, but it was not clear whether this extended to the data extraction process. There was little detail on the included patient characteristics meaning that the interpretation of generalisability was difficult. The chosen
methods of synthesis appeared to be appropriate, and statistical heterogeneity was explored.

The authors’ conclusion reflected the evidence presented, but due to some of the methodological limitations previously described, the extent to which this is reliable is unclear.

The authors declared financial relationships with Medtronic, Boston Scientific, Abbott Vascular, St Jude Medical, Cordis, Merck, AstraZeneca.

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

**Practice:** The authors stated that DES were safe for both on-label and off-label use and had comparable efficacy.

**Research:** The authors stated that large-scale RCTs were needed to ascertain the true effects of DES compared with BMS in mortality and myocardial infarction.

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