Safety and efficacy of everolimus-versus sirolimus-eluting stents: a systematic review and meta-analysis of 11 randomized trials


CRD summary
This was a generally well-conducted review which concluded that treatment with everolimus-eluting stents significantly reduced the risk of repeat revascularisation and definite stent thrombosis compared to sirolimus-eluting stents, with no significant differences in the risk of cardiac death or heart attack. Given the clinical variability across the studies and imprecision of the results, the conclusions may be overly strong.

Authors’ objectives
To compare the efficacy and safety of everolimus-eluting stents with those of sirolimus-eluting stents in patients who underwent percutaneous coronary intervention (PCI).

Searching
PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), two clinical trials registries and four news/discussion websites were searched to December 2011; search terms were reported. Conference proceedings of five relevant societies were searched. Relevant reviews and editorials from major medical journals published in the prior year were sought.

Study selection
Eligible studies were randomised controlled trials (RCT) that compared everolimus-eluting stents and Promus sirolimus-eluting stents in patients with coronary artery disease. The primary endpoint was major adverse cardiac events (MACE) at the longest available follow-up; a range of secondary outcomes were also assessed.

Mean age of patients ranged from 61 to 69 years. From 59% to 80% of the participants were men. The proportion of patients with diabetes ranged from 10% to 100%. Approximately 45% of patients had acute coronary syndrome. Most RCTs administered clopidogrel for 12 months. Definitions of MACE differed between studies.

Two independent reviewers selected studies for the review; disagreements were resolved by discussion.

Assessment of study quality
The quality of the RCTs was assessed by two independent reviewers using the Cochrane risk of bias tool; disagreements were resolved by discussion.

Data extraction
Two independent reviewers extracted data on outcomes to calculate odds ratios (OR) and 95% confidence intervals (CI); disagreements were resolved by discussion.

Methods of synthesis
Pooled odds ratios with 95% CI were calculated using the DerSimonian and Laird random-effects model and the Mantel–Haenszel fixed-effect model. Heterogeneity was assessed using the $X^2$ and $I^2$ statistics. Meta-regression was used to investigate the impact on results of sample size and prevalence of patients with diabetes and acute coronary syndrome. Stratification was used to assess treatment effects according to the protocol-mandated angiographic follow-up and clopidogrel duration, follow-up duration and study quality. Publication bias was assessed using a funnel plot and the Egger’s test.

Results of the review
Eleven RCTs were included in the review (12,869 patients, range 100 to 3,197). All RCTs were described as randomised, eight adequately concealed allocation and nine blinded outcome assessors. Follow-up ranged from six to 36 months.
There were no statistically significant differences between patients with everolimus-eluting stents and those with sirolimus-eluting stents in terms of MACE (OR 0.90, 95% CI 0.77 to 1.04; 11 RCTs; I²=16%), cardiac death (OR 0.97, 95% CI 0.74 to 1.27; 10 RCTs; I²=0%), myocardial infarction (OR 0.95, 95% CI 0.75 to 1.20; 11 RCTs; I²=0%), repeat revascularisation (OR 0.85, 95% CI 0.72 to 1.00; 11 RCTs; I²=0%) and stent thrombosis (OR 0.68, 95% CI 0.45 to 1.02; 11 RCTs; I²=0%). Definite stent thrombosis was significantly reduced with everolimus-eluting stents (OR 0.47, 95% CI 0.26 to 0.85; 10 RCTs; I²=0%). Results for the stratified analyses and meta-regression were given. There was no evidence of publication bias.

Authors' conclusions
Treatment with everolimus-eluting stents significantly reduced the risk of repeat revascularisation and definite stent thrombosis compared to sirolimus-eluting stents; no significant differences were found in the risk of cardiac death or myocardial infarction.

CRD commentary
The review addressed a clear review question supported by reproducible inclusion criteria. The extensive search included attempts to identify unpublished studies; it was unclear whether language restrictions were applied. Each stage of the review process was conducted in duplicate to reduce risks of error and bias. Appropriate criteria were used to assess study quality and the results were published in full.

The two meta-analytical models had different assumptions that needed to be met; data from the included studies would meet the assumptions of one of these models. Clinical differences between the studies meant that the random-effects model was more suitable. The authors stated that there was a statistically significant reduction in repeat revascularisation with everolimus-eluting stents compared to sirolimus-eluting stents, but the 95% confidence intervals for the pooled result included a value of 1.00. The larger trials in this meta-analysis were not statistically significant and some of the smaller trials showed an opposite direction of effect. As a result, it was unclear in which direction a further good quality RCT would influence the pooled result were one to become available.

This was a generally well-conducted review but clinical heterogeneity across studies and the imprecision of results from these studies suggest that the conclusions should be treated with some caution as they may be overly strong.

Implications of the review for practice and research
Practice: The authors stated that the practice of widespread use of everolimus-eluting stents in the field of interventional cardiology was justified with its proven efficacy and safety.

Research: The authors stated that future studies and analyses with longer duration of follow-up were needed to confirm the results in the long-term perspectives. The authors stated that everolimus-eluting stents should be considered the most competitive comparator in future clinical trials.

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