Everolimus-eluting versus sirolimus-eluting stents: a meta-analysis of randomized trials


CRD summary
The review concluded that no significant differences were found between everolimus-eluting stents and sirolimus-eluting stents for clinical efficacy or safety, including major adverse cardiac events, cardiac death, myocardial infarction, repeat vascularisation, and definite/probable stent thrombosis combined. Given limitations in the review process limitations and the unclear quality of included trials, the reliability of these conclusions is unclear.

Authors' objectives
To compare the efficacy and safety of everolimus-eluting versus sirolimus-eluting stents in patients with cardiac disease.

Searching
PubMed, ClinicalTrials.gov and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched up to April 2011; search terms were not reported. The websites of relevant organisations (Cardiosource, theheart.org, tctmd.com), ongoing trials (clinicaltrialresults.com) and relevant conference proceedings were scanned. Bibliographies of reviews and editorials in major relevant medical journals over the previous year were handsearched and experts in the field were contacted to identify unpublished trials.

Study selection
Randomised controlled trials (RCTs) that compared everolimus-eluting stents (second generation stents) with sirolimus-eluting stents (first generation stents) in patients with cardiac disease were eligible for inclusion. The primary outcome was major adverse cardiac events.

The major cardiac adverse events included in the review definitions were myocardial infarction, target vessel/lesion revascularisation, cardiac death or death, and definite stent thrombosis reported in one trial. The mean age of included patients ranged from 63 to 67 years; the proportion of men ranged from 59% to 77%. Patient exclusion criteria (where stated) were: left main or graft vessel stenosis; in-stent restenosis; vessel size less than range 2.25 to 3.0mm in some trials and >4.25 mm in one trial; and bifurcation lesion in one trial. One trial was of patients with diabetes mellitus. Duration of clopidogrel therapy ranged from six to 12 months or longer. Protocol mandated follow-up angiography was performed in 60% trials.

The authors did not report how many reviewers performed the study selection.

Assessment of study quality
The criteria assessed in trial quality were allocation concealment, intention-to-treat analysis, and blinding.

The authors did not report how many reviewers performed the quality assessment.

Data extraction
Numbers of events were used to calculate hazard ratios (HR) with 95% confidence intervals (CI). To permit analysis, a value of 0.5 was added to any trial treatment arms that reported zero events.

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

Methods of synthesis
Pooled hazard ratios with 95% confidence intervals were calculated using a random-effects model (DerSimonian-Laird). The Cochrane Q and I² were used to determine trial heterogeneity, where I² below 25% indicated low heterogeneity, I² of 25% to 50% indicated medium heterogeneity, and I² over 50% indicated high heterogeneity.

Results of the review
Five RCTs were identified (7,370 participants, range 300 to 2,774). Follow-up ranged from nine to 36 months (median
There was no significant difference in risk between everolimus-eluting and sirolimus-eluting stents for major adverse events (HR 0.91, 85% CI 0.77 to 1.08; I²=0%; five trials), cardiac death (HR 1.02, 95% CI 0.73 to 1.41; I²=0%; five trials), myocardial infarction (HR 0.97, 95% CI 0.66 to 1.35; I²=0%; five trials), repeat revascularisation (HR 0.85, 95% CI 0.68 to 1.07; I²=0%; five trials), or for definite and probable stent thrombosis (HR 0.79, 95% CI 0.49 to 1.27; I²=0%; five trials).

Sensitivity analysis found no significant difference in results when one trial, which excluded lesions in vessels under 3mm in size, was omitted from the analysis of repeat vascularisation. There were also no differences in the results when all the analyses were repeated for the two trials without scheduled follow-up angiography.

**Authors’ conclusions**
This meta-analysis did not show significant differences between everolimus-eluting and sirolimus-eluting stents for clinical efficacy or safety.

**CRD commentary**
The review addressed a well-defined question for study design, participants, interventions, and relevant outcomes. The search appeared to be comprehensive and included unpublished studies (three included trials were in press). However, it was not clear whether studies published in any language were included. No measures to reduce error and bias in the review process were reported.

Trial quality was assessed using some relevant criteria, but little relevant data was provided to assess trial quality. It was not clear whether a trued time-to-event analysis was performed to obtain hazard ratios. It may have been informative to have shown the results of a fixed-effect model for the pooled analysis (in addition to those of a random-effects model), since there was no evidence for heterogeneity. The authors noted that the definitions of major adverse events were not consistent across trials, particularly for stent thrombosis.

In view of limitations in the review process and unclear trial quality, the reliability of the authors' conclusions is unclear.

**Implications of the review for practice and research**
**Practice:** The authors noted that good first-generation drug-eluting stents such as sirolimus-eluting stents may still represent a valid treatment option for patients with coronary heart disease.

**Research:** The authors recommended future studies to better define the relative merits of everolimus-eluting and sirolimus-eluting stents.

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