Comprehensive meta-analysis on drug-eluting stents versus bare-metal stents during extended follow-up

Roukoz H, Bavry AA, Sarkees ML, Mood GR, Kumbhani DJ, Rabbat MG, Bhatt DL

CRD summary
The authors concluded that drug-eluting and bare metal stents were associated with similar mortality rates. Drug-eluting stents reduced target lesion revascularisation with sustained effects and may also reduce non-Q-wave myocardial infarction. However, they increased late stent thrombosis. Suboptimal reporting in the review, particularly with regard to study validity and statistical heterogeneity, means that these conclusions require a degree of caution.

Authors' objectives
To compare the safety and efficacy of drug-eluting versus bare metal stents over short- and long-term follow-up.

Searching
MEDLINE was searched from 2000 to 2007. Search terms were reported. Relevant journal supplements and abstracts from cardiology meetings were checked. Science Citation Index was used to cross-reference eligible studies. The search was limited to studies in English.

Study selection
Randomised controlled trials (RCTs) that compared paclitaxel- or sirolimus-eluting versus bare metal stents that had at least six months’ follow-up were eligible for inclusion. Eligible indications for stent placement included myocardial infarction, stable or unstable angina and total coronary occlusion. Antiplatelet therapy was required to consist of lifelong aspirin and a specified duration of a thienopyridine (clopidogrel or ticlopidine). Outcomes of interest in the review were all-cause and cardiovascular mortality, Q-wave and non-Q-wave myocardial infarction, target lesion revascularisation and stent thrombosis. All outcomes were defined in detail in the review. Studies that used non-polymeric stent platforms, next-generation drug-eluting stents, venous bypass graft revascularisation or treatment of in-stent restenosis were excluded. Studies that compared paclitaxel versus sirolimus stents or that used cilostazol instead of a thienopyridine were excluded.

The mean or median age of participants in included studies ranged from 58 to 70 years. The proportion of women ranged from 11.5% to 44.7%. From 9.5% to 100% of participants had diabetes mellitus, 18% to 68% were smokers and 0% to 52% had a history of myocardial infarction (where reported). From 1.6% to 38.8% of participants had a history of percutaneous coronary intervention and 0.3% to 19.3% had a history of coronary artery bypass grafting. Most participants had stable coronary artery disease; for about one quarter the indication for stent placement was acute ST-elevation myocardial infarction. Mean reference vessel diameter ranged from 2.20mm to 3.17mm. Mean lesion length ranged from 9.6mm to 20.6mm. Mean/median stent diameter ranged from 2.5mm to 3.7mm. Mean stent length ranged from 15mm to 34mm. There was a mean of one to 1.9 stents per patient (where reported). All participants (where reported) received clopidogrel; periods ranged from six to 12 months. Glycoprotein IIb/IIIa inhibitor use varied widely (range 0% to 100%). Mean duration of study follow-up was 29.6 months (range six to 60 months).

The authors stated neither how the papers were selected for the review nor how many reviewers performed the selection.

Assessment of study quality
Two reviewers independently assessed studies for adequacy of treatment allocation and analysis.

Data extraction
Risk ratios (RRs) were calculated from the numbers of events in the control and intervention groups of each study, with 95% confidence intervals (CIs). Where studies reported no events, automatic zero-cell correction was used. Event rates were extracted for the entire follow-up period (overall) and classified as early or late (under or over one year). An exception was the outcome of stent thrombosis, which was classified as early, late or very late (under 30 days, 30 days
to one year and more than one year). Data were analysed in the review by intention to treat.

Three reviewers independently extracted data. Discrepancies were resolved by a fourth reviewer.

**Methods of synthesis**

Studies were combined using the DerSimonian and Laird random-effects model. Heterogeneity was assessed with the Q statistic. Publication bias was assessed by Begg's method. Where data were available, subgroup analyses were conducted by type of myocardial infarction (ST-elevation/non-ST elevation), solely diabetic participants, drug-eluting stent type (paclitaxel/sirolimus), reference vessel and stent dimensions, and glycoprotein IIb/IIIa inhibitor use. Cut-off thresholds for these characteristics (where relevant) were based on the medians in the included studies.

**Results of the review**

Twenty-eight RCTs were included in the review (n=10,727, range 61 to 1,314).

**Drug-eluting versus bare metal stents:** There was no statistically significant difference between the groups in overall, early or late rates of all-cause or cardiovascular mortality or in rates of Q-wave or non-Q-wave myocardial infarction/re-infarction. There was a non-statistically-significant trend for reduced early non-Q-wave myocardial infarction with drug-eluting stents (RR 0.78, 95% CI 0.61 to 1.00). There was a significantly lower rate of early non-Q-wave myocardial infarction in the drug-eluting stent group in studies with mean stent length under 22mm (p=0.01) and where more than 50% of patients used glycoprotein IIb/IIIa inhibitors (p=0.047). There were no statistically significant findings in other subgroup analyses for these outcomes.

**Target lesion revascularisation:** Rates of target lesion revascularisation were significantly lower in the drug-eluting stent group at early follow-up (RR 0.28, 95% CI 0.21 to 0.38) and overall (p<0.001), but did not differ significantly at late follow-up. Subgroup analyses had similar findings to the main analysis.

**Stent thrombosis:** There was no statistically significant difference between the groups in early stent thrombosis, but the rate of very late stent thrombosis was significantly higher in the drug-eluting stent group (RR 4.57, 95% CI 1.54 to 13.57). Subgroup analyses showed a similar trend, but the results did not reach statistical significance in all subgroups.

**Authors’ conclusions**

Drug-eluting and bare metal stents were associated with similar mortality rates. Drug-eluting stents reduced target lesion revascularisation with sustained effects and may also reduce non-Q-wave myocardial infarction. However, they increased late stent thrombosis.

**CRD commentary**

The objectives and inclusion criteria of the review were clear, review outcomes were well-defined and relevant sources were searched for published and unpublished studies. Only one database was used and the search was limited by language, so it was possible that studies were missed. Steps were taken to minimise risks of reviewer bias and error by having more than one reviewer independently assess study validity and extract data; it was unclear whether similar steps were applied to study selection. Study validity was assessed, but the results were not reported. Suitable statistical methods were used to combine studies and subgroup analyses were used to explore differences between them. However, no results of tests for statistical heterogeneity and publication bias were reported and forest plots were not presented for all analyses, which made it difficult to evaluate the consistency of study findings. Potential biases such as lack of long-term data and suboptimal definition of outcomes were acknowledged in the text. Suboptimal reporting in the review, in particular with regard to study validity and statistical heterogeneity, means that the authors’ conclusions require a degree of caution.

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

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that studies with long-term follow-up were needed to assess safety of drug-eluting stents in patients with ST-elevation myocardial infarction.
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