Long-term safety and efficacy of drug-eluting stents in patients with acute myocardial infarction: a meta-analysis of randomized trials

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CRD summary
The review concluded that, compared to bare-metal stents, percutaneous coronary intervention with drug-eluting stents reduced the long-term need for target-vessel revascularisation without increasing the risk of death and reinfarction, but the rate of very late stent thrombosis increased. The review was generally well conducted and the authors’ conclusions are likely to be reliable.

Authors’ objectives
To assess the long term effectiveness of drug-eluting stents versus bare-metal stents in patients with ST-segment elevation myocardial infarction (STEMI).

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched without language restrictions to September 2010; search terms were reported. Scientific session abstracts in relevant journals and websites and reference lists of retrieved studies were searched.

Study selection
Randomised controlled trials (RCTs) that compared drug-eluting stents against bare-metal stents in patients with STEMI were eligible for inclusion. Eligible studies had a mean follow-up period of at least three years. The primary outcome was target-vessel revascularisation (TVR) or target-lesion revascularisation (where TVR was unavailable). Secondary outcomes included death, recurrent myocardial infarction and stent thrombosis. Ongoing studies and studies with irretrievable or duplicated data were excluded.

Mean age of participants in the included studies was 62 years (range of means was 59 to 64 years). Drug-eluting stents included sirolimus-, paclitaxel- and zotarolimus-eluting stents. Percutaneous coronary intervention (PCI) was performed for all participants except for 57 people in one trial. Participants in most of the trials were treated with glycoprotein IIb/IIIa inhibitors and dual oral antiplatelet therapy. In all studies, participants received a 300mg to 600mg loading dose of clopidogrel. The outcome endpoints were measured according to how they were defined in the individual studies.

Two reviewers independently selected studies for the review, with disagreements resolved by consensus.

Assessment of study quality
Studies were assessed for quality using Cochrane Collaboration criteria that included adequacy of sequence generation, adequacy of allocation concealment, blinding, incomplete data, selective outcome reporting, other potential sources of bias and sample size calculation. These criteria were individually scored.

Two reviewers independently assessed studies for quality, with disagreements resolved by consensus.

Data extraction
Data were extracted on the primary and secondary outcomes and odds ratios (ORs), together with 95% confidence intervals (CIs), were calculated.

The authors did not state how many reviewers extracted data from the studies.

Methods of synthesis
Studies were pooled in meta-analyses and summary odds ratios and their 95% confidence intervals were calculated using a fixed-effect model; where significant heterogeneity was identified, a random-effects model was used instead. Where summary effect measures were significant, numbers needed to treat (NNT) or numbers needed to harm (NNH), each with CIs, were calculated. Heterogeneity was assessed with $\chi^2$ and $I^2$. Publication bias was assessed by visual
inspection of funnel plots and by Harbord and Peters tests. Weighted random effect meta-regression was performed to assess the relationship between drug-eluting stents efficacy and baseline risk of TVR.

Sensitivity analyses were performed according to follow-up duration (≥4 years versus <4 years), state of publication (full versus not yet published articles), sample size (trials with ≥400 participants versus <400 participants), routine angiographic follow-up (trials with angiographic follow-up in all participants or in prespecified subgroups versus no routine angiographic follow-up) and enrolling centres (multi- versus single-centre trials). An influence analysis was performed to compare estimates based on the elimination of one study at a time.

**Results of the review**

Ten RCTs (6,774 participants, range 175 to 3,006) were included in the review. Most of the included studies had adequate sequence generation, allocation concealment, blinding (either of patients or outcome assessors), description of incomplete data, freedom from selective reporting and other sources of bias and sample size calculations. Follow-up ranged from three to five years (mean 3.6 years).

**Primary outcome:** Compared to bare-metal stents, drug-eluting stents significantly reduced the odds of TVR (OR 0.51, 95% CI 0.43 to 0.59, NNT=15, 95% CI 12 to 18; 10 studies, no significant heterogeneity).

**Secondary outcomes:** There was no evidence of a significant difference in the incidence of death, recurrent myocardial infarction or overall stent thrombosis between groups. Compared to bare-metal stents, drug-eluting stents were significantly associated with a higher rate of very late (one year after revascularisation) stent thrombosis (OR 1.71, 95% CI 1.05 to 2.79, NNH=146, 95% CI 58 to 2,022; nine trials, no significant heterogeneity).

Meta-regression revealed a significant relationship between Log odds ratio for TVR and TVR rates in bare-metal stents groups (exponent 0.94, 95% CI 0.89 to 0.98). There was no evidence of interaction between subgroups in sensitivity analyses or marked change in results with influence analyses. However, compared to bare-metal stents, a significant reduction in mortality was associated with drug-eluting stents with the exclusion of one study (OR 0.80, 95% CI 0.65 to 0.98; nine studies, no significant heterogeneity). There was no evidence of publication bias.

**Authors’ conclusions**

Compared to bare-metal stents, percutaneous coronary intervention with drug-eluting stents at long-term follow-up reduced the need for target-vessel revascularisation without increasing risks of death and reinfarction, but the rate of very late stent thrombosis increased.

**CRD commentary**

The review addressed a clear research question. Inclusion criteria appeared appropriate. A wide range of relevant sources was used to search for studies and there were no language and publication restrictions, so language or publication bias was unlikely. Adequate methods were used to select studies and assess studies for quality, but the number of reviewers was not reported for data extraction, so reviewer error and bias from this process cannot be ruled out. Studies appear to be of good quality.

Appropriate methods were used to synthesize studies and assess heterogeneity. Meta-regression was used to determine whether risk of TVR influenced the results. Sensitivity and influence analyses assessed the reliability of results according to different study characteristics through subgroup analyses and omission of individual studies from the overall analyses.

The review was generally well conducted and the authors’ conclusions are likely to be reliable.

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

**Practice:** The authors stated that clinicians needed to balance the clinical benefit in re-intervention gained from drug-eluting stents during STEMI against a possible increase in late stent thrombosis. They suggested that drug-eluting stent implantation should be reserved for STEMI patients with an intermediate or high risk for clinical restenosis.

**Research:** The authors stated that further research should evaluate new stent platforms and drugs in patients who underwent primary PCI and should determine characteristics of patients that most benefit from drug-eluting stents.
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