Meta-analysis of long-term outcomes for drug-eluting stents versus bare-metal stents in primary percutaneous coronary interventions for ST-segment elevation myocardial infarction

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CRD summary
The authors concluded that use of drug-eluting stents resulted in decreased repeat revascularisation with no increase in stent thrombosis, mortality or recurrent myocardial infarction. Varying definitions of outcomes across the studies and limited reflection for the entirety of the evidence presented suggest that the authors' conclusions may not be wholly reliable.

Authors' objectives
To evaluate outcomes of first generation drug-eluting stents and bare-metal stents after three or more years of follow-up.

Searching
MEDLINE, The Cochrane Library, EMBASE and CINAHL were searched from January 1980 to February 2011 (Cochrane databases were searched to January 2011). Search terms were reported. The US Food and Drug Administration web site and BIOSIS Previews were searched using the same dates. Reference lists of included articles, relevant review articles and published abstracts of international meetings were handsearched for further studies.

Study selection
Eligible studies were randomised controlled trials (RCTs) and observational studies that examined use of drug-eluting stents versus bare-metal stents during primary percutaneous coronary intervention (PPCI) with a long-term follow-up (≥3 years). Prespecified outcomes were death, myocardial infarction, target vessel revascularisation, target lesion revascularisation, stent thrombosis and major adverse cardiac events at three or more years follow-up.

Mean patient age per study group ranged from 58 to 67 years. From 19% to 32% of patients in the included studies were female and from 7% to 41% had diabetes. Drug eluting stents were paclitaxel-eluting or sirolimus-eluting; half of the studies included both. All studies were published between 2008 and 2011.

Two reviewers independently selected the studies for inclusion.

Assessment of study quality
Quality of RCTs was assessed according to adequacy of allocation, randomisation, baseline comparability of study groups, blinding, loss to follow-up and use of intention-to-treat analysis (providing percentages for loss to follow-up and yes/no ratings for all other domains). Quality of registry studies was assessed using a modified version of the Newcastle-Ottawa Scale to give ratings of A, B or C (A was the highest quality).

It appeared that at least two reviewers were involved in the assessment of study quality.

Data extraction
Data were extracted to calculate odds ratios and 95% confidence intervals per study group. Results were expressed as a ratio of total participants with complete follow-up. The longest follow-up data available per study were extracted.

Two reviewers independently extracted the data; disagreements were resolved by consensus with a third reviewer.

Methods of synthesis
Separate meta-analyses were performed for RCTs and observational studies. Odds ratios (ORs) and 95% confidence intervals (CIs) per outcome were pooled using the random-effects DerSimonian-Laird method. Statistical heterogeneity was assessed using the I² statistical test (25% was considered low, 50% moderate and 75% high).
Subgroup analysis was based on type of drug-eluting stent used. Sensitivity analysis removed the largest RCT and the study with the greatest percentage of loss to follow-up. Absolute risk decrease (ARD) and number needed to treat (NNT) were estimated to assess the clinical relevance of results. Publication bias was assessed using funnel plots.

**Results of the review**

Thirteen studies were included in the review (10,447 patients): eight RCTs (5,797 patients) and five observational studies (4,650 patients). Study sample size ranged from 175 to 3,006. Follow-up ranged from 2.1 years to 5.8 years. All RCTs were evaluated as having adequate allocation, randomisation, baseline comparability of groups and intention-treat analysis. Seven RCTs reported that the outcome had been measured blindly but did not report that patients or caregivers had been blinded to the intervention. Percentage loss to follow-up ranged from 0% to 29% (where reported). All observational studies received the highest quality rating (A) for six of the eight domains measured; generally lower scores (range A to D) were given for assessment of the outcome and adequacy of follow-up.

**RCTs:** There were statistically significant lower odds of target lesion revascularisation (OR 0.48, 95% CI 0.37 to 0.61; seven trials) and major adverse cardiac events (OR 0.67, 95% CI 0.56 to 0.79; seven trials) with use of drug-eluting versus bare-metal stents. There was no evidence of significant statistical heterogeneity for target lesion revascularisation ($I^2=31.5\%$) and major adverse cardiac events ($I^2=17.8\%$).

No statistically significant differences were identified between drug-eluting stents and bare-metal stents for mortality, stent thrombosis and recurrent myocardial infarction. Significant heterogeneity was found for recurrent myocardial infarction.

Sensitivity analyses for all outcomes (excluding the largest RCT and then a trial with 29% loss to follow-up) yielded similar findings. Stratified analyses (by type of drug-eluting stent) revealed larger increases in all outcomes (except mortality) with sirolimus versus paclitaxel-eluting stents.

**Observational studies:** There were statistically significant lower odds of mortality (OR 0.65, 95% CI 0.53 to 0.80; four studies) and significantly higher odds for stent thrombosis (OR 1.62, 95% CI 1.18 to 2.21; five studies) were found with use of drug-eluting versus bare-metal stents. No statistical heterogeneity was indicated in either meta-analysis ($I^2=0\%$).

No statistically significant differences between drug-eluting stents and bare-metal stents were found for target lesion revascularisation and recurrent myocardial infarction. Statistically significant heterogeneity was identified for both outcomes.

Subgroup analyses revealed comparable results between sirolimus and paclitaxel-eluting stent registries for all of the outcomes except lower incidence of recurrent myocardial infarction in studies that used sirolimus-eluting stents.

**Additional findings:** All findings remained unchanged when meta-analyses were re-performed using fixed-effect models. Asymmetry in funnel plots suggested possible publication bias for target lesion revascularisation, mortality and myocardial infarction.

**Authors' conclusions**

That authors concluded that use of drug-eluting stents resulted in decreased repeat revascularisation with no increase in stent thrombosis, mortality or recurrent myocardial infarction.

**CRD commentary**

The review question was clear. The inclusion criteria seemed sufficiently replicable. Relevant data sources were accessed and attempts were made to reduce error and bias throughout the review process. Suitable quality assessment criteria were employed and all studies were evaluated as being of mostly high quality. Publication bias was shown but the authors stated that any assessment of the publication bias might be deemed inconclusive because there were fewer than 10 studies per outcome.

Study details were presented and methods of synthesis seemed appropriate. Attempts were made to explore statistical and methodological heterogeneity via subgroup and sensitivity analyses, although the authors stated that overall conclusions may have been influenced by differing definitions of outcomes across the studies.
The overall conclusions seem mainly based on the findings from the meta-analyses of RCTs. In particular, the conclusion that drug-eluting stents did not increase the risk of stent thrombosis compared with bare-metal stents appeared overly optimistic in light of the evidence from the observational studies. Thus, the authors' conclusions do not truly reflect the entirety of the evidence presented and may not be wholly reliable.

Implications of the review for practice and research
The authors did not state any implications for practice or future research.

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