Drug-eluting stents: a systematic review and economic evaluation

CRD summary
This review assessed the clinical effectiveness of drug-eluting coronary artery stents in percutaneous coronary intervention in patients with coronary artery disease and concluded that they should be targeted at the subgroups of patients with the highest risks of requiring reintervention. A number of areas were highlighted for further research. The conclusions are likely to be reliable.

Authors' objectives
To assess the clinical effectiveness of drug-eluting coronary artery stents in percutaneous coronary intervention in patients with coronary artery disease.

Searching
Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, DARE, EMBASE, HTA database, Web of Science Proceedings, Science Citation Index, MEDLINE and NHS EED were searched from December 2002 to August 2005. Reference lists of included studies and device manufacturer submissions were searched for relevant studies. Handsearches of cardiology conference abstracts and conference proceedings from various meetings were performed. Internet resources were searched. Search terms were reported.

Study selection
Randomised controlled trials (RCTs), non-RCTs and non-controlled studies in adults with coronary artery disease undergoing treatment of native and intervention naive vessel by percutaneous coronary intervention with the use of drug-eluting coronary artery stents were eligible for inclusion. Studies were required to report on one or more of the following outcomes: combined event rate or event-free survival; mortality; acute myocardial infarction; target lesion revascularisation; target vessel revascularisation; repeat revascularisation; adverse effects; angiographic binary restenosis; late loss; and health-related quality of life. Where reported, the mean age of patients in the included studies ranged from 35.1 to 67.4 years. Most patients were male (62.5 to 94%). All studies permitted the recruitment of people with diabetes.

The outcomes assessed included mortality, acute myocardial infarction, composite event rate, target lesion revascularisation, target vessel revascularisation, angiographic binary restenosis rates and late luminal loss. The mean age of patients in the included studies ranged from 60 to 68 years. Most patients were male (72-83%). The studies included a range of vessel diameters and proportions of complex lesions. The outcomes assessed included mortality, acute myocardial infarction, composite event rate, target lesion revascularisation, target vessel revascularisation, composite event rate, angiographic binary restenosis rates and late luminal loss.

Two pairs of reviewers independently screened studies for relevance, with disagreements resolved by discussion to reach consensus.

Assessment of study quality
The quality of the included studies was assessed using previously published criteria, including items on randomisation, baseline comparability, eligibility criteria specified, co-interventions identified, blinding, withdrawals and intention-to-treat analysis.

Two reviewers assessed studies for validity. Any disagreements were resolved by consensus.

Data extraction
Pre-tested data extraction forms were used to extract odds ratios and 95% confidence intervals (CIs) for binary outcomes and weighted-mean differences for continuous outcomes.
Two reviewers independently performed the data extraction. Extractions were checked for accuracy by a second reviewer.

Methods of synthesis
Studies that compared drug-eluting stents with non-drug-eluting bare metal stents and drug-eluting stents of different design were included and analysed separately. The studies were combined in a fixed-effects meta-analysis where appropriate; a random-effects model was applied where quantitative heterogeneity was indicated. Pooled odds ratios were calculated for dichotomous outcomes and pooled weighted mean differences were calculated for continuous outcomes. Statistical heterogeneity was investigated using $\chi^2$ and $I^2$ statistics. Subgroup analyses by eluted drug subgroup were undertaken.

Results of the review
Included studies comprised 17 RCTs that compared drug-eluting stents with bare metal stents with all included for at least one outcome. A range of eluting agents were included: paclitaxel (n=11); sirolimus (n=5); everolimus (n=1); and ABT-578 (n=1). Most studies (11) were restricted to the treatment of single lesions. The studies included a range of vessel diameters and lesion lengths. Eight RCTs compared drug-eluting stents with other drug-eluting stents designs and six compared Taxus and Cypher directly.

Seventeen RCTs with 8,464 participants compared drug-eluting stents versus bare metal stents and eight RCTs with 4,474 participants compared drug-eluting stents with other drug-eluting stent designs.

Significant reductions in repeat revascularisations were noted for drug-eluting stents compared with bare metal stents. After one year target lesion revascularisation had a relative risk of 0.24 (95% CI: 0.19 to 0.31) and target vessel revascularisation a relative risk of 0.43 (95% CI: 0.33 to 0.55). These benefits were considered to be stable from one to three years. Binary restenosis and late luminal loss also favoured drug-eluting stents. At angiographic follow-up between six and nine months, binary restenosis rates were found to be statistically significantly lower for all drug-eluting stents except everolimus-eluting stents. The pooled estimate for binary restenosis in the paclitaxel-eluting stents group was an odds ratio of 0.27 (95% CI: 0.20 to 0.35) and for sirolimus-eluting stents 0.08 (95% CI: 0.06 to 0.11). High levels of heterogeneity for the pooled analysis of all trials and the sirolimus-eluting stents subgroup were indicated by the $I^2$ statistic. Late loss analysis at follow-up ranging from six to nine months favoured drug-eluting stents (weighted mean difference -0.59, 95% CI: -0.62 to -0.56). Mean late loss was reduced by 0.45mm for paclitaxel-eluting stents (weighted mean difference -0.45, 95% CI: -0.50 to -0.40) and by 0.79mm for sirolimus-eluting stents (weighted mean difference -0.79, 95% CI: -0.84 to -0.74).

In studies that compared drug-eluting stents versus other drug-eluting stents, target lesion revascularisation and composite event rate exhibited marginal improvement in efficacy of Cypher over Taxus. In the six to nine month analysis of target lesion revascularisation a statistically significant advantage of sirolimus-eluting stents over paclitaxel-eluting stents was noted (odds ratio 0.68, 95% CI: 0.51 to 0.91). For target vessel revascularisation, analysis of Cypher sirolimus-eluting stents and Taxus paclitaxel-eluting stents trials suggested a statistically significant advantage for sirolimus-eluting stents over paclitaxel-eluting stents (odds ratio 0.59, 95% CI: 0.39 to 0.89) at six to nine months. Composite event rates analysed at six to nine months for Cypher sirolimus-eluting stents versus Taxus paclitaxel-eluting stents appeared to favour sirolimus-eluting stents over paclitaxel-eluting stents, but with 95% CIs that were only just within statistical significance (odds ratio 0.75, 95% CI: 0.59 to 0.96).

Non-RCT findings were also reported in the review.

Cost information
The cost per quality adjusted life year (QALY) ratios (£183,000 to £562,000) exceeded the normal range of acceptability. Cost effectiveness occured only for those non-elective patients who underwent a previous coronary artery bypass graft and had small vessels.

Authors' conclusions
Drug-eluting stents should be targeted at the subgroups of patients with the highest risks of requiring reintervention.
CRD commentary
The review addressed a clear question and included appropriate inclusion criteria. An extensive search for studies was undertaken by searching electronic databases and other appropriate sources. No mention was made of the language(s) in which papers were searched, therefore, it was not possible to eliminate the potential for language bias. Appropriate attempts were made to minimise the potential for reviewer error and bias at each stage of the review process. Suitable methods were undertaken to assess statistical heterogeneity and subgroup analyses were explored. This was generally a well-conducted systematic review with conclusions that are likely to be reliable.

Implications of the review for practice and research
Practice: The authors did not state any further implications for practice.

Research: There should be more trials of drug-eluting stents compared with new generation bare metal stents and trials of drug-eluting stents compared with drug-eluting stents, plus further evaluation of newer bare metal stents in combination with drug administration.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.