Drug-eluting balloons for coronary artery disease: an updated meta-analysis of randomized controlled trials

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CRD summary
This review update concluded that efficacy and safety of drug-eluting balloons were comparable to those of drug-eluting stents and superior to plain old balloon angioplasty for angiographic end points, target lesion revascularisation, major adverse cardiac events and mortality. Limited reporting of the results and the paucity of the evidence base suggest that these conclusions may be overly strong.

Authors' objectives
To update a meta-analytic review evaluating the efficacy and safety of drug-eluting balloons in the treatment of coronary artery disease.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to December 2011 in the original search and to December 2012 in the update search. No language restrictions were applied. Search terms were reported. Web of Science conference proceedings, ClinicalTrials.gov, reference lists of retrieved articles and relevant reviews, editorials and letters were searched in December 2011.

Study selection
Eligible studies were randomised controlled trials (RCTs) that compared the use of drug-eluting balloons versus usual care in adult patients (aged 18 years or older) with coronary artery disease. Usual care was defined as the use of bare metal or drug-eluting stents, or plain old balloon angioplasty. The primary outcomes of interest included target lesion revascularisation, major adverse cardiac events, mortality, myocardial infarction and stent thrombosis. Secondary outcomes of interest included in-stent and in-segment measurements of late lumen loss, mineral lumen diameter and binary restenosis (as defined in the original review paper).

The included studies were published between 2009 and 2012. Mean ages of patients in trial arms ranged from 64 to 69.9 years and 57% to 96% of the patients were men. One study enrolled patients with de novo lesions (stable or unstable angina); the other studies enrolled patients with in-stent restenosis. All of the balloon systems used were coated with paclitaxel. In most studies, postintervention antiplatelet therapy consisted of aspirin (usually 100mg once daily for life) and/or clopidogrel (75mg once daily; durations varied across studies). One study had three arms and compared drug-eluting balloons with drug-eluting stents and plain old balloon angioplasty. The other studies compared drug-eluting balloons versus drug-eluting stents or plain old balloon angioplasty.

Two authors independently selected studies for inclusion in the review. Any disagreements were resolved by discussion.

Assessment of study quality
The quality of studies included in the original review was assessed by an unknown number of reviewers who used criteria from the Cochrane Collaboration's risk of bias tool. No quality assessment was reported for the additional studies included in the updated review.

Data extraction
Data on outcomes were extracted to calculate odds ratios (dichotomous data) or mean differences (continuous data), and their corresponding 95% confidence intervals.

The authors did not state how many reviewers were involved in the data extraction process.

Methods of synthesis
Effect estimates and 95% confidence intervals from individual studies were pooled using random-effects models. Statistical heterogeneity was assessed using Cochran's Q statistic and the I² statistic (I² values of 25% or more indicated
low heterogeneity, 50% or more indicated moderate heterogeneity and 75% or more indicated high heterogeneity). Data from the longest follow-up period were used in the main analyses. Sensitivity analyses explored the influences of follow-up duration and the inclusion of small studies.

**Results of the review**

Six publications describing seven RCTs were included in the updated review (861 patients). Five RCTs were located through the original searches (349 patients) and two RCTs were located though the update searches (512 patients). The five trials assessed for quality in the original review were all assessed as having low risks of bias for randomisation and incomplete outcome data/selective reporting. Results for other quality domains were variable. Length of follow-up across all seven RCTs ranged from six months to five years.

**Drug-eluting balloons versus drug-eluting stents (three comparisons):** No statistically significant differences were observed between groups in relation to target lesion revascularisation, major adverse cardiac events, mortality, myocardial infarction and stent thrombosis. Similar results were shown when analyses were restricted to populations with in-stent restenosis. Only one RCT reported in-stent angiographic observations (results not reported). No statistically significant differences between groups were observed in relation to late lumen loss, minimal lumen diameter and binary restenosis.

**Drug-eluting balloons versus plain old balloon angioplasty (five comparisons):** Statistically significant reductions in target lesion revascularisation (OR 0.27, 95% CI 0.15 to 0.48), major adverse cardiac events (OR 0.30, 95% CI 0.20 to 0.44) and mortality (OR 0.39, 95% CI 0.16 to 0.92) were observed with the use of drug-eluting balloons. No statistically significant difference between groups was found in relation to myocardial infarction. Stent thrombosis reportedly occurred only in one RCT; rates for this outcome were comparable across the trial arms. Use of drug-eluting balloons was also associated with statistically significant reductions in late lumen loss (in-stent MD -0.61, 95% CI -0.77 to -0.46; in-segment MD -0.55, 95% CI -0.74 to -0.35, I²=71%), minimal lumen diameter (in-stent MD 0.68, 95% CI 0.50 to 0.85; in-segment MD 0.60, 95% CI 0.48 to 0.72) and binary restenosis (in-stent OR 0.12, 95% CI 0.06 to 0.34; in-segment OR 0.14, 95% CI 0.06 to 0.34, I²=70%).

No substantial changes to the primary outcome results were observed when the meta-analyses were performed using fixed-effect models instead (to explore the influence of small studies). Similarly, no substantial changes were apparent when primary outcome results were calculated separately according to length of follow-up (6-12 months, up to 2 years, up to 5 years).

**Authors’ conclusions**

This updated analysis re-confirmed that the efficacy and safety of drug-eluting balloons are comparable to those of drug-eluting stents and are superior to plain old balloon angioplasty regarding angiographic end points, target lesion revascularisation, major adverse cardiac events and mortality.

**CRD commentary**

The review question and inclusion criteria were clearly defined. During the original search, no language restrictions were applied and an extensive range of relevant data sources (including unpublished literature) were accessed. The update search was less extensive but still included major databases; it is possible that a small number of potentially relevant studies may have been missed at this stage. The study selection process was performed in duplicate; this was not reported for the process of data extraction so the presence of reviewer error and/or bias could not be ruled out completely. No quality assessment was reported for the two additional studies included in this review update. These two studies contributed a substantial amount of data to the analyses; the lack of information regarding quality means that we could not ascertain their potential risks of within-study bias. Study characteristics and meta-analysis results were reported in limited detail so we could not be sure of the amount of heterogeneity between the studies synthesised.

Limitations in the reporting of the results and the paucity of the evidence base suggest that the authors’ conclusions may be overly strong.

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

**Practice:** The authors did not state any implications for clinical practice.
Research: The authors stated that further RCTs were needed to compare balloons coated with other antiproliferative agents versus different types of comparator intervention in a range of lesion types. Further research on the effects of drug-eluting balloons in de novo lesions and on the comparison of drug-eluting balloons versus drug-eluting stents was recommended.

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