Intracoronary ultrasound-guided stenting improves outcomes: a meta-analysis of randomized trials
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CRD summary
The authors concluded that, compared to angiographic-guided stenting, intracoronary ultrasound-guided stenting significantly reduced angiographic restenosis and target lesion revascularization but did not reduce major adverse cardiac events. The authors made a good effort in producing this well-conducted review, however clinical differences between studies and unexplained statistical heterogeneity mean that their conclusions may not be wholly reliable.

Authors' objectives
To assess the impact of routine intracoronary ultrasound-guided coronary stent implantation on long-term clinical and angiographic outcomes.

Searching
PubMed, Cochrane Central Register of Controlled Trials (CENTRAL) and EMBASE were searched from 1982 to 2010. Studies had to be in English, Spanish or Portuguese. Search terms were reported. Bibliographies of published studies were handsearched to locate further studies.

Study selection
Eligible studies were randomised controlled trials (RCTs) that compared angiography plus intracoronary ultrasound-guided versus angiography alone-guided coronary stent implantation. Patients had symptomatic coronary lesion or silent ischaemia. The primary outcome of interest was major adverse coronary events, defined as all-cause mortality, myocardial infarction and revascularisation. Revascularisation included new percutaneous coronary intervention, coronary artery bypass grafting, target vessel revascularisation and target lesion revascularisation. Secondary outcomes included the individual components above in addition to angiography restenosis, defined as more than 50% diameter stenosis at six months. Trials with follow-up shorter than six months were excluded.

Included trials had been published between 1998 and 2010. Patient conditions were reported as being angina, ischaemia, single-vessel or native multivessel disease, and coronary artery disease. Diameters of vessels for stenting ranged from less than 2.5mm to more than 2.75mm; lengths of lesions varied across the studies (where reported).

Two reviewers independently selected studies for inclusion; disagreements were resolved by consensus or by evaluation from a third reviewer (whenever disagreements persisted).

Assessment of study quality
Presence of risk or of bias (yes/no) was assessed according to studies' descriptions for the following domains: adequate sequence generation, allocation concealment, blinding of assessors, drop-outs and exclusions, and use of intention-to-treat analysis.

Overall quality of the evidence for each outcome was evaluated using the GRADE (Grades of Recommendation Assessment Development and Evaluation) tool to assess the following: limitations of the study design, consistency of results, directness, precision and potential for publication bias. Evidence quality could be score as high, moderate, low or very low.

Quality assessment was performed independently by two reviewers; the authors did not state how any discrepancies were resolved.

Data extraction
Numbers of events per outcome were extracted to calculate risk ratios with 95% confidence intervals, as reported in original studies or sub-studies using intention-to-treat analysis. Available case analyses were used for the outcome of angiographic restenosis. Corresponding authors were contacted for any missing data or clarification of results required.
Two reviewers independently extracted the data; disagreements were resolved by consensus or by evaluation from a third reviewer (where disagreements persisted).

**Methods of synthesis**

Risk ratios (RRs) and 95% confidence intervals (CIs) were pooled for each outcome, using the Mantel-Haenszel random-effects model. Statistical heterogeneity was assessed using Cochran’s Q and $I^2$ ($I^2$ values above 25% indicated moderate heterogeneity, above 50% indicated high heterogeneity).

Sensitivity analyses were conducted according to methodological features of studies for major adverse cardiac events, and by use of intention-to-treat analysis for angiographic restenosis.

**Results of the review**

Eight RCTs (2,397 participants) were included in the review. Length of follow-up ranged from six to 30 months. Thirty-seven percent reported adequate sequence generation, 62% reported allocation concealment, 62% had blinded outcome assessors, 87% described drop-outs and exclusions and 100% presented intention-to-treat analyses.

**Primary outcome: major adverse cardiac events**

Risk of major adverse cardiac events was 21% lower for intracoronary ultrasound stenting compared with angiography alone-guided stenting, this difference was not statistically significant (RR 0.79, 95% CI 0.61 to 1.03; seven trials). Moderate statistical heterogeneity was observed ($I^2=44\%$). Sensitivity analyses according to methodological features of these studies revealed similar findings; in these analyses statistical heterogeneity was moderate or high ($I^2$ values ranged from 35% to 53%).

Assumption of a 20% control rate, a 20% relative risk reduction with 90% power, and a 0.01 two-sided alpha revealed that the optimal information size needed to reliably detect a plausible treatment effect for this outcome was at least 4,655 patients.

**Secondary outcomes**

Risk of angiographic restenosis was 27% lower for intracoronary ultrasound stenting than with angiography alone-guided stenting (RR 0.73, 95% CI 0.54 to 0.97; six trials), this difference was of borderline statistical significance. High statistical heterogeneity was observed ($I^2=51\%$). Non-use of intention-to-treat analysis did not influence this finding (RR 0.80, 95% CI 0.64 to 0.98) and still revealed moderate statistical heterogeneity ($I^2=45\%$). To prevent one case of angiographic restenosis, the number-needed-to-treat was 11.

Risk of target lesion revascularization was 38% lower for intracoronary ultrasound stenting than with angiography alone-guided stenting (RR 0.62, 95% CI 0.47 to 0.83; five trials), this difference was statistically significant. No statistical heterogeneity was observed ($I^2=0\%$). To prevent one case of target lesion revascularization, the number-needed-to-treat was 20.

No statistically significant differences were found for individual risks of all-cause mortality and myocardial infarction between intracoronary ultrasound and angiography alone-guided stenting. No statistical heterogeneity was observed for the all-cause mortality meta-analysis ($I^2=0\%$); moderate statistical heterogeneity was observed for the myocardial infarction meta-analysis ($I^2=37\%$).

No statistically significant differences were found between intracoronary ultrasound stenting and angiography alone-guided stenting for risks of target vessel revascularization, new percutaneous coronary intervention or coronary artery bypass grafting surgery. Statistical heterogeneity was high in the meta-analysis for new percutaneous coronary intervention ($I^2=84\%$) and was not present in the target vessel revascularization and coronary artery bypass grafting surgery meta-analyses ($I^2=0\%$).

**Quality of evidence for all outcomes**

Quality of overall evidence per outcome was assessed as being mostly moderate, except for new percutaneous coronary intervention (very low quality), myocardial infarction (low quality) and target lesion revascularization (high quality).
Authors' conclusions
Compared to angiographic-guided stenting, intracoronary ultrasound-guided stenting significantly reduced angiographic restenosis and target lesion revascularization but did not reduce major adverse cardiac events.

CRD commentary
The review question was clear and inclusion criteria appeared sufficiently replicable. Relevant electronic databases were accessed, and the screening process including publications printed in three different languages. Efforts were made to minimise error and bias during the various stages of the review. Study quality was assessed using suitable standardised criteria and results indicated fairly high quality across the studies. Quality of overall evidence per outcome was also evaluated with a standardised tool and suggested that the quality of most evidence was moderate.

Study details were presented clearly. Methods of synthesis appeared appropriate, but statistically significant heterogeneity might have been better explained by sensitivity analyses according to length of follow-up, because one follow-up (clinical outcomes only) was five times longer than the minimal follow-up of six months. It was also uncertain whether clinical differences (for study population, or stent brand used) between the included studies might have influenced the results. In particular, the result for risk of angiographic restenosis did not appear reliable because it was of borderline statistical significance and significant statistical heterogeneity was demonstrated, even following non-use of the intention-to-treat analysis principle.

The authors have made a good effort in producing a well-conducted review but clinical differences between studies and some unexplained statistical heterogeneity suggest that their conclusions may not be wholly reliable.

Implications of the review for practice and research
Practice: The authors stated that this evidence supported recently updated guidelines, which suggested that intracoronary ultrasound-guided stenting should be assigned a class IIa recommendation and a level of evidence B. The high economical cost of this technology also needed to be considered.

Research: The authors stated that large scale and high-quality RCTs were required to examine the potential benefit of intracoronary ultrasound guidance for hard endpoints.

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