Outcome after treatment of coronary in-stent restenosis: results from a systematic review using meta-analysis techniques
Radke P W, Kaiser A, Frost C, Sigwart U

CRD summary
This review evaluated the clinical outcome after treatment of coronary in-stent restenosis. Treatment of in-stent restenosis was associated with an overall 30% rate of major adverse cardiac events. The review's findings should be interpreted with caution given the lack of clarity in the statistical analysis, the lack of details on included studies and a confusing presentation of the results.

Authors' objectives
To evaluate the clinical outcome after treatment for coronary in-stent restenosis.

Searching
MEDLINE was searched from January 1987 to March 2001, with restrictions (type of study: human), using a combination of the terms 'Coronary', 'Stent', 'Restenosis' and 'Treatment'. The reference lists of all retrieved articles were checked for additional relevant articles.

Study selection
Study designs of evaluations included in the review
The inclusion criteria specified all randomised or non-randomised clinical trials conducted since 1987 that enrolled at least 30 patients and included a follow-up period of at least 3 months. In the included studies, the majority of the data originated from retrospectively analysed databases; there were only two randomised controlled trials (RCTs).

Specific interventions included in the review
The inclusion criteria specified any treatment for in-stent restenosis. Six treatment modalities for restenosis were evaluated in the included studies: stent-in-stent therapy, rotational atherectomy, balloon angioplasty, excimer laser angioplasty, directional coronary atherectomy and intracoronary radiation. There was no comparison intervention.

Participants included in the review
The participants included in the review were patients undergoing treatment for in-stent restenosis; 72% were male. The authors did not specify any inclusion or exclusion criteria for the participants. The participants suffered from hypertension (61%), diabetes mellitus (29%), hyperlipidaemia (55%) and unstable angina (36%).

Outcomes assessed in the review
The main outcome measure was the proportion of patients experiencing a major adverse cardiac event (MACE). This was defined as a composite of either death, myocardial infarction, or target lesion revascularisation.

How were decisions on the relevance of primary studies made?
Two authors independently assessed study eligibility.

Assessment of study quality
Validity was assessed using a series of weighted criteria based on items such as description of the population, interventions, outcomes and study design. Details were provided in the review. The authors do not state how the papers were assessed for validity, or how many of the reviewers performed the validity assessment.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. Detailed baseline characteristics, aggregated across all studies and split by treatment modality, were presented. The proportion of participants experiencing a MACE, along with the standard error, was obtained for each study. Where the event rate was zero the number of events was taken to be 0.5.

**Methods of synthesis**

**How were the studies combined?**
Random-effects meta-analyses were used to combine the results, both for individual treatment modalities and overall. A meta-regression was used to evaluate and adjust for the effects of patient, lesion and procedural variables on the primary outcome measure.

**How were differences between studies investigated?**
The authors do not state how differences between the studies were investigated, but P-values for heterogeneity between studies were reported.

**Results of the review**
Twenty-eight studies with a total of 3,012 participants were included in the analysis. Six different treatment modalities were reported: stent-in-stent therapy (3 studies, 200 participants), rotational atherectomy (8 studies, 675 participants), balloon angioplasty (13 studies, 1,305 participants), excimer laser angioplasty (6 studies, 474 participants), directional coronary atherectomy (2 studies, 75 participants) and intracoronary radiation (4 studies, 283 participants). Some of the studies included more than one treatment modality.

The mean modified validity score for all 28 studies was 18 (standard deviation 3) out of a maximum of 25.

The estimated average probability of experiencing a MACE after any of the treatments for in-stent restenosis with a follow-up period of 9 (+/- 4) months was 30.0% (95% confidence interval, CI: 25.0, 34.9). There was significant heterogeneity between the studies (P=0.0001). This outcome (MACE) was not significantly different between differing treatments: the mean adjusted probability of MACE according to treatment modality was: 28.9% (95% CI: 20.1, 35.1) for balloon angioplasty, 31.4% (95% CI: 20.5, 42.3) for stent-in-stent, 29.7% (95% CI: 15.8, 43.7) for high-speed rotational atherectomy, 34.8% (95% CI: 25.1, 44.5) for excimer laser angioplasty, 30.6% (95% CI: 20.2, 41.0) for directional coronary atherectomy, and 28.9% (95% CI: 23.6, 34.2) for intracoronary radiation therapy.

The meta-regression model estimated differences between modalities, adjusting for clinical confounding factors (lesion length, prevalence of diabetes mellitus, pre-procedural diameter stenosis). Compared with balloon angioplasty, the relative probability of MACE was -12.4% (95% CI: -39.7, 14.9) for stent-in-stent, -9.3% (95% CI: -31.0, 12.5) for high speed rotational atherectomy, -10.3% (95% CI: -28.2, 7.6) for excimer laser angioplasty, -12.1% (95% CI: -41.0, 16.8) for directional coronary atherectomy, and -16.9% (95% CI: -37.7, 4.0) for intracoronary radiation. The meta-regression analysis showed a significant and positive correlation between diameter stenosis post-intervention and the probability of experiencing a MACE.

**Authors’ conclusions**
Treatment of in-stent restenosis is associated with an overall 30% rate of MACEs, irrespective of the treatment modality used. The acute procedural result is a major predictor for the long-term outcome after treatment of in-stent restenosis.

**CRD commentary**
The review question was addressed using adequately defined inclusion criteria, except for those relating to study design. While the authors stated that their aim was to include all relevant trials, it appears that the majority of the included data have been taken from observational studies and not trials. The search strategy was not comprehensive, being restricted to a single database, and published papers may have been missed. The authors made no attempt to obtain unpublished data.
The validity of the included studies was assessed, but this was not useful given the (unknown) range of designs. No sensitivity analyses were conducted to investigate the effect of excluding studies of lower quality.

The statistics were not well reported, and the meta-analysis and meta-regression used in this study may not have been the most appropriate statistical analyses. Different types of studies were combined and indirect comparisons were made (or implied) for the different treatment modalities. Direct comparisons from RCTs were ignored. Insufficient attention was paid to the significant heterogeneity between the studies, and possible sources of this heterogeneity were not investigated. The authors stated that over-dispersed logistic regression models were used to validate the consistency of the findings, but the results of these analyses were not presented.

There was very little information on the individual included studies, such as the study designs and patient characteristics. The lack of details relating to the primary studies makes it difficult for the reader to fully appreciate the nature of the included data.

The conclusions of the authors are rather too definite in view of the lack of data from RCTs included in the meta-analysis. The review's findings should be interpreted with caution given the lack of clarity in the statistical analysis, the primary studies and a confusing presentation of the results, which are mixed up with the 'Discussion' section.

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

Practice: The authors state that balloon angioplasty should be considered as the treatment of choice, especially in short and focal lesions, as long as a sufficient acute procedural result can be achieved. In patients with the therapy-refractory form of diffuse in-stent restenosis, intracoronary radiation should be considered.

Research: The authors do not directly recommend the need for a randomised trial comparing different treatment modalities for in-stent restenosis, but it would appear to be a clear practice recommendation arising from the review.

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