Effect of thiazolidinediones on in-stent restenosis in patients after coronary stenting: a meta-analysis of randomized controlled trials

CRD summary
This review found that thiazolidinedione therapy for six months following coronary stenting significantly reduced in-stent restenosis in both diabetic and non-diabetic patients. The review was generally well conducted and the conclusions are likely to be reliable but should be interpreted with some caution due to the possibility of publication bias.

Authors’ objectives
To determine the effects of thiazolidinediones on in-stent restenosis after coronary stenting.

Searching
PubMed, EMBASE, BIOSIS Previews and Cochrane Central Register of Controlled Trials were searched from inception to May 2007. Search terms were reported. References from retrieved studies and five relevant conference proceedings were screened to identify additional relevant studies. No language or publication restrictions were applied.

Study selection
Randomised controlled trials (RCTs) that compared thiazolidinedione treatment with placebo, no treatment or conventional anti-diabetic therapy in patients with coronary artery disease undergoing coronary stenting, irrespective of whether or not they had diabetes, were eligible for inclusion. Trials that evaluated troglitazone, which has been withdrawn from the market, were excluded. Trials had to report in-stent restenosis, late lumen loss, diameter stenosis or target lesion revascularisation evaluated by quantitative coronary angiography during at least six months follow-up.

The primary outcome measure was in-stent restenosis, defined as greater than 50% diameter stenosis measured by quantitative coronary angiography. Secondary outcomes included diameter stenosis, late lumen loss and target lesion revascularisation evaluated by quantitative coronary angiography, and in-stent neointimal area/volume on intravascular ultrasound (if performed).

Trials included both diabetic and non-diabetic patients. The proportion of men was 72%. Thiazolidinediones evaluated were pioglitazone (30 mg/day) and rosiglitazone (4mg/day).

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Two reviewers independently assessed study quality using the Jadad score (maximum score of 5). Discrepancies were resolved through consensus or referral to a third reviewer.

Data extraction
Data were extracted as relative risks for dichotomous outcomes, weighted mean differences for continuous outcomes in which units of measurement were consistent across trials, and as standard mean differences if inconsistent. 95% confidence intervals (CI) were extracted for all measures of effect.

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Methods of synthesis
Measures of effect were pooled using random-effects models. Heterogeneity was assessed using the $\chi^2$ test with $p < 0.10$ considered as evidence of heterogeneity. The $I^2$ statistic was used to quantify heterogeneity with $I^2 > 50\%$ considered as significant heterogeneity. Subgroup analysis was used to investigate differences between diabetic versus non-diabetic
Results of the review
Eight RCTs (n=366) were included. Jadad quality scores ranged from 2 to 4.

All outcomes assessed using quantitative coronary angiography were significantly lower in patients treated with thiazolidinediones compared to those treated with placebo:

In-stent restenosis (seven RCTs, n=377): Relative risk 0.32 (95% CI: 0.21, 0.49), p<0.00001. There was no evidence of heterogeneity (p=0.42, I²=0.8%).

Late lumen loss (four RCTs, n=252): Weighted mean difference -0.54 (95% CI: -0.87, -0.22), p=0.001. There was some evidence of heterogeneity (p=0.01, I²=72%).

Diameter stenosis (four RCTs, n=242): Weighted mean difference -15.7% (95% CI: -19.4%, -12.0%), p<0.00001. There was no evidence of heterogeneity (p=0.71, I²=0%).

Neointimal area/volume (three RCTs, n=136): Standard mean difference -0.76 (95% CI: -1.13, -0.39), p<0.0001. There was no evidence of heterogeneity (p=0.33, I²=8.8%).

Target lesion revascularisation (six RCTs, n=225): Relative risk 0.34 (95% CI: 0.18, 0.62), p=0.0005. There was no evidence of heterogeneity (p=0.45, I²=0%).

All findings were consistent for both diabetic and non-diabetic patients. Exclusion of the two papers available only as conference abstracts did not alter the results.

There were no serious adverse events associated with thiazolidinediones. There were four cases of non-serious (oedema and dizziness and headache) in patients treated with thiazolidinediones.

Authors' conclusions
Thiazolidinedione therapy for six months following coronary stenting significantly reduces in-stent restenosis, diameter stenosis, late lumen loss and neointimal area/volume in both diabetic and non-diabetic patients.

CRD commentary
The review addressed a focused question supported by clearly defined inclusion criteria. The literature search was appropriate but did not include specific attempts to locate unpublished studies but conference abstracts were sought. Consequently, there is a possibility of publication bias. Appropriate steps were taken to minimise bias and errors in the extraction of data and assessment of quality but it is unclear whether such steps were also taken in the selection of studies. Relevant details were reported for the trials published as full publications but details were lacking on the trials published only as abstracts. The methods of analysis were appropriate and results were clearly presented in the text and using forest plots. The authors' conclusions are supported by the results presented and are likely to be reliable but should be interpreted with some caution due to the possibility of publication bias.

Implications of the review for practice and research
Practice: The authors stated that thiazolidinedione therapy is effective in preventing in-stent restenosis in both diabetic and non-diabetic patients who are undergoing coronary stenting.

Research: The authors stated that large multi-centre RCTs are needed to clarify the anti-restenotic effect of thiazolidinedione therapy in diabetic and non-diabetic patients undergoing coronary stenting.

Funding
Not stated.

Bibliographic details

PubMedID
18602105

DOI
10.1016/j.atherosclerosis.2008.05.029

Indexing Status
Subject indexing assigned by NLM

MeSH
Angioplasty, Balloon, Coronary; Coronary Artery Disease /therapy; Coronary Restenosis /drug therapy; Humans; Hypoglycemic Agents /therapeutic use; Randomized Controlled Trials as Topic; Stents; Thiazolidinediones /therapeutic use

AccessionNumber
12009102732

Date bibliographic record published
15/04/2009

Date abstract record published
17/06/2009

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.