Effects of ranolazine in symptomatic patients with stable coronary artery disease. A systematic review and meta-analysis


CRD summary
The review concluded that ranolazine significantly reduced angina incidence and sublingual nitroglycerin consumption, and improved exercise tolerance, in patients with coronary artery disease. The authors' conclusions appear to fairly reflect the evidence presented in a broad sense, but limitations of the meta-analysis methods (and reporting) suggests the accuracy of the actual results is questionable.

Authors' objectives
To assess the effects of ranolazine on symptoms, electrocardiographic signs of ischaemia, and haemodynamic changes in patients with chronic coronary artery disease.

Searching
MEDLINE, The Cochrane Library, ISI Web of Science and SCOPUS were searched until May 2013 for published studies by combining the terms “ranolazine” and “randomized”. There were no language restrictions. Reference lists of relevant articles were also searched and experts in the field contacted to identify further relevant studies.

Study selection
Randomised studies of ranolazine versus control were eligible providing they reported at least one of the following outcomes: evaluation of exercise duration; time to onset of angina; time to 1mm ST-segment depression; weekly nitroglycerin consumption; weekly angina frequency; comparison of glycaemic control by glycated haemoglobin (HbA1c) in type II diabetic patients; and supine or standing heart rate and blood pressure variations from baseline to the end of follow-up.

All included studies were placebo-controlled. Some were multi-armed trials investigating different doses of ranolazine; one trial also had atenolol as a comparator. Ranolazine doses ranged from 500mg twice a day, to 1500mg twice a day, though in the largest trial a dose range (of 375mg to 1000mg twice daily) was reported. The mean age of participants was 63 years and 31% were women. Most participants had hypertension.

Two reviewers independently selected studies for inclusion; disagreements were resolved by discussion.

Assessment of study quality
Methodological quality of trials was assessed by Detsky method which scored items such as method of randomisation, blinding and outcome assessment. Studies that scored below 50% were considered low quality, those with a score greater than 75% were high quality, and those with a score between 50% and 75% were moderate quality.

It appeared that one reviewer assessed study quality, with the results being checked by a second reviewer.

Data extraction
Data were extracted in order to calculate mean differences with 95% confidence intervals. If data were missing, the trial authors or the product manufacturers were contacted. One reviewer extracted data which were then checked by a second reviewer.

Methods of synthesis
Meta-analyses were performed to calculate pooled weighted mean differences at both peak and trough levels of ranolazine; the type of model used was varied "as appropriate" (no specific details were provided). Heterogeneity was assessed using the Q-test and I². The effect of numerous possible effect modifiers (listed in the paper) was explored using meta-regression with a weighted random-effects model. Publication bias was assessed using Egger's test.

Results of the review
Six trials were included (9,223 patients; range 158 to 6,560). Study quality scores ranged between 90% and 95%. Two studies used a cross-over design. Duration of follow-up ranged from one to 50 weeks.

At trough levels (six placebo comparisons from three studies) ranolazine significantly improved exercise duration (WMD 31.90 seconds, 95% CI 20.98 to 42.82) time to onset of angina (WMD 37.98 seconds, 95% CI 26.15 to 49.81) and time to 1mm ST-segment depression (36.21 seconds, 95% CI 24.27 to 48.15). There was no evidence of statistical heterogeneity. Results for peak levels were similar, except that significant heterogeneity was seen in the angina, and ST-segment depression analyses.

From four placebo comparisons in three studies, ranolazine significantly reduced weekly angina frequency (WMD -0.69, 95% CI -0.97 to -0.40; I²=11%) and weekly nitroglycerin consumption (WMD -0.53; 95% CI -0.79 to -0.28; I²=38%). Ranolazine did not significantly reduce supine systolic and diastolic blood pressure, heart rate, standing heart rate and diastolic blood pressure; a small but statistically significant reduction was found for standing systolic blood pressure (WMD -1.55mm Hg, 95% CI -2.36 to -0.74; I²=0%).

Compared to placebo ranolazine significantly reduced HbA1c levels in type II diabetic patients by 0.43% (95% CI -0.75 to -0.11; three comparisons, two studies; I²=68%).

Results of the meta-regressions did not indicate the presence of any significant effect modifiers. Sensitivity analyses found that no individual study drove the analyses. There was some evidence of publication bias for time to onset of angina at trough levels, supine systolic blood pressure, and standing heart rate.

**Authors’ conclusions**
In symptomatic patients with chronic coronary artery disease, ranolazine added to conventional therapy effectively reduced angina frequency and sublingual nitroglycerin consumption. Ranolazine also prolonged exercise duration, as well as time to onset of ischaemia and to onset of angina with no substantial effects on blood pressure and heart rate. Additionally, in type II diabetic patients ranolazine improved glycaemic control reducing HbA1c levels.

**CRD commentary**
The review addressed a clear question and was supported by reproducible eligibility criteria in terms of study design, intervention and outcomes; though no definition of chronic coronary artery disease was reported. Several databases were searched for relevant studies in any language, using limited search terms. There was evidence that publication bias may have affected some results. Suitable methods (such as independent duplicate processes) were used to reduce the risk of reviewer error and bias throughout the review.

It was unclear which type of model was used for individual meta-analyses. Furthermore, the double-counting of some comparator groups in many of the analyses meant that the accuracy and precision of some effect estimates was questionable. Study quality was assessed with the results used in a meta-regression analysis. Adequate primary study details were provided. Two of the included trials had follow-up durations of only one week.

Although the authors' conclusions appear to fairly reflect the evidence presented in a broad sense, limitations in the methods and reporting of meta-analysis suggests the accuracy of the actual results is questionable.

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

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Not reported.

**Bibliographic details**

**PubMedID**
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.