Authors' objectives
To determine the relative efficacy of anti-anginal drugs administered as monotherapy or in combination, in patients with chronic stable angina.

Searching
MEDLINE, the Cochrane Library and the reference lists of relevant reviews and identified studies were searched. The search was limited to studies published in the English language from 1980 to December 1999.

Study selection
Study designs of evaluations included in the review
Only double-blind randomised controlled trials (RCTs) were sought. The included studies were of both parallel and crossover design. Studies of less than one week in duration were excluded.

Specific interventions included in the review
The inclusion criteria specified combined anti-anginal drug therapies (beta-blockers, calcium-channel antagonists or long-acting nitrates) compared with the same drugs administered individually. In the included studies, beta-blocker monotherapy or calcium-channel blockers were compared with a combination of beta-blockers and calcium-channel antagonists. The specific drugs and dosages were given in the paper. The duration of the active treatment ranged from 2 to 16 weeks.

Participants included in the review
Both males and females with stable chronic angina were included. The mean ages ranged from 58 to 60 years. Documented coronary angiography, or history of myocardial infarction (MI), were criteria for inclusion in some of the studies. Some studies specified that at least two exercise tests had to have been performed before randomisation.

Outcomes assessed in the review
The outcomes to be assessed were measures of anti-anginal efficacy, as evaluated by exercise testing (treadmill or bicycle), total duration of exercise, time to onset of pain and time to 1mm ST-segment depression. The authors implied they were interested in clinical outcomes, but the data were either unavailable or not reported consistently in the included studies; these outcomes were subsequently excluded. Tolerance data were also sought.

How were decisions on the relevance of primary studies made?
A cardiologist assessed the full texts of all the retrieved publications, following which the cardiologist and a clinical statistician selected the articles.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The cardiologist extracted the data. The exercise-test data entry was double-checked.

Methods of synthesis
How were the studies combined?
Two separate analyses were performed: one comparison of beta-blockers in single or combination therapy, and one comparison of calcium-channel blockers in single or combination therapy. Trials that compared the two drugs separately and in combination were included in both analyses. Trials that compared several doses of a drug to a combination were included as many times as the number of tested doses. The absolute and the percentage differences of combined therapy to monotherapy were estimated for each trial and for all trials together. Standardised mean differences (SMDs) were estimated using Hedges' method that remains adapted for smaller sample sizes. Unbiased SMDs and their 95% confidence intervals were estimated for each trial and for all the studies together. The percentage of participants with no angina and the percentage without 1 mm ST-segment depression at the end of the study were compared using the Mantel-Haenszel adjusted chi-squared.

How were differences between studies investigated?
An overall heterogeneity test was performed for each exercise-test parameter. Subgroup analyses were carried out on groups defined by the time to exercise testing (within or later than 6 hours of drug intake), on crossover and parallel trials, and on the use of short- or long-acting calcium antagonists.

Results of the review
Twenty-two studies were included: 12 compared beta-blocker monotherapy with the combination therapy of beta-blocker and calcium antagonist (three parallel design, 284 participants; nine crossover design, 286 participants), while 10 compared beta-blockers and calcium-channel blockers individually and in combination (four parallel design, 1,617 participants; six crossover design, 166 participants).

Only one study was found that compared nitrates in monotherapy with combination therapy. Therefore, no meta-analysis was carried out for these drugs.

No overall heterogeneity test was statistically significant.

Comparison of betablockers and combination therapy: the time (seconds, s) to ST-segment depression was 8% (33 s) higher with the combination therapy (p<0.001). There was a statistically-significant difference of 9% (43 s) at peak (p<0.001), while the difference of 3% (10 s) at trough was not statistically significant (p<0.21). The adjusted difference in total exercise duration was 5% (23 s) in favour of combination therapy (p=0.002). There was a significant increase of 12% (42 s) in time to onset of pain with combination therapy (p<0.001). The difference of +8% (+38 s) in the subgroup of exercise testing within 6 hours of drug intake was significant (p=0.039). No statistical difference was shown for the 'after six hours' group (difference: 0%,-4 s; p=0.65). Similar results were noted when short- and long-acting calcium antagonists were evaluated separately, and for the subgroup analysis of parallel and crossover trials. The exception was total duration of exercise test where the difference of +2% (11 s) was not statistically significant in the parallel trials (p=0.24).

Comparison of calcium antagonist with combination therapy: the time to 1 mm ST-segment depression was 9% (41 s) higher with the combined therapy (p<0.001). There was a statistically-significant difference of 10% (46 s) for exercise test performed within 6 hours of drug intake (p<0.001), but no statistical difference in the only trial where the exercise test was performed after 6 hours (difference: 2%, 10 s; p=0.66). There was a non statistically-significant increase of 4% (17 s) in total duration of exercise with combined therapy (p=0.35). The difference in time to onset of pain (9%, 30 s) was statistically borderline, favouring combination therapy (p=0.067). There were insufficient trials to conduct a subgroup analyses of short- and long-acting calcium antagonists. There were also insufficient studies and patients to perform subgroup analyses of parallel and crossover studies.

There were insufficient data to enable a comparison of the safety data.

Authors’ conclusions
In terms of exercise testing, the combination of a calcium antagonist and beta-blocker is statistically more effective than either monotherapy. However, the difference seems restricted to the first 6 hours following drug intake.

CRD commentary
This was generally a clearly written review. The aims were well defined but the search strategy appeared rather limited, especially regarding the terms used and the limited number of references the authors say they found from the initial search. It is possible that studies were missed. The outcomes were given as times, apparently in seconds, but the authors did not clearly state what units were used. The authors included a combination of parallel and crossover studies; combining these in meta-analyses may be problematic. The authors did, however, perform a subgroup analysis by study design. Further problems relating to drug washout periods (in crossover studies) were not discussed. Some studies appear to have been included several times in the analyses since more than one drug dose was being compared. It was not clear how this issue was dealt with. The use of the same control group more than once may have influenced the results.

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

Research: The authors state that further studies are needed to confirm the higher efficacy (of combination therapy) after the first 6 hours following drug intake.

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