Efficacy and tolerability of trimetazidine in stable angina: a meta-analysis of randomized, double-blind, controlled trials

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CRD summary
This manufacturer-funded review assessed the efficacy of trimetazidine (TMZ) alone or in combination compared with placebo or other drugs. The authors concluded that TMZ is effective compared with placebo and as effective as other anti-anginal agents. The review had reporting and methodological weaknesses, and some conclusions did not follow from the evidence presented and hence may not be reliable.

Authors' objectives
To evaluate the efficacy and tolerance of trimetazidine (TMZ), both in monotherapy and in combination with other agents, in the treatment of stable effort angina pectoris.

Searching
MEDLINE and EMBASE were searched from 1985 to April 2001; the search terms used were listed. The bibliographies of identified articles and reviews were handsearched. It appears that the search was not restricted by language. Articles in English, French and Turkish were included.

Study selection
Study designs of evaluations included in the review
The inclusion criteria specified double-blind, randomised controlled trials (RCTs).

Specific interventions included in the review
The inclusion criteria specified TMZ, either alone or in combination with other treatments, compared with placebo or other drugs. The comparison groups in the included studies were placebo or other drug treatment (prenylamine, propranolol, nifedipine or isosorbide dinitrate). Other concomitant drug treatments in both arms of some studies were diltiazem, metoprolol, nifedipine, propranolol or an anti-anginal drug (not specified). The duration of treatment ranged from 2 weeks to 6 months. The drug doses and treatment duration for each trial were given in the review. The authors stated that in most studies short-acting nitrates were allowed during exercise testing, if needed.

Participants included in the review
The inclusion criteria specified participants who had stable angina. Men and women were included in the review, but the majority of the participants were men. The mean age ranged from 50 to 62 years; all participants were under 75 years. The patients in the included studies had stable angina for at least one month. Angina severity varied from three attacks per week to at least one attack per day. Sublingual nitroglycerin consumption varied from two to nine tablets per week at baseline. The individual studies all excluded patients who had unstable angina or a myocardial infarction during the 3 months prior to the start of the study.

Outcomes assessed in the review
Four outcomes were assessed in the review: the number of weekly angina attacks, the time to 1-mm ST-segment depression, the total work at peak exercise (kilopond-metres), and exercise duration at peak exercise. Tolerability was assessed by the reporting of any adverse events.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
A qualitative assessment of study methodology was performed, which considered the randomisation procedure, sample size, study design, patient withdrawals and ergonomic parameters assessed. The authors did not state how the papers were assessed for validity, or how many reviewers performed the validity assessment.

**Data extraction**

Three reviewers independently collected the data. Any discrepancies were discussed and a consensus reached. Data on the study design, trial quality, participant characteristics and treatments were tabulated. The authors stated that the extracted data were checked for accuracy.

**Methods of synthesis**

How were the studies combined?

The authors stated that they calculated effect sizes as standardised mean differences (SMDs) with 95% confidence intervals (CIs) for continuous outcomes. Results from fixed-effect and random-effects models were reported for each outcome. Standard meta-analytical statistical techniques appear to have been used.

How were differences between studies investigated?

Heterogeneity was investigated by determining the percentage of the variance explained by sampling error. Sensitivity analyses were performed by studying the influence of individual studies on the results.

**Results of the review**

From the results tabulated (Table 2), it appears that 12 RCTs with data on 921 participants were included in the review (see CRD Commentary with respect to which studies were included). Two studies were crossover studies and the rest were parallel studies. Eight studies evaluated TMZ against placebo and four against other drugs. Six studies were on TMZ as monotherapy and six were on TMZ combined with other drugs.

All the following results are the effect of TMZ compared with the comparator group, from random-effects models.

Number of weekly angina attacks (8 studies): TMZ reduced the number of weekly angina attacks; the SMD was 0.39 (95% CI: 0.08, 0.70, P=0.013). This statistically-significant effect was only seen in studies where TMZ was compared with placebo (P<0.001) and not when TMZ was compared to another drug (P>0.05). TMZ reduced the number of weekly angina attacks when taken on top of conventional treatment, but not when taken as monotherapy (this was stated in the text, but the results were not shown).

Time to 1-mm ST-segment depression (7 studies): TMZ increased the time to 1-mm ST-segment depression; the SMD was 0.23 (95% CI: 0.09, 0.38, P=0.002). This statistically-significant effect was only seen in studies where TMZ was compared with placebo (P<0.05) and not when TMZ was compared to another drug (P>0.05). TMZ improved the time to 1-mm ST-segment depression when taken on top of conventional treatment, but not when taken as monotherapy.

Total work at peak exercise (8 studies): TMZ increased the total work time at peak exercise, but the result was not statistically significant; the SMD was 0.15 (95% CI: -0.03, 0.33, P=0.11). The subgroup analyses showed that TMZ did not significantly improve the total work at peak exercise, whether given as monotherapy or in combination therapy.

Exercise duration at peak exercise (7 studies): TMZ did not alter the exercise duration at peak exercise; the SMD was 0.12 (95% CI: -0.09, 0.33, P=0.28). The subgroup analyses showed that TMZ did not increase the exercise duration at peak exercise, whether given as monotherapy or in combination therapy.

Tolerability was assessed by the reporting of any adverse events (8 studies). No patient withdrawals due to side-effects of TMZ or any other drug were mentioned. The authors reported that there were fewer adverse events (gastrointestinal, headaches or muscular cramps) in the TMZ groups in comparison with nifedipine, propranolol or metoprolol. No quantitative data on tolerability were presented.

**Authors' conclusions**
The study confirmed that TMZ is effective in angina pectoris in monotherapy, as compared with placebo, and is as effective as other first-line anti-anginal agents. The authors also concluded that TMZ provided additional efficacy in combination with other agents and had good tolerability.

CRD commentary
This review had clearly stated aims. The search strategy may have missed relevant studies since little attempt was made to identify unpublished data. The authors noted that they searched for conference proceedings, but they did not report the searching of grey literature such as FDA submissions or pharmaceutical company reports. The search terms used also appear to have been limited.

It was unclear from the paper exactly which studies were included in the meta-analysis. Twelve papers were listed in Table 2, but the references to the included studies referred to a different 12 studies. There were also inconsistencies in the reporting of which studies were parallel and which were crossover studies.

Some of the conclusions in the paper (e.g. comparisons of the effect of TMZ in monotherapy and combination therapy) were based on subgroup analyses in which single studies were excluded. Insufficient justification for this approach to the analysis was given.

The reporting of the results in the paper was confused. The authors stated that they calculated the SMDs in the 'Methods' section, then in the 'Results' section they stated that they reported the pooled odds ratios when it was actually SMDs that were given. Differences between the results in the text and the tables further confuses the interpretation of the results. For example, the authors stated that TMZ reduces the number of weekly angina attacks, whereas Figure 1 indicated that it increases this number. The result for the random-effects model of the effect of TMZ on total work at peak exercise was given in the text as 0.166 (95% CI: 0.33, 0.334), which cannot be correct. This was different to the random-effects and fixed-effect results tabulated.

There were also discrepancies when referring to the individual references within the text and in tables.

In the opinion of the reviewer, the authors' conclusions do not follow from their results. For example, the authors did not present any data to show that TMZ is as effective as other first-line anti-anginal agents. For none of the outcomes studied was TMZ beneficial when taken as monotherapy.

There were insufficient data on tolerability to support the authors' claims that TMZ is well tolerated.

This study was funded by Servier, the pharmaceutical company which manufactures TMZ.

Implications of the review for practice and research
Practice: The authors stated that TMZ can be proposed as a first-line treatment for coronary patients.

Reviewer's comment: Better information is required before such a recommendation can be made.

Research: The authors did not state any implications for further research.

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Bibliographic details

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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.