Additional use of trimetazidine in patients with chronic heart failure: a meta-analysis


CRD summary
This review concluded that trimetazidine may have decreased hospitalisation for cardiac causes, improved clinical symptoms and cardiac function, and ameliorated left ventricular modelling in patients with chronic heart failure. Despite some uncertainties in the methods used to select studies, the authors cautious conclusions reflect the evidence presented and are likely to be reliable.

Authors' objectives
To assess the effects of additional trimetazidine treatment in patients with chronic heart failure.

Searching
PubMed, EMBASE and EBM Reviews databases were searched up to November 2010. Search terms were reported. The reference lists of retrieved studies were screened for additional studies.

Study selection
Randomised controlled trials (RCTs) that compared trimetazidine with placebo in patients with chronic heart failure were eligible for inclusion. Studies with treatment duration of less than four weeks were excluded, as were cross-over trials without a washout period between treatments. The review outcomes of interest included all-cause mortality, hospitalisation for cardiac causes, change in left ventricular ejection fraction, New York Heart Association functional class, left ventricular end-systolic diameter, left ventricular end-diastolic diameter, left ventricular end-systolic volume, left ventricular end-diastolic volume, resting systolic and diastolic blood pressure, B-type natriuretic peptide, high-sensitivity C-reactive protein and corrected QT interval.

The included studies used trimetazidine at 60mg or 70mg per day. The New York Heart Association functional class of included patients ranged from I to IV where reported. The percentage of included patients with ischaemic aetiology ranged from zero to 100%. Most included patients were male. The mean left ventricular ejection fraction at baseline ranged from 29 to 55%. The duration of follow-up ranged from one to 23 months. The mean age of patients ranged from 50 to 78 years.

The authors did not report how many reviewers assessed studies for inclusion.

Assessment of study quality
The quality of studies was assessed using the Jadad scale, a five-point scale evaluating randomisation, blinding and withdrawals/drop-outs.

Two reviewers independently performed study quality.

Data extraction
For continuous outcomes, data were extracted on mean and standard deviations to enable the calculation of mean differences (MDs) with 95% confidence intervals (CIs). For dichotomous outcomes, data were extracted on event rates to enable the calculation of relative risks (RRs) with 95% confidence intervals.

Two reviewers independently performed data extraction.

Methods of synthesis
The studies were combined in a meta-analysis. The weighted mean differences (WMDs) and standardised mean differences (SMDs) with 95% confidence intervals were calculated. The pooled relative risks with 95% confidence intervals were also calculated. A random-effect model was used when there was significant heterogeneity; otherwise a fixed-effect model was employed. Statistical heterogeneity was assessed using I². Meta-regression was used to assess the influence of age, aetiology, baseline left ventricular ejection fraction, type of trimetazidine, baseline New York Heart Association functional class and length of follow-up. Sensitivity analyses were performed by excluding one study at a time.
times. Publication bias was assessed using the Begg adjusted rank correlation test and Egger regression asymmetry test.

**Results of the review**

Sixteen RCTs (884) were included in the review. Sample size ranged from 19 to 200. Jadad score ranged from 1 to 5. Ten trials had a Jadad score of at least three. Six studies reported allocation concealment; four studies adequately described method of randomisation; eight studies were double-blind, two studies were single-blind; thirteen studies ascertained outcomes blindly; fifteen studies described loss to follow-up; and no studies used intention-to-treat analysis.

Compared with placebo, trimetazidine therapy was found to have significantly improved left ventricular ejection fraction (WMD 6.46%; 95% CI 5.20% to 7.73%; 14 RCTs; Ι²=71%). There was no significant difference in all-cause mortality between the trimetazidine and placebo groups.

Compared with placebo, trimetazidine therapy was associated with a significant reduction in hospitalisation due to cardiac causes (RR 0.43, 95% CI 0.21 to 0.91; four RCTs; Ι²=0%), left ventricular end-systolic diameter (WMD -6.67 mm, 95% CI -9.29 to -4.06; three RCTs; Ι²=95%), left ventricular end-diastolic diameter (WMD -6.05 mm, 95% CI -7.57 to -4.52; three RCTs; Ι²=56%), left ventricular end-systolic volume (WMD -0.61, 95% CI -1.14, -0.09; six RCTs; Ι²= 80%), New York Heart Association functional class (WMD -0.57, 95% CI -0.88 to -0.26; seven RCTs; Ι²=75%) and B-type natriuretic peptide (WMD -203.40pg/ml, 95% CI -308.99 to -97.81; two RCTs; Ι²=63%).

Results for left ventricular end-diastolic volume, resting systolic and diastolic blood pressure, high-sensitivity C-reactive protein, and corrected QT interval were not statistically significant.

Results for the meta-regression analysis were also reported. There was no evidence of publication bias.

**Authors’ conclusions**

Trimetazidine may have decreased hospitalisation for cardiac causes, improved clinical symptoms and cardiac function, and ameliorated left ventricular remodelling in patients with chronic heart failure.

**CRD commentary**

The review question and inclusion criteria were clearly stated and the search appeared adequate, however it was not reported whether methods to reduce error and bias in the selection of studies was undertaken. It was unclear whether any language restriction was applied, which made it difficult to assess the risk of language bias. Study quality was assessed using reasonable criteria and efforts were made to reduce the likelihood of error or bias in the assessment of quality and extraction of data. A reasonable level of information about individual studies was provided. Given the high levels of between-study heterogeneity for many outcomes, a narrative synthesis may have been more appropriate, however, the authors assessed outcomes for different subgroups. Despite some uncertainties in the methods used to select studies, the authors’ cautious conclusions reflect the evidence presented and are likely to be reliable.

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

The authors did not state any implications for practice or research.

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