Trimetazidine: a meta-analysis of randomised controlled trials in heart failure
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CRD summary
This review concluded that trimetazidine might be effective in treating heart failure, but routine use could not be recommended and further research was needed. Data came from small studies some of which were of lower quality. The authors’ conclusions included a need for further research and appear suitably conservative.

Authors’ objectives
To assess the effects of trimetazidine in the management of heart failure.

Searching
PubMed, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from inception to June 2010. Search terms were reported. No language restrictions were applied. Conference proceedings from three societies (2005 to 2010) and ClinicalTrials.gov were searched. Bibliographies of identified papers were checked. Manufacturers were contacted.

Study selection
Randomised controlled trials (RCTs) that compared trimetazidine to placebo in adults with chronic heart failure were included. The outcomes of interest were mortality, hospitalisation, cardiovascular events, changes in cardiac function parameters (left ventricular ejection fraction, left ventricular end-diastolic volume, left ventricular end-systolic volume), New York Heart Association (NYHA) classification and exercise duration.

In the included studies included men and women. Mean ages ranged from 50 to 67 years in the trimetazidine group and 53 to 78 years in the placebo group. Most of the participants the aetiology of heart failure was ischaemic heart disease. Left ventricular ejection fraction ranged from 28% to 40% in the trimetazidine group and 29% to 40% in the placebo group. Most participants (where reported) had NYHA Class II or III symptoms. Some participants had diabetes. Trimetazidine doses ranged from 40mg to 70mg per day; most received 60mg per day. Concomitant treatments included betablockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), digitalis, aldosterone antagonists, diuretics and statins. Follow-up ranged from four weeks to 48 months.

Two authors selected studies for inclusion. Disagreements were resolved by consensus or, where necessary, a third author.

Assessment of study quality
Quality was assessed by two authors independently using the Jadad scale of reporting of randomisation, generation of random sequence, blinding, completeness of follow-up and description of drop-outs. The maximum score was 5. Disagreements were resolved by consensus.

Data extraction
For crossover trials, where data were not reported as mean differences between treatment and control but separately as two groups, data were extracted as two separate parallel trials. Risk ratio (RR) and 95% confidence intervals (CI) were calculated for dichotomous data. Weighted mean difference (WMD) and 95% CI were calculated for continuous data.

Data were extracted by two authors and checked by a third. Authors were contacted for missing information.

Methods of synthesis
Pooled risk ratios and weighted mean differences, with 95% CIs, were calculated using a random-effects model. Heterogeneity was assessed using X² and I². Sensitivity analyses were undertaken to investigate effects of study quality (score ≥3) and longer follow-up (≥3 months). Subgroup analysis investigated aetiology of disease (ischaemic versus non-ischaemic), presence of diabetes, trials with concomitant use of ACE inhibitors/ARBs and betablockers.
Funnel plots were used to assess publication bias.

Results of the review
Seventeen RCTs (905 participants) were included: 14 parallel trials and three crossover trials. Most studies were small with study sizes that ranged from 19 to 200 participants. Funnel plot indicated a low likelihood of publication bias.

Four trials scored 5 for quality, seven scored 4, three scored 3 and three scored 2. Only four trials reported adequate methods of randomisation. Eleven trials were double blind, four were single blind and two were open studies. Fourteen trials reported on withdrawals.

Compared to placebo, trimetazidine was associated with a reduction in all-cause mortality (RR 0.29, 95% CI 0.17 to 0.49, I²=0%; four trials) and cardiovascular events and hospitalisation (RR 0.42, 95% CI 0.30 to 0.58, I²=0%; four trials). There was an improvement in NYHA symptom classification (WMD -0.41, 95% CI -0.51 to 0.31, I²=15%; seven trials) and in exercise capacity (WMD 30.26 seconds, 95% CI 8.77 to 51.75, I²=31%; six trials) with trimetazidine.

Trimetazidine was associated with an improvement in left ventricular ejection fraction (WMD 7.49%, 95% CI 6.26 to 8.71%, I²=50%; 17 trials). All subgroup and sensitivity analyses showed similar results to the main analysis. Left ventricular end-systolic volume was lower in those treated with trimetazidine (WMD -10.37, 95% CI -15.46 to -5.29, I²=66%; 10 trials). There was no statistically significant effect on left ventricular end-diastolic volume.

Authors' conclusions
Trimetazidine might be effective in treating heart failure, but routine use could not be recommended and further research was needed.

CRD commentary
The aims of this review were clearly stated in terms of the inclusion criteria. The search covered a number of relevant sources and included looking for unpublished studies and those in any language; this was likely to have reduced the possibility of language and publication biases. The methods of the review were aimed at reducing reviewer error and bias. Quality was assessed using a scoring system and useful details were reported. The methods of synthesis were generally appropriate. Heterogeneity was assessed. It was unclear whether the methods for inclusion of data from crossover trials were appropriate. In particular some crossover trials (participants) appeared to have been included twice inappropriately. There were some discrepancies between numbers in the text and tables. The authors acknowledged that data came from small studies, some of which were of lower quality.

The authors' conclusions included a need for further research and appear suitably conservative.

Implications of the review for practice and research
Practice: The authors stated that routine use of trimetazidine could not be recommended until further research was undertaken.

Research: The authors stated that large-scale RCTs were needed to assess the effects of trimetazidine in people with heart failure.

Funding
National Natural Science Foundation of China (no 30900617); Research Fund for the Doctoral Program of Higher Education of China (no 2008.6981036); Major Basic Research Development Program of China from the Ministry of Science and Technology (no 2006CB503802).

Bibliographic details
Heart 2011; 97(4): 278-286

PubMedID
21134903

DOI
10.1136/hrt.2010.208751

Original Paper URL
http://heart.bmj.com/content/97/4/278.abstract

Indexing Status
Subject indexing assigned by NLM

MeSH
Acetyl-CoA C-Acyltransferase /antagonists & inhibitors; Adult; Chronic Disease; Enzyme Inhibitors /therapeutic use; Exercise Tolerance; Heart Failure /drug therapy /physiopathology; Humans; Randomized Controlled Trials as Topic; Stroke Volume /drug effects; Treatment Outcome; Trimetazidine /therapeutic use; Vasodilator Agents /therapeutic use; Ventricular Remodeling

AccessionNumber
12011001467

Date bibliographic record published
18/05/2011

Date abstract record published
07/09/2011

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.