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Additional Use of Trimetazidine in Patients With Chronic Heart Failure

A Meta-Analysis

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Objectives The aim of this meta-analysis was to evaluate the effects of additional trimetazidine (TMZ) treatment on patients with chronic heart failure (CHF).

Background Conflicting results currently exist on the clinical use of TMZ in CHF patients.

Methods PubMed, MEDLINE, EMBASE, and EBM Reviews databases were searched through November 2010 for randomized controlled trials (RCTs) assessing TMZ treatment in CHF patients. Data concerning the study design, patient characteristics, and outcomes were extracted. Risk ratio (RR) and weighted mean differences (WMD) were calculated using fixed or random effects models.

Results Sixteen RCTs involving 884 CHF patients were included. Hospitalization for cardiac causes (RR: 0.43, $p = 0.03$), but not all-cause mortality (RR: 0.47, $p = 0.27$), was reduced by TMZ treatment. Moreover, TMZ therapy was associated not only with the increase of left ventricular ejection fraction (WMD: 6.46%, $p < 0.0001$) and total exercise time (WMD: 63.75 seconds, $p < 0.0001$), but also with the decrease of New York Heart Association functional class (WMD: −0.57, $p = 0.0003$), left ventricular end-systolic diameter (WMD: −6.67 mm, $p < 0.0001$), left ventricular end-diastolic diameter (WMD: −6.05 mm, $p < 0.0001$), and B-type natriuretic peptide (WMD: −203.40 pg/ml, $p = 0.0002$).

Conclusions Additional use of TMZ in CHF patients may decrease hospitalization for cardiac causes, improve clinical symptoms and cardiac function, and simultaneously ameliorate left ventricular remodeling. (J Am Coll Cardiol 2012;59:913–22) © 2012 by the American College of Cardiology Foundation

Despite therapeutic advances, chronic heart failure (CHF) remains a major cause of mortality in the worldwide. Evidence suggests that the alterations in energy metabolism, such as high rates of fatty acid oxidation, may lead to abnormal function of the failing heart (1,2).

Trimetazidine (1-[2,3,4-trimethoxybenzyl] piperazine dihydrochloride, TMZ), which shifts energy production from fatty acid oxidation to glucose oxidation (3), is effective in stable angina pectoris (4). Studies have shown that TMZ exerted cardioprotective effects by reducing oxidative damage, inhibiting inflammation and apoptosis, and improving endothelial function (5–7). TMZ was, therefore, considered a promising candidate for the treatment of CHF.

This meta-analysis of randomized controlled trials (RCTs) was performed to estimate the effects of TMZ treatment on CHF patients.

Methods

Search strategy and selection criteria. We performed an electronic literature search of PubMed, MEDLINE, EMBASE, and EBM Reviews databases through November 2010, using the terms "trimetazidine," "Vastarel," "Idaptan," "heart failure," "cardiac dysfunction," "cardiac insufficiency," "cardiac inadequacy," "cardiomyopathy," and "ventricular dysfunction." The references of the studies were also searched for relevant titles.

RCTs in which CHF patients were assigned to TMZ or placebo were included. Exclusion criteria were: 1) treatment interval <4 weeks; 2) cross-over trials without washout

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Abbreviations and Acronyms

BNP = B-type natriuretic peptide
CHF = chronic heart failure
hsCRP = high-sensitivity C-reactive protein
LVEF = left ventricular ejection fraction
NYHA = New York Heart Association
RCT = randomized controlled trial
RR = risk ratio
SMD = standardized mean differences
TMZ = trimetazidine
WMD = weighted mean differences

period; and 3) no access to full text for quality assessment and data extraction.

Data extraction and quality assessment. Two investigators independently reviewed all potentially eligible studies and collected data on patient and study characteristics. Quality assessments were evaluated with Jadad quality scale.

Data synthesis and analysis. Dichotomous data were analyzed using risk ratio (RR) with 95% confidence intervals, whereas continuous variables (change from baseline to follow-up) were analyzed using weighted mean differences (WMD) or standardized mean differences (SMD). Pooled analyses were calculated using fixed-effect models, whereas random-effect models were applied in case of significant heterogeneity across studies. When no events were observed, 0.5 was added to both arms of the trial. Statistical heterogeneity were measured using the I^2 statistic. Meta-regression analyses were conducted to estimate the extent to which other covariates might have influenced the treatment effects. Sensitivity analyses (exclusion of 1 study at a time) were performed to determine the stability of the overall treatment effects. Additionally, publication bias was assessed using the Begg adjusted rank correlation test and Egger regression asymmetry test. All p values were 2-tailed, and the statistical significance was set at 0.05. Statistical analyses were performed using RevMan 5.0 (The Cochrane Collaboration, Copenhagen, Denmark), STATA software 10.0 (StataCorp, College Station, Texas), and nlme package in R Language 2.12.1.

Results

Eligible studies. The flow of selecting studies for the meta-analysis is shown in Figure 1. Briefly, of the initial 499 hits, 84 articles were retrieved for detailed evaluation, and 16 RCTs (8–23) satisfying the inclusion criteria were finally analyzed.

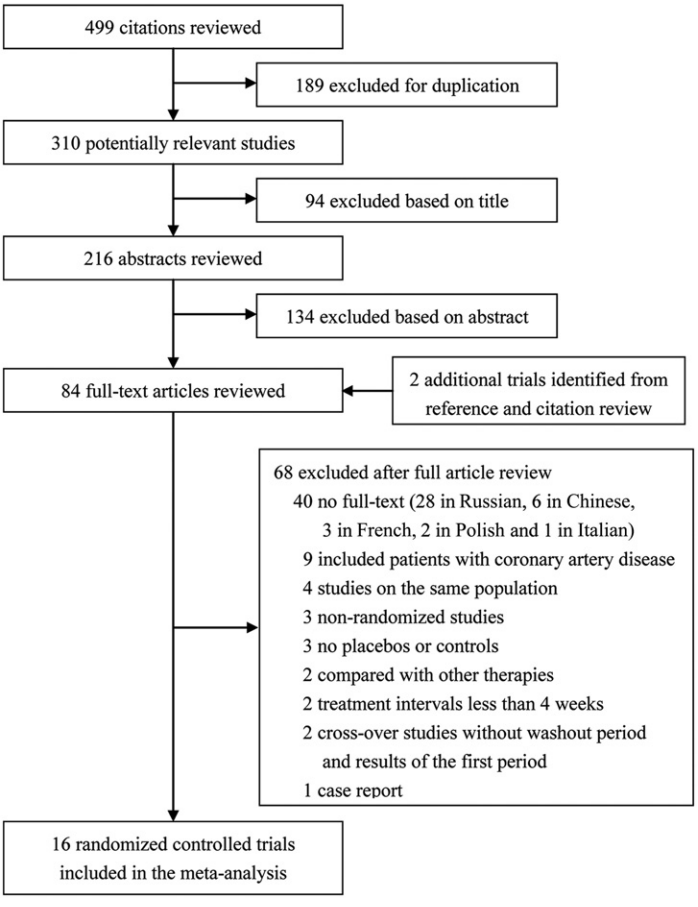

Figure 1 Search Flow Diagram for Studies Included in the Meta-Analysis