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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.

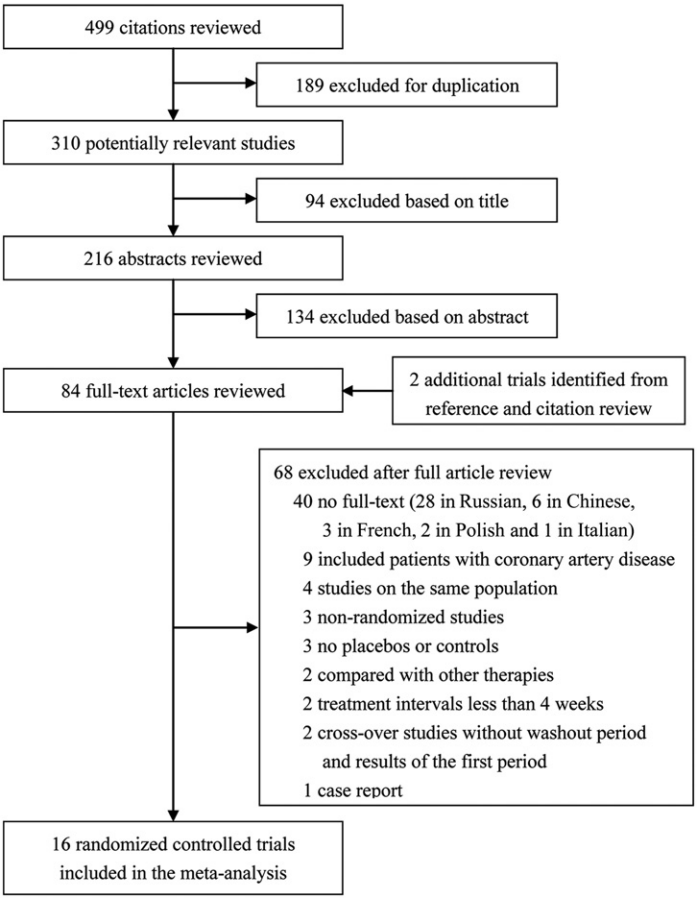

Figure 1 Search Flow Diagram for Studies Included in the Meta-Analysis

Table 1 Characteristics of 16 Clinical Trials Included in the Meta-Analysis

First Author, Year (Ref. #)	Individuals Randomized, n		Age (Mean, yrs)		Female (%)		Etiology (Ischemic, %)	DM (%)	NYHA Functional Class
	TMZ	Control	TMZ	Control	TMZ	Control			
Belardinelli et al., 2001 (8)	19	19	50	54	21	16	100	NA	II–III
Belardinelli et al., 2007 (9)	27	24	51	52	35	23	100	33	NA
Belardinelli et al., 2008 (10)	19	16	54	54	16	13	100	100	NA
Brottier et al., 1990 (11)	9	11	57	62	5 (overall)*		100	NA	III–IV
Cera et al., 2010 (12)	17	13	65	70	12	15	60	37	I–III
Di Napoli et al., 2005 (13)	30	31	67	69	43	42	100	20	II–IV
Di Napoli et al., 2007 (14)	25	25	64	63	40	28	100	24	II–IV
El-Kady et al., 2005 (15)	100	100	53	53	14	22	100	34	NA
Fragasso et al., 2006 (16)	34	31	64	66	11	7	54	7	II–IV
Gunes et al., 2009 (17)	51	36	59	57	27	42	66	29	II–III
Rosano et al., 2003 (18)	16	16	66	65	31	19	100	100	NA
Sisakian et al., 2007 (19)	42	40	64	66	12	17	100	0	II–III
Thrainsdottir et al., 2004 (20)	10	10	67	66	10	20	100	100	II–III
Tuunanen et al., 2008 (21)	12	7	59	57	17	29	0	0	2.2 ± 0.3†
Vitale et al., 2004 (22)	23	24	77	78	22	8	100	26	I–III
Zemljic et al., 2010 (23)	25	22	65	66	18	25	100	NA	II–III

First Author, Year (Ref. #)	LVEF (Mean, %)	TMZ (Dose, mg/Day)	Follow-Up (Mean)	Endpoints
Belardinelli et al., 2001 (8)	33	60	2 months	Adverse events, contractile response to dobutamine, left ventricular systolic function and functional capacity
Belardinelli et al., 2007 (9)	33	60	4 weeks	Adverse events, endothelium-dependent relaxation, functional capacity and indices of cardiovascular efficiency
Belardinelli et al., 2008 (10)	38	60	3 months	Adverse events, left ventricular function and structure, blood biochemical indices
Brottier et al., 1990 (11)	25	60	6 months	Adverse events, left ventricular function and structure
Cera et al., 2010 (12)	36	60	6 months	Adverse events, left ventricular function, NYHA functional class, electrophysiological indices
Di Napoli et al., 2005 (13)	31	60	18 months	Adverse events, Left ventricular function and structure, NYHA functional class, CRP
Di Napoli et al., 2007 (14)	29	60	6 months	Adverse events, left ventricular function, NYHA functional class, 6-minute walk, BNP, cTnT
El-Kady et al., 2005 (15)	36	60	23 months	Adverse events, anginal attacks/weekly, left ventricular function and structure, exercise capacity
Fragasso et al., 2006 (16)	35	60	13 months	Adverse events, left ventricular function and structure, NYHA functional class, QOL, heart rate, blood pressure, BNP
Gunes et al., 2009 (17)	32	60	3 months	Left ventricular function and structure, NYHA functional class, heart rate, blood pressure
Rosano et al., 2003 (18)	33	60	6 months	Left ventricular function and structure, heart rate, blood pressure
Sisakian et al., 2007 (19)	33	70§	3 months	Adverse events, left ventricular function and structure, NYHA functional class, 6-minute walk
Thrainsdottir et al., 2004 (20)	31	60	4 weeks	Adverse events, left ventricular function, exercise capacity
Tuunanen et al., 2008 (21)	34	70§	3 months	Adverse events, left ventricular function and structure, heart rate, blood pressure, myocardial metabolism
Vitale et al., 2004 (22)	29	60	6 months	Adverse events, left ventricular function and structure, NYHA functional class, anginal attacks/week, QOL
Zemljic et al., 2010 (23)	55‡	70§	1 month	Electrophysiological index (corrected QT interval)

*Percentage in all included patients; †Mean NYHA functional class in all included patients; ‡LVEF in all included patients were <55%; §Modified form of TMZ.

BNP = brain natriuretic peptide; CRP = C-reactive protein; cTnT = cardiac troponin T; DM = diabetes mellitus; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; QOL = quality of Life; TMZ = trimetazidine.

Quality assessments of the RCTs are shown in Online Table 1. Table 1 summarizes the characteristics of the included trials. Specifically, 459 patients were assigned to TMZ, whereas 425 subjects were assigned to control. All studies have enrolled patients with reduced left ventricular ejection fraction (LVEF).

All-cause mortality and hospitalization for cardiac causes. On the whole, TMZ treatment was well tolerated in CHF patients. The results showed all-cause mortality in the TMZ group was not lower than control (RR: 0.47, p = 0.27). Nevertheless, 7 of 80 patients with TMZ treatment needed hospitalization for cardiac causes, which was significantly <17 of 76 patients assigned to control (RR: 0.43, p = 0.03) (Fig. 2). Sensitivity analyses suggested that this beneficial effect was concealed when the study by Fragasso et al. (16) (p = 0.08) or by Vitale et al. (22) (p = 0.07) was omitted.

Left ventricular structure and function. The results indicated that additional TMZ therapy was superior to standard therapy in terms of LVEF improvement (WMD: 6.46%, p < 0.0001). Furthermore, TMZ therapy was similarly found to reduce 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 left ventricular end-systolic volume (SMD: −0.61, p = 0.02). Additionally, TMZ therapy tended to decrease left ventricular end-diastolic volume (SMD: −0.38, p = 0.10) (Fig. 3).

Sensitivity analyses confirmed in direction and magnitude of statistical significance the results regarding LVEF. According to the results of meta-regression analyses, no statistically significant association was found between: the benefits of TMZ therapy and year of publication, age of patients, etiology of CHF, baseline LVEF, baseline New York Heart Association (NYHA) functional class, and follow-up duration. Nevertheless, we found a statistically significant association between patients' sex and LVEF improvement (p = 0.03) (Fig. 4). Subgroup analyses showed the original form of TMZ significantly increased LVEF (p < 0.0001), whereas the modified form did not (Table 2). Moreover, the difference in LVEF improvement was not shown on etiology, as indicated by indirect comparison (p = 0.99). No publication bias was found, as shown by Egger's test (p = 0.16) and Begg's test (p = 0.83) (Online Fig. 1).

Functional capacity. Benefits of TMZ treatment were shown on both NYHA functional class (WMD: −0.57, p = 0.0003) and total exercise time (WMD: 63.75 seconds, p < 0.0001) (Figs. 5A and 5B). Subgroup analyses indicated that ischemic CHF patients with baseline LVEF ≥30% were more likely to get such benefits from TMZ treatment (Table 2).

Blood pressure and heart rate. Resting heart rate in the TMZ group was slightly lower than that of the control group (WMD: −2.62 beats/min, p = 0.04), whereas no significant differences were observed in resting systolic blood pressure (WMD: −0.94 mm Hg, p = 0.42) or resting diastolic blood pressure (WMD: −1.86 mm Hg, p = 0.27) (Figs. 5C to 5E).

Serum markers. B-type natriuretic peptide (BNP) level was significantly down-regulated by TMZ treatment (WMD: −203.40 pg/ml, p = 0.0002), whereas high-sensitivity C-reactive protein (hsCRP) level was not (WMD: −2.45 mg/l, p = 0.10) (Figs. 6A and 6B).

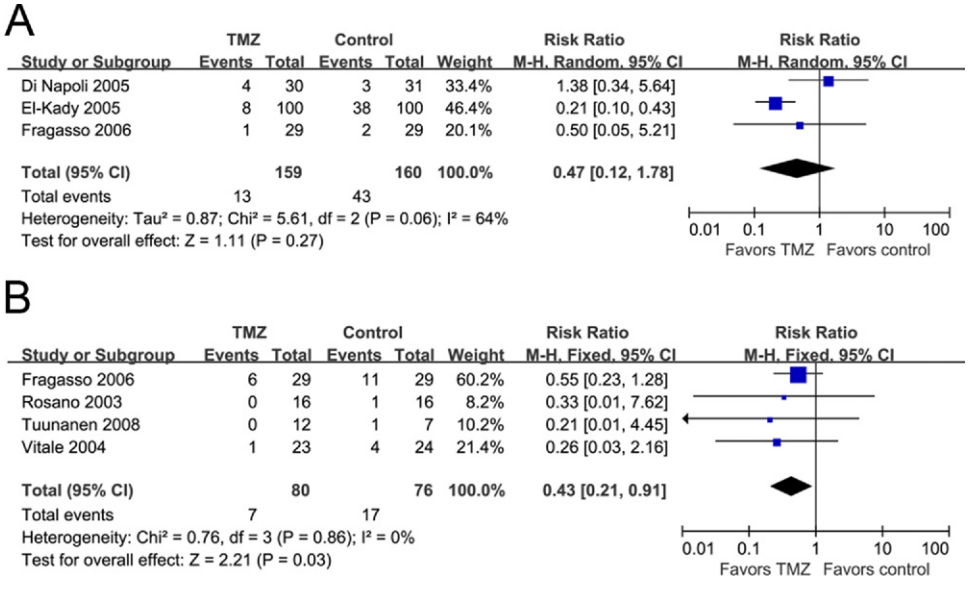

Figure 2 Forest Plots for All-Cause Mortality and Hospitalization for Cardiac Causes

(A) All-cause mortality; **(B)** hospitalization for cardiac causes. CI = confidence intervals; M-H = Mantel-Haenszel; RR = relative risk; TMZ = trimetazidine.

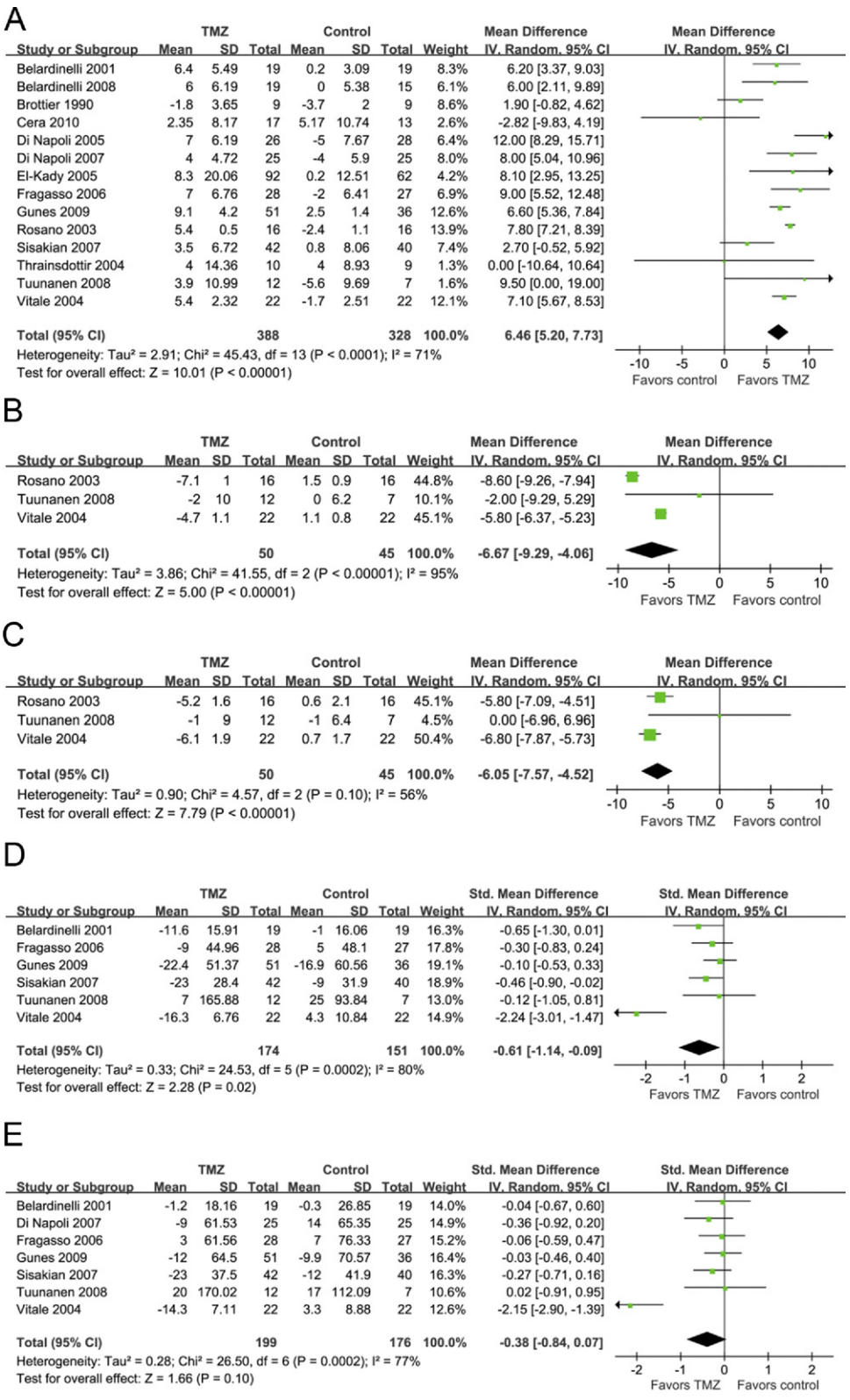

Figure 3 **Forest Plots for Left Ventricular Structure and Function**

(A) Left ventricular ejection fraction; **(B)** left ventricular end-systolic diameter; **(C)** left ventricular end-diastolic diameter; **(D)** left ventricular end-systolic volume; **(E)** left ventricular end-diastolic volume. IV = inverse variance; other abbreviations as in Figure 2.

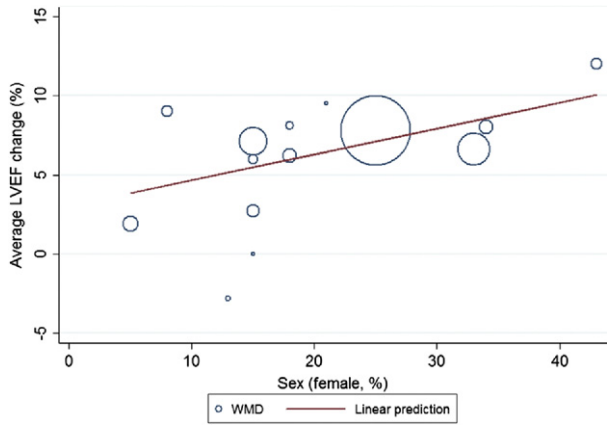

Figure 4 Meta-Regression Between Patient Sex and LVEF Improvement

LVEF = left ventricular ejection fraction; WMD = weighted mean differences.

Corrected QT interval. As shown in Figure 6C, TMZ therapy tended to be, albeit nonsignificantly, associated with corrected QT interval shortening (WMD: −31.32 ms, p = 0.07).

Discussion

The main findings of this meta-analysis are that although the additional use of TMZ failed to reduce all-cause mortality in CHF patients, the beneficial effects have been demonstrated by the increase of LVEF and total exercise time, and by the decrease of hospitalization for cardiac causes, NYHA class and of left ventricular end-systolic diameter, left ventricular end-diastolic diameter, left ventricular end-systolic volume, and serum BNP level. Moreover, as illustrated by the unchanged resting blood pressure and an average decrease of a mere 2.6 beats/min in resting heart rate, our study indicated that the aforementioned beneficial effects may be hemodynamically neutral.

The well-established anti-ischemic effects of TMZ are thought to be mediated by reducing fatty acid β-oxidation and increasing glucose oxidation, resulting in higher ATP production (3,24). Combining these findings with the "energy starvation" hypothesis, which suggests that inadequate ATP supply underlies the contractile dysfunction presenting in heart failure (25), it seems plausible that TMZ improves energy metabolism in cardiomyocytes, which may finally translate into mechanical efficiency and contribute to the improvement of cardiac function and clinical symptoms. Besides, it is noteworthy that TMZ exerts cardioprotective effects by restoring phosphorylation processes, inhibiting inflammatory response, oxidative damage, and apoptosis, as well as by improving endothelial function and coronary microcirculation (5-7,26,27), which may account for the amelioration of left ventricular remodeling. Furthermore, it seems reasonable that the BNP level could be downregulated by TMZ treatment, considering that the BNP level is negatively related to the alteration of cardiac structure and function (28).

TMZ treatment may play beneficial roles, not only in cardiac structural remodeling, but in electrical remodeling (29). Moreover, inflammatory mediators are involved in the pathogenesis of CHF (e.g., hsCRP), whereas the anti-inflammatory effects of TMZ have been observed (6,30). Unexpectedly, we failed to show the beneficial effects of TMZ either on corrected QT interval or on hsCRP, which may be due to the insufficiently powered studies included.

Subgroup estimation indicated that clinical symptoms and left ventricular structure in ischemic CHF patients were more likely to be ameliorated with TMZ treatment, nevertheless, such superiority may not totally deny the utility of TMZ in nonischemic CHF, with respect to LVEF improvement. Furthermore, modified TMZ may yield less benefits than the original form in LVEF enhancement, which may be associated with the difference in pharmacokinetics (31). Additionally, it was shown that female patients were more likely to get benefits from TMZ therapy regarding LVEF, suggesting that the difference in the proportion of female patients might be an origin of the interstudy discrepancy.

Study limitations. Drawbacks pertinent to this meta-analysis were the differences in characteristics among included studies, encompassing patients' age, follow-up duration, and so on. Moreover, it is worth noticing that only 884 patients were involved in the 16 RCTs, which justifies the performance of more large-scale RCTs for evaluating the impact of TMZ treatment on CHF patients.

Conclusions

The additional use of TMZ in CHF patients may exert beneficial effects, not only in ameliorating clinical symptoms and left ventricular structure and function, but in reducing hospitalization for cardiac causes, indicating that it may be an additional therapeutic agent for CHF.

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Table 2 Subgroup Estimation of the Effects of TMZ Therapy on Patients With CHF

	LVEF			NYHA Functional Class			LVEDV		
Subgroup	Studies/Patients, n/N	WMD [95% CI]	p Value	Studies/Patients, n/N	WMD [95% CI]	p Value	Studies/Patients, n/N	SMD [95% CI]	p Value
Age, yrs									
≥65	7/319	6.72 [4.76 to 8.69]	<0.0001	5/268	−0.70 [−1.09 to −0.30]	0.0006	3/181	−0.79 [−1.85 to 0.28]	0.15
<65	7/400	6.07 [4.39 to 7.76]	<0.0001	2/137	−0.30 [−0.54 to −0.06]	0.01	4/194	−0.11 [−0.40 to 0.17]	0.44
Etiology (ischemic, 100%)									
Yes	10/528	6.45 [4.92 to 7.99]	<0.0001	4/233	−0.62 [−1.01 to −0.23]	0.002	4/214	−0.67 [−1.45 to 0.11]	0.09
No	4/191	6.10 [2.47 to 9.73]	0.001	3/172	−0.46 [−1.11 to 0.20]	0.17	3/161	−0.03 [−0.35 to 0.28]	0.83
All pts with DM									
Yes	3/85	7.11 [4.98 to 9.24]	<0.0001	—	—	—	—	—	—
No	9/575	7.00 [5.27 to 8.73]	<0.0001	7/402	−0.57 [−0.88 to −0.26]	0.0003	6/337	−0.45 [−0.97 to 0.08]	0.10
Baseline LVEF									
≥30%	11/604	6.74 [5.28 to 8.21]	<0.0001	5/308	−0.62 [−1.00 to −0.24]	0.001	5/281	−0.11 [−0.34 to 0.13]	0.38
<30%	3/115	5.72 [2.36 to 9.08]	0.0008	2/97	−0.37 [−0.78 to 0.04]	0.08	2/94	−1.23 [−2.99 to 0.52]	0.17
Type of TMZ									
Modified form (70 mg/day)	2/101	4.57 [−1.38 to 10.53]	0.13	1/82	−0.48 [−0.73 to −0.23]	0.0002	2/101	−0.22 [−0.62 to 0.17]	0.27
Original form (60 mg/day)	12/618	6.74 [5.49 to 7.99]	<0.0001	6/323	−0.57 [−0.97 to −0.18]	0.005	5/274	−0.49 [−1.13 to 0.16]	0.14
Follow-up, months									
≥12	3/263	9.96 [7.68 to 12.23]	<0.0001	2/109	−1.01 [−1.38 to −0.83]	<0.0001	1/55	−0.06 [−0.59 to 0.47]	0.83
<12	11/456	5.76 [4.40 to 7.12]	<0.0001	5/296	−0.38 [−0.54 to 0.21]	<0.0001	6/320	−0.45 [−0.99 to 0.09]	0.10

	LVESV			Resting HR			Resting SBP		
	Studies/Patients, n/N	SMD [95% CI]	p Value	Studies/Patients, n/N	WMD [95% CI]	p Value	Studies/Patients, n/N	WMD [95% CI]	p Value
Age, yrs									
≥65	3/181	−0.95 [−1.95 to 0.05]	0.06	2/87	−2.70 [−7.27 to 1.87]	0.25	2/87	−1.96 [−4.76 to 0.84]	0.17
<65	3/144	−0.24 [−0.58 to 0.09]	0.15	4/189	−2.58 [−5.65 to 0.48]	0.10	4/189	1.05 [−2.86 to 4.97]	0.60
Etiology (ischemic, 100%)									
Yes	3/164	−1.08 [−2.08 to −0.08]	0.03	3/115	−5.83 [−9.26 to −2.41]	0.0008	3/115	−1.83 [−4.33 to 0.67]	0.15
No	3/161	−0.17 [−0.48 to 0.14]	0.29	3/161	1.35 [−2.46 to 5.15]	0.49	3/161	3.45 [−2.10 to 9.01]	0.22
All pts with DM									
Yes	—	—	—	1/32	−6.00 [−11.59 to −0.41]	0.04	1/32	−2.00 [−4.86 to 0.86]	0.17
No	5/287	−0.61 [−1.24 to 0.02]	0.06	4/206	−0.79 [−4.04 to 2.45]	0.63	4/206	1.73 [−2.20 to 5.65]	0.39
Baseline LVEF									
≥30%	5/281	−0.32 [−0.56 to −0.08]	0.009	6/276	−2.62 [−5.16 to −0.07]	0.04	6/276	−0.94 [−3.22 to 1.34]	0.42
<30%	1/44	−2.24 [−3.01 to −1.47]	<0.0001	—	—	—	—	—	—
Type of TMZ									
Modified form (70 mg/day)	2/101	−0.40 [−0.80 to −0.00]	0.05	1/19	3.00 [−7.89 to 13.89]	0.59	1/19	7.00 [−3.05 to 17.05]	0.17
Original form (60 mg/day)	4/224	−0.78 [−1.59 to 0.04]	0.06	5/257	−2.94 [−5.56 to −0.32]	0.03	5/257	−1.37 [−3.71 to 0.972]	0.25
Follow-up (months)									
≥12	1/55	−0.30 [−0.83 to 0.24]	0.27	1/55	4.00 [−3.96 to 11.96]	0.32	1/55	−1.00 [−15.26 to 13.26]	0.89
<12	5/270	−0.69 [−1.34 to −0.04]	0.04	5/221	−3.37 [−6.06 to −0.69]	0.01	5/221	−0.94 [−3.25 to 1.37]	0.43

CHF = chronic heart failure; CI = confidence interval; HR = heart rate; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; NYHA = New York Heart Association; SBP = systolic blood pressure; SMD = standardized mean differences; WMD = weighted mean differences; other abbreviations as in Table 1.

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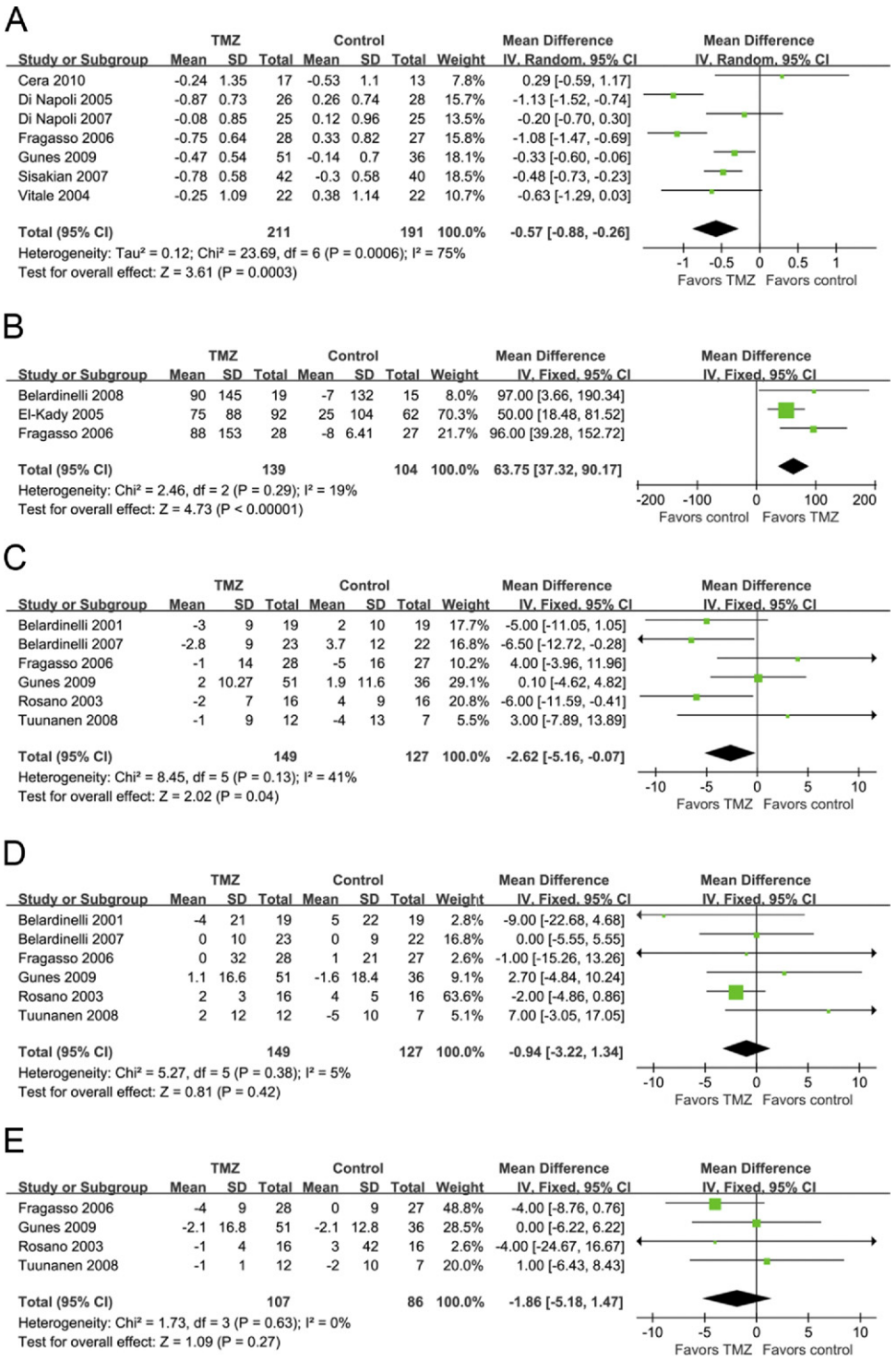

Figure 5 Forest Plots for Functional Capacity, Blood Pressure, and Heart Rate

(A) New York Heart Association functional class; **(B)** total exercise time; **(C)** resting heart rate; **(D)** resting systolic blood pressure; **(E)** resting diastolic blood pressure. Abbreviations as in Figures 2 and 3.

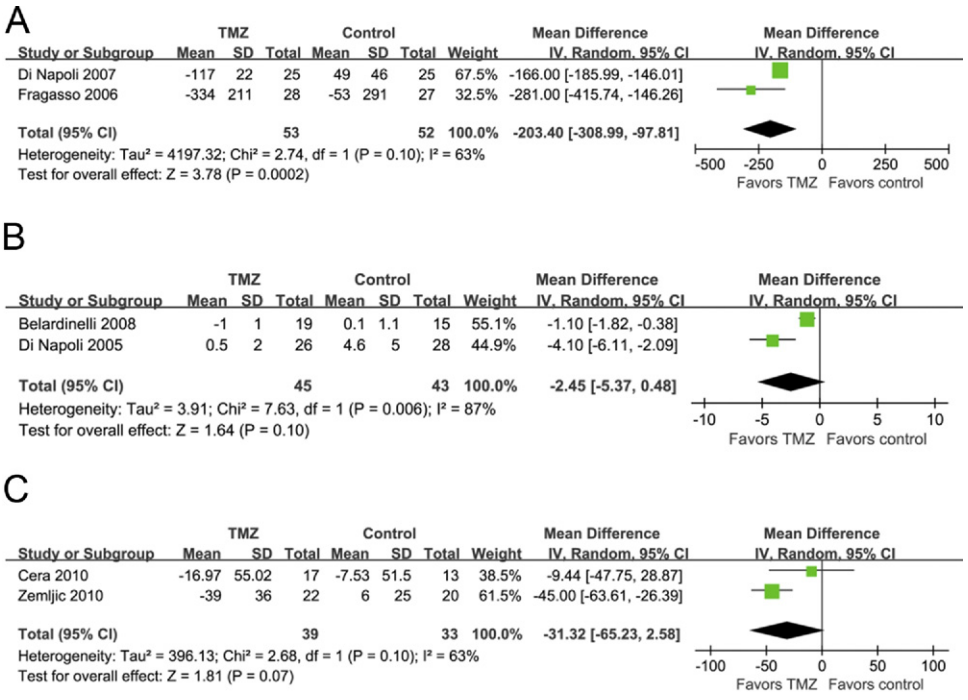

Figure 6 **Forest Plots for Serum Markers and Corrected QT Interval**

(A) B-type natriuretic peptide; **(B)** high-sensitivity C-reactive protein; **(C)** corrected QT interval. Abbreviations as in Figures 2 and 3.

REFERENCES

1. Ingwall JS. Energy metabolism in heart failure and remodelling. Cardiovasc Res 2009;81:412–9.
2. Clarke B, Wyatt KM, McCormack JG. Ranolazine increases active pyruvate dehydrogenase in perfused normoxic rat hearts: evidence for an indirect mechanism. J Mol Cell Cardiol 1996;28:341–50.
3. Kantor PF, Lucien A, Kozak R, Lopaschuk GD. The antianginal drug trimetazidine shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting mitochondrial long-chain 3-ketoacyl coenzyme A thiolase. Circ Res 2000;86:580–8.
4. Marzilli M, Klein WW. Efficacy and tolerability of trimetazidine in stable angina: a meta-analysis of randomized, double-blind, controlled trials. Coronary Artery Dis 2003;14:171–9.
5. Ruixing Y, Wenwu L, Al-Ghazali R. Trimetazidine inhibits cardiomyocyte apoptosis in a rabbit model of ischemia-reperfusion. Transl Res 2007;149:152–60.
6. Williams FM, Tanda K, Kus M, Williams TJ. Trimetazidine inhibits neutrophil accumulation after myocardial-ischemia and reperfusion in rabbits. J Cardiovasc Pharmacol 1993;22:828–33.
7. Di Napoli P, Chierchia S, Taccardi AA, et al. Trimetazidine improves post-ischemic recovery by preserving endothelial nitric oxide synthase expression in isolated working rat hearts. Nitric Oxide-Biol Ch 2007;16:228–36.
8. Belardinelli R, Purcaro A. Effects of trimetazidine on the contractile response of chronically dysfunctional myocardium to low-dose dobutamine in ischaemic cardiomyopathy. Eur Heart J 2001;22:2164–70.
9. Belardinelli R, Solenghi M, Volpe L, Purcaro A. Trimetazidine improves endothelial dysfunction in chronic heart failure: an antioxidant effect. Eur Heart J 2007;28:1102–8.
10. Belardinelli R, Cianci G, Gigli M, Mazzanti M, Lacalaprice F. Effects of trimetazidine on myocardial perfusion and left ventricular systolic function in type 2 diabetic patients with ischemic cardiomyopathy. J Cardiovasc Pharmacol 2008;51:611–5.
11. Brottier L, Barat JL, Combe C, Boussens B, Bonnet J, Bricaud H. Therapeutic value of a cardioprotective agent in patients with severe ischaemic cardiomyopathy. Eur Heart J 1990;11:207–12.
12. Cera M, Salerno A, Fragasso G, et al. Beneficial electrophysiological effects of trimetazidine in patients with postischemic chronic heart failure. J Cardiovasc Pharmacol Ther 2010;15:24–30.
13. Di Napoli P, Taccardi AA, Barsotti A. Long term cardioprotective action of trimetazidine and potential effect on the inflammatory process in patients with ischaemic dilated cardiomyopathy. Heart 2005;91:161–5.
14. Di Napoli P, Di Giovanni P, Gaeta MA, D'Apolito G, Barsotti A. Beneficial effects of trimetazidine treatment on exercise tolerance and B-type natriuretic peptide and troponin T plasma levels in patients with stable ischemic cardiomyopathy. Am Heart J 2007;154:602.e1–5.
15. El-Kady T, El-Sabban K, Gabaly M, Sabry A, Abdel-Hady S. Effects of trimetazidine on myocardial perfusion and the contractile response of chronically dysfunctional myocardium in ischemic cardiomyopathy: a 24-month study. Am J Cardiovasc Drugs 2005;5:271–8.
16. Fragasso G, Palloshi A, Puccetti P, et al. A randomized clinical trial of trimetazidine, a partial free fatty acid oxidation inhibitor, in patients with heart failure. J Am Coll Cardiol 2006;48:992–8.
17. Gunes Y, Guntekin U, Tuncer M, Sahin M. Improved left and right ventricular functions with trimetazidine in patients with heart failure: a tissue Doppler study. Heart Vessels 2009;24:277–82.
18. Rosano GM, Vitale C, Sposato B, Mercuro G, Fini M. Trimetazidine improves left ventricular function in diabetic patients with coronary artery disease: a double-blind placebo-controlled study. Cardiovasc Diabetol 2003;2:16.
19. Sisakian H, Torgomyan A, Barkhudaryan A, Sisakian H, Torgomyan A, Barkhudaryan A. The effect of trimetazidine on left ventricular systolic function and physical tolerance in patients with ischaemic cardiomyopathy. Acta Cardiol 2007;62:493–9.
20. Thrainsdottir IS, von Bibra H, Malmberg K, Ryden L. Effects of trimetazidine on left ventricular function in patients with type 2 diabetes and heart failure. J Cardiovasc Pharmacol 2004;44:101–8.

21. Tuunanen H, Engblom E, Naum A, et al. Trimetazidine, a metabolic modulator, has cardiac and extracardiac benefits in idiopathic dilated cardiomyopathy. Circulation 2008;118:1250–8.
22. Vitale C, Wajngaten M, Sposato B, et al. Trimetazidine improves left ventricular function and quality of life in elderly patients with coronary artery disease. Eur Heart J 2004;25:1814–21.
23. Zemljic G, Bunc M, Vrtovec B. Trimetazidine shortens QTc interval in patients with ischemic heart failure. J Cardiovasc Pharmacol Ther 2010;15:31–6.
24. Stanley WC, Lopaschuk GD, Hall JL, McCormack JG. Regulation of myocardial carbohydrate metabolism under normal and ischaemic conditions - Potential for pharmacological interventions. Cardiovasc Res 1997;33:243–57.
25. Katz AM. Is the failing heart energy depleted? Cardiol Clin 1998;16: 633–44.
26. Lee L, Horowitz J, Frenneaux M. Metabolic manipulation in ischaemic heart disease, a novel approach to treatment. Eur Heart J 2004;25:634–41.
27. Deleiris J, Boucher F. Rationale for trimetazidine administration in myocardial-ischemia reperfusion syndrome. Eur Heart J 1993;14:34–40.
28. Levin ER, Gardner DG, Samson WK. Mechanisms of disease - Natriuretic peptides. New Engl J Med 1998;339:321–8.
29. Kiyosue T, Nakamura S, Arita M. Effects of trimetazidine on action potentials and membrane currents of guinea-pig ventricular myocytes. J Mol Cell Cardiol 1986;18:1301–11.
30. Mann DL. Inflammatory mediators and the failing heart: past, present, and the foreseeable future. Circ Res 2002;91:988–98.
31. Genissel P, Chodjania Y, Demolis JL, Ragueneau I, Jaillon P. Assessment of the sustained release properties of a new oral formulation of trimetazidine in pigs and dogs and confirmation in healthy human volunteers. Eur J Drug Metab Pharmacokinet 2004;29:61–8.

Key Words: cardiac function ■ chronic heart failure ■ meta-analysis ■ prognosis ■ trimetazidine.

APPENDIX

For a supplementary table and figure, please see the online version of this paper.