ORIGINAL ARTICLE

Effect of Trimetazidine on Diabetic Patients with Coronary Heart Diseases: A Meta-Analysis of Randomized, Controlled Trials

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Objective To explore the therapeutic effects of trimetazidine (TMZ) on diabetic patients with coronary heart diseases.

Methods We conducted a comprehensive electronic search of PubMed, EMBASE, and Cochrane databases between the inception dates of databases and May 2019 (last search conducted on 30 May 2019) to identify randomized controlled trials. The evaluation method recommended by Cochrane Collaboration for bias risk assessment was employed for quality assessment. Random or fixed models were used to investigate pooled mean differences in left ventricular function, serum glucose metabolism, serum lipid profile, myocardial ischemia episodes and exercise tolerance with effect size indicated by the 95% confidence interval (CI).

Results Additional TMZ treatment contributed to considerable improvement of left ventricular ejection fraction ($WMD=4.39$, 95%CI: 3.83, 4.95, $P<0.00001$), left ventricular end diastolic diameter ($WMD=-3.17$, 95%CI: -4.90, -1.44, $P=0.0003$) and left ventricular end systolic diameter ($WMD=-4.69$, 95%CI: -8.66, -0.72, $P=0.02$). TMZ administration also significantly decreased fasting blood glucose ($SMD=-0.43$, 95%CI: -0.70, -0.17, $P=0.001$), glycosylated hemoglobin level ($WMD=-0.59$, 95%CI: -0.95, -0.24, $P=0.001$), serum level of total cholesterol ($WMD=-20.36$, 95%CI: -39.80, -0.92, $P=0.04$), low-density lipoprotein cholesterol ($WMD=-20.12$, 95%CI: -32.95, -7.30, $P=0.002$) and incidence of myocardial ischemia episodes ($SMD=-0.84$, 95%CI: -1.50, -0.18, $P=0.01$). However, there were no significant differences in serum triglyceride level, high-density lipoprotein cholesterol, exercise tolerance between the TMZ group and the control group.

Conclusion TMZ treatment in diabetic patients with coronary heart disease is effective to improve cardiac function, serum glucose and lipid metabolism and clinical symptoms.

WITH lifestyle changes, diabetes mellitus (DM) is gradually becoming one of the most common chronic diseases.^[1] It is estimated that by 2040, more than 642 million people worldwide will suffer from diabetes.^[2] DM as a group of metabolic disorders characterized by increased blood glucose levels and altered lipid profile can cause many complications, among which coronary heart disease (CHD) is highly prevalent. CHD and DM pose a synergistic threat to more severe cardiovascular diseases such as myocardial infarction (MI), arrhythmia, sudden cardiac death (SCD) and congestive heart failure,^[3, 4] resulting in poor quality of life and high mortality among the patients.

Although it still remains controversial whether CHD occurs after DM or they coexist in the early stage, the notion that oxidative stress triggered by DM is detrimental for endothelial function and consequently leads to CHD is widely accepted.^[5] It is believed that hyperglycemia can rapidly decrease NO generation possibly by increasing reactive oxygen species (ROS) production and thereby suppressing endothelium-dependent vasodilatation.^[6] In addition, the detrimental metabolic products caused by hyperglycemia result in intima thickening and arterial stiffness,^[7] which play important roles in the development and progression of atherosclerosis and CHD. Owing to the narrowed lumen of arteries and reduced blood flow to the heart,^[8] patients with CHD may perceive typical symptoms associated with myocardial ischemia such as chest pain. However, some diabetic patients are not able to perceive the typical manifestations of CHD owing to diabetic autonomic neuropathy. As a result, more severe ischemic diseases such as acute MI and SCD may appear as the first clinical presentations of CHD in DM patients, accounting partly for the higher cardiovascular death rate than that of non-diabetic patients.^[9-12] Hence, more emphasis should be placed on the prevention and treatment of CHD in DM patients.

Trimetazidine (2, 3, 4-trimethoxybenzyl-piperazine dihydrochloride; TMZ) is an anti-ischemia agent that optimizes the energy metabolism of the myocardium. TMZ not only preserves necessary adenosine triphosphate (ATP) level in cardiomyocytes by shifting fatty acid β -oxidation to glucose oxidation, but also improves the intracellular concentration of superoxide dismutase (SOD), thereby decreasing the oxygen-free radicals and protecting the myocardium against oxidative stress.^[13-18] The pharmacological effects of TMZ indicate that diabetic

patients with glucose and lipid metabolism disorders may benefit more than other non-diabetic patients.

In the past two decades, several randomized controlled trials (RCTs) investigating TMZ administration in diabetic patients with CHD have been reported. These trials focused on the cardiac function, glucose and lipid metabolism, exercise tolerance, clinical symptoms and so on. However, some of the results were not consistent and no previous meta-analysis focused on the efficacy of TMZ on patients with both CHD and DM. Therefore, we performed a meta-analysis with the purpose to provide more convincing evidence for TMZ therapy in diabetic patients with CHD.

MATERIALS AND METHODS

Search strategy

We performed a comprehensive search of PubMed, EMBASE, and Cochrane databases between the inception dates of databases and May 2019 (last search conducted on 30 May 2019), using the following key words "Trimetazidine" or "Vastarel" or "Vasartel" "Idaptan" in combination with "diabetes" or "diabetic". No restrictions were imposed. In addition, we reviewed the reference lists of retrieved literatures and recent reviews.

Selection criteria

Inclusion criteria for studies were listed as follows: (1) The search was in English, on human subjects; (2) The study type was limited to RCTs; (3) The purpose of the study was to compare the efficacy between the TMZ and control groups in diabetic patients with CHD; (4) Studies included at least one of the outcome indicators were considered eligible: cardiac function parameters [i.e., left ventricular ejection fraction (LVEF), left ventricular end diastolic diameter (LVEDD), left ventricular end systolic diameter (LVESD), and left ventricular end-diastolic volume (LVEDV)], serum glucose metabolism [i.e., fasting blood glucose (FBG) and glycosylated hemoglobin (HbA_{1c}) level], serum lipid metabolism [i.e., triglycerides, total cholesterol, low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C)], myocardial ischemia episodes and exercise tolerance.

Exclusion criteria were shown as follows: (1) retrospective, nonrandomized trial; (2) data were incomplete, erroneous or unavailable for statistical analysis; (3) studies were not original, such as reviews, letters, case reports, etc.; (4) duplicate publication; (5) over-

lapping data, only latest report was included and prior reports were excluded.

Data extraction and quality assessment

Two authors (LY and WZL) independently extracted the following contents of retrieved articles: basic data (i.e., first author, publication year, research location and duration, the number, age and gender ratio of patients), intervention strategies and outcomes.

The evaluation method recommended by Cochrane Collaboration for bias risk assessment was employed for quality assessment. If there was dispute between the two authors, the third author (YM) would be invited for consultation.

Statistical analysis

Continuous variables were analyzed using weighted mean differences (*WMD*) with effect size indicated by 95% confidence intervals (*CI*s). Summary effect was calculated as the standard mean difference (*SMD*) for fasting blood glucose level and incidence of myocardial ischemia episodes, together with their 95% *CI*s. Sub-group analysis was performed based on the treatment duration and sensitivity analysis was also conducted by removing individual studies sequentially. Statistical heterogeneity across trials was measured using the I^2 statistic. Fixed-effect models were applied if there was a lack of heterogeneity across studies ($P > 0.05$ and $I^2 < 50\%$). Otherwise, random-effect models were used. $P < 0.05$ was considered statistically significant. Statistical analyses were performed using the RevMan 5.3 software (Cochrane Collaboration, Oxford, UK). No registered protocol was reported for the present meta-analysis.

RESULTS

Study selection

A flow chart of the selection process of literatures is shown in **Figure 1**. Based on our inclusion criteria, 405 articles were retrieved by using the search strategy. After removing duplicate literatures, 302 literatures were retained. After browsing the headlines and abstracts, 281 papers were excluded, including 170 articles which were obviously irrelevant, 28 animal experiments, 83 reviews, conference papers and case reports. 21 potential trials were identified, of which 13 trials were excluded after reading the full text. Only 8 RCTs^[19-26] met our inclusion criteria.

Figure 1. Flow diagram of selecting eligible studies included in the meta-analysis.

RCT: randomized controlled trials.

Characteristics of studies

The general features of the 8 RCTs were described in **Table 1**. Selected articles were published between 2003 and 2017. The study sites were mainly in China, Italy, Brazil and Egypt. 2 studies used a crossover design, of these, the wash out period of a Brazilian study^[23] was 2 weeks, but the authors of the Italian study considered the wash out period unnecessary in the TMZ trials.^[26] TMZ dosage was 20 mg tid in 6 trials,^[20, 22-26] while in 2 trials, patients were provided a loading dose at admission,^[19, 21] then followed by daily dose. The follow-up time ranged from 0.5 to 24 months.

The results of the quality assessment were shown in **Figure 2**. Briefly, of all the eight studies, six studies^[19-24] adequately reported the random sequence generation procedures. In addition, six of them were designed with blinded methods.^[20-23, 25, 26] Five studies^[19, 21, 22, 24, 26] were classified as high-risk studies with incomplete outcome data due to loss of large numbers of patients during follow-up. The risk of selective reporting and other biases were considered low in all the studies.

Table 1. The general features of the 8 trials

Study	Study design	Location	Number of case	Group (n)	Male (n)	Age (mean, yrs)	Treatment	Inclusion criteria	Outcomes	Follow-up (mon)
Fragasso <i>et al.</i> ^[26]	Crossover	Canada	16	T (8) C (5)	8 5	64 64	20 mg TMZ tid placebo	DM, ischemic cardiomyopathy, LVEF≤45%	Echocardiogram, exercise tolerance, glucose levels, HbA _{1c} , ET-1	6
Rosano <i>et al.</i> ^[25]	Parallel	Italy	32	T (16) C (16)	11 13	66 65	20 mg TMZ tid placebo	DM, ischemic cardiomyopathy, LVEF<50%	Echocardiogram	6
Marazzi <i>et al.</i> ^[24]	Parallel	Italy	63	T (15) C (15)	12 10	66 68	20 mg TMZ tid placebo	DM, chronic stable angina	Number and duration of silent and symptomatic ischemia episodes	6
Ribeiro <i>et al.</i> ^[23]	Crossover	Brazil	10	T (5) C (5)	6	62	20 mg TMZ tid placebo	DM, stable angina	Clinical and biochemical evaluations, exercise testing, 24-hour ambulatory blood pressure, Holter monitoring	1.5
Belardinelli <i>et al.</i> ^[22]	Parallel	Italy	35	T (19) C (15)	16 13	54 54	20 mg TMZ tid placebo	DM, ischemic cardiomyopathy	Myocardial scintigraphy, blood chemistry	3
Shehata <i>et al.</i> ^[21]	Parallel	Egypt	100	T (50) C (50)	31 29	60 59	70 mg LD+35 mg TMZ bid placebo	DM, anterior wall STEMI treated with thrombolysis	Myocardial enzyme, degree of ST-segment resolution, echocardiogram, adverse events	6
Xu <i>et al.</i> ^[20]	Parallel	China	510	T (255) C (255)	172 174	69 69	20 mg TMZ tid placebo	DM, multivessel CHD after DES implantation	Incidence of recurrent angina pectoris, echocardiographic, clinical outcomes	24
Li <i>et al.</i> ^[19]	Parallel	China	180	T (89) C (84)	62 58	63 64	60 mg LD+20 mg TMZ tid placebo	DM, AMI undergoing PCI	Myocardial enzyme, liver function, glucose levels, echocardiogram	0.5

T: trimetazidine group; C: control group; TMZ: trimetazidine; LD: loading dose; DM: diabetes mellitus; LVEF: left ventricular ejection fraction; STEMI: ST elevated myocardial infarction; CHD: coronary heart disease; DES: drug-eluting stent; AMI: acute myocardial infarction; PCI: percutaneous coronary intervention; HbA_{1c}: glycosylated hemoglobin; ET-1: endothelin-1.

Figure 2. Quality assessment of included studies.

A. Risk of bias summary: The assessment of the percentage of all RCTs that have the risk of bias in the analysis; B. Risk of bias summary: The assessment of all the biases of each study in the analysis. +: low risk; -: high risk; ?: unclear.

Left ventricular function

Among the included studies, 6 trials described LVEF (involving a total of 859 patients, 437 in the TMZ group and 422 in the control group).^[19-22, 25, 26] According to the test of heterogeneity ($I^2=36\%$, $P=0.17$), a fixed-effects model was used to analyze the data. Our results indicated that additional use of TMZ in diabetic patients with CHD was superior to conventional treatment in terms of LVEF improvement ($WMD=4.39$, $95\%CI: 3.83, 4.95$, $P<0.00001$, **Figure 3A**). In addition, 4 trials described LVEDD (including 728 patients, 368 in the TMZ group and 360 in the control group)^[19, 20, 25, 26] and 3 described LVESD (including 555 patients, 279 in the TMZ group and 276 in the control group).^[20, 25, 26] A random-effects model was used to analyze the data according to the test of heterogeneity ($I^2=81\%$, $P=0.001$; $I^2=98\%$, $P=0.00001$, respectively). The results showed that LVEDD and LVESD were significantly lower in patients treated with additional TMZ ($WMD=-3.17$, $95\%CI: -4.90, -1.44$, $P=0.0003$, **Figure 3B**; $WMD=-4.69$, $95\%CI: -8.66, -0.72$, $P=0.02$, **Figure 3C**, respectively). Meanwhile, one trial reported LVEDV

and LVESV as the outcomes.^[26] Compared with the control group, additional use of TMZ reduced LVESV significantly ($85.0\pm36.5\text{ cm}^3$ vs. $98.8\pm47.5\text{ cm}^3$, $P=0.02$), but the reduction of LVEDV was not significant ($150.3\pm47.9\text{ cm}^3$ vs. $152.9\pm57.9\text{ cm}^3$, $P=0.7$).

Serum glucose metabolism

A total of 4 trials described FBG levels (involving 230 patients, 121 in the TMZ group and 109 in the control group).^[19, 22, 23, 26] Owing to the test of heterogeneity ($I^2=48\%$, $P=0.12$), a fixed-effects model was used. After pooling the data, the TMZ group achieved significant reduction in the FBG level compared with the control group ($SMD=-0.43$, $95\%CI: -0.70, -0.17$, $P=0.001$, **Figure 4A**). The serum level of HbA_{1c} was also measured in 3 trials (involving 57 patients, 32 in the TMZ group and 25 in the control group).^[22, 23, 26] A fixed-effects model was used after observing the heterogeneity ($I^2=0\%$, $P=0.94$). Pooled analysis showed that the serum level of HbA_{1c} was significantly reduced in the TMZ group ($WMD=-0.59$, $95\%CI: -0.95, -0.24$, $P=0.001$, **Figure 4B**).

Serum lipid profile

Only 2 trials described the serum lipid profile (including 44 patients, 24 in the TMZ group and 20 in the control group).^[22, 23] A random-effects model was used to analyze the serum level of triglyceride according to the heterogeneity ($I^2=83\%$, $P=0.02$). The results showed no significant difference in the serum triglyceride level between the TMZ and control group ($WMD=-37.33$, $95\%CI: -129.46, 54.81$, $P=0.43$, **Figure 5A**). A fixed-effects model was used to analyze the serum level of total cholesterol, LDL-C and HDL-C according to the heterogeneity ($I^2=38\%$, $P=0.20$; $I^2=0\%$, $P=0.32$; $I^2=0\%$, $P=0.87$ respectively). The results indicated that the serum total cholesterol and LDL-C levels in the TMZ group were lower than those in the control group, and the differences were statistically significant ($WMD=-20.36$, $95\%CI: -39.80, -0.92$, $P=0.04$, **Figure 5B**; $WMD=-20.12$, $95\%CI: -32.95, -7.30$, $P=0.002$, **Figure 5C**, respectively). However, compared with the control group, the serum level of HDL-C in the TMZ group was not statistically significant ($WMD=2.75$, $95\%CI: -2.50, 8.00$, $P=0.30$, **Figure 5D**).

Myocardial ischemia episodes

Only 2 trials described the ischemia episodes (involving a total of 40 patients, 20 in the TMZ group and

A

B

C

Figure 3. Forest plots for left ventricular function of diabetic patients with CHD additionally used TMZ vs. the controls.

A. LVEF; B. left ventricular end diastolic diameter; C. left ventricular end systolic diameter.

A

B

Figure 4. Forest plots for serum glucose metabolism of diabetic patients with CHD treatment with TMZ vs. those with conventional treatment.

A. fasting blood glucose; B. HbA_{1c}.

Figure 5. Forest plots for serum lipid profile of the TMZ and the control groups.

A. triglyceride; B. total cholesterol; C. low-density lipoprotein cholesterol; D. high-density lipoprotein cholesterol.

20 in the control group).^[23, 24] A fixed-effects model was used to analyze the data ($I^2 = 0\%$, $P = 0.47$). The results showed that the incidence of myocardial ischemic episodes was significantly reduced in the TMZ group compared with the control group ($SMD = -0.84$, $95\%CI$: $-1.50, -0.18$, $P = 0.01$, **Figure 6**).

Exercise tolerance

3 included trials reported exercise tolerance (involving a total of 57 patients, 32 in the TMZ group and 25 in the control group).^[22, 23, 26] A fixed-effects model was used to analyze the data ($I^2 = 0\%$, $P = 0.77$). The results suggested that there was no significant difference in exercise tolerance between the TMZ and control groups ($WMD = 49.50$, $95\%CI$: $-21.19, 120.20$, $P = 0.17$, **Figure 7**).

Subgroup and sensitivity analysis

Since significant heterogeneity across studies was

observed for LVEDD, we conducted a subgroup analysis based on the treatment duration. The result suggested that TMZ treatment significantly decreased LVEDD in patients with intervention periods longer than 6 months ($WMD = -4.01$, $95\%CI$: $-5.59, -2.42$, $P < 0.00001$), but not in patients treated within 6 months ($P = 0.13$). Besides, the heterogeneity of the longer treatment subgroup was also lower ($I^2 = 66\%$, $P = 0.05$). Testing for subgroup differences between the two subgroups found significant differences in LVEDD ($P = 0.007$, **Figure 8**).

As for the sensitivity analysis of LVESD, when two of the included studies were removed, I^2 of the heterogeneity declined to 0% . The results still favored additional TMZ treatment as a superior therapy (**Table 2**).

DISCUSSION

DM is a well-recognized risk factor for CHD with a

Figure 6. Forest plot for myocardial ischemia episodes of the TMZ and the control groups.

Figure 7. Forest plot for exercise tolerance of the TMZ and the control groups.

Figure 8. Forest plot of subgroup analysis for left ventricular end diastolic diameter based on treatment duration.

Table 2. Sensitivity analysis of left ventricular end systolic diameter

Study omitted	WMD (95%CI)	P for heterogeneity	I ² (%)
Fragasso <i>et al.</i> ^[26]	-4.83 (-9.08, -0.59)	<0.00001	99
Rosano <i>et al.</i> ^[25]	-2.67 (-3.31, -2.03)	0.88	0
Xu <i>et al.</i> ^[20]	-6.99 (-7.64, -6.33)	0.51	0

WMD: weighted mean difference; CI: confidence interval.

wide range of clinical presentations, including angina, MI, ischemic cardiomyopathy or SCD.^[27-30] The main reason for CHD is coronary atherosclerosis manifested by the formation of lipid plaque.^[31] In clinical practice, diabetic patients with CHDs are often traditionally treated with hypoglycemic agent, aspirin, angioten-

sin-converting enzyme inhibitors (ACEI), beta-blocker, statin, etc. to reduce blood glucose level and ameliorate cardiac dysfunction. A large number of traditional ant-ischemic drugs which have been used clinically may affect hemodynamics (i.e., vasodilation, arrhythmia, decreased myocardial contractility) or increase cardiac oxygen consumption. Since TMZ is a cardiac metabolite with little hemodynamic impact, we performed the current meta-analysis to evaluate the effect of TMZ in diabetic patients with CHD. Our results confirmed that additional use of TMZ significantly increased LVEF and decreased LVEDD and LVESD levels, indicating considerable improvement in left ventricular systolic function and remodeling. The results of subgroup analysis based on treatment time showed that the LVEDD of patients with TMZ treatment duration over 6 months

was significantly reduced, suggesting that long-term TMZ treatment could improve left ventricular reconstruction. The study also found that the adjunct of TMZ reduced myocardial ischemia episodes in patients with both CHD and diabetes, indicating an improvement in myocardial ischemia and an improvement in their quality of life.

By selective inhibition of mitochondrial long-chain 3-ketoacyl coenzyme A thiolase (3-KAT), TMZ switches cardiac energy metabolism from free fatty acid oxidation to glucose oxidation, improving glucose utilization as well as ATP production with less oxygen required than traditional anti-ischemic drugs.^[32] Due to the insulin resistance of DM, the uptake and utilization of glucose by cardiomyocytes are reduced with increasing free fatty acid oxidation serving as compensation. Therefore, the preferential oxidation of glucose should be more beneficial to diabetic patients. There is increasing evidence that oxidative stress is integral to the development and progression of CHD, especially in patients with diabetes.^[33-36] Hyperglycemia resulting from diabetes causes the mitochondria to overproduce ROS such as hydrogen peroxide, superoxide ion and peroxy radical, establishing a vicious circle of oxidative stress.^[37, 38] As an initiating factor of atherosclerosis, excessive ROS production can not only cause direct injury to endothelial cells, but also promote the expression of various inflammatory factors and adhesive molecules in endothelial cells.^[39] Long-term exposure of cardiomyocytes to ROS results in apoptosis and inflammatory cell infiltration, leading to impaired excitation-contraction coupling, progressive deterioration of cardiac function and cardiac remodeling.^[40-43] Many researches^[44-46] have confirmed that TMZ can decrease the production of ROS and increase the intracellular concentration of SOD. Moreover, TMZ plays a critical role in reducing apoptosis and inflammation of cardiomyocytes, enhancing mitochondrial integrity and activity as well as increasing mitochondrial calcium retention capacity, thereby demonstrating cardioprotective effects.^[47-49]

In the past few years, some studies have investigated the effects of TMZ treatment on blood glucose metabolism in patients with diabetes and CHD. Some RCTs reported that TMZ treatment was associated with a considerable improvement in FBG and HbA_{1c}, while some other RCTs revealed little effect on serum glucose levels. In our meta-analysis, FBG and HbA_{1c} were both significantly reduced by TMZ treatment. The

observed improvement in blood glucose level could be partly ascribed to the effect of TMZ on glucose utilization in both cardiac and skeletal muscles.^[50] Besides, some studies^[49, 51] revealed increased systemic insulin sensitivity and glucose tolerance in insulin-resistant patients treated with TMZ and the mechanism might be related to the translocation of GLUT4 by activating PI3 K/AKT and AMPK pathways.^[49, 52] Our meta-analysis also showed that TMZ was associated with a reduction in serum total cholesterol and LDL-C levels, which were crucial elements in development of atherosclerotic lesions especially in diabetic patients. By reducing blood lipid levels, TMZ was likely to attenuate the progress of atherosclerosis and enhance the stability of atherosclerotic plaques.^[53, 54]

Recently, several researches demonstrated that TMZ treatment was associated with better exercise tolerance in patients suffering from stable angina^[32, 55, 56] or ischemic heart disease.^[57] However, this study showed no significant difference in the improvement of exercise tolerance in diabetic patients with CHD using TMZ. As is known, exercise capacity is a strong health predictor determined by cardiac and pulmonary function as well as the strength and metabolism of skeletal muscles, which were the main insulin-mediated glucose disposal. Besides, normal endothelial vasodilation function is also associated with exercise tolerance.^[58] In diabetic patients, insulin resistance may lead to severe metabolic disorders and skeletal muscle inflammation,^[59, 60] accounting partly for the indistinguishable difference of exercise tolerance between the TMZ and control groups. Meanwhile, diabetes is linked to impaired endothelial-dependent vasodilation,^[61] which may also reduce the effect of TMZ on exercise tolerance.

The limitations of our study are listed as follows: Firstly, for the comparisons of LVEDD, LVESD and serum level of triglyceride, the heterogeneity was very high. Some reasons might explain this phenomenon: 1. The number of articles included in our meta-analysis was relatively small, the population might not have a good representation; 2. Inconsistency existed in study design (crossover & parallel); 3. The population included Asia, Europe, Africa, which might also lead to the heterogeneity. 4. In addition, there were some differences in the types of CHD and follow-up duration in each study. Secondly, due to some incomplete outcome data, attribution bias couldn't be ruled out. Thirdly, owing to the limited number of articles, publi-

cation bias assessments could not be processed. These potential confounding factors might affect the statistical power to interpret the results.

Our study suggests that following aspects should be noted in subsequent studies: 1. Studies with large samples in multiple regions are needed in the future. 2. The medication strategy of TMZ remains to be regulated according to different pathological situations and clinical presentations. 3. The follow-up of patients should be strengthened in order to decrease the potential bias, and the follow-up time should be extended for the detection of the long-term effect of TMZ. 4. A number of outcomes such as glucose level, lipid profile, exercise tolerance and life quality remain to be included in the further research. 5. Whether TMZ therapy could decrease the morbidity of CHD in diabetic patients needs to be further investigated.

In conclusion, this meta-analysis indicates that additional TMZ treatment in diabetic patients with CHD is effective to improve cardiac function, blood glucose level, lipid profile and clinical symptoms. Thus, it is recommended that patients with CHDs especially combined with diabetes receive the medication of TMZ in addition to conventional drugs. However, there is insufficient evidence to support the relation between TMZ administration and increased exercise tolerance. Further large scale, long time follow-up RCTs are warranted in the future to validate the conclusion drawn by this meta-analysis.

Conflict of Interests Statement

The authors declare that they have no competing interests.

REFERENCES

1. Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. *Nature* 2001; 414(6865):782-7. doi: 10.1038/414782a.
2. Ogurtsova K, da Rocha Fernandes JD, Huang Y, et al. IDF Diabetes Atlas: global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes Res Clin Pract* 2017; 128:40-50. doi: 10.1016/j.diabres.2017.03.024.
3. Haffner SM, Lehto S, Ronnema T, et al. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *NEJM* 1998; 339(4):229-34. doi: 10.1056/NEJM199807233390404.
4. Aune D, Schlesinger S, Norat T, et al. Diabetes mellitus and the risk of sudden cardiac death: a systematic review and meta-analysis of prospective studies. *Nutr Metab Cardiovasc Dis* 2018; 28(6):543-56. doi: 10.1016/j.numecd.2018.02.011.
5. Esper RJ, Vilarino JO, Machado RA, et al. Endothelial dysfunction in normal and abnormal glucose metabolism. *Adv Cardiol* 2008; 45:17-43. doi: 10.1159/000115120.
6. Kawano H, Motoyama T, Hirashima O, et al. Hyperglycemia rapidly suppresses flow-mediated endothelium-dependent vasodilation of brachial artery. *J Am Coll Cardiol* 1999; 34(1):146-54. doi: 10.1016/s0735-1097(99)00168-0.
7. Yoshida N, Okumura K, Aso Y. High serum pentosidine concentrations are associated with increased arterial stiffness and thickness in patients with type 2 diabetes. *Metabolism* 2005; 54(3):345-50. doi: 10.1016/j.metabol.2004.09.014.
8. Li L, Pan Y, Dai L, et al. Association of genetic polymorphisms on vascular endothelial growth factor and its receptor genes with susceptibility to coronary heart disease. *Med Sci Monit* 2016; 22:31-40. doi: 10.12659/msm.895163.
9. Bravo PE, Psaty BM, Di Carli MF, et al. Identification of coronary heart disease in asymptomatic individuals with diabetes mellitus: to screen or not to screen. *Columbia Med (Cali)* 2015; 46(1):41-6.
10. Chiha M, Njeim M, Chedrawy EG. Diabetes and coronary heart disease: a risk factor for the global epidemic. *Int J Hypertens* 2012; 2012:697240. doi: 10.1155/2012/697240.
11. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics—2011 update: a report from the American Heart Association. *Circulation* 2011; 123(4):e18-e209. doi: 10.1161/CIR.0b013e3182009701.
12. Donahoe SM, Stewart GC, McCabe CH, et al. Diabetes and mortality following acute coronary syndromes. *JAMA* 2007; 298(7):765-75. doi: 10.1001/jama.298.7.765.
13. Ussher JR, Lopaschuk GD. Targeting malonyl CoA inhibition of mitochondrial fatty acid uptake as an approach to treat cardiac ischemia/reperfusion. *Basic Res Cardiol* 2009; 104(2):203-10. doi: 10.1007/s00395-009-0003-9.
14. Monti LD, Setola E, Fragasso G, et al. Metabolic and endothelial effects of trimetazidine on forearm skeletal muscle in patients with type 2 diabetes and ischemic

- cardiomyopathy. *Am J Physiol* 2006; 290(1):E54-E9. doi: 10.1152/ajpendo.00083.2005.
15. Kantor PF, Lucien A, Kozak R, et al. 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(5):580-8. doi: 10.1161/01.res.86.5.580.
 16. Onay-Besikci A, Ozkan SA. Trimetazidine revisited: a comprehensive review of the pharmacological effects and analytical techniques for the determination of trimetazidine. *Cardiovas Ther* 2008; 26(2):147-65. doi: 10.1111/j.1527-3466.2008.00043.x.
 17. Chrusciel P, Rysz J, Banach M. Defining the role of trimetazidine in the treatment of cardiovascular disorders: some insights on its role in heart failure and peripheral artery disease. *Drugs* 2014; 74(9):971-80. doi: 10.1007/s40265-014-0233-5.
 18. Tsioufis K, Andrikopoulos G, Manolis A. Trimetazidine and cardioprotection: facts and perspectives. *Angiology* 2015; 66(3):204-10. doi: 10.1177/0003319714530040.
 19. Li R, Tang X, Jing Q, et al. The effect of trimetazidine treatment in patients with type 2 diabetes undergoing percutaneous coronary intervention for AMI. *Am J Emerg Med* 2017; 35(11):1657-61. doi: 10.1016/j.ajem.2017.05.024.
 20. Xu X, Zhang W, Zhou Y, et al. Effect of trimetazidine on recurrent angina pectoris and left ventricular structure in elderly multivessel coronary heart disease patients with diabetes mellitus after drug-eluting stent implantation: a single-centre, prospective, randomized, double-blind study at 2-year follow-up. *Clin Drug Investig* 2014; 34(4):251-8. doi: 10.1007/s40261-014-0170-9.
 21. Shehata M. Cardioprotective effects of oral trimetazidine in diabetic patients with anterior wall myocardial infarction treated with thrombolysis. *Cardiol Res* 2014; 5(2):58-67. doi: 10.14740/cr330w.
 22. Belardinelli R, Cianci G, Gigli M, et al. Effects of trimetazidine on myocardial perfusion and left ventricular systolic function in type 2 diabetic patients with ischemic cardiomyopathy. *J Cardiovas Pharmacol* 2008; 51(6):611-5. doi: 10.1097/FJC.0b013e31817bdd66.
 23. Ribeiro LW, Ribeiro JP, Stein R, et al. Trimetazidine added to combined hemodynamic antianginal therapy in patients with type 2 diabetes: a randomized cross-over trial. *Am Heart J* 2007; 154(1):78.e1-7. doi: 10.1016/j.ahj.2007.04.026.
 24. Marazzi G, Wajngarten M, Vitale C, et al. Effect of free fatty acid inhibition on silent and symptomatic myocardial ischemia in diabetic patients with coronary artery disease. *Int J Cardiol* 2007; 120(1):79-84. doi: 10.1016/j.ijcard.2006.08.082.
 25. Rosano GMC, Vitale C, Sposato B, et al. Trimetazidine improves left ventricular function in diabetic patients with coronary artery disease: A double-blind placebo-controlled study. *Cardiovas Diabetol* 2003; 2:16. doi: 10.1186/1475-2840-2-16.
 26. Fragasso G, Piatti Md PM, Monti L, et al. Short- and long-term beneficial effects of trimetazidine in patients with diabetes and ischemic cardiomyopathy. *Am Heart J* 2003; 146(5):E18. doi: 10.1016/S0002-8703(03)00415-0.
 27. D'Souza A, Hussain M, Howarth FC, et al. Pathogenesis and pathophysiology of accelerated atherosclerosis in the diabetic heart. *Mol Cell Biochem* 2009; 331(1-2):89-116. doi: 10.1007/s11010-009-0148-8.
 28. Gartner V, Eigentler TK. Pathogenesis of diabetic macro- and microangiopathy. *Clin Nephrol* 2008; 70(1):1-9. doi: 10.5414/cnp70001.
 29. Vinik A, Flemmer M. Diabetes and macrovascular disease. *J Diabetes Complications* 2002; 16(3):235-45. doi: 10.1016/s1056-8727(01)00212-4.
 30. Natali A, Vichi S, Landi P, et al. Coronary atherosclerosis in type II diabetes: angiographic findings and clinical outcome. *Diabetologia* 2000; 43(5):632-41. doi: 10.1007/s001250051352.
 31. Dalen JE, Alpert JS, Goldberg RJ, et al. The epidemic of the 20(th) century: coronary heart disease. *Am J Med* 2014; 127(9):807-12. doi: 10.1016/j.amjmed.2014.04.015.
 32. Danchin N, Marzilli M, Parkhomenko A, et al. Efficacy comparison of trimetazidine with therapeutic alternatives in stable angina pectoris: a network meta-analysis. *Cardiology* 2011; 120(2):59-72. doi: 10.1159/000332369.
 33. Jandeleit-Dahm K, Watson A, Soro-Paavonen A. The AGE/RAGE axis in diabetes-accelerated atherosclerosis. *Clin Expe Pharmacol Physiol* 2008; 35(3):329-34. doi: 10.1111/j.1440-1681.2007.04875.x.
 34. Wautier JL, Schmidt AM. Protein glycation: a firm link to endothelial cell dysfunction. *Circ Res* 2004; 95(3):233-8. doi: 10.1161/01.RES.0000137876.28454.64.
 35. Xanthis A, Hatzitolios A, Koliakos G, et al. Advanced glycosylation end products and nutrition—a possible

- relation with diabetic atherosclerosis and how to prevent it. *J Food Sci* 2007; 72(8):R125-9. doi: 10.1111/j.1750-3841.2007.00508.x.
36. Katakami N, Kaneto H, Matsuoka TA, et al. Accumulation of oxidative stress-related gene polymorphisms and the risk of coronary heart disease events in patients with type 2 diabetes--an 8-year prospective study. *Atherosclerosis* 2014; 235(2):408-14. doi: 10.1016/j.atherosclerosis.2014.05.936.
37. Chen YR, Zweier JL. Cardiac mitochondria and reactive oxygen species generation. *Circ Res* 2014; 114(3):524-37. doi: 10.1161/CIRCRESAHA.114.300559.
38. Blake R, Trounce IA. Mitochondrial dysfunction and complications associated with diabetes. *Biochim Biophys Acta* 2014; 1840(4):1404-12. doi: 10.1016/j.bbagen.2013.11.007.
39. van den Oever IA, Raterman HG, Nurmohamed MT, et al. Endothelial dysfunction, inflammation, and apoptosis in diabetes mellitus. *Mediators Inflamm* 2010; 2010:792393. doi: 10.1155/2010/792393.
40. Maack C, Dabew ER, Hohl M, et al. Endogenous activation of mitochondrial KATP channels protects human failing myocardium from hydroxyl radical-induced stunning. *Circ Res* 2009; 105(8):811-7. doi: 10.1161/CIRCRESAHA.109.206359.
41. Giordano FJ. Oxygen, oxidative stress, hypoxia, and heart failure. *J Clin Invest* 2005; 115(3):500-8. doi: 10.1172/JCI24408.
42. Akar FG, Aon MA, Tomaselli GF, et al. The mitochondrial origin of postischemic arrhythmias. *J Clin Invest* 2005; 115(12):3527-35. doi: 10.1172/JCI25371.
43. Kurokawa S, Niwano S, Niwano H, et al. Progression of ventricular remodeling and arrhythmia in the primary hyperoxidative state of glutathione-depleted rats. *Circulation J* 2011; 75(6):1386-93. doi: 10.1253/circj.cj-10-1089.
44. Monteiro P, Duarte AI, Goncalves LM, et al. Protective effect of trimetazidine on myocardial mitochondrial function in an *ex-vivo* model of global myocardial ischemia. *Eur J Pharmacol* 2004; 503(1-3):123-8. doi: 10.1016/j.ejphar.2004.09.003.
45. Wu Q, Qi B, Liu Y, et al. Mechanisms underlying protective effects of trimetazidine on endothelial progenitor cells biological functions against H₂O₂-induced injury: involvement of antioxidation and Akt/eNOS signaling pathways. *Eur J Pharmacol* 2013; 707(1-3):87-94. doi: 10.1016/j.ejphar.2013.03.027.
46. Dehina L, Vaillant F, Tabib A, et al. Trimetazidine demonstrated cardioprotective effects through mitochondrial pathway in a model of acute coronary ischemia. *Naunyn Schmiedebergs Arch Pharmacol* 2013; 386(3):205-15. doi: 10.1007/s00210-012-0826-z.
47. Senturk T, Cavun S, Avci B, et al. Effective inhibition of cardiomyocyte apoptosis through the combination of trimetazidine and N-acetylcysteine in a rat model of myocardial ischemia and reperfusion injury. *Atherosclerosis* 2014; 237(2):760-6. doi: 10.1016/j.atherosclerosis.2014.10.091.
48. Zhou X, Li C, Xu W, et al. Trimetazidine protects against smoking-induced left ventricular remodeling *via* attenuating oxidative stress, apoptosis, and inflammation. *PloS One* 2012; 7(7):e40424. doi: 10.1371/journal.pone.0040424.
49. Zhang L, Ding WY, Wang ZH, et al. Early administration of trimetazidine attenuates diabetic cardiomyopathy in rats by alleviating fibrosis, reducing apoptosis and enhancing autophagy. *J Transl Med* 2016; 14(1):109. doi: 10.1186/s12967-016-0849-1.
50. Vitale C, Marazzi G, Pelliccia F, et al. Trimetazidine improves exercise performance in patients with peripheral arterial disease. *Pharmacol Res* 2011; 63(4):278-83. doi: 10.1016/j.phrs.2011.01.003.
51. Tuunanen H, Engblom E, Naum A, et al. Trimetazidine, a metabolic modulator, has cardiac and extra-cardiac benefits in idiopathic dilated cardiomyopathy. *Circulation* 2008; 118(12):1250-8. doi: 10.1161/CIRCULATIONAHA.108.778019.
52. Fazakerley DJ, Holman GD, Marley A, et al. Kinetic evidence for unique regulation of GLUT4 trafficking by insulin and AMP-activated protein kinase activators in L6 myotubes. *J Bio Chem* 2010; 285(3):1653-60. doi: 10.1074/jbc.M109.051185.
53. Orekhov AN, Bobryshev YV, Sobenin IA, et al. Modified low density lipoprotein and lipoprotein-containing circulating immune complexes as diagnostic and prognostic biomarkers of atherosclerosis and type 1 diabetes macrovascular disease. *Int J Mol Sci* 2014; 15(7):12807-41. doi: 10.3390/ijms150712807.
54. Yang H, Mohamed AS, Zhou SH. Oxidized low density lipoprotein, stem cells, and atherosclerosis. *Lipids Health Dis* 2012; 11:85. doi: 10.1186/1476-511X-11-85.
55. Peng S, Zhao M, Wan J, et al. The efficacy of trimetazidine on stable angina pectoris: a meta-analysis of randomized clinical trials. *Int J Cardiol* 2014; 177(3):780-5. doi: 10.1016/j.ijcard.2014.10.149.
56. Marzilli M, Klein WW. Efficacy and tolerability of

- trimetazidine in stable angina: a meta-analysis of randomized, double-blind, controlled trials. *Coron Artery Dis* 2003; 14(2):171-9. doi: 10.1097/00019501-200304000-00010.
57. Zhao Y, Peng L, Luo Y, et al. Trimetazidine improves exercise tolerance in patients with ischemic heart disease: a meta-analysis. *Herz* 2016; 41(6):514-22. doi: 10.1007/s00059-015-4392-2.
58. Borlaug BA, Melenovsky V, Russell SD, et al. Impaired chronotropic and vasodilator reserves limit exercise capacity in patients with heart failure and a preserved ejection fraction. *Circulation* 2006; 114(20):2138-47. doi: 10.1161/CIRCULATIONAHA.106.632745.
59. Wei Y, Chen K, Whaley-Connell AT, et al. Skeletal muscle insulin resistance: role of inflammatory cytokines and reactive oxygen species. *Am J Physiol* 2008; 294(3):R673-80. doi: 10.1152/ajpregu.00561.2007.
60. Zeyda M, Stulnig TM. Obesity, inflammation, and insulin resistance—a mini-review. *Gerontology* 2009; 55(4):379-86. doi: 10.1159/000212758.
61. Roberts AC, Porter KE. Cellular and molecular mechanisms of endothelial dysfunction in diabetes. *Diab Vasc Dis Res* 2013; 10(6):472-82. doi: 10.1177/1479164113500680.