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Systematic Review

The efficacy of trimetazidine in non-ischemic heart failure patients: a meta-analysis of randomized controlled trials

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Trimetazidine has been reported to benefit patients with heart failure (HF) and angina. The impact of trimetazidine on non-ischemic HF remains unclear. We reviewed clinical trials to investigate whether trimetazidine could improve exercise endurance, life quality, and heart function in non-ischemic HF patients. We searched the Cochrane Central Register of Controlled Trials, EMBASE, PubMed, and Web of science for randomized clinical trials published before April 30th, 2020; Studies limited to patients with non-ischemic HF, aged $\geq$18 years, comparing trimetazidine with conventional therapy with/without placebo. Outcome measurements included primary outcomes (6 minutes walking test (6-MWT)) and secondary outcomes (life quality scores, echocardiography parameters, biomarker, peak oxygen consumption). The follow-up period was longer than three months. This study was registered with international prospective register of systematic reviews (PROSPERO) (CRD42020182982). Six studies with 310 cases were included in this research. Trimetazidine significantly improved 6-MWT (weighted mean difference (WMD) = 48.51 m, 95% confidence interval (CI) [29.41, 67.61], $p < 0.0001$, $I^2 = 0\%$), left ventricle ejection fraction (LVEF) (WMD = 3.09%, 95% CI [1.09, 5.01], $p = 0.002$, $I^2 = 0\%$) at 3 months, and LVEF (WMD = 6.09%, 95% CI [3.76, 8.42], $p < 0.0001$, $I^2 = 12\%$) at 6 months. Furthermore, it reduced peak oxygen consumption (WMD = –2.24 mL/kg per minute, 95% CI [–4.09, –0.93], $p = 0.02$). This meta-analysis suggested that trimetazidine might be an effective strategy for improving exercise endurance and cardiac function in patients with non-ischemic HF.

Keywords

Trimetazidine; Non-ischemic heart failure; Exercise endurance; Heart function

1. Introduction

Heart failure (HF) is the leading cause of morbidity and mortality worldwide; it is the end-stage of multiple cardiovascular diseases that affects more than 26 million people in the global population [1]. The past decades have witnessed remarkable progress in HF treatment, including digitalis, diuretics, angiotensin-converting enzyme inhibitors (ACEI)/(angiotensin receptor antagonists) ARB, β blockers, aldosterone antagonists, neprilysin (NEP) inhibitor sacubitril, and resynchronization therapy [2, 3]. Nevertheless, heart failure patients with preserved ejection fraction (HFpEF) have been increasing and remaining undiscovered and untreated [4].

Metabolism seems to be a promising therapeutic target in HF patients when a failing heart exhibits energetic impairment, characterized by a lower phosphocreatine/adenosine triphosphate ratio and elevated utilization of the ketone body [5–9]. Multiple studies confirmed trimetazidine, a fatty acid oxidation inhibitor, has beneficial effect on HF patients [10–13]. Mechanistic studies [14] *in vivo* and *in vitro* demonstrated that trimetazidine could reduce fatty acid utilization and shift to glucose metabolism.

Trimetazidine has been recommended for HF patients with stable angina pectoris, according to the European Society of Cardiology guidelines [3, 15]. Several small-scale, single-center randomized clinical trials demonstrated that it improves cardiac function and life quality in HF patients. However, there has been no consistent conclusion concerning its efficacy on exercise endurance, life quality, and heart function for non-ischemic HF patients [11–13, 16–21].

Our study aims to perform a meta-analysis with randomized clinical trials investigating the efficacy of trimetazidine versus control or placebo therapy in non-ischemic HF patients.

2. Method

2.1 Protocol and registration

This study was registered with international prospective register of systematic reviews (PROSPERO), numbered CRD42020182982, and was abided by the Cochrane Handbook for Systematic Reviews of Interventions [22] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [23].

2.2 Search strategy

Two authors independently searched the Cochrane Central Register of Controlled Trials, EMBASE, PubMed, and Web of science for randomized clinical trials published before April 30th, 2020. The search terms were 'trimetazidine' [Mesh terms] OR 'VASTAREL' [Mesh terms] AND 'heart failure' [Mesh terms] or 'cardiomyopathy' [Mesh terms]. The

search was limited to human subjects, with no restriction for language. Database searches were supplemented by searching the reference of studies and reviews. We also contacted authors for unpublished data when missing data. The search was finished on May 1st, 2020.

2.3 Selection criteria

Two authors screened the abstract of the studies independently. Studies were included if they met the criteria below: (1) randomized clinical trial comparing trimetazidine with conventional therapy with/without placebo; (2) non-ischemic HF patient including dilated cardiomyopathy, hypertrophic cardiomyopathy, metabolic disorders associated heart failure, and patients with abnormal loading conditions (arrhythmia and hypertension); (3) outcome measurements including the result of 6 minutes walking test (6-MWT), life quality scores (including Minnesota heart failure score and left ventricular dysfunction 36 (LVD-36)), echocardiography parameters (left ventricular ejection fraction (LVEF), left ventricular end-systolic volume (LVESV) and left ventricular end-diastolic volume (LVEDV)), biomarker (B-type natriuretic peptide (BNP), N -terminal pro-brain natriuretic peptide (NT-pro BNP)), peak oxygen consumption (peak VO2); (4) follow up period longer than three months; (5) full article and data available. Studies that had not specified the cause of HF or exhibit non-ischemic HF data alone were excluded. Observational studies, preclinical studies, reviews, and animal experiment studies were excluded (Fig. 1).

2.4 Data collection

Two authors validated the studies included independently and discussed when divergence existed. The quality of the included studies was assessed using the criteria below, following Cochrane Handbook for Systematic Reviews of Interventions: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective reporting were used for the methodological quality of each included trials. The quality of each item was classified using a nominal scale: "Yes" (low risk of bias), "No" (high risk of bias), or "Unclear" (unclear risk of bias).

Data were abstracted by the use of data collection forms specially designed. The basic information of the articles was extracted, such as the first author, year of publication, intervention, and follow-up months. Patient information included age, sex, body mass index (BMI), history of other diseases (diabetes (DM), hypertension (HBP), atrial fibrillation (AF)), treatment (cardiac resynchronization therapy (CRT), β-blocker, ACEI/ARB, aldosterone antagonist, diuretics, statins, digitalis) were also extracted. Outcomes of interest were: (1) result of 6-MWT, (2) life quality scores (including Minnesota heart failure score and LVD-36), (3) echocardiography parameters (LVEF, LVESV, and LVEDV), (4) biomarker (BNP, NT-pro BNP), (5) peak VO2.

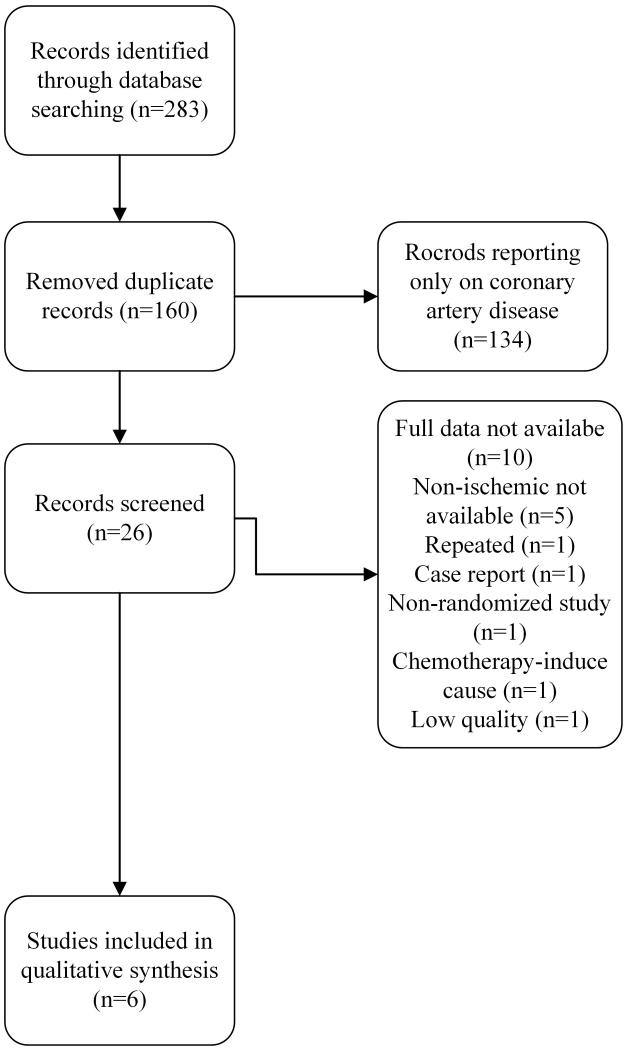

Fig. 1. Research screen chart.

2.5 Statistical analysis

Statistical analysis was performed by Review Manager 5.3 software (The Cochrane Collaboration, Copenhagen, The Nordic Cochrane Centre). Dichotomous variables were presented as hazard ratio (HR), while continuous outcomes were presented as the weighted mean difference (WMD) with a 95% confidence interval (CI). Summary measures were pooled using the I-square (I^2) statistic to assess heterogeneity, and $p < 0.1$ was defined as statistically significant. A fixed-effect model was performed for minor heterogeneity when I^2 was $<50\%$ or p was >0.1. A random-effect model was applied when I^2 was $>50\%$, and p was <0.1. Subgroup analysis was used to assess the possible effect. Moreover, a sensitivity analysis was performed to evaluate the reliability of the meta-analysis results. Publication bias was evaluated using funnel plot analyses and statistically by the Egger test. Except for the heterogeneity assessment, a two-sided p-value of 0.05 or less was considered to indicate a statistically significant difference.

3. Result

3.1 Study characteristics

There are 283 records obtained from the databases, and after removing the duplicates, 160 records were identified. After eliminating the records related to coronary artery disease, 26 records are finally included. We attempted to acquire the full texts of the researches, of which six researches were qualified. The other records were excluded for the following reasons: 10 records were not acquirable for unpublished data or full texts, five records had not listed the non-ischemic HF data alone (neither acquirable after contacted the author), one record was a case report, one record was a non-randomized trial, one record reported cardiomyopathy after chemotherapy, one record was repeatedly reported in a different year, one record was reported as a randomized clinical trial with low quality (failed to report the specific method of randomization, blindness and registration information after contact with the authors). One study included the non-ischemic HF outcome measurement data separately but lacked other data.

The trials included 310 patients with 161 patients in the trimetazidine group and 149 patients in the control group, reported patients with nonobstructive hypertrophic cardiomyopathy [16], dilated cardiomyopathy [17–19], idiopathic dilated cardiomyopathy [20], other causes of non-ischemic HF [13] (Table 1, Ref. [13, 16, 18–20]). Two studies were conducted in Asia, three studies were conducted in Europe, and one study was conducted in South America. Five studies defined the dose of trimetazidine as 60 mg/day, one defined as 70 mg/day. The age of these patients ranged from 47.1 to 66 years old. The follow-up period was three to 13 months. Baseline characteristics of NYHA classification, other conditions, including diabetes, hypertension, atrial fibrillation, and cardiac resynchronization therapy, were partially reported in these studies. Conventional treatment with β-blocker, ACEI/ARB, aldosterone antagonist, diuretic, statins, digitalis were listed in Table 1.

3.2 Quality assessment

The quality assessment of these six included studies was conducted according to the Cochrane risk of bias estimation (Fig. 2). Two studies using a computer-generated number as randomization were defined as low risk in random sequence generation [13, 16, 17], and another two studies reported randomly without specifying the method [18, 20], one study used the sequential number as randomization was defined as high risk [19]. Four studies [13, 16, 17] used the envelope as allocation concealment were defined as low risk, while others [18–20] failed to report specific methods. Three studies reported blindness of participants [16, 17, 19], and all the studies reported blindness of outcome measurement, which was defined as low risk. Attribution bias and selective reporting existed in 2 studies [13, 20] due to the lack of primary outcome (**Supplementary Fig. 1**).

3.3 6-MWT

Four studies [16–19] reported the full data of 6-MWT comparing the trimetazidine and the control group. The result showed that the improvement of 6-MWT was non-significant (WMD = 14.58 m, 95% CI [–46.10, 75.27], p = 0.64) due to the substantial heterogeneity ($p < 0.00001$, I^2 = 93%). Sensitivity analysis suggested that the effect was concealed when the study by Winter *et al.* [19] was omitted. A fixed-effect model was used to pool this meta-analysis in the remaining studies [16–18]. The result showed that trimetazidine improved 6-MWT (WMD = 48.51 m, 95% CI [29.41, 67.61], $p < 0.0001$) without obvious heterogeneity (p = 0.45, I^2 = 0%) (Fig. 3).

3.4 Peak VO2 and life quality score

Two studies [16, 19] reported peak VO2 as outcome measurement, and there was no significant heterogeneity (p = 0.20, I^2 = 39%). A fixed-effects model was used to pool this meta-analysis, which showed that trimetazidine failed to improve peak VO2 (WMD = –2.24 mL/kg per minute, 95% CI [–4.09, –0.93], p = 0.02) (Fig. 4). Life quality score was conducted in 4 studies [13, 16, 18, 19], including Minnesota heart failure score and LVD-36. A fixed-effect model was used to pool this meta-analysis, which showed that trimetazidine failed to improve life quality score (WMD = –2.72, 95% CI [–4.19, –1.24], p = 0.0003) with no heterogeneity (p = 0.16, I^2 = 41%) (Fig. 5).

3.5 LVEF

LVEF was reported in all studies [13, 16–20, 24]. Additionally, Jatain *et al.* [18] reported LVEF in three and six months follow-up separately, and the data were presented as two studies. Due to the significant heterogeneity (p = 0.03, I^2= 70%), a random-effect model was used to pool this meta-analysis, which showed that trimetazidine improved LVEF (WMD = 4.25%, 95% CI [1.40, 7.10], p = 0.003) (Fig. 6). Subgroup analysis was performed based on the various months of follow-up. Three months follow-up group was analyzed with fixed-effect model (heterogeneity p = 1.00, I^2 = 0%), which showed that trimetazidine improved LVEF (WMD = 3.09%, 95% CI [1.09, 5.01], p = 0.002) (Fig. 7, Ref. [18]). In six months follow-up subgroup, the result showed that trimetazidine did not improve LVEF (WMD = 2.67%, 95% CI [–2.71, 8.06], p = 0.33) using random-effect model(heterogeneity p = 0.03, I^2 = 79%), sensitivity analysis showed Jatain *et al.* [18] had significant heterogeneity compared with others and was thus excluded [13, 17, 19]. The six months follow-up group was analyzed with a fixed-effect model (heterogeneity p = 0.32, I^2 = 12%), which showed that trimetazidine improved LVEF (WMD = 6.09%, 95% CI [3.76, 8.42], $p < 0.0001$) (Fig. 7). In conclusion, trimetazidine improved LVEF both in three months and six months follow-up groups.

3.6 LVESV and LVEDV

Three studies [13, 18, 20] reported peak LVESV and LVEDV as outcome measurement and there was no signif-

Table 1. Characteristics of included studies.

Study	Year	Country	Total case (T/C)	Inclusion cretia	Control	Dose of trimetazidine	Follow-up months	Outcome measurement	Age (trimetazidine versus placebo/control)	Sex (M/F)	BMI
Coats *et al.* [16]	2019	Britan	27/24	Non-obstructive HCM, NYHA 2–4	placebo+ conventional therapy	60 mg/day	3 months	CPET, exercise, echo, biomarker, questionaire	49 ± 13, 51 ± 14	18/9, 18/6	29 ± 6, 28 ± 5
Liang *et al.* [17]	2017	China	30/30	DCM with LBBB, EF 34–45, NYHA 2–3	placebo+ conventional therapy	60 mg/day	6 months	exercise, echo, biomarker	53 ± 7.5, 51 ± 8.1	24/6, 25/5	NA
Jatain *et al.* [18]	2016	India	52/48	DCM, NYHA 2–4, EF <45	conventional therapy	60 mg/day	3, 6 months	exercise, echo, biomarker, questionaire	47.1 ± 12.6, 48.31 ± 11.5	36/14, 37/13	24.6 ± 4.5, 23.3 ± 3.5
Winter *et al.* [19]	2014	Chile	30/30	DCM, NYHA 2–3, EF <45	conventional therapy	70 mg/day	6 months	CPET, exercise, echo, biomarker, questionaire, PET-CT	53 ± 13, 57 ± 13	20/10, 21/9	27 ± 4, 27 ± 3
Tuunanen *et al.* [20]	2008	Turku	12/7	IDCM, EF <47	placebo+ conventional therapy	70 mg/day	3 months	exercise, echo, biomarker, PET-CT	59 ± 8.8, 57 ± 7.3	10/2, 5/2	27.4 ± 5.3, 29.8 ± 3.6
Fragasso *et al.* [13]	2006	Italy	10/10	Non-ischemic HF	conventional therapy	60 mg/day	13 ± 3 months	exercise, echo, biomarker, questionaire, cumulative event	64 ± 7, 66 ± 7	NA	NA

Table 1. Continued.

Study	Diabetes (%)	HBP (%)	AF (%)	CRT (%)	NYHA	β-blocker (%)	ACEI/ARB (%)	Aldosterone antagonist (%)	Diuretic (%)	Statins (%)	Digitalis (%)
Coats *et al.* [16]	0	19/0	8/17	4/0	2–3	44/42	NA	30/46	NA	19/13	0
Liang *et al.* [17]	NA	NA	NA	NA	2–3	93.3/96.7	100/100	83.3/86.7	93.3/93.3	NA	NA
Jatain *et al.* [18]	19.2/20.8	29/21	NA	NA	2–4	100/100	100/100	NA	NA	NA	NA
Winter *et al.* [19]	13/3	53/60	14/14	NA	2–3	90/96	90/86	83/86	86/76	40/43	NA
Tuunanen *et al.* [20]	0	25/28.5	41.6/28.5	NA	2–3	91.6/100	83.3/66.7	NA	58.3/57.1	33.3/28.5	33.3/28.5
Fragasso *et al.* [13]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Abbreviation: NYHA, New York Heart Association functional class; EF, Ejection Fraction; HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; IDCM, idiopathic dilated cardiomyopathy; LBBB, left bundle branch block; CPET, cardio-pulmonary exercise test; BMI, body mass index; HBP hypertension; AF atrial fibrillation; CRT, cardiac resynchronize therapy; ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor antagonists.

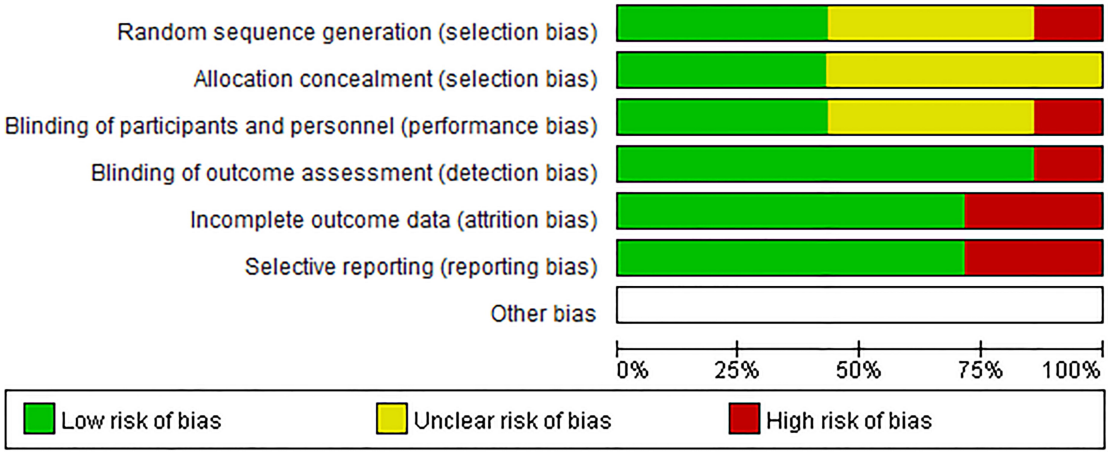

Fig. 2. Quality assessment of article.

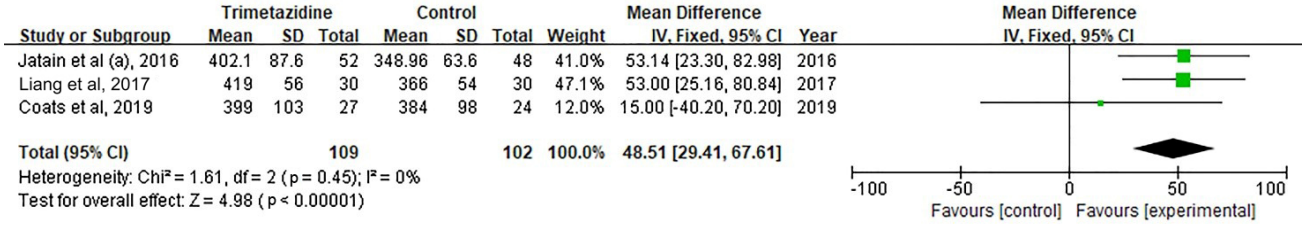

Fig. 3. Forest plot for 6-MWT. Forest plot depicting the 6-MWT difference of trimetazidine on non-ischemic HF vs. control. The size of the square corresponding to each study is proportional to the sample size.

icant heterogeneity (LVESV: $p = 0.12$, $I^2 = 49\%$; LVEDV: $p = 0.37$, $I^2 = 5\%$), a fixed-effect model was used to pool these meta-analysis, which showed that trimetazidine might reduce LVESV and LVEDV (LVESV: WMD = –11.23 mL, 95% CI [–17.63, –4.83], $p = 0.0006$; LVEDV: WMD = –6.92 mL, 95% CI [–14.46, 0.62], $p = 0.07$), while LVEDV effect reached a borderline p value (Figs. 8,9).

3.7 Biomarker

Troponin data was reported in the study by Coats *et al.* [16], NT-proBNP data was reported by Winter *et al.* [19] and Coats *et al.* [16], and BNP was acquirable in the study by Jatain *et al.* [18]. As a result of insufficient data, we reviewed these studies systemically. Coats *et al.* [16] reported that trimetazidine did not change troponin T level at 3 months (mean difference, 0.001ng/L [95% CI, -0.013 to 0.016 ng/L]) or NT-proBNP level (mean difference, -0.07 pmol/L [95% CI, -0.28 to 0.14 pmol/L]) compared with placebo. Winter *et al.* [19] reported that trimetazidine did not improve the NT-proBNP values compared with baseline during follow-up period (paired t-test $p = 0.66$ in TMZ and $p = 0.18$ in placebo). However, Jatain *et al.* [18] showed that trimetazidine reduced BNP level both in three months (712.9 ± 606.8 pg/mL to 455.44 ± 475.87 pg/mL, $p = 0.001$) and six months (712 pg/mL to 382 pg/mL, lack of SD) when compared with baseline and follow-up, respectively; Due to no adjustment for factors or comparison of trimetazidine and control, these positive results were not convincible. Conclusively, there was no significant improvement in laboratory biomarkers in the trimetazidine group.

3.8 Adverse events and reactions

There were four studies that recorded the adverse events. Coats *et al.* [16] reported total nonserious adverse events during follow-up (33 times in trimetazidine, 24 times in the control group). Fragasso *et al.* [13] reported that trimetazidine reduced the incidence of cumulative adverse cardiovascular events compared with patients randomized to the control group (13 times in trimetazidine, 26 times in control). Two studies [18, 19] reported no adverse event.

3.9 Publication bias

Publication bias was performed by the use of a funnel plot based on the LVEF results. Six studies were included in the funnel plot, which suggested no asymmetry in LVEF (Fig. 10).

4. Discussion

The main findings of this meta-analysis are that trimetazidine improved exercise endurance and cardiac function. Besides, long-term and short-term usage of trimetazidine seemed to achieve similar results. However, trimetazidine seemed neutral in improving adverse events, life quality, and biomarkers, and Peak VO2.

Previous studies demonstrated that trimetazidine benefits patients with HF, including decreased re-hospitalization and mortality, improved cardiac function, and exercise en-

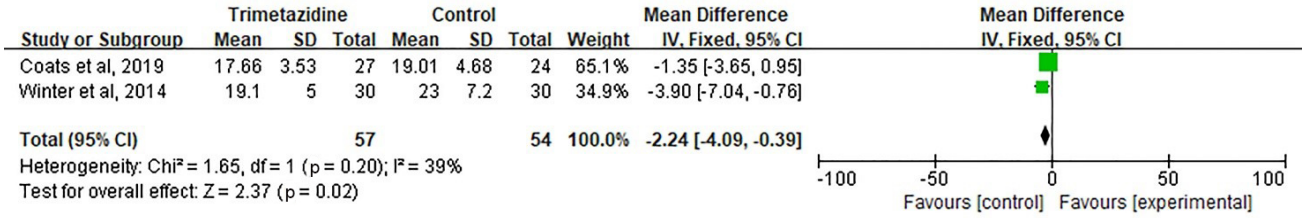

Fig. 4. Forest plot for peak VO2. Forest plot depicting the peak VO2 difference of trimetazidine on non-ischemic HF vs. control. The size of the square corresponding to each study is proportional to the sample size.

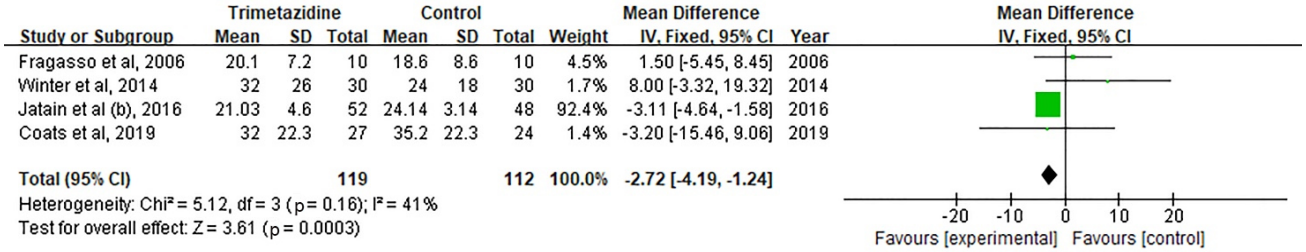

Fig. 5. Forest plot for life quality score. Forest plot depicting the life quality score difference of trimetazidine on non-ischemic HF vs. control. The size of the square corresponding to each study is proportional to the sample size.

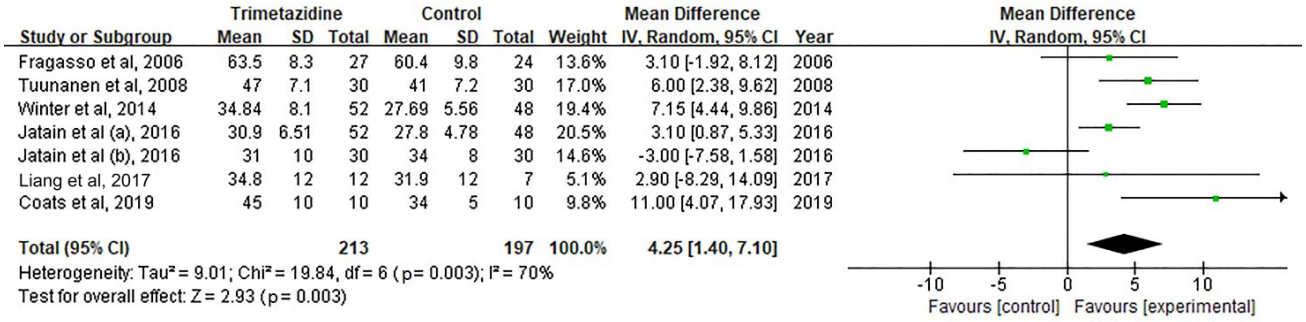

Fig. 6. Forest plot for LVEF. Forest plot depicting the LVEF difference of trimetazidine on non-ischemic HF vs. control. The size of the square corresponding to each study is proportional to the sample size.

durance. However, the non-ischemic HF was discussed in subgroup analysis, and studies included were not designed separately for non-ischemic HF. Our study included trials that focused on non-ischemic HF published in recent years and updated the knowledge of trimetazidine use in non-ischemic HF.

Consistent with previous findings [12, 25], this study demonstrated that trimetazidine could improve 6-MWT, a test for exercise endurance, in non-ischemic HF. However, the result was inconsistent with sensitivity analysis, which showed that the study by Winter *et al.* [19] was the cause of heterogeneity. The study by Winter *et al.* [19] did not set a placebo control group compared with the others, and it was conducted earlier, which might cause the heterogeneity. After excluding it, the result showed that trimetazidine improved 6-MWT with low heterogeneity.

The recovery of cardiac function might drive the benefit of trimetazidine on exercise endurance. Trimetazidine protects cardiac function by inhibiting long-chain 3-ketoacyl coenzyme A thiolase, which catalyzes the final step of fatty acid β-oxidation. It subsequently reduces the fatty acid utilization and shifts to glucose metabolism, which enables the heart to produce more ATP [26, 27]. In addition, trimetazidine might inhibit cardiac fibrosis, ischemia/reperfusion injury, cardiomyocyte apoptosis, and oxidative stress through the following pathways: (1) Nicotinamide adenine dinucleotide phosphate oxidase/reactive oxygen species/connective tissue growth factor pathway [28]; (2) Akt/endothelial nitric oxide synthase signaling pathway [29]; (3) mitochondrial pathway [30]; (4) Bcl-2/Bax pathway [31]; (5) Adenosine monophosphate (AMP)-activated protein kinase/extracellular signal-regulated kinase signaling pathway [32]; (6) Nuclear factor E2-related factor 2/nuclear factor-kappaB signaling pathway [33]; (7) AMP-activated protein kinase/mechanistic target of rapamycin/autophagy pathway [34]. Given the facts listed above, it is reasonable to believe that trimetazidine serves as a cardiac protective agent.

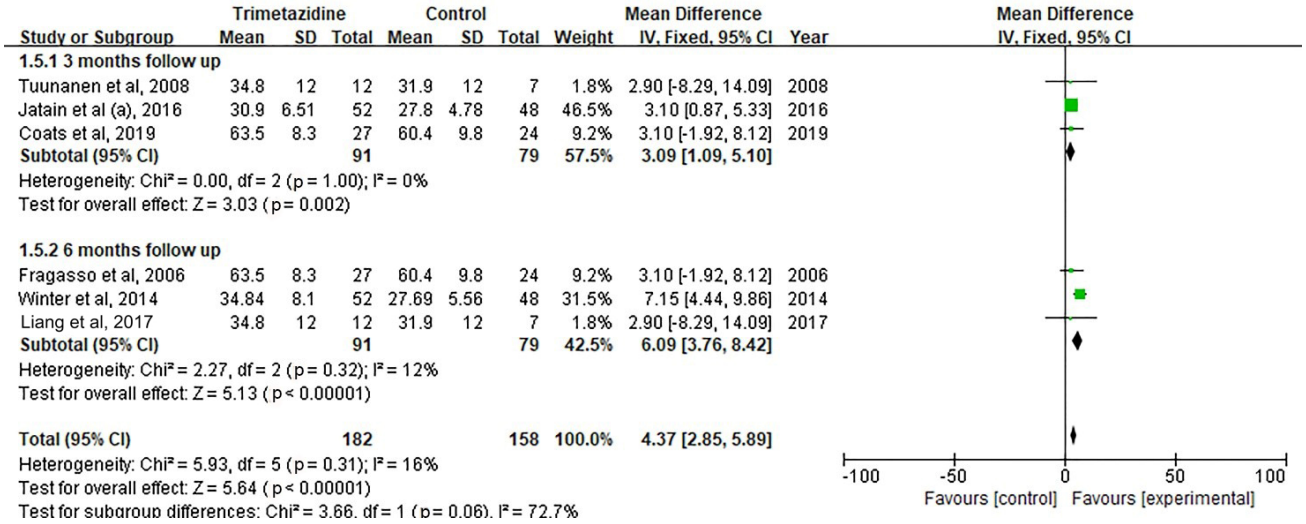

Fig. 7. Forest plot for the subgroup of LVEF. Follow-up months of three months and longer than six months were analyzed separately. Jatain *et al.* (a) and Jatain *et al.* (b) [18] were acquired from the same research but at different follow-up months. Forest plot depicting the LVEF difference of trimetazidine on non-ischemic HF vs. control.

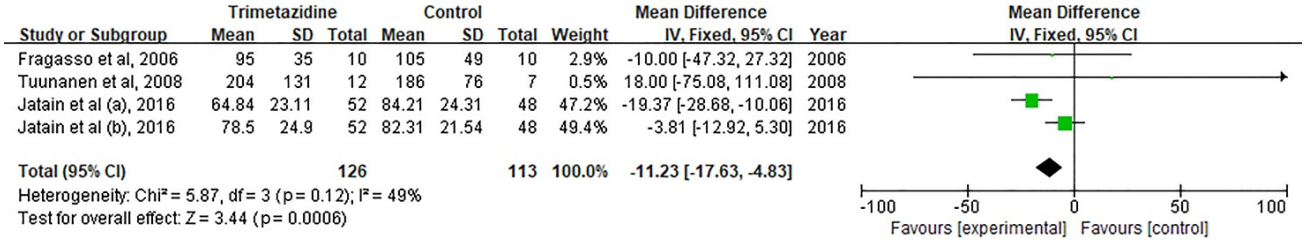

Fig. 8. Forest plot for LVESV. Forest plot depicting the LVESV difference of trimetazidine on non-ischemic HF vs. control. The size of the square corresponding to each study is proportional to the sample size.

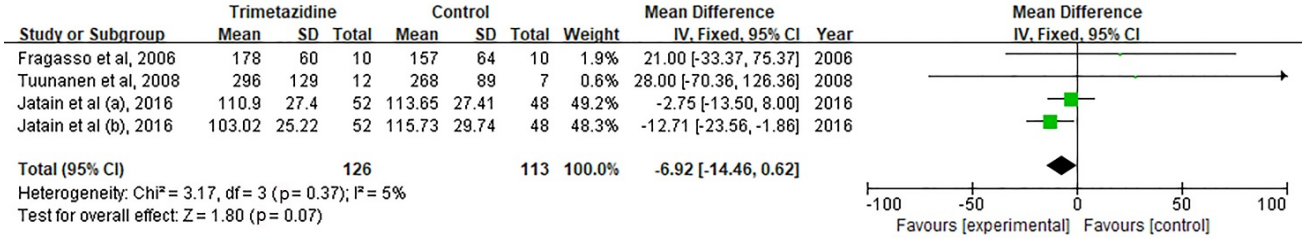

Fig. 9. Forest plot for LVEDV. Forest plot depicting the LVEDV difference of trimetazidine on non-ischemic HF vs. control. The size of the square corresponding to each study is proportional to the sample size.

This study suggested that trimetazidine increased LVEF value in the follow-up period, especially in six months, while LVESV and LVEDV were reduced. Another meta-analysis published previously demonstrated that trimetazidine improved LVEF (WMD 8.72%; 95% CI 5.51 to 11.92; $p < 0.01$) and increased exercise duration (WMD 30.26 s; 95% CI 8.77 to 51.75; $p < 0.01$) in HF [12]. Hence, it is reasonable to believe that trimetazidine protects cardiac function, which is associated with exercise endurance improvement.

Of note, trimetazidine may not exert exercise improvement beyond the cardiac effect. It is demonstrated to improve skeletal muscle strength, enhance expression of slow myosin heavy chain isoform, and increase the number of small-sized myofibers in mice [35]. Due to the mechanism mentioned above, trimetazidine was added to the World Anti-Doping Agency prohibited list on January 1st, 2014 [36–38].

Studies included in this meta-analysis reported adverse events with trimetazidine, including chest pain, palpitations, syncope, and noncardiac disorders. In terms of insufficient evidence, this meta-analysis failed to reveal the association between trimetazidine and mortality. Another meta-analysis published in 2011 indicated that trimetazidine lowered the mortality in patients with HF (RR 0.29; 95% CI 0.17 to 0.49; $p < 0.01$), although controversy existed due to the limited

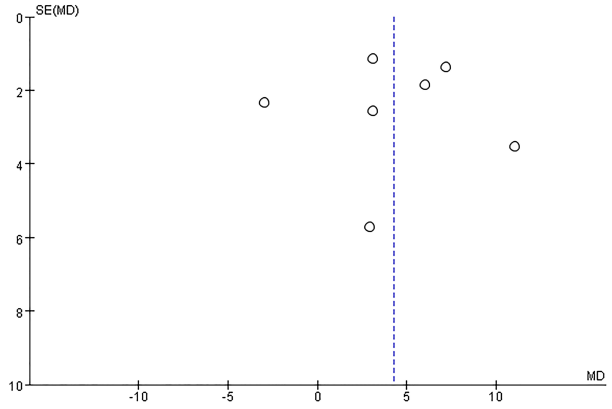

Fig. 10. The publication bias. The symmetrical funnel plot indicated no publication bias.

number of participants [12]. Furthermore, a systemic review summarized several case reports and observational studies that pointed out that trimetazidine might induce Parkinsonism while trials found no such incident [13, 39, 40].

There is ample room for further investigation of trimetazidine usage in different etiology of HF. It might have a protective effect in anthracycline-induced cardiotoxicity with conservation of diastolic function [41]. A clinical trial is conducting in the meanwhile to investigate the role in HF patients with preserved ejection function [42].

There were limitations to this study. Firstly, the studies included were small-scale, single-center trials, and only six randomized clinical trials were included. Thus, the reliability of the efficacy of trimetazidine on outcomes was limited. Secondly, only two studies were described with double blind [16, 19], leading to the potential of bias existed. Thirdly, we were unable to obtain the original data of these trials, such as mortality rate, re-hospitalization rate, and cumulative adverse events rate, accounting for missed essential assessment of drug efficacy. Furthermore, subgroup analysis was only adopted in the follow-up duration when sex, age, and comorbidities were not available.

5. Conclusions

Our meta-analysis demonstrated that trimetazidine benefits non-ischemic HF patients by improving exercise endurance and cardiac function. Trimetazidine might serve as an additional therapeutic strategy for patients with non-ischemic HF, and further progress are needed in determining the role of trimetazidine in various type of HF.

Author contributions

Conceived and designed the experiment—CZ and MX. Data curation—CJ and CZ. Formal analysis and data curation—CZ and XH. Writing, review and editing—CZ, CJ, XH and MX. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at https://rcm.imrpress.com/EN/10.31083/j.rcm2204149.

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