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Original Article

Combination of trimetazidine and coenzyme Q10 for the treatment of acute viral myocarditis: a systematic review and meta-analysis

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Abstract

Introduction: Coenzyme Q10 (CoQ10) is considered to be beneficial for patients with acute viral myocarditis (AVM). In addition, trimetazidine may be also beneficial to patients with AVM by promoting cardiac energy metabolism. This systematic review and meta-analysis examined the efficacy and safety of combining trimetazidine and CoQ10 with respect to CoQ10 alone in patients suffering from AVM.

Methodology: PubMed, Embase, the Cochrane Library, Wanfang, and China National Knowledge Infrastructure (CNKI) databases were searched for relevant randomized controlled trials (RCTs). An analysis of random effects was employed to combine the results.

Results: Sixteen RCTs that included 1,364 patients with AVM contributed to the meta-analysis. Overall, 687 patients received the combined treatment, while 677 received the CoQ10 alone for a duration of 2-12 weeks (mean: 5.2 weeks). In contrast to monotherapy with CoQ10, combined treatment with trimetazidine and CoQ10 significantly improved overall therapy effectiveness (risk ratio [RR]: 1.19, 95% confidence interval [CI]: 1.13 to 1.24, $p < 0.001$; $I^2 = 0\%$). Differences in study parameters such as the incidence of heart failure upon admission, dosage of CoQ10, or length of treatment did not significantly alter the outcomes (p for all subgroup analyses > 0.05). The combined treatment was associated with improved myocardial enzyme levels and recovery of cardiac systolic function as compared to CoQ10 alone (p all < 0.05). In addition, trimetazidine combined with CoQ10 caused no greater increase in adverse events than CoQ10 alone.

Conclusions: Trimetazidine combined with CoQ10 is an effective and safe treatment for AVM.

Key words: myocarditis; coenzyme Q10; trimetazidine; efficacy; meta-analysis.

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Introduction

Acute viral myocarditis (AVM) refers to a type of myocarditis that is characterized by viral infection-related myocardial interstitial inflammation and cardiomyocyte injury [1,2]. Viruses such as the Coxsackie virus, adenoviruses, and influenza viruses are common pathogens causing AVM in humans [3,4]. The clinical manifestations of patients with AVM may vary significantly depending on the severity of the disease. Mild to moderate symptoms include palpitations and chest tightness; and severe presentations include heart failure (HF), malignant arrhythmia, and even cardiogenic shock [3]. Currently, the main treatments for patients with AVM include the use of antiviral medications, inflammation control, improvement of myocardial energy metabolism, and possibly immunomodulation [5]. However, the clinical outcome of some patients with AVM remains poor despite the above treatments [5,6]. Therefore, continuous efforts are still needed to develop effective treatment strategies in patients with AVM.

Coenzyme Q10 (CoQ10) plays an essential role in human metabolism by facilitating electron transfer and adenosine triphosphate production in the mitochondria [7]. As evidence grows that CoQ10 plays an important role in various cardiovascular disorders, CoQ10 supplementation has been proposed as an effective adjunctive treatment for these disorders, including myocardial infarction, HF, and AVM [8,9]. Trimetazidine is an anti-anginal agent that switches the myocardial biogenesis from fatty acid oxidation to glucose oxidation [10]. Accumulating evidence suggests that many other mechanisms are involved in the cardiovascular benefits of trimetazidine [11]. Accordingly, trimetazidine has also been proposed as a potentially effective treatment for AVM [12]. However, even if both trimetazidine and CoQ10 improve the mitochondrial biogenesis of the heart, it remains to be confirmed if trimetazidine and CoQ10 can be combined

to achieve superior treatment efficacy over CoQ10 alone in patients suffering from AVM. Thus, we conducted a systematic review and meta-analysis to better understand the treatment of patients with AVM using trimetazidine and CoQ10.

Methodology

This study was designed and implemented according to Cochrane Handbook guidelines [13] and the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [14,15].

Search strategy

A combination of strategies was used to search CENTER (Cochrane Library), Medline (PubMed), Embase (Ovid), China National Knowledge Infrastructure (CNKI), and Wanfang databases for relevant studies with the following key words: (1) "trimetazidine" OR "vastarel" OR "metacard" OR "idaptan"; (2) "myocarditis"; and (3) "randomized" OR "randomised" OR "random" OR "randomly" OR "placebo" OR "RCT". Relevant studies were limited to those that included human subjects. We did not limit the outcome of the studies in the search strategy to avoid missing potentially relevant records. We also searched for references to reviews and original articles related to the topic manually. Database searches were conducted on December 26, 2022.

Study selection

Studies with the following criteria were included: (1) full-length English or Chinese articles; (2) RCTs with parallel groups; (3) patients with AVM were randomly assigned to a trimetazidine and CoQ10-combination treatment group or to a CoQ10-only control group; and (4) one or more of the selected efficacy outcomes were reported. The efficacy rate served as the main outcome indicator. The following were the key reference standards: (1) markedly effective: symptoms improved or disappeared, cardiac troponin markers (cardiovascular injury markers) returned to normal; (2) effective: there was some improvement in clinical symptoms, but myocardial injury markers did not return to completely normal; and (3) invalid: no improvement in clinical symptoms was noted, and myocardial injury markers also did not improve. In general, the effectiveness rate was equal to n (the number of cases noted as highly effective and effective) / N (the total number of cases) × 100%. Among the secondary outcomes were: (1) biomarkers of myocardial injury: creatine kinase (CK), creatine kinase-MB (CK-MB), lactate dehydrogenase (LDH), and cardiac troponin I (cTnI); (2) left ventricular ejection fraction (LVEF) measured on echocardiograms to assess cardiac systolic function; and (3) and adverse events (AEs) related to the treatment. Non-randomized studies, studies including patients not with AVM, studies not in patients treated with trimetazidine or CoQ10, or studies that failed to report the outcome of interest were excluded. Grey literature such as conference abstracts or unpublished data were not included because these are generally not peer-reviewed, and incorporating these studies could affect the reliability of the findings.

Data extraction and quality assessment

Data extraction, data mining, and quality evaluation were handled by two independent authors. If disagreements arose, the corresponding author was consulted. Information regarding publication detail, study design (blinded or open-label), patient characteristics (demographic information, presentation with heart failure, and LVEF at baseline), intervention (dosages and durations of combined treatment, regimens of controls), and outcomes reported were extracted. We evaluated the quality of the study using Cochrane's Risk of Bias Tool [13] in accordance with the following criteria: (1) random generation of sequences; (2) concealing allocations; (3) blinding of participants and staff; (4) blinding outcome assessors; (5) presenting incomplete outcome data; (6) reporting selective results; and (7) other potential bias.

Statistical analysis

The influences of combined therapy on the proportions of patients who achieved the overall effectiveness rate were presented as risk ratios (RRs) and corresponding 95% confidence intervals (CIs). Changes in the myocardial injury markers and LVEF after treatment were summarized as mean differences (MDs) and corresponding 95% CIs. Besides, the influences of the combined therapy on the risks of common adverse events were also summarized as RRs and 95% CIs. We used Cochrane's Q test for the detection of heterogeneity [16]. A statistical analysis of heterogeneity was also conducted using the I^2, and an I^2 > 50% confirmed significant heterogeneity [17]. A random effect model was used in the pooled analyses to account for potential heterogeneity and provide a more general conclusion [13]. We conducted a sensitivity analysis to assess whether each study contributed to the pooled meta-analysis results irrespective of whether it was included or excluded [13]. A subgroup analysis was also conducted if more than ten datasets were

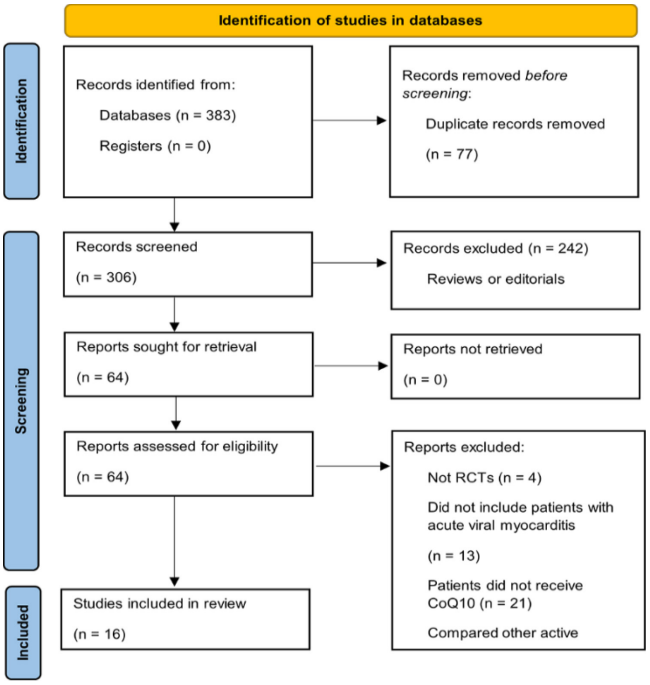
available, to assess the influence of defined study characteristics on the outcome, including the presentation with HF, dose of CoQ10, and treatment duration. An analysis of funnel plots and Egger's regression asymmetry test was conducted when at least ten studies were included in order to determine publication bias [18]. Statistically significant differences were determined at $p < 0.05$. The software Stata (version 12.0; Stata Corporation) and RevMan (version 5.1; Cochrane, Oxford, UK) were used.

Results

Search results

A diagram showing how we searched databases and identified studies is shown in Figure 1. A total of 383 articles were obtained by searching the database and 306 were identified after excluding duplicates. Out of these, 242 were subsequently excluded based on the title and abstract mainly because their objectives were irrelevant. Forty-eight articles were further excluded after full-text review due to the reasons illustrated in Figure 1. The final analysis included 16 RCTs [19-34].

Figure 1. Flowchart of literature search.



RCT: Randomized control trial.

Table 1. Characteristics of the included randomized control trials (RCTs).

Study	Country	Design	No. of patients	Age (years)	Men (%)	Baseline LVEF (%)	HF at admission	Intervention (TiD)	Control (Tid)	Treatment duration (weeks)	Outcomes reported
Zhao *et al* [19]	China	R, SB	64	Mean: 27.3	43.8	NR	None	TMZ 20 mg +CoQ10 20 mg	CoQ10 20 mg	12	1, 7
Wang *et al* [20]	China	R, SB	52	Range: 12~45	46.2	NR	NR	TMZ 20 mg +CoQ10 10 mg	CoQ10 10 mg	12	1
Hu *et al* [21]	China	R	86	Mean: 24.8	47.7	NR	NR	TMZ 20 mg +CoQ10 10 mg	CoQ10 10 mg	6	1, 5
Mu *et al* [22]	China	R	66	Mean: 26.2	45.5	NR	None	TMZ 20 mg +CoQ10 20 mg	CoQ10 20 mg	8	1
Fang *et al* [23]	China	R	48	Mean: 25.2	56.3	37.5	All	TMZ 20 mg +CoQ10 20 mg	CoQ10 20 mg	4	1, 6, 7
Zhang [24]	China	R	50	Mean: 27.1	54	36.4	All	TMZ 20 mg +CoQ10 20 mg	CoQ10 20 mg	8	1, 6, 7
Zhou [25]	China	R	64	Mean: 26.5	70.3	NR	None	TMZ 20 mg +CoQ10 20 mg	CoQ10 20 mg	4	1, 5
Yue *et al* [28]	China	R	65	Mean: 26.5	58.5	NR	NR	TMZ 20 mg +CoQ10 20 mg	CoQ10 20 mg	4	1
Yang [27]	China	R	80	Mean: 26.3	46.3	NR	None	TMZ 20 mg +CoQ10 20 mg	CoQ10 20 mg	6	1
Wang *et al* [26]	China	R	50	Mean: 26.5	50	NR	None	TMZ 20 mg +CoQ10 20 mg	CoQ10 20 mg	4	1
Zhu [30]	China	R	96	Mean: 42.9	57.3	NR	NR	TMZ 20 mg +CoQ10 20 mg	CoQ10 20 mg	4	1
Shen [29]	China	R	42	Range: 14~41	52.4	NR	NR	TMZ 20 mg +CoQ10 20 mg	CoQ10 20 mg	2	1
Liang *et al* [31]	China	R, SB	85	Mean: 23.5	52.9	46.5	NR	TMZ 20 mg +CoQ10 10 mg	CoQ10 10 mg	2	2, 4 6
Sun [32]	China	R	114	Mean: 67.9	56.1	36.5	NR	TMZ 20 mg +CoQ10 20 mg	CoQ10 20 mg	6	1, 2, 3, 6
Wang [33]	China	R	312	Mean: 31.3	48.7	NR	NR	TMZ 20 mg +CoQ10 20 mg	CoQ10 20 mg	4	1, 2, 3, 4
Zhao [34]	China	R	90	Mean: 31.1	54.4	NR	None	TMZ 20 mg +CoQ10 20 mg	CoQ10 20 mg	4	1, 2, 3, 4

Outcomes reported: 1, Effectiveness rate; 2, CK; 3, CK-MB; 4, LDH; 5, cTnI reduced to normal; 6, LVEF; 7, AE: GI discomfort. LVEF, left ventricular ejection fraction; HF, heart failure; R, randomized; SB, single-blind; NR, not reported; TMZ, trimetazidine; CoQ10, coenzyme Q10; , three times per day; CK, creatine kinase; CK-MB, creatine kinase isoenzyme MB; LDH, lactate dehydrogenase; cTnI, cardiac troponin I; AE, adverse events; GI, gastrointestinal.

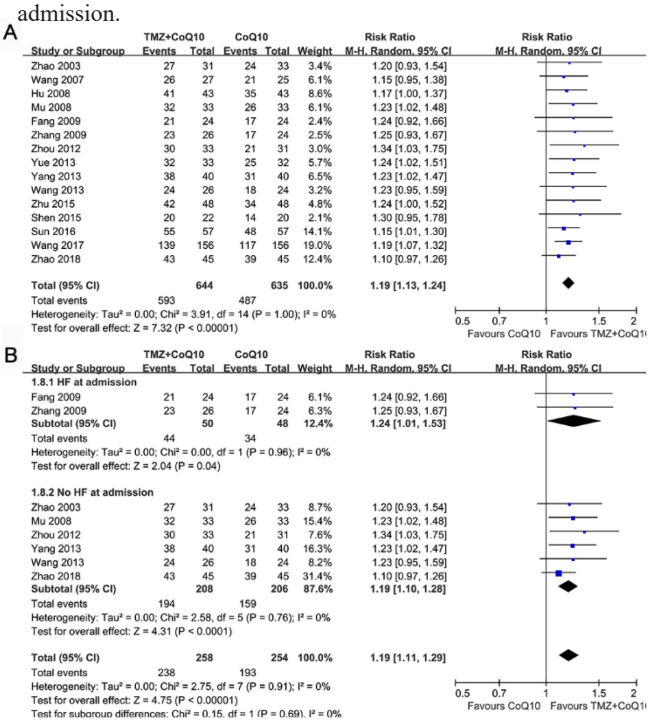
Study characteristics and data quality

An overview of the included studies is presented in Table 1. Overall, 16 RCTs [19-34] including 1,364 patients with AVM contributed to the meta-analysis. These studies were all performed in China and published between 2003 and 2018. The age of the patients, ranged between 23 and 68 years, and most of the patients were males (43-71%). Six of the included studies enrolled AVM patients without HF at admission [19,22,25-27,34], while two studies included AVM patients with HF [23,24]. Overall, 687 patients received the combined treatment, and 677 received CoQ10 alone. The dose of trimetazidine was 20 mg 3 times per day for all the studies, and the dose of CoQ10 was 10 mg 3 times per day in 3 studies [20,21,31] and 20 mg 3 times per day in the remaining 13 studies [19,22-30,32-34]. Treatment duration was between 2 and 12 weeks (mean: 5.2 weeks). As shown in Table 2, each RCT included in the review was assessed with Cochrane's Risk of Bias Tool. Three of the included studies were single-blind. [19,20,31]. Three studies [26,32,34] described how random sequences are generated, but none described how allocation concealment was achieved.

Efficacy outcomes

Pooled results of 15 RCTs [19-30,32-34] showed that compared to patients receiving CoQ10 alone, the combination of trimetazidine and CoQ10 was associated with significantly improved overall effectiveness (RR: 1.19, 95% CI: 1.13 to 1.24, $p < 0.001$; Figure 2A) without significant heterogeneity ($I^2 = 0\%$). Consistent results were shown by excluding one study at a time in sensitivity analyses (data not shown). Additionally, subgroup analyses revealed that study characteristics, including HF morbidity at admission (Figure 2B), dose of CoQ10 (Figure 3A), or treatment durations (Figure 3B), were not significantly correlated with the results (p for all subgroup analyses > 0.05).

Figure 2. Forest plots for the meta-analysis of the overall effectiveness rate of the combined trimetazidine and CoQ10 for patients with AVM; A, results of the overall meta-analysis; and B, subgroup analysis according to the presentation with HF at admission.

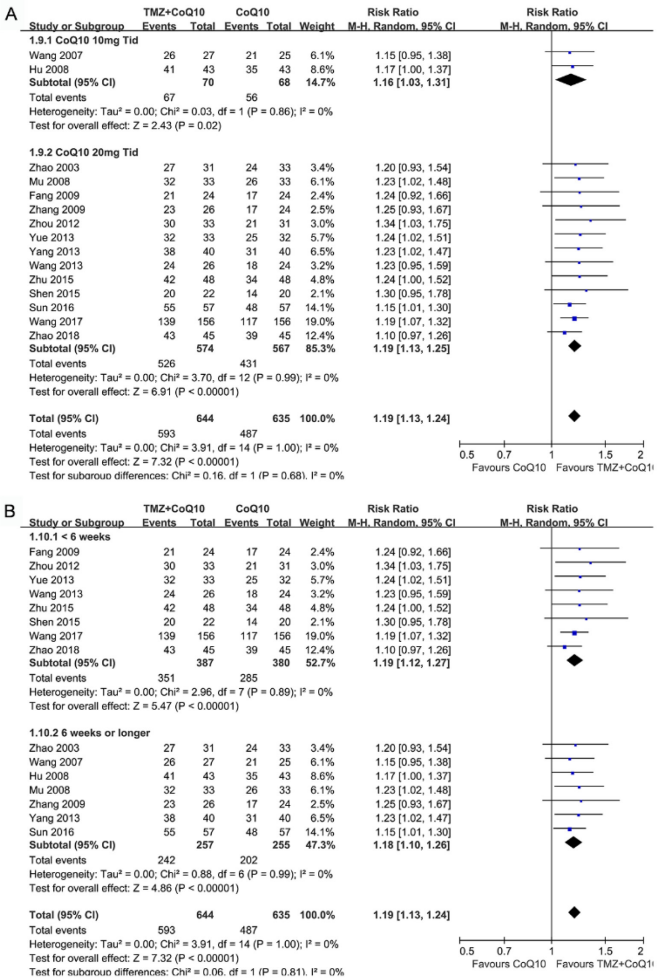


CI: confidence interval; HF, heart failure; M-H, Mantel-Haenszel; TMZ, trimetazidine; CoQ10, coenzyme Q10.

Table 2. Details of study quality evaluation with Cochrane's Risk of Bias Tool.

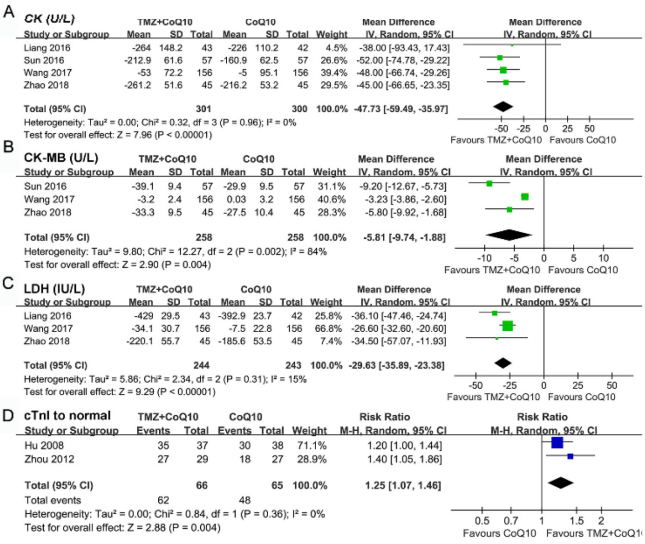
	Random sequence generation	Allocation concealment	Blinding in performance	Blinding in outcome detection	Incomplete outcome data	Reporting bias	Other bias
Zhao *et al* [19]	Unknown	Unknown	Low	High	Low	Low	Low
Wang *et al* [20]	Unknown	Unknown	Low	High	Low	Low	Low
Hu *et al* [21]	Unknown	Unknown	High	High	Low	Low	Low
Mu *et al* [22]	Unknown	Unknown	High	High	Low	Low	Low
Fang *et al* [23]	Unknown	Unknown	High	High	Low	Low	Low
Zhang [24]	Unknown	Unknown	High	High	Low	Low	Low
Zhou [25]	Unknown	Unknown	High	High	Low	Low	Low
Yue *et al* [28]	Unknown	Unknown	High	High	Low	Low	Low
Yang [27]	Unknown	Unknown	High	High	Low	Low	Low
Wang *et al* [26]	Low	Unknown	High	High	Low	Low	Low
Zhu [30]	Unknown	Unknown	High	High	Low	Low	Low
Shen [29]	Unknown	Unknown	High	High	Low	Low	Low
Liang *et al* [31]	Unknown	Unknown	Low	High	Low	Low	Low
Sun [32]	Low	Unknown	High	High	Low	Low	Low
Wang [33]	Unknown	Unknown	High	High	Low	Low	Low
Zhao [34]	Low	Unknown	High	High	Low	Low	Low

Figure 3. Forest plots for the subgroup analyses of the overall effectiveness rate of the combined trimetazidine and CoQ10 for patients with AVM; Subgroup analysis according to the dose of CoQ10 (A) or to treatment duration (B).



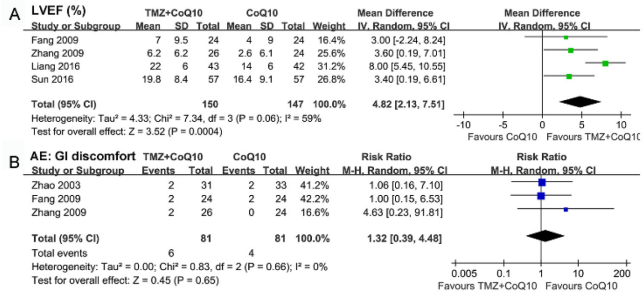
CoQ10, coenzyme Q10; AVM, acute viral myocarditis

Figure 4. Forest plots for the meta-analyses of the combined trimetazidine and CoQ10 on myocardial injury markers in patients with AVM; CK alterations after treatment (A), CK-MB changes after treatment (B), LDH changes after treatment (C) and rate of cTnI reduced to normal level after treatment (D).



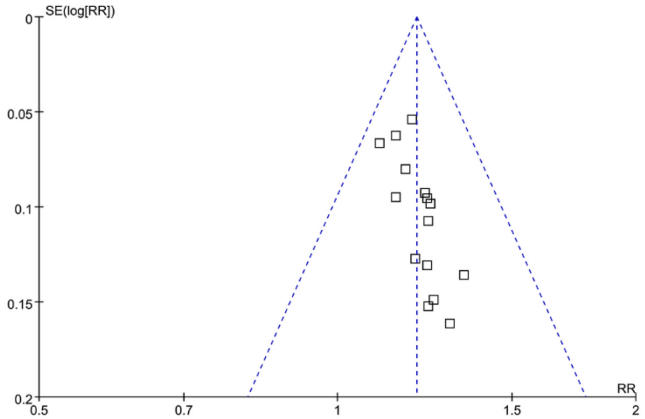
CoQ10, coenzyme Q10; AVM, acute viral myocarditis; CK, creatine

Figure 5. Forest plots for the meta-analysis of the effect of the combined trimetazidine and CoQ10 on LVEF and incidence of drug-related AEs in patients with AVM; Changes of LVEF after treatment (A) and B incidence of drug-related AEs (B).



CoQ10, coenzyme Q10; AVM, acute viral myocarditis; LVEF, left ventricular ejection fraction; AE, adverse events

Figure 6. Funnel plots for the publication biases underlying the meta-analysis of the overall effectiveness rate of the combined trimetazidine and CoQ10 for patients with AVM.



CoQ10, coenzyme Q10; AVM, acute viral myocarditis.

Further meta-analyses showed that the combined treatment was associated with reduced myocardial enzyme levels, including CK (MD: -47.73 U/L, 95% CI: -59.49 to -35.97, $p < 0.001$, $I^2 = 0\%$; Figure 4A), CK-MB (MD: -5.81 U/L, 95% CI: -9.74 to -1.88, $p = 0.004$, $I^2 = 84\%$; Figure 4B), LDH (MD: -29.63 IU/L, 95% CI: -35.89 to -23.38, $p < 0.001$, $I^2 = 15\%$; Figure 4C), and an improved rate of patients with cardiac troponin I (cTnI) reduced to normal level (RR: 1.25, 95% CI: 1.07 to 1.46, $p = 0.004$, $I^2 = 0\%$; Figure 4D). Besides, combined treatment with trimetazidine and CoQ10 also significantly improved the recovery of LVEF as compared to the treatment with CoQ10 alone (MD: 4.82%, 95% CI: 2.13 to 7.51, $p < 0.001$, $I^2 = 59\%$; Figure 5A).

Safety outcome

In most of the included studies, no drug-related AEs were reported for patients allocated to either of the treatment groups. Mild gastrointestinal (GI) discomfort which did not require further treatment was reported in three studies [19,23,24], and the incidence was not significantly different between patients of different treatments (RR: 1.32, 95% CI: 0.39 to 4.48, $p = 0.65$, $I^2 = 0\%$; Figure 5B).

Publication bias

The funnel plots for the meta-analyses of the effect of trimetazidine compared with CoQ10 on the overall effectiveness rate in patients with AVM were symmetrical, suggesting a low risk of publication biases (Figure 6). Egger's regression tests also suggested low risks of publication biases ($p = 0.83$). Meta-analyses of other outcomes did not provide adequate estimates of publication bias due to the limited number of studies included in the analysis.

Discussion

This systematic review and meta-analysis showed that combined treatment with trimetazidine and CoQ10 significantly improved the overall effectiveness rate as compared to CoQ10 alone in patients with AVM. Also, the combined treatment was associated with reduced serum levels of myocardial enzymes and a preserved LVEF after treatment, suggesting that combined treatment with trimetazidine and CoQ10 was more effective than CoQ10 alone in reducing myocardial injury and attenuating related cardiac dysfunction. Finally, the combined treatment was well tolerated by the patients. Only a few patients with mild GI discomfort were reported, and the incidence of these AEs was not significantly different between groups. Taken together, the results of the meta-analysis suggest that combined trimetazidine and CoQ10 is associated with reduced myocardial injury, preserved cardiac function, and improved clinical efficacy than CoQ10 alone in patients with AVM. Although these findings should be validated in large-scale high-quality RCTs in the future, a combined treatment with trimetazidine and CoQ10 should be considered for patients with AVM.

To the best of our knowledge, this is the first systematic review and meta-analysis comparing the efficacy and safety of the combined trimetazidine and CoQ10 with CoQ10 alone in patients with AVM. The strengths of our meta-analysis include the extensive literature search to retrieve all eligible studies, comprehensive investigation of multiple efficacy outcomes and incidence of drug-related AEs, and the series of sensitivity and subgroup analyses to indicate the stability of the findings. In this study, we chose the overall effective rate as the primary outcome of the meta-analysis because this is a practical indicator for the therapeutic efficacy based on both the clinical symptoms and the levels of myocardial biomarkers, and has been well-applied in previous clinical trials and meta-analyses evaluating the pharmacotherapy for AVM [12,35]. In addition, subgroup analyses showed that the combined therapy with trimetazidine and CoQ10 was associated with improved overall effectiveness rate than CoQ10 alone in patients with AVM, with or without HF at presentation, in studies with 10 or 20 mg 3 times per dayd CoQ10, and in studies with treatment durations $<$ or ≥ 6 weeks, which further suggested the robustness of the findings. These results are consistent with the previous studies which showed that additional trimetazidine could improve the clinical symptoms and preserve cardiac function in patients with HF [36]. Besides, it has been observed that combined trimetazidine and CoQ10 were more effective than either of the agents alone for reducing cisplatin-induced cardiotoxicity [37] and contrast-induced nephropathy (CIN) [38], probably due to the strong anti-oxidation effect of the combined treatment.

There are also some limitations in this study. First and foremost, all the RCTs were conducted in China. Further studies in other countries are required to demonstrate consistent benefits of the combined treatment. In addition, there was a lack of high-quality RCTs and sample sizes were small in the included studies. There is a need to validate the results of the meta-analysis in large-scale randomized controlled trials in the future. Moreover, arrhythmia is an early adverse event in patients with AVM, which may adversely influence the prognosis of the patients.

However, none of the included studies evaluated the combined effects on incidence of arrhythmia in patients with AVM. Studies are needed in the future for further investigation. Also, the follow-up lengths were relatively short. The long-term efficacy of the combined treatment with trimetazidine and CoQ10 for patients with AVM remains to be investigated. In the future, the effects of the combined treatment on clinical outcomes should also be evaluated, including rehospitalization risks and long-term mortality rates in patients with AVM.

Conclusions

This systematic review and meta-analysis proposed for the first time that a combined treatment with trimetazidine and CoQ10 is associated with improved symptoms, reduced myocardial injury, and preserved cardiac systolic function as compared to CoQ10 alone for patients with AVM. Although the long-term influence of the combined therapy on clinical outcomes of patients with AVM should be further determined, a combined treatment with trimetazidine and CoQ10 should be considered for patients with AVM.

Authors' contributions

Min Zeng and Yusheng Pang designed the study. Min Zeng and Zhi Chen performed database search, literature review, data collection, and quality evaluation. Min Zeng and Yan Zhang performed statistical analyses and interpreted the results. Min Zeng drafted the manuscript and all authors critically revised the manuscript. All authors approved the submission of the manuscript.

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