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Effect of trimetazidine on incidence of major adverse cardiac events in coronary artery disease patients undergoing percutaneous coronary intervention

A protocol for systematic review and meta-analysis

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Abstract

Background: Percutaneous coronary intervention (PCI) is a common treatment method for coronary artery disease (CAD). PCI can cause myocardial ischemia or injury, and lead to major adverse cardiac events (MACEs). Trimetazidine has significant cardioprotective effects and improves endothelial dysfunction and myocardial injury. We will conduct a comprehensive systematic review and meta-analysis to evaluate effect of trimetazidine on incidence of MACE in CAD patients undergoing PCI.

Methods: PubMed, Embase, Web of Science, Cochrane Library, the China National Knowledge Infrastructure, Chinese Biomedical Literature Database, and China Science and Technology Journal Database will be searched to collect randomized controlled trials (RCTs) of trimetazidine for CAD patients undergoing PCI. The range of publication time will be from the inception of the database to October 2020 without language limitation. Two reviewers will independently conduct study selection, data extraction and management, and assessment of risk of bias. Any disagreement will be resolved by discussion with the third reviewer. Review Manager Software 5.3 will be used for meta-analysis. The Cochrane risk of bias tool will be used to assess the risk of bias.

Results: This study will provide a systematic synthesis of current published data to summarize the effect of trimetazidine on incidence of MACE such as stent restenosis, stent thrombosis, new significant coronary stenosis, myocardial infarction, heart failure, and cardiac arrest in CAD patients undergoing PCI.

Conclusions: This meta-analysis will provide evidence as to whether trimetazidine can reduce incidence of MACE in CAD patients undergoing PCI.

Study registration number: INPLASY202090083.

Abbreviations: CAD = coronary artery disease, PCI = percutaneous coronary intervention, MACE = major adverse cardiac events, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RCTs = randomized controlled trials.

Keywords: trimetazidine, major adverse cardiac event, coronary artery disease, percutaneous coronary intervention, protocol, systematic review

1. Introduction

With the rapid economic development, changes in lifestyles, and adoption of unhealthy diet, coronary artery disease (CAD) has become a major problem worldwide and the leading global cause of mortality in recent years.[1–3] Percutaneous coronary intervention (PCI) is a primary and common treatment method for CAD.[4] PCI can dilate stenotic or obstructed coronary artery, relieve clinical symptoms, and decrease mortality from CAD.[5,6] However, PCI may induce coronary spasm, endothelial cell injury, and coronary artery distal embolization, which causes myocardial ischemia or injury.[7–9] Major adverse cardiac events (MACEs) such as stent restenosis, stent thrombosis, new significant coronary stenosis, myocardial infarction, heart failure, and cardiac arrest are the main causes of mortality in CAD patients undergoing PCI.[10,11] Obviously, it is of great significance to prevent the occurrence of MACE following PCI.

Trimetazidine is an anti-ischemic agent that exerts its cardioprotective effects by shifting cardiac energy metabolism from fatty acid oxidation to glucose oxidation, and reducing intracellular accumulation of hydrogen ions, lactate, sodium ions

and calcium ions.[12–14] One study showed that trimetazidine treatment could prevent the increase in creatine kinase-MB, cardiac troponin I, and von Willebrand factor and the decrease in nitric oxide induced by PCI, and improve endothelial dysfunction and myocardial injury.[15] A meta-analysis showed that additional use of trimetazidine significantly improved the left ventricular ejection fraction and reduced elevated cardiac troponin I level and angina attacks during PCI.[16]

While up to now, no systematic review and meta-analysis has been performed on the effect of trimetazidine on incidence of MACE in CAD patients undergoing PCI. In view of this, we will conduct a comprehensive systematic review and meta-analysis to evaluate effect of trimetazidine for CAD patients undergoing PCI.

2. Methods

2.1. Study registration

This study has been registered on INPLASY (INPLASY202090083). This meta-analysis will be performed according the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement checklist.[17]

2.2. Eligibility criteria for study selection

2.2.1. Types of studies. All randomized controlled trials (RCTs) of trimetazidine for CAD patients undergoing PCI will be considered for inclusion without language limitation. Case reports, non-RCTs, animal experiments, reviews, and repeatedly published studies will be excluded.

2.2.2. Types of participants. Participants who suffer from CAD and receive PCI treatment will be included without restrictions of the nationality, age, gender, and race.

2.2.3. Types of interventions. In the treatment group, patients were given trimetazidine with no limitations of administration routes, dosage, or duration of intervention.

RCTs that have control groups with conventional treatments (such as drug therapy and physical therapy), or no treatment will be included.

2.2.4. Types of outcomes. The incidence of MACE (such as stent restenosis, stent thrombosis, new significant coronary stenosis, myocardial infarction, heart failure, and cardiac arrest) will be designated as the outcomes.

2.3. Search strategy

PubMed, Embase, Web of Science, Cochrane Library, the China National Knowledge Infrastructure, Chinese Biomedical Literature Database, and China Science and Technology Journal Database will be searched to collect RCTs of trimetazidine for CAD patients undergoing PCI. The range of publication time will be from the inception of the database to October 2020 without language limitation. The detailed search strategy of PubMed is summarized in Table 1. The similar search strategies will be used for other electronic databases.

2.4. Selection of studies

All the searched articles will be exported to EndNote 7.0 (Thomas Reuters, CA) and duplicates will be excluded by software. Two reviewers will independently scan titles and abstracts to eliminate all irrelevant records. Then, the remaining

Table 1

Search strategy of PubMed.

Number	Search terms
1	coronary artery disease
2	coronary heart disease
3	coronary atherosclerotic heart disease
4	coronary disease
5	angina pectoris
6	Or 1–5
7	percutaneous coronary intervention
8	endovascular procedures
9	Angioplasty
10	Atherectomy
11	Revascularization
12	Or 7–11
13	major adverse cardiac event
14	stent restenosis
15	stent thrombosis
16	new significant coronary stenosis
17	myocardial infarction
18	heart failure
19	cardiac arrest
20	Or 13–19
21	Trimetazidine
22	Vastarel
23	trimetazidine dihydrochloride
24	Or 21–23
25	Randomized controlled trial
26	Clinical trial
27	Random
28	Randomized
29	Randomly
30	Trial
31	Placebo
32	Or 25–31
33	6 and 12 and 20 and 24 and 32

records will be read by full texts in further assessing the inclusion of the study. Any disagreement about the selection of studies will be resolved by discussion with the third reviewer. A PRISMA flowchart will be designed to describe the details of selection process.

2.5. Data extraction and management

Data extraction will be conducted by 2 reviewers independently. A standard data extraction table will be designed according to Cochrane guidelines, including first author's name, country of publication, year of publication, title of journal, study design, patient information, intervention, control, duration of intervention, and specific details about MACE (number of persons experiencing stent restenosis, stent thrombosis, new significant coronary stenosis, myocardial infarction, heart failure, or cardiac arrest). Any disagreement about the data extraction will be resolved by discussion with the third reviewer. If some important information is missing, we will contact original authors by email to request detailed information about the research.

2.6. Assessment of risk of bias

Two reviewers will independently assess the risk of bias using the Cochrane risk of bias assessment tool. Seven items will be assessed, including random sequence generation, allocation concealment,

blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. A bias value of "high," "unclear," or "low" was evaluated for each item. Any disagreement about assessment of risk of bias will be resolved by discussion with the third reviewer.

2.7. Data synthesis and analysis

2.7.1. Data synthesis. Review Manager Software 5.3 will be used for data synthesis. Risk ratio will be used for dichotomous outcomes with 95% confidence interval. The random effects model or fixed effects model will be selected according to the I^2 value. Heterogeneity will be examined using the I^2 test. The I^2 value > 50% means significant heterogeneity, and the random effects model will be used. Otherwise, the I^2 value ≤ 50% means minor heterogeneity, and the fixed effects model will be utilized. If significant heterogeneity still exists after subgroup analysis, meta-analysis will not be pooled, and descriptive summary will be reported.

2.7.2. Subgroup analysis. Subgroup analysis will be performed to check the potential heterogeneity and inconsistency based on the different participant characteristics, administration routes and dose of trimetazidine, control methods, and outcome indicators.

2.7.3. Sensitivity analysis. Sensitivity analysis will be applied to check the robustness and reliability of pooled results. We will perform meta-analysis again after eliminating studies in low quality and will apply different statistical methods.

2.7.4. Reporting bias. Publication bias will be assessed with funnel plot and Egger regression test if sufficient trials (≥10 trials) are included.[18,19]

2.8. Ethics and dissemination

Ethical approval is not necessary because this study is based on literature analysis. The results of this study will be published in a peer-reviewed journal.

3. Discussion

To our knowledge, this is the first systematic review and meta-analysis to conduct a comprehensive literature search and provide a systematic synthesis of current published data to summarize the effect of trimetazidine on incidence of MACE in CAD patients undergoing PCI. We will search 7 electronic literature databases to avoid missing any potential eligible studies, and apply rigorous methodology to examine studies reporting the MACE of trimetazidine for CAD patients undergoing PCI. We believe that this systematic review and meta-analysis will provide clinical evidence for the trimetazidine treatment of CAD patients undergoing PCI, inform our understanding of the value of trimetazidine in treating CAD and reducing incidence of MACE following PCI, and provide helpful evidence for clinical practice, patients, and future research.

Author contributions

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Writing – original draft: Kun Zhu, Yu-shui Zheng.
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References

[1] Head SJ, Milojevic M, Daemen J, et al. Mortality after coronary artery bypass grafting versus percutaneous coronary intervention with stenting for coronary artery disease: a pooled analysis of individual patient data. Lancet 2018;391:939–48.

[2] Motwani M, Dey D, Berman DS, et al. Machine learning for prediction of all-cause mortality in patients with suspected coronary artery disease: a 5-year multicentre prospective registry analysis. Eur Heart J 2017;38:500–7.

[3] John J, Parikh PB, Thippeswamy G, et al. Sex-related disparities in obstructive coronary artery disease, percutaneous coronary intervention, and mortality in adults with cardiac arrest. Int J Cardiol 2018;269:23–6.

[4] Al-Lamee RK, Nowbar AN, Francis DP. Percutaneous coronary intervention for stable coronary artery disease. Heart 2019;105:11–9.

[5] Mahmoud AN, Elgendy IY, Mentias A, et al. Percutaneous coronary intervention or coronary artery bypass grafting for unprotected left main coronary artery disease. Catheter Cardiovasc Interv 2017;90:541–52.

[6] Grines CL, Harjai KJ, Schreiber TL. Percutaneous coronary intervention: 2015 in review. J Interv Cardiol 2016;29:11–26.

[7] Mehta SR, Wood DA, Storey RF, et al. Complete revascularization with multivessel PCI for myocardial infarction. N Engl J Med 2019;381:1411–21.

[8] Miyoshi T, Ejiri K, Kohno K, et al. Effect of remote ischemia or nicorandil on myocardial injury following percutaneous coronary intervention in patients with stable coronary artery disease: a randomized controlled trial. Int J Cardiol 2017;236:36–42.

[9] Goliasch G, Winter MP, Ayoub M, et al. A contemporary definition of periprocedural myocardial injury after percutaneous coronary intervention of chronic total occlusions. JACC Cardiovasc Interv 2019;12:1915–23.

[10] Aghajani H, Nezami P, Shafiee A, et al. Predictors of long-term major adverse cardiac events following percutaneous coronary intervention in the elderly. Arch Iran Med 2018;21:344–8.

[11] Guy JM, Wilson M, Schnell F, et al. Incidence of major adverse cardiac events in men wishing to continue competitive sport following percutaneous coronary intervention. Arch Cardiovasc Dis 2019;112:226–33.

[12] Kallistratos MS, Poulimenos LE, Giannitsi S, et al. Trimetazidine in the prevention of tissue ischemic conditions. Angiology 2019;70:291–8.

[13] Costa LM, Rezende PC, Garcia RM, et al. Role of trimetazidine in ischemic preconditioning in patients with symptomatic coronary artery disease. Medicine (Baltimore) 2015;94:e1161.

[14] Dézsi CA. Trimetazidine in practice: review of the clinical and experimental evidence. Am J Ther 2016;23:e871–9.

[15] Shao S, Shi Z, Tse G, et al. Effects of trimetazidine pretreatment on endothelial dysfunction and myocardial injury in unstable angina patients undergoing percutaneous coronary intervention. Cardiol Res Pract 2019;2019:4230948.

[16] Zhang Y, Ma XJ, Shi DZ. Effect of trimetazidine in patients undergoing percutaneous coronary intervention: a meta-analysis. PLoS One 2015;10:e0137775.

[17] Moher D, Liberati A, Tetzlaff J, et al. PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.

[18] Sutton AJ, Duval SJ, Tweedie RL, et al. Empirical assessment of effect of publication bias on meta-analyses. BMJ 2000;320:1574–7.

[19] Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.