Impact of Trimetazidine on Major Adverse Cardiac Events in Asian Patients with Acute Myocardial Infarction: A Systematic Review

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ABSTRACT

Aims: The review aims to assess the effect of ongoing treatment with trimetazidine on the incidence of major adverse cardiac events (MACE) in Asian patients with acute myocardial infarction (AMI).

Methodology:A systematic literature review of the journal articles evaluating the impact of trimetazidine on the incidence of MACE was performed. Two real-world studies recruiting Asian patients who were hospitalized and on trimetazidine treatment for AMI were included. Both the studies evaluated the incidence of MACE post-AMI.

Results: The KAMIR study (N=1304), with a 12-month follow-up period, reported that the risk of all-cause death was lower by 59% (incidence rate 2.3 vs 6.4%; hazard ratio 0.41, 95% CI 0.18–0.97, *P* = .042) and the risk of MACE was lower by 76% (incidence rate 2.3 vs 9.5%; hazard ratio 0.24, 95% CI 0.10–0.56, *P* = .001) in the trimetazidine group vs the non-trimetazidine group. According to the METRO study (N=353), with a 6-month follow-up period, the mean discharge-to-6-month all-cause mortality risk was predicted to be 5% as per the Global Registry of Acute Coronary Events (GRACE) prediction score card and nomogram. All 353 patients receiving antianginal drugs prior to MI had lower predicted discharge-to-6-month all-cause mortality score; however, the reduction was only significant in patients receiving trimetazidine (*P* = .022).

Conclusion: The analysis of data suggests that the use of trimetazidine as an antianginal medication does have a beneficial effect in patients with AMI: it decreases the incidence of MACE post-AMI in patients.

Keywords: acute myocardial infarction, trimetazidine, cardiovascular disease, mortality

1. INTRODUCTION

Preventing and managing the cardiovascular disease (CVD) burden in Asia has been a challenge because of the high population, different ethnicities, and cultural diversity in this continent. This issue is even more critical as CVD has emerged a leading cause of death in Asia.The American College of Cardiology/American Heart Association (ACC/AHA) recommends that CVD treatment should chiefly focus on the following aspects: (1) reduction in the symptoms of angina and occurrence of ischemia and (2) prevention of myocardial infarction (MI) or death.Nevertheless, acute myocardial infarction (AMI) remains a common cause for hospitalization of patients with CVD. Although advances in healthcare have reduced mortality from AMI in patients, the long-term clinical outcomes in patients remain elusive. Major adverse cardiac events (MACE) is a term given to post-AMI adverse events such as heart failure, re-infarction, persistent angina pain, re-hospitalization for CVD-related ailment, repeat percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), and all-cause mortality [3].The incidence of MACE depends on the health status, age, gender, race, co-morbidities of the patient, among other factors. One such important factor is the effect of ongoing treatment for angina or other cardiac ailments[3].

In routine clinical practice, many antianginal drugs with different mechanisms of action are prescribed depending on the type of angina and patient comorbidities [12-14]. However, their effectiveness in preventing subsequent MACE and mortality due to episodes like MI may vary in the real-world scenario. Presently, the effectiveness of different antianginal drugs such as β-blockers or calcium-channel antagonists (CCAs) and metabolic modulators in the real-world scenario is being evaluated in many studies [15-17]. Trimetazidine acts at the cellular level by inhibiting free fatty acid oxidation and shifting cardiac cell metabolism to glucose oxidation, thereby improving the energy metabolism in the ischemic heart [4,18-20]. Given that trimetazidine is an antianginal drug without any hemodynamic effect, it can be administered to patients with different cardiovascular comorbidities, making it an ideal option in addition to the conventional antianginal agents such as β-blockers or CCAs. Trimetazidine also corrects disturbances in myocardial cellular homeostasis resulting from acute ischemic damage, thus protecting against cardiomyocyte injury [5,6]. Trimetazidine, when regularly consumed as an antianginal medication, may also exert continued cardioprotective effect should an unfortunate AMI event occur [7].
In this review, we systematically examined the real-world evidence evaluating the impact of trimetazidine therapy on clinical outcomes (mortality, MACE) in Asian patients with AMI.

2. MATERIAL AND METHODS

To identify observational studies assessing the effectiveness, safety, and tolerability of trimetazidine in real-world settings in Asian populations, we performed a systematic literature search and developed a search string to capture different aspects of the research question in order to retrieve articles from MEDLINE/PubMed. The search string was based on three facets: trimetazidine, observational studies, and Asia. The various tenets of the search strategy are described below as per the PICOTS guidelines recommended by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The included studies recruited patients (P) with AMI who were admitted in a hospital for further management and were receiving trimetazidine at the time (treatment ongoing before the MI episode) as part of an intervention (I), with a non-restrictive comparator (C; any or none antianginal drug). The outcomes (O) of interest were incidence of MACE or all-cause death over subsequent follow-up. We used no limit for time frame (T) and included only observational studies (study type, S). We restricted the search to human studies that were published as journal articles in English language only. We excluded clinical trials, systematic literature reviews, meta-analyses, narrative reviews, case series, case studies, and editorials. We extracted relevant data on the incidence of MACE or all-cause death up to 12 months of follow-up post AMI.

3. RESULTS AND DISCUSSION

3.1 Literature search

Using the search string, 22 relevant articles were retrieved from PubMed (**Fig. 1**), of which six non-English articles were excluded. Furthermore, seven articles were excluded based on the study design and two more based on the outcomes data. Further, five studies were excluded because the patient population did not experience an episode of AMI. Thus, following the application of critical selection criteria, two most relevant observational studies were identified for the detailed analysis and review as per PRISMA guidelines.

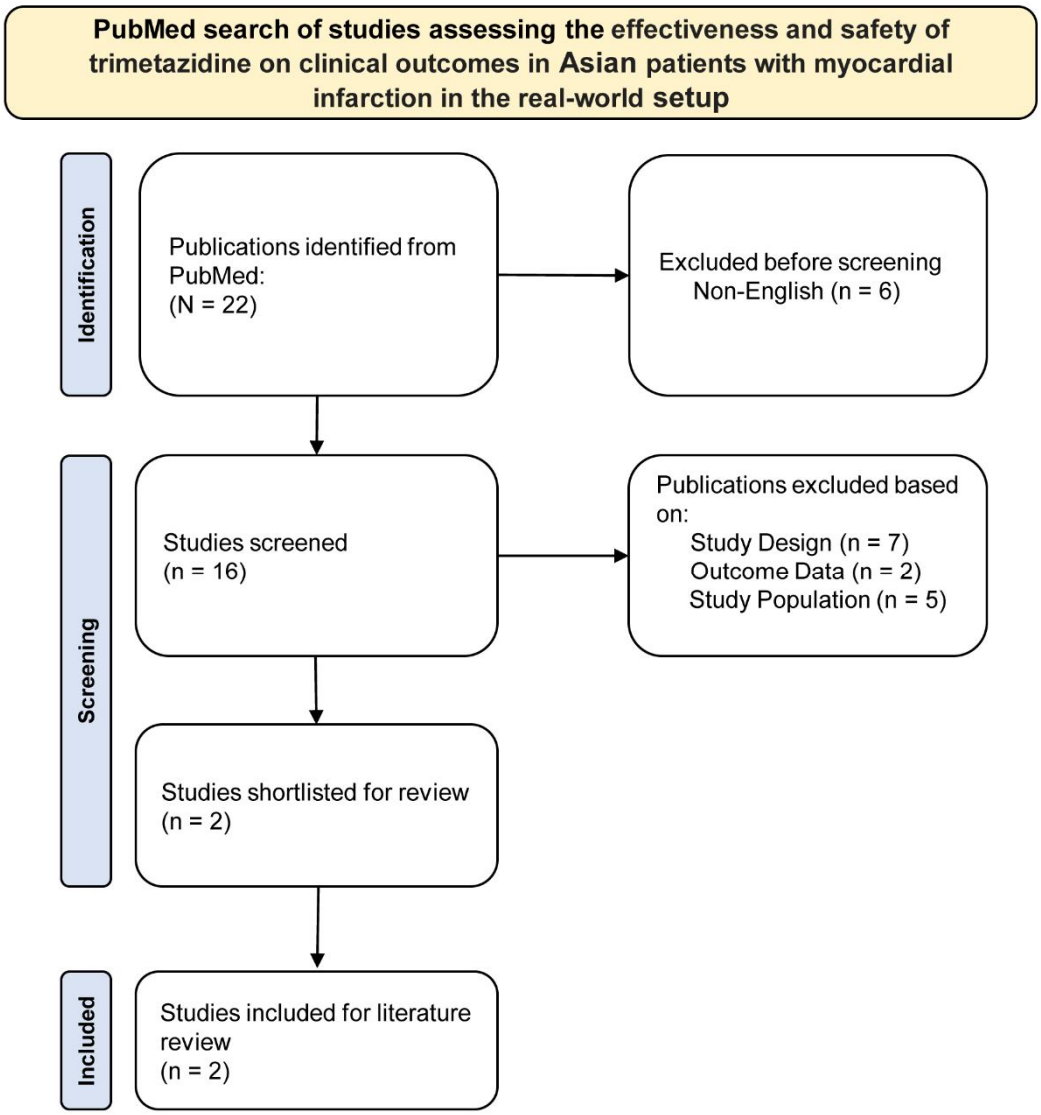

Fig. 1. PRISMA flow diagram for systematic reviews of observational studies

3.2 Study settings

A retrospective analysis was conducted in South Korea, using the data of patients registered in the Korean Acute Myocardial Infarction Registry (KAMIR) [7]. The KAMIR is a Korean multicentre prospective online registry maintained since 2005; it provides an overview of the latest status of AMI in Korea and the leading trends in demographic characteristics, risk factors, medications, treatment strategies, and clinical outcomes in patients with AMI. The data from 41 community or teaching hospitals in South Korea were analysed in this study [7]. The METRO (ManagEment of angina: a reTRospectivecOhort) study was the other observational study that assessed post-AMI outcomes in India across five centres. It

assessed the independent effect of using different antianginal drugs on subsequent mortality risk in patients surviving an episode of AMI [8].

3.3 Sample size

Of the 13,733 patients registered from 2005 to 2008 in the KAMIR study, 271 were receiving trimetazidine when hospitalized for AMI [7]. For further analysis, the authors selected a propensity-matched study population (trimetazidine and non-trimetazidine groups that were matched using baseline and clinical characteristics). For propensity score analysis, the variables matched included age, gender, CV risk factors (hypertension, diabetes mellitus, dyslipidaemia, smoking status, and family history of coronary heart disease) and co-morbidities, diagnosis (non-ST elevation MI or ST elevation MI), left ventricular ejection fraction (LVEF), creatinine level on admission, and type of implanted coronary stent. Furthermore, indications such as treatments with betablockers, statins, angiotensin-converting enzyme inhibitors, and/or angiotensin II receptor blockers, aspirin, clopidogrel, cilostazol, heparin, glycoprotein IIb/IIIa receptor blocker were recorded and matched. A total population of 1304 patients was selected (trimetazidine group, n = 261; non-trimetazidine group, n = 1043) [7].

In the KAMIR study, of the propensity-matched patients, nearly 75% were receiving β-blockers and 90% were prescribed statins and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker. More than 95% were on clopidogrel and aspirin. The other medications were cilostazol, heparin, and GP IIb/IIIa receptor blocker [7].

The METRO study included 353 patients who were admitted to the hospital after an AMI and were receiving antianginal drugs such as monotherapy or combination therapy. At the time of hospitalization, 48 (13.6%) were receiving trimetazidine, 282 (79.9%) were receiving β-adrenoceptor antagonist, 25 (7.1%) were being treated with CCAs, 198 (56.1%) were being treated with nitrates, and 77 (21.8%) were receiving nicorandil for angina [8].

3.4 Patient characteristics

In both the studies, the majority of the patients were men. The number of patients with hypertension was higher in the METRO vs the KAMIR study (80.7% vs 44.8%), whereas the number of smokers was more in the KAMIR than in the METRO study (64.4% vs 38.5%). Details of patient characteristics are presented in **Table 1**.

Table 1.Patient Characteristics in the KAMIR and the METRO studies

Patient Characteristics	**KAMIR**[*] [7]	**METRO**[†] [8]
Total patients (patients in the trimetazidine group)	1304 (261)	353 (48)
Age (y), mean ± SD	62.4 ± 12.6	55.0 ± 10.2
Male, n (%)	191 (73.2)	287 (81.3)
Hypertension, n (%)	117 (44.8)	285 (80.7)
Diabetes, n (%)	63 (24.1)	106 (30.0)
Dyslipidaemia, n (%)	16 (6.1)	56 (15.9)

Smoking, n (%)	168 (64.4)	136 (38.5)
History of MI, n (%)	13 (5.0)	30 (8.5)
Total cholesterol (mg/dL), mean ± SD	181.5 ± 42.8	229.1 ± 37.9
LDL (mg/dL), mean ± SD	113.2 ± 38.1	136.0 ± 26.3
HDL (mg/dL), mean ± SD	44.9 ± 11.2	45.4 ± 12.6
Serum creatinine (mg/dL), mean ± SD	1.08 ± 0.28	1.1 ± 0.3

** Patient characteristics for N = 261 patients*

†Patient characteristics for N = 353 patients

HDL, high-density lipoprotein; KAMIR, Korean Acute Myocardial Infarction Registry; LDL, low-density lipoprotein; METRO, METRO ManagEment of angina: a reTRospectivecOhort; MI, myocardial infarction; SD, standard deviation.

3.5 Patient outcome

In the KAMIR study, patients had a follow-up period of up to 12 months during which they recorded the all-cause death, combined in-hospital and 12-month death and MACE; MACE included all-cause death, recurrent MI, repeated percutaneous coronary intervention (PCI) for target lesion revascularization (TLR), and coronary artery bypass graft. Over the period of 12 months, the risk of all-cause death was 59% lower (incidence rate 2.3 vs 6.4%; hazard ratio (HR) 0.41, 95% CI 0.18–0.97, *P* = .042) in the trimetazidine group compared with the non-trimetazidine group. Correspondingly, the risk of MACE was lower by 76% (incidence rate 2.3 vs 9.5%; HR 0.24, 95% CI 0.10–0.56, *P* = .001) [7].

The METRO study had a follow-up of 6 months after an AMI episode [8]. In these patients (N = 353), the mean discharge-to-6-months all-cause mortality risk was predicted to be 5%. The risk was derived from the widely accepted Global Registry of Acute Coronary Events (GRACE) prediction score card and nomogram. For the GRACE risk prediction score, the METRO study analysed characteristics such as age, history of congestive heart failure, history of previous MI, resting heart rate, systolic BP, serum creatinine, elevated cardiac enzymes, etc. These factors were considered significant predictors of the 6-month post-AMI mortality risk [8].

The odds ratios (95% CI) for predicted all-cause mortality after surviving an MI, from discharge to 6 months, were derived from the validation dataset for treatment and were as follows: β-adrenoceptor antagonist, 0.63 (0.26, 1.52; *P* = .309); a calcium-channel antagonist, 0.76 (0.12, 2.89; *P* = .638); a nitrate, 0.52 (0.26, 1.05; P = .070); nicorandil, 0.62 (0.29, 1.33; *P* = .221); and trimetazidine, 0.36 (0.15, 0.86; *P* = .022). In these 353 patients, all antianginal drugs given prior to an MI reduced the predicted discharge-to-6-month all-cause mortality independent of each other. However, the reduction was only significant in patients receiving a metabolic agent (trimetazidine) (*P* = .022) [8].

4. DISCUSSION

In cardiology, trimetazidine has been used as an antianginal agent for more than 40 years. However, real-world data on its cardioprotective effects in patients with acute ischemic conditions are scarce [5]. This systematic review intended to find evidence for the effectiveness of trimetazidine in preventing MACE following an AMI.

AMI is one of the common causes for hospitalization of patients with cardiovascular ailments. During an episode of AMI, the acute ischemia and reperfusion injury (IRI) can damage the cardiomyocytes in the myocardium. The cardiac mitochondria play a dual role as the mediator of cell survival and death. Therefore, preventing mitochondrial dysfunction induced by acute myocardial IRI is an important therapeutic approach for the protection of myocardium [9]. To reduce the size of the infarcted myocardium, preserve cardiac function, and improve patient outcomes, newer treatments must protect the myocardium from the detrimental effects of acute myocardial injury. The term metabolic modulator has been used to describe the use of drugs that improve the function of cardiomyocytes.

Myocardial ischemia and infarction are the consequences of pathological processes associated with metabolic and functional aberrations. During ischemia, free fatty acid oxidation increases and glucose oxidation reduces. These changes lead to reduction in the adenosine triphosphate (ATP) available for myocardial contraction as well as cell acidosis and calcium overload. Trimetazidine increases the phosphocreatine (PCr)/ATP ratio by 33%, thereby reserving the high-energy phosphate levels in the cardiac muscle. It is an effective antianginal agent that has a selective inhibitory effect on long chain 3-ketoacyl CoA thiolase activity, which reduces fatty acid oxidation and stimulates glucose oxidation without any negative inotropic effect [7].

Trimetazidine has a cytoprotective effect that can modify cardiac muscle metabolism, leading to anti-ischemic benefits. It inhibits β-oxidation of free fatty acids (FFA) and then shifts FFA to the more efficient glucose oxidation, thus helping preserve the ATP level in myocardial cells and result in a positive effect [7].

The METRO study had relatively small number of patients receiving trimetazidine (n = 48); however, the narrow confidence interval of the odds ratio 0.36 (0.15, 0.86; *P* = .022) indicates a strong and positive association between survival benefit post-MI and administration of trimetazidine [8].

The KAMIR study showed a significant reduction in all-cause death (2.3% vs 6.4%; *P* = .010) and total MACE (2.3% vs 9.5%; *P* = .001) in patients in the trimetazidine group vs the non-trimetazidine group [7].

A recent Asian study examined myocardial enzymes as an indicator of the amount of infarcted myocardium. Although the study did not establish a significant effect on the left ventricular diastolic diameter, cardiac output, and cardiac troponin (cTNI) on the second day of hospitalization, the results did show that trimetazidine statistically increased LVEF after 10 to 14 days in the hospital (*P* = .039) and 6 months after discharge *(P* = .047) [6]. Trimetazidine also reduced the size of infarcted myocardium and improved heart function. The trimetazidine groups showed reduction in the circulating biomarkers of MI and improved cardiac function compared with the control group, thereby emphasizing on the cardioprotective effect of trimetazidine. The study also speculated on the possibility that patients treated with trimetazidine may recover faster, leading to reduced hospital stay and lower healthcare costs [6].

An international multicentre retrospective cohort study data from 669 patients suggests that trimetazidine is effective in reducing mortality and event-free survival in patients with chronic heart failure (CHF). The addition of trimetazidine along with optimal medical therapy improved the long-term survival in patients with CHF. The Kaplan–Meier analysis performed to estimate the global mortality indicated that in the trimetazidine group,the global survival (*P* = .015) was improved by 11.3%, and the survival for cardiovascular death (*P* = .050) was

improved by 8.5%. The 5-year rate of hospitalization due to cardiovascular causes was reduced by 10.4% and hospitalization-free survival was increased by 7.8 months [10].

Trimetazidine is also believed to reduce the infarct size, restrict myocardial neutrophil buildup, and prevent intracoronary platelet aggregation in animal models of ischemia-reperfusion [11].Thus, it can be assumed that trimetazidine is effective in improving the clinical outcomes in CHF as well as stable coronary artery disease patients.

CONCLUSION

Myocardial ischemia and infarction are the result of pathological processes associated with metabolic and functional irregularities. A treatment targeted toward metabolic stabilization during the process can improve post-MI outcome and reduce the mortality risk. An analysis of data from the KAMIR and METRO studies suggests that ongoing trimetazidine treatment as an antianginal medication does yield a beneficial effect on the clinical outcomes of patients who have experienced an AMI. Trimetazidine is observed to decrease the all-cause mortality and MACE over the follow-up period of 6 to 12 months post-MI in such a patient population in the real-world scenario. More observational studies with larger sample sizes and longer follow-up duration would add to the available evidence identified in this review.

LIMITATIONS

Both the studies show a positive impact of treatment with trimetazidine in lowering the incidence of all-cause mortality and MACE; however, the evidence of its effect in reducing MACE is based mainly on the relatively small sample sizes of patients receiving trimetazidine (METRO study, n = 48; KAMIR study, propensity-matched n = 261). Since both the studies are multicentre and real-world studies, there may be differences in the protocol for AMI management in these settings, which can affect the overall outcome. Since patients with MI are hospitalized, there can be selection bias such as Berkson's bias. Moreover, there is a possibility of inaccurate clinical assessment by clinicians or maintenance of records for MACE or cause of death over the 12-month follow-up period. Considering all these limitations in the current studies, it is advisable to conduct a more focused and structured study with a bigger sample population.

CONSENTAND ETHICAL APPROVAL

It is not applicable.

DEFINITIONS, ACRONYMS, ABBREVIATIONS

ACC/ AHA: American College of Cardiology/American Heart Association
AMI: Acute Myocardial Infarction
CVD: Cardiovascular Disease
CABG: Coronary Artery Bypass Grafting
CCAs: Calcium-Channel Antagonists
cTNI: Cardiac Troponin
CHF: Chronic Heart Failure
GRACE: Global Registry of Acute Coronary Events
FFA: Free Fatty Acids
KAMIR: Korean Acute Myocardial Infarction Registry
LVEF: Left Ventricular Ejection Fraction

METRO: ManagEment of angina: a reTRospectivecOhort
MI: Myocardial Infarction
MACE: Major Adverse Cardiac Events
PCI: Percutaneous Coronary Intervention
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
TLR: Target Lesion Revascularization

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