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Focus on trimetazidine in acute coronary syndrome

Luis Henrique W. Gowdak, MD, PhD
Heart Institute (InCor), School of Medicine, University of São Paulo

Correspondence: Luis Henrique W. Gowdak, MD, PhD, Heart Institute (InCor), School of Medicine, University of São Paulo, Av. Dr. Enéas de Carvalho Aguiar, 44, 05403-000 São Paulo, SP, Brazil
E-mail: luis.gowdak@gmail.com

Abstract

Trimetazidine is an anti-ischemic agent that acts at the cellular level by shifting the cardiac energy metabolism from β-oxidation of free fatty acids to the more efficient glucose oxidation. In patients with an acute myocardial infarction (AMI) who are treated with thrombolysis and/or a percutaneous coronary intervention (PCI), ischemia-reperfusion injury may occur after reestablishing myocardial blood supply to an ischemic region. In animal models of ischemia-reperfusion injury, trimetazidine markedly reduced casein kinase and lactate dehydrogenase activities and decreased the infarct size. In patients with an AMI, trimetazidine reduced the rate of any form of reperfusion arrhythmias, more so with potentially life-threatening arrhythmias. In the EMPI-FR study (European Myocardial Infarction Project – Free Radicals), in the subset of patients not receiving thrombolysis assessed as per-protocol analysis, there was an 11.9% and 13.8% risk reduction in 35-day mortality and in-hospital mortality, respectively, in patients receiving trimetazidine. More recently, it was shown that trimetazidine, as an adjunctive therapy to PCI, reduced myocardial damage and preserved left ventricular function more than PCI alone. In a large registry of patients with AMI, the use of trimetazidine was associated with significant reductions in all-cause mortality and combined major adverse cardiac events (MACE), a finding that was confirmed in the first meta-analysis to report these benefits in patients with AMI treated with trimetazidine, showing a 67% risk reduction for MACE, which was defined as the composite of death, recurrent nonfatal MI, target vessel revascularization, coronary artery bypass graft, recurrence of angina, and/or hospitalization for heart failure. ■ *Heart Metab*. 2018;75:22-27

Keywords: arrhythmia; myocardial infarction; prognosis; treatment; trimetazidine

Introduction

Until the early 1960s, in-hospital mortality due to acute myocardial infarction (AMI) was approximately 30%, not counting those dying before being admitted to a hospital.[1] Advances in both adjuvant pharmacological therapy (modern antithrombotic therapy and secondary prevention) along with early reperfusion (thrombolysis or percutaneous coronary intervention [PCI]) in patients with ST-segment elevation MI (STEMI) are responsible for a significant decrease in acute and long-term mortality following an acute coronary syndrome (ACS). Still, in the national registries of the European Society of Cardiology countries, mortality of unselected patients with STEMI varies between 4% and 12%.[2] Therefore, it is fair to say that there is an ongoing challenge to achieve a greater reduction in morbidity and mortality in patients with ACS.

Abbreviations

ACS: acute coronary syndrome; **AMI:** acute myocardial infarction; **CK-MB:** creatinine kinase–myoglobin isoenzyme; **cTnI:** cardiac troponin I; **EMPI-FR:** European Myocardial Infarction Project – Free Radicals; **KAMIR:** Korean Acute Myocardial Infarction Registry; **LIST:** Limitation of Infarct Size by trimetazidine Trial; **MACE:** major adverse cardiovascular events; **METRO:** ManagEment of angina: a reTRospective cOhort [study]; **PCI:** percutaneous coronary intervention; **STEMI:** ST-segment elevation myocardial infarction

The potential role for cardioprotection at the cellular level during acute ischemia

Trimetazidine is an anti-ischemic agent that acts at the cellular level by shifting the cardiac energy metabolism from β-oxidation of free fatty acids to the more efficient glucose oxidation.[3] The use of trimetazidine in patients with stable angina has been extensively documented to significantly reduce angina attacks,[4] increase exercise tolerance,[5] and improve quality of life.[6] In patients with left ventricular dysfunction, trimetazidine in addition to optimal medical therapy improves cardiac function[7] and decreases cardiovascular events, including hospitalizations and all-cause death.[8,9]

In patients with AMI who are treated with thrombolysis and/or PCI, ischemia-reperfusion injury may occur after reestablishing myocardial blood supply to an ischemic region.[10] Several studies have shown that ischemia-reperfusion injury may not only precipitate arrhythmias and suppress or delay the recovery of contractile function, but may also cause cell death in potentially salvable ischemic tissue. In an animal model of ischemia-reperfusion injury, trimetazidine markedly reduced casein kinase and lactate dehydrogenase activities *(Figure 1)* and decreased the infarct size *(Figure 2)* compared with the control group.[11]

The activation of AMP-activated protein kinase (AMPK), an energy sensor that controls ATP supply from substrate metabolism and protects the heart from energy stress, exerts a protective effect against ischemia-reperfusion injury.[12] In a mouse model of in vivo regional ischemia and reperfusion, ie, by ligation of the left anterior descending coronary artery, trimetazidine significantly stimulated cardiac AMPK and extracellular signal-regulated kinase (ERK) signaling pathways, thereby reducing myocardial infarct size.[13]

Due to the aforementioned actions of trimetazidine at the cellular level during acute ischemia, its role in patients with ACS has long been explored.

Effects of trimetazidine on patients with AMI in the thrombolytic era

One of the first clinical demonstrations of the effects of trimetazidine on reperfusion arrhythmias in patients with an AMI came from the work of Papodopoulos et al[14] in the mid–1990s. In this controlled, randomized trial, 169 patients with a first AMI were included and

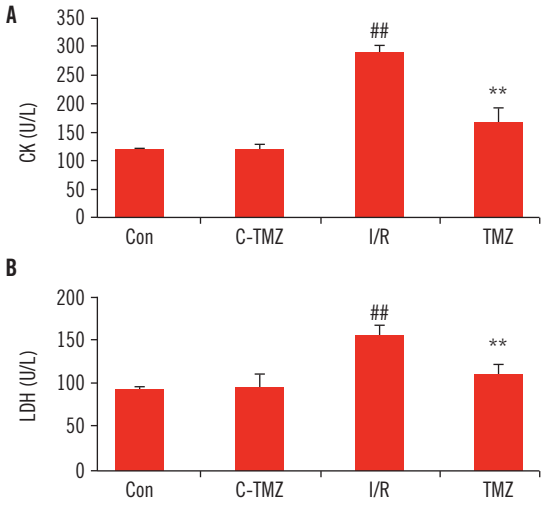

Fig. 1 *Trimetazidine exerts protective effects against CK (**A**) and LDH (**B**) activities in rats following cardiac I/R injury.*
Abbreviations: *##P<0.05 vs control group; **P<0.05 vs I/R group; Con, control group; CK, casein kinase; C-TMZ, control-trimetazidine group; I/R, cardiac ischemia/reperfusion injury model group; LDH, lactate dehydrogenase; TMZ, trimetazidine (30 mg/kg) treatment group.*
From reference 11: *Ma et al.* Mol Med Rep. *2016;14(5):4216-4222. © 2016, Ma et al.*

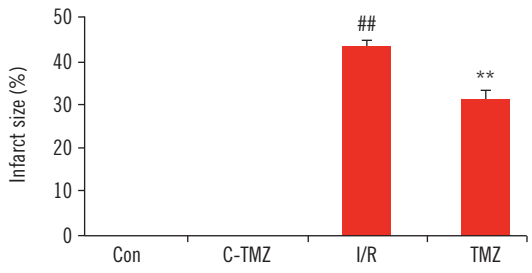

Fig. 2 *Trimetazidine reduces infarct size.*
Abbreviations: *##P<0.05 vs control group; **P<0.05 vs I/R group; Con, control group; CK, casein kinase; C-TMZ, control-trimetazidine group; I/R, cardiac ischemia/reperfusion injury model group; LDH, lactate dehydrogenase; TMZ, trimetazidine (30 mg/kg) treatment group.*
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underwent thrombolytic treatment with intravenous administration of recombinant tissue plasminogen activator. Trimetazidine was given at an initial single oral dose of 60 mg on admission, followed by 20 mg twice a day for the next 5 days. There was a significant reduction in the rate of any form of reperfusion arrhythmias in the trimetazidine-treated group vs controls (30.1% vs 56.3%; *P*<0.01). The beneficial effects of trimetazidine were more evident in patients with more severe and potentially life-threatening arrhythmias (sustained ventricular tachycardia, ventricular fibrillation); in this group of patients, arrhythmias were almost totally suppressed by trimetazidine vs controls (1.2% vs 7.0%; *P*<0.05), an effect that is possibly related to trimetazidine's ability to reduce late potentials after an AMI.[15] Similar findings were found in another small trial on 81 patients with an anterior MI in which trimetazidine was given before thrombolysis, which led to a decrease in the occurrence of ventricular arrhythmias, a reduction in infarct size, and less left ventricular remodeling after 6 months.[16]

Due to the clinical benefits observed with trimetazidine in small trials in patients with an AMI, a large, randomized, double-blind, placebo-controlled trial was performed. The EMIP-FR trial (European Myocardial Infarction Project – Free Radicals) was a prospective European multicenter trial in which 19 725 patients presenting with symptoms of an AMI within the previous 24 hours were randomized. An intravenous bolus injection of trimetazidine (40 mg) was given just before or simultaneously with thrombolysis, followed by continuous infusion (60 mg/day) for 48 hours. Overall, there was no difference between trimetazidine and placebo for short-term mortality (35 days) in an intention-to-treat analysis. However, in the subset of nonthrombolysed patients (corresponding to 44% of all patients included in the trial), a nonsignificant reduction in mortality was observed for patients receiving trimetazidine in the intention-to-treat analysis, which became significant in the per-protocol population analysis for 35-day mortality (13.3% vs 15.1%; *P*=0.027) and in-hospital mortality (11.9% vs 13.8%; *P*=0.013).[17]

More recently, the cardioprotective effect of trimetazidine was tested in 100 diabetic patients with an anterior MI who were treated with thrombolysis.[18] Confirming previous study results, the use of trimetazidine in this high-risk population was associated with a 2-fold increase in the proportion of patients achieving resolution of their ST-segment elevation (70% vs 36%; *P*<0.05). Total serum creatinine kinase and creatinine kinase–myoglobin isoenzyme (CK-MB) levels were significantly lower in the trimetazidine group at different sampling times. Taken together, trimetazidine-treated patients had significantly lower myocardial damage and faster reperfusion times at the 6-month follow-up, with fewer cardiac events.

Effects of trimetazidine on patients with AMI in the PCI era

According to the most recent international guidelines, primary PCI is the preferred reperfusion strategy in patients with STEMI within 12 hours of symptom onset, provided it can be performed <120 minutes from the time of diagnosis.[19] The first clinical trial exploring the benefits of trimetazidine in 94 patients undergoing primary PCI for an AMI was the LIST trial (Limitation of Infarct Size by trimetazidine Trial).[20] Trimetazidine was given intravenously before angioplasty and continued for 48 hours, and, compared with placebo, it yielded a significantly more important and faster reduction in ST-segment elevation with a trend to lower ST-segment exacerbation.[21]

Due to its mode of action at the cellular level, trimetazidine may protect cardiomyocytes in patients with an ACS who are undergoing a PCI, thus minimizing myocardial damage and improving left ventricular function. This hypothesis was tested in a study involving 52 patients hospitalized for a recent ACS (17 STEMI, 11 non–STEMI [NSTEMI], and 24 unstable angina patients), in whom a primary PCI had not been performed.[22] Trimetazidine was given 15 days prior to PCI and serum troponin I and CK-MB levels were measured before PCI and up to 48 hours after the procedure. *Figure 3* shows that fewer patients treated with trimetazidine vs placebo had higher levels of CK-MB at 24 and 48 hours after a PCI. Due to the lower amount of myocardial damage, left ventricular function, as assessed by echocardiography in the first 3 months after the PCI, improved in trimetazidine-treated patients compared with placebo-treated patients. While left ventricular ejection fraction (%) increased significantly from 51.7±7.9 (baseline) to 58.6±5.5 in trimetazidine-treated patients, it remained unchanged in the placebo group (53.5±7.5 vs 54.7±6.0).

To further test the capability of trimetazidine in protecting the cardiac cells during PCI, a single, oral

loading dose (60 mg) of trimetazidine was given to 136 patients 30 minutes before recanalization, whereas the 130 patients in the control group did not receive trimetazidine. Cardiac troponin I (cTnI) levels were significantly reduced in the trimetazidine group at each time point *(Figure 4)*[23]; moreover, the total amount of cTnI released after PCI was significantly reduced in the trimetazidine group ($P<0.05$). Although this trial was performed in patients with stable angina, the cardioprotection demonstrated during the study may be extrapolated to patients undergoing PCI for ACS.

In a similar study, but which is now enrolling 45 patients with NSTEMI undergoing PCI,[24] trimetazidine, given prior to the intervention, was associated with a greater improvement in the myocardial performance index as well as a decrease in both left ventricular end-diastolic volume and brain natriuretic peptide levels compared with standard care.

Clinical benefits of trimetazidine in patients with ACS

The comparative effect of antianginal drugs in patients with stable angina on the predicted mortality risk after surviving an MI was the main objective of the METRO study (ManagEment of angina: a reTRospective cOhort).[25] In 353 consecutive patients with stable angina who were selected if they were discharged following an AMI, the effect of the prior use of any antianginal drug (nitrates, β-adrenoceptor antagonists, calcium channel antagonists, trimetazidine, or nicorandil) on mortality was assessed. In a multivariate logistic regression model, the prior use of trimetazidine was the only factor independently associated with a significant reduction in mortality compared with other antianginal drugs. A recent study demonstrated that pretreatment with trimetazidine can significantly inhibit coronary microembolization–induced myocardial apoptosis, improving cardiac function in a swine model of coronary microembolization,[26] a well-described complication in patients undergoing PCI and which is usually associated with an acute elevation in cardiac troponins and adverse long-term outcomes.[27]

The KAMIR registry (Korean Acute Myocardial Infarction Registry) was a large registry comprising 13 733 patients with AMI, where the effect of adding trimetazidine to standard treatment was assessed on clinical outcomes.[28] Patients were divided into two groups: those treated with trimetazidine during their in-hospital management period and those who were not. During the first year after a PCI, trimetazidine lowered the relative risk of all-cause mortality by 59% and major adverse cardiovascular events (MACE) by 76%. The positive findings in this registry prompted investigators from China to run a controlled, randomized trial in 173 diabetic patients with AMI who were undergoing a PCI to compare the effects of trimetazidine on the release of cardiac markers and improvement in cardiac function. All patients received 300 mg of aspirin and 180 mg of ticagrelor upon admission, followed by 100 mg of aspirin once a day and 90 mg of ticagrelor twice a day. Trimetazidine-treated pa-

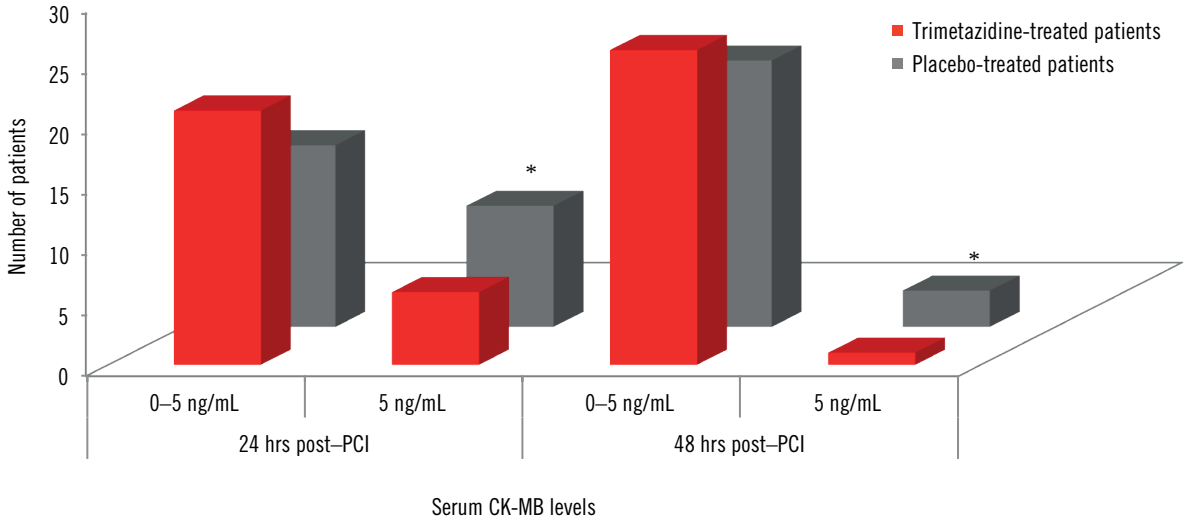

Fig. 3 *Histogram of CK-MB levels in patients at 24 and 48 hours post–PCI who were treated with trimetazidine or placebo.*
Abbreviations: *##P<0.05 vs group B; CK-MB, creatinine kinase–myoglobin isoenzyme; PCI, percutaneous coronary intervention.*
Based on data from reference 22: *Labrou et al.* Am J Cardiovasc Drugs. *2007;7(2):143-150.*

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tients received a loading dose of 60 mg trimetazidine at admission, followed by 20 mg twice a day. There were no significant between-group differences at baseline; on the second day post–PCI, trimetazidine significantly reduced total creatinine kinase and CK-MB levels by as much as 27% and 24%, respectively, compared with the control group; in addition, after days 1 and 6, trimetazidine significantly reduced cTnI levels by 32% and 31%, respectively. At 14 days post–MI, the left ventricular ejection fraction was greater in trimetazidine-treated patients (58.4%±8.6%) compared with controls (54.9%±8.4%).[29]

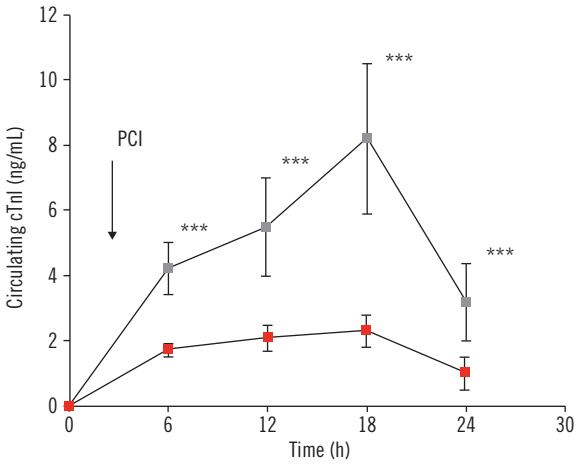

Fig. 4 *Time course of cTnI release. cTnI levels were measured in blood samples collected from patients before (T0) and 6, 12, 18 and 24 hours after PCI. Values are the means ± SD obtained for 130 (control, open symbols) and 136 (TMZ, filled symbols) patients. The arrow indicates the time of PCI.* ***P<0.001.
Abbreviations: ##P<0.05 *vs group B; cTnI, cardiac troponin I; PCI, percutaneous coronary intervention; TMZ, trimetazidine.*
From reference 23: *Bonello et al.* Heart. *2007;93(6):703-707. © 2007, BMJ Publishing Group and British Cardiovascular Society*

Conclusions

Due to its unique mode of action at the cellular level, there was a strong physiopathological rationale for trimetazidine to be effective in patients with ACS. ACS is a condition in which the myocardial cells are at great risk due to the low blood supply before recanalization ensues. Moreover, even after blood supply has been restored, the cells must deal with the ischemia-reperfusion phenomena. In fact, experimental and clinical data obtained in the past 30 years confirmed that trimetazidine might protect the cells during ischemia and after reperfusion to consistently prevent myocardial damage, preserve left ventricular function, and improve outcomes. The first meta-analysis to report these benefits in patients with AMI who were treated with trimetazidine *(Figure 5)*[30] showed no effect on ear-

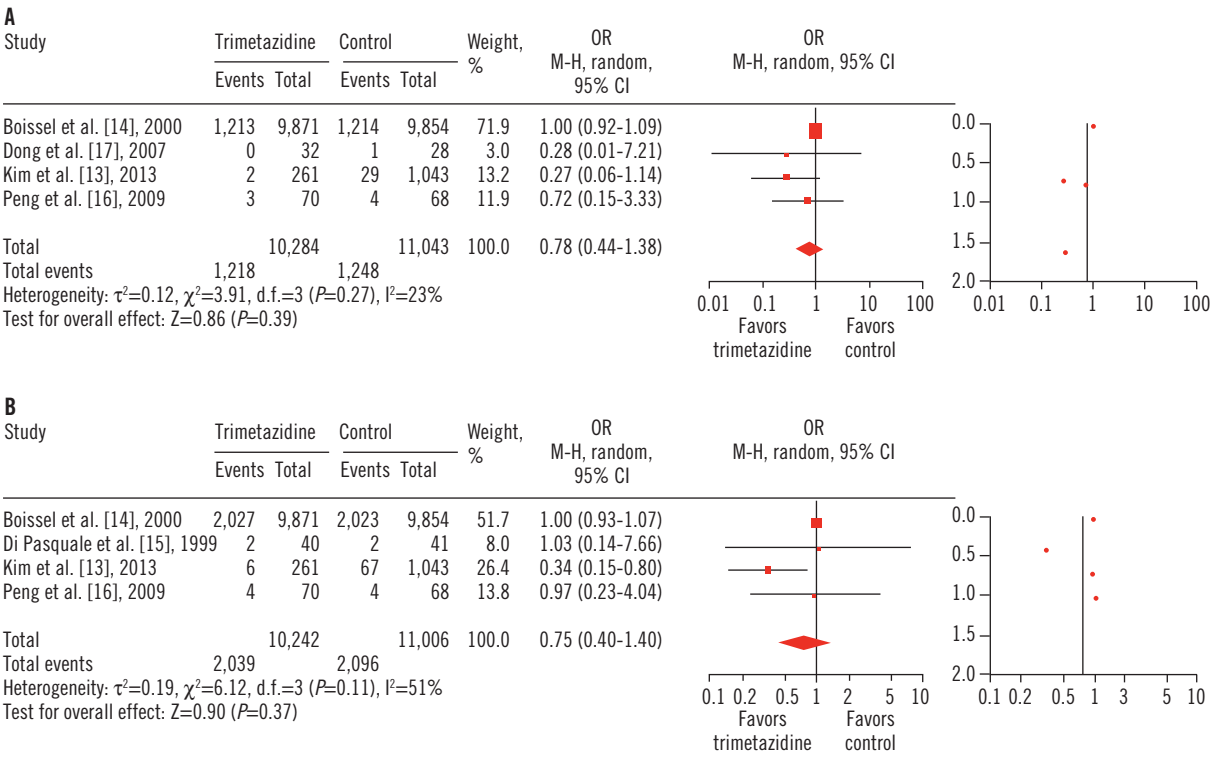

Fig. 5 *Forest plot and funnel plot of early/short-term all-cause mortality (**A**) and total major adverse cardiovascular events (**B**).*
Abbreviations: *M-H, Mantel-Haenszel; OR, odds ratio.*
From reference 30: *Li et al.* Cardiology. *2016;135:188-195. © 2016, Karger AG, Basel.*

ly/short-term all-cause mortality, but a 67% risk reduction for MACE, which was defined as the composite of death, recurrent nonfatal MI, target vessel revascularization, coronary artery bypass graft, recurrence of angina, and/or hospitalization for heart failure.

Despite clear signs of benefit and due to the lack of a large, properly designed clinical trial that is powered to assess hard end points, with the use of primary PCI and contemporary adjuvant therapy, trimetazidine in patients with ACS has not made it into the guidelines. Until then, it is up to the clinician's discretion to consider adding trimetazidine in the management of this high-risk population of patients with ACS. ■

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