International Journal of
Cardiovascular Diseases & Diagnosis

Research Article

# Protective Effect of Trimetazidine on Myocardial Injury in Patients with Non-ST Segment Elevation Acute Coronary Syndromes Undergoing Percutaneous Coronary Intervention -

**Jiang-you Wang, Han Chen, Dan Song, Jian Peng, Xi Su and Hua Yan***

*Department of Cardiology, Wuhan Asia Heart Hospital, Wuhan, PR China*

***Address for Correspondence:** Hua Yan, Department of Cardiology, Wuhan Asia Heart Hospital, Wuhan, PR China. E-mail: yanhua0807@aliyun.com

**Submitted:** 22 August 2017; **Approved:** 01 September 2017; **Published:** 05 September 2017

**Citation this article:** Jiang-you Wang, Chen H, Song D, Peng J, Su X, et al. Protective Effect of Trimetazidine on Myocardial Injury in Patients with Non-ST Segment Elevation Acute Coronary Syndromes Undergoing Percutaneous Coronary Intervention. Int J Cardiovasc Dis Diagn. 2017;2(1): 029-032.

**Copyright:** © 2017 Jiang-you Wang, et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

## ABSTRACT

**Background:** To investigate the effects of loading dose of trimetazidine therapy on periprocedural myocardial injury in patients with Non-ST Segment Elevation (NSTE) acute coronary syndromes (unstable angina or NSTE acute myocardial infarction).

**Method:** The study included 82 patients who were undergoing PCI with the diagnosis of NSTACS. The patients were randomized into two groups. The first group (n=42) of the patients hospitalized with the diagnosis of NSTACS was given conventional therapy plus 60 mg TMZ just prior to PCI. Treatment with TMZ was continued for one month after the procedure. TMZ treatment was not given to the second group (n=40). The main end point was a 30-day incidence of major adverse cardiac events (cardiac death, nonfatal acute myocardial infarction, or revascularization with either PCI or coronary artery bypass grafting). Cardiac troponin I and high-sensitivity C-reactive protein levels were measured at the baseline and at 16-18h after the procedure.

**Result:** Major adverse cardiac events occurred in 10.0% of patients in the control group and 4.76% of those in the TMZ group (*P<0.05*). This difference was mostly because of reduction in the incidence of per procedural myocardial infarction (7.50 vs. 4.76%; *P<0.05*). Markers of the two groups were elevated after PCI; however, the serum levels of cardiac troponin I and high-sensitivity C-reactive protein in the TMZ group were significantly lower than those in the control group (*P<0.01*).

**Conclusion:** Short-term pretreatment with the TMZ administration prior to PCI can prominently reduce myocardial injury caused by PCI.


**Keywords:** Trimetazidine; Percutaneous Coronary Intervention; Ctni; Inflammatory Reaction

## INTRODUCTION

Despite rapid advancements in the therapeutic field of cardiovascular diseases, Acute Coronary Syndromes (ACSs) are still the leading cause of morbidity and mortality worldwide. Increased numbers of coronary intensive care units, reperfusion techniques for Percutaneous Coronary Interventions (PCIs), and advanced medical therapies, including several pharmacological agents, have resulted in a significantly prolonged life expectancy. However, despite intensive therapies with hemodynamically effective agents, many patients with ischemic disease do not recover fully and remain at high risk for undesired further events. Hence, attempts to develop novel therapies are currently ongoing.

Trimetazidine (TMZ) has an anti-ischemic effect through the selective inhibition of long-chain 3-ketoacyl-CoA thiolase and the direct stimulation of pyruvate dehydrogenase, which provides a shift in cardiac energy metabolism from fatty acid oxidation to glucose oxidation [1]. As a result, TMZ preserves the necessary ATP level in cardiomyocytes, promotes a decrease in intracellular acidosis, and prevents intracellular calcium overload [2,3]. It reduces myocardial injuries caused by free radicals and, therefore, modulates the inflammatory response. It can limit the necrotic area of the myocardium. Therefore, TMZ preserves the contractile function of myocardium, reducing ischemia and reperfusion damage following an ischemic attack [4]. To investigate the effects of loading dose of trimetazidine therapy on periprocedural myocardial injury in patients with Non-ST Segment Elevation (NSTE) acute coronary syndromes (unstable angina or NSTE acute myocardial infarction).

## METHODS

### Patient Population and Study Protocol

This was a random, prospective, double-blind, placebo-controlled clinical trial performed in the Department of Cardiology, Wuhan Asia Heart Hospital. A total of 130 patients fulfilling the inclusion criteria from August 2016 to February 2017 were initially evaluated. Eighteen patients were excluded because of current or earlier treatment with statins or trimetazidine, six because of low ejection fraction, two for liver or muscle disease, and two for renal failure. A total of 98patients fulfilling the inclusion criteria were included in the study. Eligible patients (n=98) were randomized into two groups. The first group (n=42) of the patients hospitalized with the diagnosis of NSTACS was given conventional therapy plus 60 mg TMZ just prior to PCI. After coronary angiography, 16 patients were excluded from the study (four were treated medically and six with bypass surgery, Thus, 82 patients were enrolled and they were the study population. Patients were randomly divided independent of their lipid levels. According to our standard protocol, all patients without contraindications were pretreated with aspirin (100mg/d) and with Ticagrelor (180mg) or Clopidogrel (300-600mg) at least 6h before the procedure. Physicians performing the procedure and the follow-up assessment were not aware of the random assignment.

Inclusion criteria were the presence of a NSTE-ACS (unstable angina or NSTE acute myocardial infarction) sent for early coronary angiography (<4 days). Exclusion criteria were as follows: (1) ST-segment elevation acute myocardial infarction, (2) NSTE-ACS with high-risk features needing emergency coronary angiography, (3) renal failure with creatinine of more than 3mg/dl, (4) history of liver or muscle disease, (5) earlier or current treatment with statins or trimetazidine, (6) any increase in liver enzymes[alanine transferase (ALT)/aspartate transferase (AST)], (7) left ventricular ejection fraction of less than 30%.

### Interventional procedure

PCI was performed using a standard technique, through the radial artery route. Routine care was taken before and after the procedure for all patients, including pretreatment with a loading dose of Ticagrelor (180mg) or clopidogrel (300 mg initial oral bolus) the day before the procedure, followed by Ticagrelor (90mg/bid) or clopidogrel (75mg/day) for 12 month, in addition to lifelong aspirin medication (100mg/day). Intravenous bolus of unfractionated heparin (100 IU/kg), with activated coagulation time adjusted (200–300 s with Hemochron devices), was administered at the beginning of the procedure. The radial artery sheath was removed immediately after the end of the procedure.

### Angiographic Analysis

Classification of coronary artery morphology based on the report of the American Heart Association/American College of Cardiology Task Force [9], was used. Coronary angiograms were reviewed by

independent observers blinded to the results of biochemical assays. Intimal major or minor dissection, thrombus, abrupt closures in a previously patent vessel, no-reflow, spasm and side-branch occlusion were assessed. The degree of perfusion was evaluated according to TIMI criteria [5]. No-reflow phenomenon was defined as TIMI flow grade 0, 1, or 2 without a mechanical obstruction on angiograms after PCI. Left ventricular function was assessed by angiography in all patients.

### Blood Sampling and Analyzing

Venous blood samples for measurement of cTnI and hs-CRP were obtained from all patients before PCI and at16-18 h after the procedure. The samples were drawn into tubes without anticoagulant and were kept at room temperature for 20 min to allow clotting. The samples were centrifuged at 3000g for10 min, and the serum was stored in aliquots at a temperature of-80˚C until analysis. Serum samples were analyzed for cTnI using BECKMANLX-20 fully automatic biochemical analyzer (Beckman Coulter, Inc.USA) normal limits were less than0.04ng/ml for cTnI.

### Statistical Analysis

Statistical analyses were performed with SPSS version 17.0 software. Categorical variables were presented as frequency counts and percentages, two group comparison was performed by using chi-square statistics or the Fisher exact test (if the expected cell value was <5). Continuous variables were presented as median and inter-quartile range [Mean (SD)], two group comparison was performed by using Student's t tests or the Mann–Whitney U test. Correlation between two variables was analyzed with linear correlation. A p value<0.05 was considered statistically significant.

## RESULTS

### Study Population

The studied population was composed of 40 patients in the control group, 42 patients in the TMZ group. A CONSORT (Consolidated Standards of Reporting Trials) flow diagram is shown in (Figure 1). Clinical and procedural variables in the control and TMZ groups are shown in (Tables 1, 2 and 3), respectively. The two groups were similar with regard to age, sex, cardiovascular risk factors, left ventricular function, mean time to angiography, and medical therapy at the time of intervention. Coronary anatomy, lesion type, procedural characteristics, use of drug-eluting stents, diameter and length of

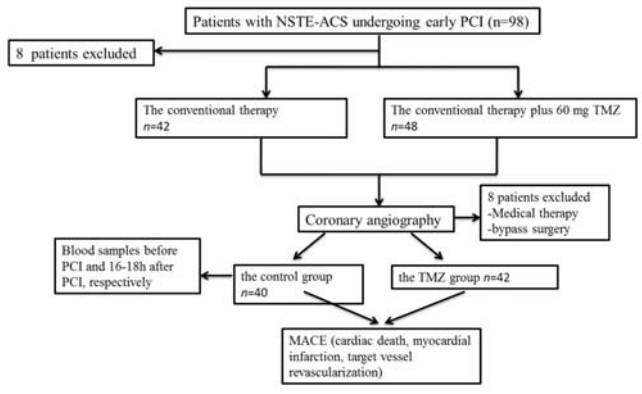


**Figure 1:** shows A CONSORT (Consolidated Standards of Reporting Trials) flow diagram.
Patients with non-ST segment elevation acute coronary syndromes (NSTE-ACS) undergoing early percutaneous coronary intervention (PCI); cTn- I, cardiac troponin I; hs-CRP, high-sensitivity C-reactive protein; MACE, major adverse cardiac events

Table 1: Patient clinical characteristics, ACEI, angiotensin-converting enzyme inhibitors; CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction; PCI, percentaneous coronaryintervention; NSTEMI, non-ST segment elevation myocardial infarction; BMI indicates body mass index. ATV, atorvastatin; TMZ ,trimetazidine.

| Variables | Control group(n=40) | TZM group(n=42) | P Value |
|---|---|---|---|
| Mean (SD) age (years) | 62.24±12.84 | 63.32±14.58 | NA |
| Sex, male, n (%) | 20(50) | 22(52) | NA |
| History, n (%) | | | NA |
| Earlier myocardial infarction | 4(10) | 6(14) | NA |
| Earlier PCI | 6(15) | 8(19) | NA |
| Earlier CABG | 2(5) | 3(7) | NA |
| LVEF (%) | 50.42±4.43 | 50.98±5.14 | NA |
| Unstable angina | 25(62) | 26(62) | NA |
| NSTEMI | 15(38) | 16(38) | NA |
| Risk factors, n (%) | | | NA |
| Smoking (past or current) | 26(65) | 28(67) | NA |
| Hypercholesterolaemia | 23(58) | 26(62) | NA |
| Hypertension | 25(63) | 28(67) | NA |
| Diabetes mellitus | 18(45) | 19(45) | NA |
| Family history | 9(23) | 10(24) | NA |
| Mean (SD) BMI (kg/m$^2$) | 26.83±3.45 | 25.98±3.95 | NA |
| Medication, n (%) | | | NA |
| ACE inhibitors or ARB | 30(75) | 32(76) | NA |
| β Blockers | 35(88) | 37(88) | NA |
| Calcium antagonist | 10(25) | 11(26) | NA |
| Aspirin | 40(100) | 42(100) | NA |
| Clopidogrel | 10(25) | 11(26) | NA |
| Ticagrelor | 30(75) | 31(74) | NA |
| Insulin | 6(15) | 8(19) | NA |
| Nitrates | 32(80) | 35(83) | NA |

**Table 2:** Angiographic characteristics, VEF indicates left ventricular ejection fraction; ATV, atorvastatin; TMZ, trimetazidine; *According to the American Heart Association/American College of Cardiology classification.

| Variable, n (%) | Control group(n=40) | TMZ group(n=42) | P Value |
|---|---|---|---|
| Lesion class* | | | |
| A+B1 | 12(30) | 14(33) | NA |
| B2+C | 28(70) | 28(67) | NA |
| Artery involved | | | NA |
| Left main artery | 0 | 0 | NA |
| Left anterior descending artery | 30(75) | 33(78) | NA |
| Left circumflex artery | 15(38) | 28(38) | NA |
| Right coronary artery | 22(55) | 23(55) | NA |
| Single-vessel disease | 12(30) | 13(30) | NA |
| Double-vessel disease | 10(25) | 12(29) | NA |
| Three-vessel disease | 18(45) | 17(41) | NA |

implanted stents were similar. Primary composite end point: 30 days incidence of major adverse cardiac events (MACE; death, myocardial infarction, or target vessel revascularization). The result shows MACE in 10 % of patients (four of 40) in the control arm and in 4.76% (two of 42) of those in the TMZ arm (*P<0.05*). The incidence of MACE at 1 month was mostly because of post-procedural myocardial infarction (7.50% vs 4.76%, *P<0.05*, and no patient died.

### Markers of Myocardial Injury and Inflammatory Reaction

Markers of the two groups were elevated after PCI; however, the higher values of cTnI, hs-CRP in the TMZ treatment group were significantly lower than those of the control group (*P<0.01*, Table 4).

## DISCUSSION

This study demonstrates that pretreatment with a 60 mg acute oral loading dose of TMZ before elective PCI alleviates myocardial damage.

Trimetazidine (TMZ; 1-[2, 3, 4-trimethoxybenzyl] piperazine) is a cellular anti-ischemic agent that selectively inhibits the activity of the final enzyme of the fatty acid oxidation pathway, 3-ketoacylcoenzyme A thiolase. Clinical studies have shown that TMZ has cardio protective effects in the setting of myocardial ischemia including acute myocardial infarction [1]. The effect of TMZ on myocardial necrosis could be explained by its metabolic and biological effects in mechanism while TMZ has been shown to have no any haemodynamic effects [2]. It acts by improving cardiac energy metabolism through switching ATP production from lipid to glucose oxidation, thus enhancing intra-mitochondrial coupling and favoring a more efficient mode of ATP production per mole of oxygen [3]. Moreover, TMZ reduces intracellular acidosis and protects against oxygen free radical induced toxicity. The drug therefore directly protects myocyte structure and function, and increases cell resistance to hypoxic stress [6-7].Those effects might be highly relevant in the setting of PCI.TMZ is also beneficial in preventing ischemia-reperfusion injury. In fact, an animal experiment demonstrated that TMZ could limit lethal ischemia-reperfusion injury by inhibiting mitochondrial permeability transition pore opening, which represents a crucial event in cardiomyocyte death following myocardial ischemia-reperfusion[8] Altogether, these effects could explain the reduction of cardiac myonecrosis in patients pretreated with TMZ before angioplasty. Our result is consistent with a previous report by Kober et al. [9] and Bonello et al. [8], who observed that TMZ administration before PCI reduces periprocedural myocardial cells ischemia, and further demonstrates that TMZ effect does translate into less myocardial necrosis assessed by cTnI measurement.

In conclusion, the TMZ could mitigate the myocardial damage following PCI through different pathways and various effects. We concluded that the beneficial effects of PCI could be reinforced with a combination of PCI and TMZ treatment.

**Table 3:** Procedural characteristics and complications, IMIindicatesThrombolysis in Myocardial Infarction Trial; Values are represented as mean (SD) unless otherwise specified; ATV, atorvastatin; TMZ, trimetazidine.

| parameters | control group(n=40) | TMZ group(n=42) | P Value |
|---|---|---|---|
| Stent length (mm) | 23.28±3.89 | 22.82±2.08 | NA |
| Stent diameter (mm) | 2.88±0.69 | 2.91±0.76 | NA |
| Total inflation time (s) | 38.53±8.98 | 39.65±5.98 | NA |
| Inflation maximal pressure (atm) | 14.38±3.68 | 15.45±4.28 | NA |
| TIMI flow grade≤1, n (%) | 2(5) | 1(2) | NA |
| TIMI flow grade=2, n (%) | 2(5) | 2(5) | NA |
| TIMI flow grade = 3, n (%) | 36(90) | 39(93) | NA |
| Procedural complication, n (%) | | | NA |
| Side-branch occlusion | 2(5) | 2(5) | NA |
| Coronary dissection | 1(2.5) | 2(5) | NA |
| Coronary spasm | 5(13) | 6(14) | NA |
| Coronary embolisation | 1(2.5) | 1(2) | NA |

**Table 4:** Markers of myocardial injury and inflammatory reaction
cTnI, cardiac troponin I; hs-CRP, high-sensitivity C-reactive protein; PCI, percutaneous coronary intervention; ATV , atorvastatin ; TMZ ,trimetazidine. Comparison before PCI, **p*<0.05, ***p*<0.01; Comparison ATV, #*p*<0.05.

| | Makers | Before PCI | 16-18h after PCI |
|---|---|---|---|
| control | | | |
| (n=40) | cTnI(ng/ml) | 0.98(0.23) | 1.68(0.98)** |
| | hsCRP(mg/l) | 3.68(1.38) | 10.27(1.38)** |
| TMZ | | | |
| (n-42) | cTnI(ng/ml) | 1.06(0.35) | 1.32(0.68)*# |
| | hsCRP(mg/l) | 3.26(1.02) | 6.34(0.89)*# |

## ACKNOWLEDGEMENTS

This study was supported by a grant from Wuhan Health and Family Planning Commission Research Foundation funded (Grant No.WX17Q36).

## REFERENCES

1. Szwed H, Sadowski Z, Elikowski W, et al. Combination treatment in stable effort angina using trimetazidine and metoprolol: results of a randomized, double-blind, multicentre study (TRIMPOL II). TRIMetazidine in POLand. Eur Heart J 2001; 22: 2267-74. https://goo.gl/3pqFfb
2. Lopaschuk GD, Kozak R. Trimetazidine inhibits fatty acid oxidation in the heart. J Mol Cell Cardiol 1998; 30: A112.
3. Aussedat J, Ray A, Kay L, Verdys M, Harpey C, Rossi A. Improvement of long-term preservation of isolated arrested rat heart: beneficial effect of the anti-ischemic agent trimetazidine. J Cardiovasc Pharmacol. 1993; 21: 128-35. https://goo.gl/hP3wjV
4. American Heart Association. 1999 heart and stroke statistical update. Chicago: American Heart Association; 1999.
5. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction. Results of the TIMI IIIB Trial. Thrombolysis in Myocardial Ischemia. Circulation. 1994; 89: 1545-56. https://goo.gl/14KjSa
6. Lopaschuk GD, Barr R, Thomas PD, Dyck JR. Beneficial effects of trimetazidine in ex vivo working ischemic hearts are due to a stimulation of glucose oxidation secondary to inhibition of long-chain 3-ketoacyl coenzyme a thiolase. Circ Res. 2003; 93: e33-7. https://goo.gl/nBwZDa
7. Kantor PF, Lucien A, Kozak R, Lopaschuk GD. The antianginal drug trimetazidine shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting mitochondrial long-chain 3-ketoacyl coenzyme A thiolase. Circ Res. 2000; 86: 580-8. https://goo.gl/dptetd
8. Argaud L, Gomez L, Gateau-Roesch O, Couture-Lepetit E, Loufouat J, Robert D, et al. Trimetazidine inhibits mitochondrial permeability transition pore opening and prevents lethal ischemia-reperfusion injury. J Mol Cell Cardiol. 2005; 39: 893-9. https://goo.gl/cQhtGH
9. Kober G, Buck T, Sievert H, Vallbracht C. Myocardial protection during percutaneous transluminal coronary angioplasty: effects of trimetazidine. Eur Heart J. 1992; 13: 1109-15. https://goo.gl/GYt4ad