

Effect of early Trimetazidine on infarct size in ST-segment-elevation myocardial infarction patients undergoing primary percutaneous coronary intervention

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Abstract

Purpose: Trimetazidine, a metabolic agent with anti-ischemic effects, was reported to reduce reperfusion injury in animal models. In this randomized double-blind placebo-controlled trial, we investigated the effects of trimetazidine on reducing infarction size in patients undergoing revascularization for ST-segment elevation myocardial infarction (STEMI).

Methods: Patients with STEMI randomly received trimetazidine (n=87) or placebo (n= 86) in a double-blind manner before primary percutaneous coronary intervention (PCI), and study treatment was maintained for 12 months after the procedure. The primary endpoint was infarction size measured by cardiac magnetic resonance (CMR) after primary PCI.

Results: The clinical characteristics of patients (90% male, mean age 57 ± 12 years) in both groups were well-matched on the baseline. Compared with patients in control group, the percentage and weight of infarction size of patients in trimetazidine group were both significantly lower ($22.1\pm 11.8\%$ [n =74] vs. $26.9\pm 11.9\%$ [n=74], $p=0.010$; $28\pm 18\text{g}$ [n =74] vs. $35\pm 19\text{g}$ [n=74], $p=0.022$), the myocardial microvascular obstruction (MVO) rate measured by CMR was lower in trimetazidine group (29.7% [22/7] vs. 52.7% [39/74], $p=0.007$), while myocardial salvage index (MSI) was significantly higher in trimetazidine group ($48\pm 20\%$ vs. $39\pm 27\%$, $p=0.008$). The incidence of readmission due to aggravated heart failure in trimetazidine group was lower than that in the control group without significance (8.0% vs 14.0% , $p=0.234$).

Conclusions: Our study provides suggests that trimetazidine initiated prior to primary PCI, improves myocardial infarct size, MVO and MSI, possibly by reducing reperfusion injury.

1. Introduction

Reperfusion injury, which occurs in ST-segment elevation myocardial infarction (STEMI) after primary percutaneous coronary intervention (PCI), could further increase myocardial infarct size and lead to poor prognosis. Reperfusion injury has been increasingly concerned on its underlying mechanism and potential treatment. There is growing evidence that trimetazidine (TMZ) applied in patients with acute myocardial ischemia is beneficial in cardioprotection and reducing major cardiac events[1–2]. A previous retrospective study showed that administration of TMZ could improve clinical outcomes in patients with acute myocardial infarction (AMI) by significantly reducing all-cause mortality in the following 12 months [3]. TMZ could protect cardiomyocytes in hypoxia-ischemia via modulating energy metabolism. Experimental studies performed in animal models of cardiac ischemia/reperfusion injury have revealed that TMZ could reduce myocardial ischemia/reperfusion injury by various mechanisms, mostly due to it facilitating energy from β -oxidation of fatty acid to more efficient glucose oxidation and antioxidant property [4–7]. However, there still lacks research to provide evidence of effects of TMZ on infarct size in STEMI patients who underwent primary PCI [8]. Cardiac magnetic resonance (CMR) has emerged as the imaging modality for assessing the cardioprotective efficacy in patients with AMI. Late gadolinium

enhancement (LGE) on CMR provides a reliable method to evaluate the infarction size. CMR could also provide the myocardial salvage index (MSI) which demonstrates efficacy of cardioprotective interventions in situations without reduction in absolute infarction size [9–10]. In this study, CMR was used to evaluate the effect of early TMZ administration on infarction size and MSI in patients who underwent primary PCI.

2. Material And Methods

2.1. Compliance with Ethical Standards

From October 2016 to October 2019, we conducted a prospective, single-center, randomized, double-blind study in the Chinese PLA General Hospital in Beijing.

The study complied with the Declaration of Helsinki, which was approved by the Beijing Ethics Association and the Ethics Committee of the Chinese PLA General Hospital.

Informed consent was obtained from all individual participants included in the study.

The trial was registered on ClinicalTrials.gov (registration number: NCT02826616). There is no potential conflicts of interest.

2.2. Study population

The study population included patients diagnosed with STEMI for the first time and underwent primary PCI within 12 hours of the onset of chest pain. Diagnosis of STEMI was based on the concurrence of symptoms consistent with STEMI for > 30 minutes; and ST-segment elevation ≥ 1 mm in at least 2 or more inferior leads or ≥ 2 mm in at least 2 or more contiguous precordial leads. Patients were excluded if they met any one of the bellow conditions: already treated with TMZ, history of myocardial infarction, mechanical complications, previous coronary artery bypass grafting (CABG) or PCI, contraindications of CMR, liver or kidney failure, malignant tumor.

2.3. PCI Procedures

Eligible patients were randomly assigned to receive TMZ or placebo before primary PCI. Primary PCI was performed by 2 operators using standard techniques. Patients took 300 mg aspirin in the emergency department, followed by 100 mg aspirin per day orally thereafter. A loading dose of 180 mg ticagrelor was administered before catheterization, followed by 90 mg ticagrelor twice daily for the next 12 months. Drug-eluting stents were the stents of choice. All patients were given enoxaparin treatment every 12 hours after primary PCI for 7 days. Blood samples were taken for troponin T testing before and at 6, 12, 24, 48 hours after PCI. The application of thrombectomy and intro-aortic balloon pump (IABP) was at the discretion of the operators. The PCI data analysts were kept blind from grouping.

2.4. Experimental Treatment Protocol

All patients were informed of the potential benefits and risks of the trial before they signed written informed consents and enrolled in the study.

Patients were randomly divided into placebo and TMZ groups by using a computer-generated sequence at a ratio of 1:1. Patients were treated with a dose of 60 mg TMZ (Servier companies) or placebo orally prior to reperfusion by primary PCI and followed by 20 mg TMZ or placebo three times a day for 12 months. Other medications including aspirin, ticagrelor, statins, β -blockers and ACEI/ARB were given in accordance with the European Cardiology Society STEMI guideline [11].

2.5. Primary endpoint and clinical Follow-Up

The primary endpoint was the infarction size measured by CMR at 7 days after primary PCI. The secondary endpoint was MSI measured by CMR at 7 days after primary PCI and main adverse cardiac events (MACEs) in following 12 months. We followed up these patients by routine clinical visits and recorded any MACEs until 12 months after the PCI.

Follow-up information was obtained at the outpatient clinic.

Good clinical practice training was required for all personnel involved in the trial. MACEs were defined as stroke, repeat revascularization, and readmission due to acute heart failure, nonfatal myocardial infarction and all-cause death. All end-point events were adjudicated by an independent clinical events committee based on medical record. All were blinded to treatment group.

2.6. Cardiovascular magnetic resonance acquisition and analysis

The scan was performed at 7 days after primary PCI so as to assess the final infarction size, microvascular obstruction (MVO), area at risk (AAR) and MSI.

All participants took a CMR examination on a 1.5T MR Scanner (Achieva; Philips Medical Systems, Best, the Netherlands), using the 32-channel phased-array body coil.

All CMR images were acquired during breath-hold and with ECG triggering. Retrospective ECG gated cine CMR imaging was performed with steady-state free precession (SSFP) sequences using the standard protocol covering short axis and long axis in the 2- and 4- chamber views. The SSFP cine images were acquired continuously from the mitral annulus to the apical level without gaps on the short-axis. Based on the retrospective triggering, 25–30 cardiac phases covering systole and diastole within a cardiac cycle were reconstructed. Infarction size was acquired by the CMR LGE method which acquired the images after 15 min injection of gadolinium (0.1 mmol/kg at 3ml/s). Inversion-recovery CMR LGE images were obtained at end-diastolic on short axis and the inversion time was manually adjusted to null the signal from remote myocardium. Myocardial edema-sensitive black-blood T2-weighted short tau inversion-recovery (STIR) sequence was performed using a fat-saturation triple inversion-recovery sequence. A full stack of LGE and T2 were acquired with about 10 slices of left ventricle (LV) chamber from base to apex, 8 mm apart. Each slice of LGE and T2 owed the same parametric location which was available for the precise analysis afterward.

The CMR data were analyzed by 2 CMR readers using the freely available validated cardiovascular image analysis software CVI42 5.11.2 (Circle Cardiovascular Imaging Inc, Calgary, Canada, version 5.10.1). Cine

images on short-axis were used to analyze LV systolic function. The LV function analysis included all slices from end-diastole to end-systole. Left ventricular ejection fraction (LVEF) was calculated by manually tracing the endocardial borders in all phases on an ECG-triggered balanced steady-state-free procession cine sequence by applying multiple slices in the short-axis image covering the entire LV. Specifically, after manual tracing of the epicardial and endocardial borders, the areas of STEMI were quantified in LGE images detected by semi-automated software, by the method of mean + 5SD Ref ROI with manual correction (Fig. 1A-B). We removed the artifact in the remote myocardium which would affect the infarction size calculation in the LGE image. Infarction size was expressed both in grams and in the percentage of the total LV mass. The myocardial AAR was assessed as edema on the CMR scan using T2-weighted STIR sequence (Fig. 1C-D). AAR was defined as the long signal area on T2-weighted images, and was semi-automated recognized by mean + 2SD Ref ROI. We removed the artifact in the remote non-infarcted myocardium in the T2 STIR image with the manual correction to analyze AAR, and the area of MVO should be manually included in AAR. The MSI was calculated as follows: (AAR, g - infarction size, g) / AAR, g. MVO was identified in LGE images as a subendocardial region with lower enhancement than the surrounding area which was semi-automated discerned via the dark areas inside the infarcted myocardium tissue with manual correction. All the data were validated by inter-and intra-observer analysis of reproducibility method.

2.7. Statistical analysis

Continuous variables were presented as mean \pm SD and compared by the *t*-test for independent samples. Non-normally distribution variables were presented as a median and interquartile range, and compared by the Wilcoxon rank-sum test. Categorical data were presented as percentages and compared by the χ^2 test or the Fisher exact test when there were less than 5 values in a given cell. All statistical analyses were performed using SPSS statistical software (version 18.0, SPSS, Chicago, Illinois).

3. Results

A total of 365 patients with STEMI planning for primary PCI were screened for eligibility, of whom 192 patients were not eligible for the following reasons: previous myocardial infarction (36 patients), previous coronary artery bypass grafting (CABG) or PCI (61 patients), renal failure (19 patients), cardiogenic shock (35 patients), pacemakers existing (8 patients), severe infectious (6 patients), malignant tumor (11 patients) and refusal (16 patients). A total of 173 patients with STEMI were randomized (1:1) to receive either TMZ or placebo prior to primary PCI. A total of 148 patients who finally received CMR were eligible for the final analysis (Figure 2).

3.1 Patient characteristics

The mean age of the total study cohort was 57 ± 12 years, and males accounted for 90%. The administrations of statins, β -blockers, and ACEI/ARB had no significant difference between the two groups. There was no significant difference in time from symptom to balloon and other baseline

characteristics between the TMZ and control group (Table 1). TIMI grade before reperfusion wasn't significant difference between the two groups. Thrombectomy occurred in 25 patients (28.7%) in the TMZ group and 23 patients (26.7%) in the control group. Compared with the control group, the proportion of patients of TIMI 3 grade after primary PCI was a little higher in TMZ group without significance (94.3% vs. 88.4%; $p=0.308$), which was shown in Table 2.

3.2. Primary endpoint

Infarction size, MVO, AAR and MSI were measured by CMR, and there were two experienced CMR readers validated the results. The intra- and inter-observer variability on infarction size were 0.01 ± 0.03 and 0.02 ± 0.05 , respectively (Figure 1). Compared with the control group, patients with STEMI who were administered TMZ prior to primary PCI had a reduction in infarction size percentage (expressed as a percentage of the LV mass, $22\pm 12\%$ [$n=74$] vs. $27\pm 13\%$ [$n=74$]; $p=0.011$), absolute infarction mass ($28\pm 18\text{g}$ [$n=74$] vs. $35\pm 19\text{g}$ [$n=74$]; $p=0.022$) and lower proportion of MVO (29.7% [$22/73$] vs. 52.7% [$39/74$]; $p=0.007$), meanwhile had an increase in MSI ($48\pm 20\%$ vs. $39\pm 27\%$; $p=0.008$), which was showed in Table 3. The plasma levels of high sensitive troponin T (hsTnT) at 12 h ($p=0.028$) and 24 h ($p=0.034$) after reperfusion in TMZ group were significantly reduced than control group, which suggested TMZ reduced reperfusion injury in primary PCI (Figure 3, Table 4).

3.3 Major adverse cardiovascular events

Compared with control group, fewer occurrences of cumulative MACEs were observed in TMZ group without significance (Figure 4). During the one-year follow-up, the incidence of readmission for acute heart failure was lower in the TMZ group than control group (8.0% vs. 14.0% , $p=0.234$). A total of 9 patients died during the follow-up, 4 in TMZ group and 5 in control group. There was no significant difference in the incidence of recurrent myocardial infarction or all-cause death (Figure 4, Table 5).

4. Discussion

TMZ is a clinically effective anti-ischemic agent, which reduces fatty acid oxidation while stimulates glucose oxidation by inhibiting long-chain 3-ketoacyl CoA thiolase. It has been reported that TMZ appeared to improve clinical outcomes in patients with AMI by significantly reducing all-cause mortality and other MACEs [3, 12]. Our trial has demonstrated improved outcomes: TMZ treatment initiated prior to primary PCI could reduce infarction size and MVO, and make improvement of MSI in patients with STEMI. Besides, CMR was firstly used to evaluate the effect of TMZ on infarction size and MSI in patients with STEMI in our trial. Other trials have proven that TMZ therapy makes improvement of LVEF, and reduce reperfusion damage for patients with STEMI, especially for non-thrombotic patients [8, 13-16], and TMZ treatment commenced prior to PCI also made improvements in left ventricular end-diastolic volume and decrease in brain natriuretic peptide (BNP) level in patients with AMI [17], all of which were in line with the results of our clinical trial.

Previous animal experiments suggested TMZ effectively reduced infarction size in animal models [18,19]. Early treatment of TMZ, especially in the acute ischemia-reperfusion phase, could reduce reperfusion myocardial injury through various mechanisms: TMZ modulates the substrate metabolism by shifting fatty acid oxidation to glucose oxidation during reperfusion [2,4,5]. TMZ could reduce the intracellular acidosis and deposition of intracellular sodium and calcium, prevent the membrane damage caused by the oxygen free radicals, and reduce white blood cells [20-22]. TMZ pretreatment could significantly inhibit myocardial apoptosis, and its cardiac protective effect appeared to be mediated by the blockade of the mitochondrial apoptotic pathway [23]. TMZ treatment significantly activates AMPK and ERK signaling pathway, and inhibits MMP-2 and MMP-9 expression, which leads to a reduction of oxidative stress in ischemia-reperfusion hearts [5, 21]. All of the above mechanisms may contribute to reducing the infarction size for STEMI

Some previous researches show no significant improvement of TMZ on the prognosis of angina pectoris after recent successful PCI [24]. However, a meta-analysis has reported that early TMZ therapy had overall benefits upon total MACEs in patients with AMI [12]. Our study provides additional evidence on the protective effect of the TMZ on relieving reperfusion injury in patients with STEMI after PCI. These inconsistent findings may be due to the following reason: The benefits efficacy of TMZ may depend on the timing and dosage of administration, and may also depend on patient status, and TMZ is likely to be more effective in the acute myocardial ischemia phase. Some previous studies did not give an adequate dosage of TMZ before the reperfusion, which might underestimate the cardioprotective effect of TMZ [13]. Our study treated STEMI patients with a loading dose of 60mg TMZ before PCI followed by TMZ for a total of 12 months to benefit these patients. It has been reported that pre-procedural oral TMZ administration significantly reduced PCI-induced myocardial injury in PCI for stable angina pectoris [25]. Our study has validated that TMZ reduces PCI-induced myocardial injury in primary PCI, and provides a reference for drug administration's dose and duration.

Infarct size is a major determinant of post STEMI mortality, so limiting the extent of infarct size in STEMI is a major therapeutic target [26]. MSI also predicts the outcome of STEMI after reperfusion, and has important implications for prognosis [9]. It is our hypothesis that TMZ reduces infarct size and improve MSI by ameliorating reperfusion injury. Here, we show that an early therapy of TMZ could significantly reduce infarct size, and increase MSI simply by being administered before reperfusion. TMZ did not reduce mortality in our study which might be due to the insufficient sample size, and further evidence is needed to assess potential longer-term clinical benefits in a larger clinical trial.

4.1. Study limitation

There were some limitations in this study. Firstly, not all the CMR exams were performed exactly on the 7th day after PCI in our study, which might affect the final results of the observed variables due to the rapidly changing pathophysiological processes of the cardiac tissue [27]. Secondly, we used CMR data at 7 days post-STEMI as the endpoint. Although scar myocardial size performed at 1 month from the acute episode should be a more reliable measurement, but previous research has taken the infarction size, MVO,

AAR and MSI measured with one week as a good alternative [28]. Furthermore, 14% of patients enrolled did not undergo the CMR for primary end-point for different reasons, and this attrition rate was as we projected and is similar to those in other STEMI trials using MRI [29]. Finally, this study was a single-center study, and our conclusion needed further validation in large-scale randomized studies.

5. Conclusions

This randomized study showed that TMZ initiated prior to primary PCI, reduced myocardial infarct size and MVO, and improved MSI significantly, possibly by reducing reperfusion injury, making it a promising treatment for evaluation in larger randomized studies.

Declarations

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Declarations: All authors have reported that they have no relationships relevant to the contents of this paper to disclose. All authors declare that they have no conflict of interest.

Availability of data: Contact the corresponding author (qiangeng9396@263.net) to get relevant data.

Authors' contributions: QG, JZC, JXS and AX analyzed and interpreted the STEMI patients' data. LT analyzed CMR data, DW, GJ, CYD enrolled patients, ZY performed the CMR examination, and QG was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

Ethics approval: The study complied with the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study. The trial was registered on ClinicalTrials.gov (registration number: NCT02826616). There is no potential conflicts of interest. The study was approved by the Beijing Ethics Association and the Ethics Committee of the Chinese PLA General Hospital.

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Tables

Table 1 Baseline characteristics of trimetazidine group and control group

	Trimetazidine group (N = 87)	Control group (N = 86)	P value
Demographic characteristics			
Male (%)	79 (90.8)	77 (89.5)	0.804
Age (years)	57±11	58±12	0.638
Medical history			
Hypertension (%)	41 (47.1)	51 (59.3)	0.128
Diabetes mellitus (%)	17 (19.5)	21 (24.4)	0.467
Hypercholesterolemia (%)	16 (18.4)	20 (23.2)	0.459
Smoker (%)	50 (57.5)	50 (58.1)	1.000
Premature CAD family (%)	14 (16.1)	13 (15.1)	1.000
Stroke (%)	4 (4.6)	6 (7.0)	0.535
Prior PCI	3 (3.4)	6 (7.0)	0.329
Prior CABG	1 (1.1)	1 (1.2)	1.000
Clinical manifestation at presentation			
Weight (kg)	74±12	75±13	0.439
SBP(mmHg)	122±22	122±23	0.866
DBP(mmHg)	71±13	72±15	0.679
Heart rate(bpm)	79±14	80±15	0.594
Symptom to balloon time (hour)	5.8±2.6	5.8±2.8	0.927
Killip class 3 or 4(%)	2 (2.3)	3 (3.5)	0.682
Hemoglobin (g/L)	145±17	147±17	0.346
White blood cell (10 ⁹ /L)	11.14±3.56	10.84±3.88	0.598
Platelet count (10 ¹² /L)	223±76	221±62	0.806
Random glucose (mmol/l)	7.54±2.50	7.55±2.47	0.995
Alanine aminotransferase	40±30	37±28	0.519
LDL-c (mmol/l)	2.90±0.94	2.94±0.92	0.772
Serum creatinine	79±34	77±18	0.589
Blood urea nitrogen	5.78±2.33	5.57±1.48	0.493
Baseline Brain Natriuretic Peptide	(74, 645)	(73, 439)	0.299 #
Treatment after primary PCI			
Aspirin and ticagrelor	87(100.0)	86 (100.0)	1.000
Statin	87(100.0)	86 (100.0)	1.000
Beta-blockers	77 (88.5)	78 (90.7)	0.804
ACEI/ARB	58 (66.7)	54 (62.8)	0.635

ACEI/ARB: angiotensin converting enzyme inhibitors or angiotensin receptor blockers, CABG: coronary artery bypass graft, DBP: diastolic blood pressure, LDL-c: low density lipoprotein cholesterol, PCI: percutaneous coronary intervention, SBP: systolic blood pressure, # non-parameter tests

Table 2 Angiographical and procedural characteristics of trimetazidine group and control group

	Trimetazidine group (N = 87)	Control group (N = 86)	P value
Pre TIMI grade flow, n (%)			0.548
0	66 (75.9)	72 (83.7)	
1	2 (2.3)	1 (1.2)	
2	7 (8.0)	7 (8.1)	
3	11 (12.6)	6 (7.0)	
Post TIMI grade flow, n (%)			0.308
0	1 (1.1)	1 (1.2)	
1	1 (1.1)	4 (4.7)	
2	3 (3.4)	5 (5.8)	
3	82 (94.3)	76 (88.4)	
Culprit Vessel, n (%)			
LM	1 (1.1)	0 (0)	0.497
LAD	39 (44.8)	37 (43.0)	0.879
LCX	7 (8.0)	13 (15.1)	0.161
RCA	40 (46.0)	35 (40.7)	0.540
Thrombectomy, n (%)	25 (28.7)	23 (26.7)	0.865
Number. of stent per patients, n (%)	1.3±0.6	1.3±0.7	0.822
IABP, n (%)	4 (4.6)	4(4.7)	1.000

IABP: intra aortic balloon pumping, TIMI: thrombolysis in myocardial infarction.

Table 3 Troponin T in trimetazidine group and control group after reperfusion

	Trimetazidine group (N =87)	Control group (N =86)	Difference (95% CI)	P value
troponin T, ng/l				
0 h	700 (2390)	685 (2580)	26 (-563 to 616)	0.763
3 h	3561(4250)	4025(5580)	-880 (-1960 to 200)	0.156
12h	3754 (5410)	5028 (4070)	-1469 (-2923 to -145)	0.028
24h	3290 (3550)	4083 (4420)	-1458 (-2719 to -197)	0.034
48h	2450 (3060)	2880 (3170)	-815 (-1900 to 269)	0.160

Table 4 Primary endpoints as measured by cardiac magnetic resonance

	Trimetazidine group (N =74)	Control group (N = 74)	P value
Left ventricle end-diastolic volume, ml	132±37	139±40	0.260
Infarct size, Proportion of LV mass, %	22±12	27±13	0.011
Infarct size, g	28±18	35±19	0.022
Area at risk, g	57±31	58±27	0.853
Myocardial salvage index, %	48±20	39±27	0.008
Prevalence of microvascular obstruction, (%)	22/74 (29.7)	39/74 (52.7)	0.007
Microvascular obstruction, g	0.8±1.8	2.0±4.0	0.017

Table 5 Main adverse cardiac events for one year follow-up

	Trimetazidine group (N = 87)	Control group (N = 86)	P value
Total adverse cardiovascular events	13 (14.9)	18 (20.9)	0.328
Stroke, n (%)	1 (1.1)	0 (0)	1.000
Recurrent myocardial infarction, n (%)	1 (1.1)	1 (1.2)	1.000
Rehospitalization for heart failure, n (%)	7 (8.0)	12 (14.0)	0.234
All cause Death, n (%)	4 (4.6)	5 (5.8)	0.747

Figures

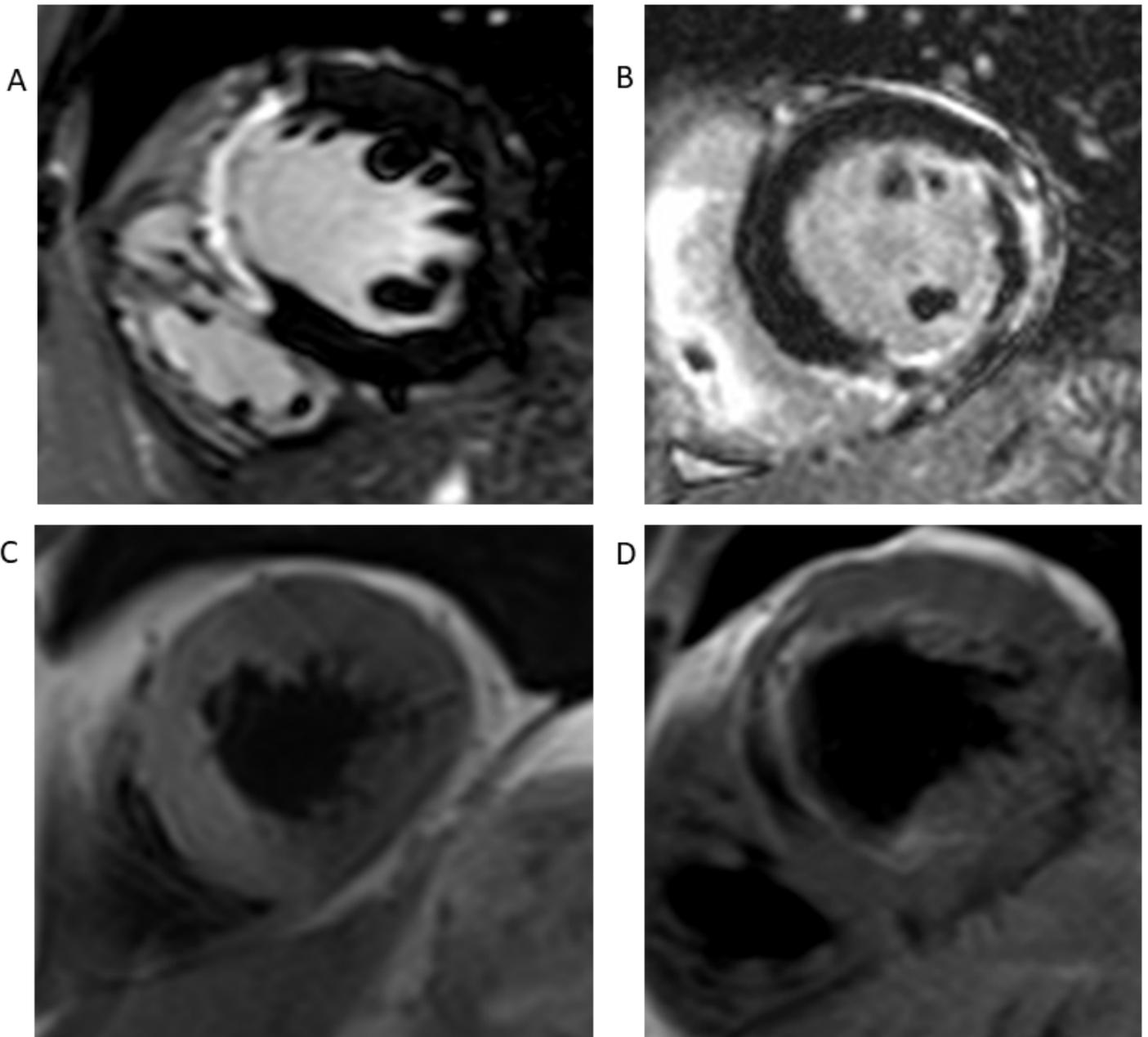


Figure 1

Examples of delayed enhancement and T2-weighted cardiac magnetic resonance images of patients with ST-segment elevation myocardial infarction (STEMI) which showed a lesion in the left anterior descending artery. Delayed enhancement image used for final infarction size analysis (A), and T2-weighted image used for area at risk analysis (C, D), late gadolinium enhancement to assess myocardial infarction size and microvascular obstruction . T2 maps depict the area of myocardial edema.

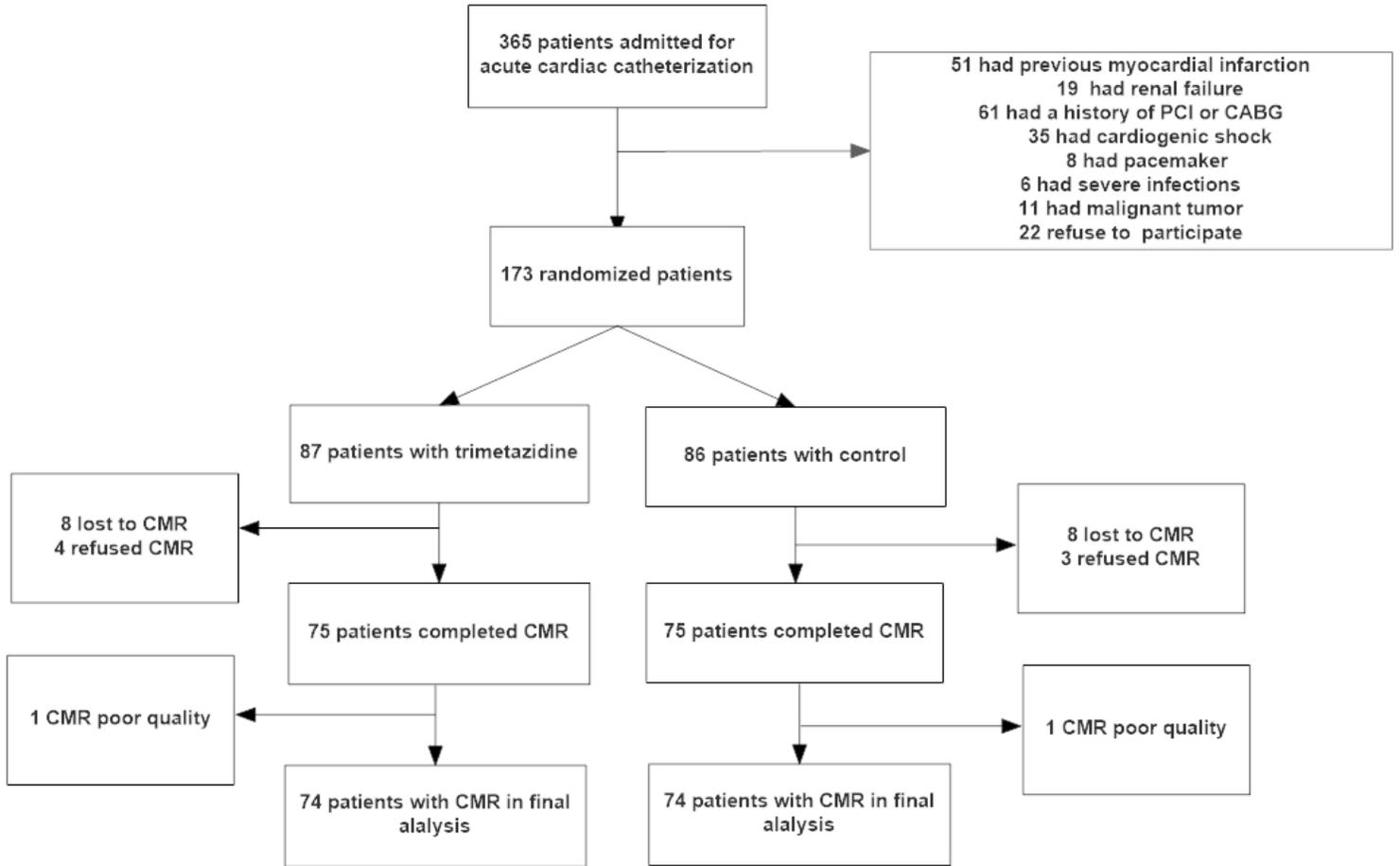


Figure 2

Flow chart of the study: A total of 173 patients were enrolled

Dynamic changes of high sensitive Troponin T in reperfusion treatment

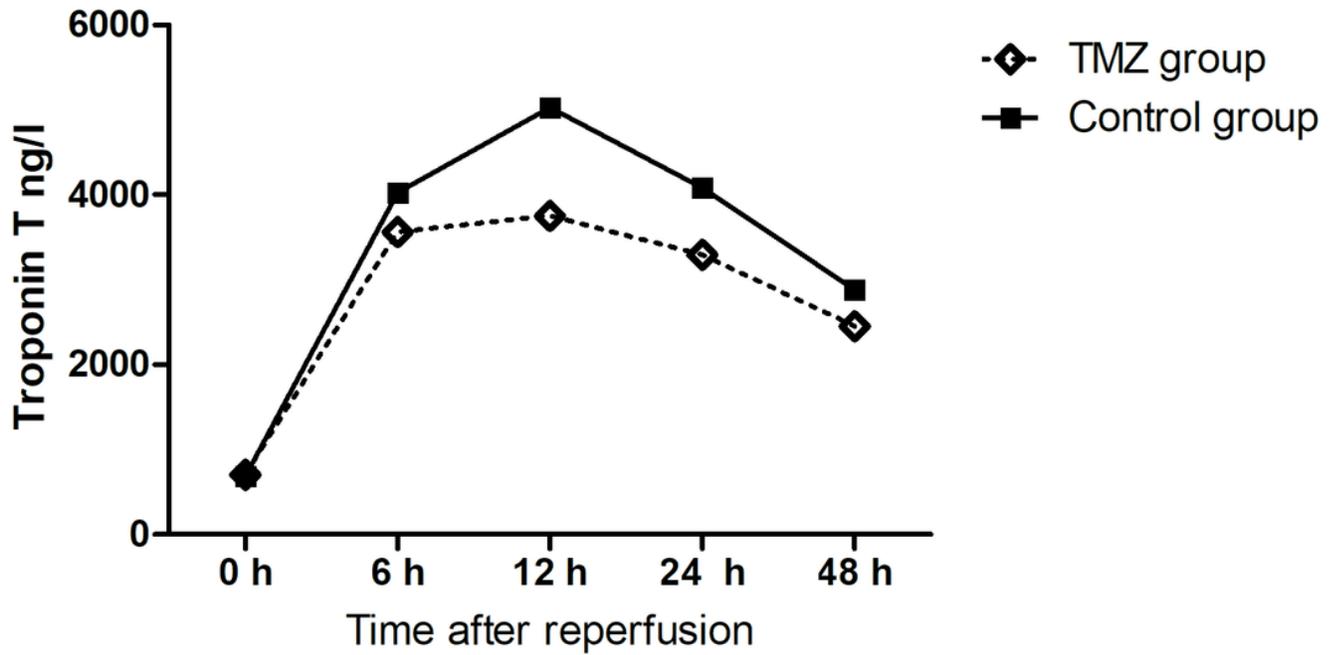


Figure 3

Dynamic changes of high sensitive Troponin T (hsTnT) in reperfusion treatment: The hsTnT level of patients in trimetazidine (TMZ) group (solid line) was significantly lower at 12h and 24 h after reperfusion when compared to control ones (dashed line).

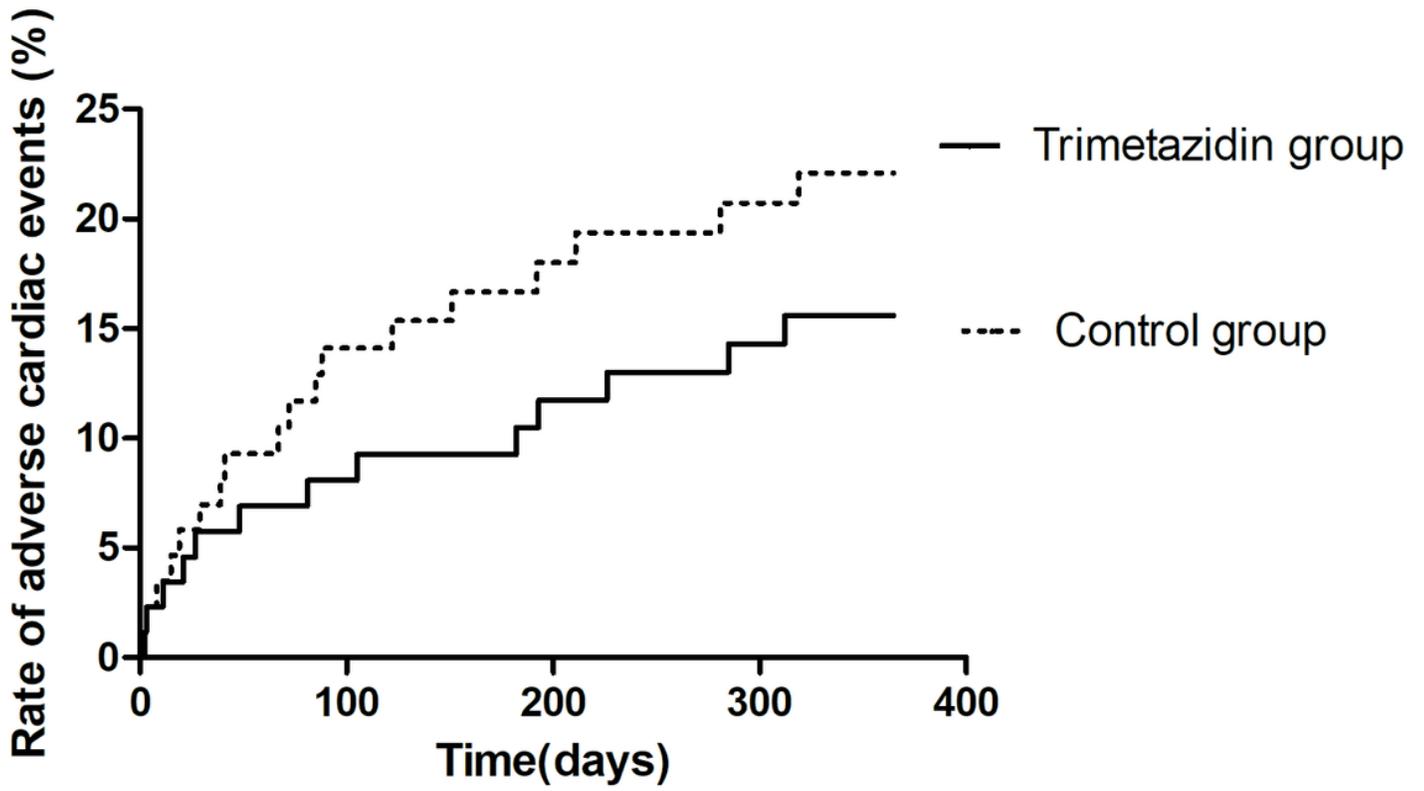


Figure 4

Main adverse cardiac events in the study patients: Less occurrences of cumulative major adverse events were observed in trimetazidine (TMZ) group compared with the control group.