Sustained nicorandil administration reduces the infarct size in ST-segment elevation myocardial infarction patients with primary percutaneous coronary intervention

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Abstract

Objective: Currently, there is still no effective strategy to diminish the infarct size (IS) in patients with ST-segment elevation myocardial infarction (STEMI). According to a previous animal study, nicorandil treatment is a promising pharmaceutical treatment to limit the infarct area. In this study, we aim to investigate the effects of continual nicorandil administration on the IS and the clinical outcomes in patients with STEMI who underwent primary percutaneous coronary intervention (pPCI).

Methods: One hundred seventeen patients with STEMI and undergoing pPCI were randomly divided into the sustained nicorandil group (5 mg, three times daily) or the control group (only single nicorandil before PCI). The primary endpoint was the IS, evaluated by single-photon emission computed tomography (SPECT) 3 months after pPCI.

Results: Eighty-five patients completed the IS assessment via SPECT, and 99 participants were available for follow-up after 6 months. Finally, there was a statistical difference in the IS between the nicorandil and control groups {13% [interquartile range (IQR), 8–17] versus 16% [IQR, 12–20.3], p=0.027}. Additionally, we observed that maintained nicorandil administration significantly improved the left ventricular ejection fraction at 3 months and enhanced the activity tolerance (physical limitation and angina stability) at 6 months after PCI.

Conclusion: Sustained nicorandil treatment reduced the IS and improved the clinical outcomes compared to the single nicorandil administration for patients with STEMI undergoing the pPCI procedure. Continuous cardioprotective therapy may be more beneficial for patients with STEMI. *(Anatol J Cardiol 2019; 21: 00-00)*

Keywords: nicorandil, ST-segment elevation myocardial infarction, infarct size, percutaneous coronary intervention, single-photon emission computed tomography

Introduction

Timely reperfusion therapy, especially via primary percutaneous coronary intervention (pPCI), plays a key role in the treatment of the ST-segment elevation myocardial infarction (STEMI), and it contributes to a marked decrease in the acute mortality of patients with STEMI (1). However, the ischemic/reperfusion injury following pPCI remains unsolved and results in a lower myocardial survival rate and a higher morbidity of heart failure (2, 3). Coronary microvascular obstruction (CMVO) and myocardial injury widely existed in patients with acute myocardial infarction (AMI) after the treatment with PCI, contributing to the final infarct size (IS) (3-6). The IS is the major determinant of the adverse cardiac remodeling associated with unfavorable prognosis. Disappointingly, a vast number of clinical studies had not yet identified a solid strategy to diminish IS (4, 6-8). Thus, it is necessary to explore novel therapeutics.

Nicorandil, a combined agent with an adenosine triphosphate-sensitive K (K_{ATP}) channel agonist and nitrate preparation, could improve clinical outcomes for ischemic heart disease through relieving both microcirculation dysfunction and myo-

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cardial injury (9-11). Additionally, several experimental studies had observed that nicorandil could reduce myocardial IS by approximately 50% (12-14). However, it is still controversial whether nicorandil diminishes IS in patients with acute myocardial infarct (15). Indeed, nicorandil was mostly administered a short time before PCI or during the perioperative period in previous trials (15, 16). However, microvascular obstruction would still deteriorate continuously after pPCI, and myocardial stunning may require several days or weeks to recover (10, 17). Thus, we decided to assess the effects of continuous oral nicorandil administration on decreasing IS and improving the outcome for STEMI patients with pPCI.

Methods

Patients

This trial was a pilot study with a prospective, randomized, open-label, and controlled design. One hundred thirty-four patients with their first STEMI were recruited consecutively in the Cardiac Care Unit of Xijing Hospital from September 2016 to February 2017. Briefly, inclusion criteria were as follows: (a) age between 18 and 79 years; (b) first STEMI diagnosis and prepared for pPCI treatment; and (c) within 12 hours from the onset of symptoms to hospital admission. The diagnosis of STEMI was given according to chest pain lasting for more than 30 minutes, at least 1 mm ST-segment elevation in two contiguous leads, and an increase in cardiospecific biomarkers.

Exclusion criteria were as follows: (a) previous myocardial infarction or cardiomyopathy; (b) culprit lesion in the left main trunk with hemodynamic instability; (c) Killip classiŞcation III or IV; (d) failure to open occlusion by pPCI or transferred to coronary artery bypass grafting; (e) glucose control with sulfonylureas (K_{ATP} channel inhibitor); (f) severe liver, kidney, or lung diseases; (g) history of drug allergy; and (h) severe glaucoma.

After meeting the eligibility criteria, patients with STEMI were assigned to the nicorandil group or the control group according to a stochastic sequence generated via the computer. All patients were given 5 mg of oral nicorandil after the hospital admission. Then, the nocorandil group was given 5 mg nicorandil three times a day for 6 months following PCI. Other treatments were completed according to the standard guidelines for both groups.

Protocols

All patients enrolled were treated on the basis of the current guidelines and recommendations for the management of patients with STEMI. Nicorandil was administered as an adjuvant treatment.

Once emergency patients were diagnosed with STEMI, dual antiplatelet therapy was given with a loading dose of aspirin, ticlopidine, or clopidogrel. Prior to catheterization, all patients received intravenous heparin (70 IU/kg). The pPCI procedure was performed in a standardized manner. Patients with no-reflow (TIMI flow grade ≤2) were treated with tirofiban, intracoronary sodium nitroprusside or adenosine in the catheterization laboratory. Statins, beta-blockers, angiotensin-converting enzyme inhibitor (ACEI), and angiotensin receptor blocker (ARB) were given according to the patient condition.

Electrocardiography was performed before entering the catheterization laboratory. Blood samples were taken to measure the levels of cardiospecific enzymes or biomarkers, such as CK-MB and Troponin I (TnI), after admission and 24 hours after PCI. Resting ECG-gated single-photon emission computed tomography (SPECT) was performed at 3 months after PCI. As described previously (18), the SPECT image acquisition began 50–60 min after the technetium-99 m-sestamibi injection (740–900 MBq, weight adjusted). After processing and reconstructing, an image analysis was performed using an Entegra (GE Medical Systems) processing station. The area of the deficiency was quantiŞed with a threshold of 50% of the peak uptake. The IS was expressed as a percentage of the left ventricle. Echocardiography (Philips Ultrasound, Washington, USA) was performed to assess the left ventricular ejection fraction (LVEF) at admission, 1, 3, and 6 months after PCI. As our previous methods (18), echocardiograms were measured by two experienced cardiac ultrasound technicians blinded to the groups. If a discrepancy between the readings of >5% was noted, a third observer participated, and a consensus was achieved. The interobserver variability analysis showed a good repeatability (LVEF, 1.2±4.1%) with the Bland–Altman test. The Seattle Angina Questionnaire (SAQ) was recorded at 6 months. SAQ was applied to measure speciŞc health conditions and the quality of life in coronary artery disease, including physical limitations, angina stability, angina frequency, treatment satisfaction and disease perception (18). Additionally, we also collected major cardiac adverse events (MACE), including all-cause death, myocardial reinfarction, severe heart failure, and unplanned rehospitalization from a cardiac cause. Those examinations were performed by experienced colleagues who were blinded.

The primary endpoint was the IS, quantiŞed as a percentage of LV wall, was evaluated by SPECT at 3 months. The secondary endpoints were LVEF and SAQ assessed at 6 months. Our study was approved by the Ethical Committee of Xijing Hospital, Fourth Military Medical University, Xi'an, Shaanxi, China. The protocol has been registered at www.chictr.org.cn/ (Clinical Trials number, ChiCTR-IPC-16009477). All of the patients gave their written, informed consent.

Statistical analysis

This study was a superiority trial, and the primary purpose was to observe whether sustained oral nicorandil reduced myocardial IS. We defined the power of the statistical test ($1-\beta$) as 0.8, the significance level α as 0.05. As in the current literature, the standard deviation (SD) of IS was assessed by SPECT, rang-

ing from 4% to 18% (18-20). We supposed that the mean±SD of IS for the nicorandil group was 15%±10% and that the IS for the control group was 20%±10%. A sample size of 50 patients would be required in each group. Given the ratio of loss for follow-up or withdrawal was 10%, the population that we needed was no less than 110. Taking into consideration that some patients refused or were unsuited for SPECT, we recruited another 10 patients consecutively.

Statistical analysis was based on the principle of Intention to Treat. Continuous data with a normal distribution were expressed as the means and standardized deviations, compared by Student's t-test. If normality tests failed, the data were described as medians and interquartile ranges (IQR) and assessed by the Mann–Whitney U test. Categorical parameters were presented as a proportion or number, compared with the chi-square test or Fisher's exact test. To perform a subgroup analysis, we transformed the primary endpoint of IS, to binary data [defining greater than or equal the median of IS (14%) as larger area]. The risk ratio and 95% confidence intervals were estimated and analyzed by a logistic regression analysis. Statistical analysis was performed with the SPSS software package (SPSS, version 14.0, Chicago, IL, USA) and STATA (StataCorp LP, version 10, College Station, Texas, USA). All tests were two-sided, and p-value of <0.05 was considered to be statistically significant.

Results

Figure 1 shows the patient profiles in the study. Of the 134 patients who were diagnosed as STEMI, 17 were excluded for

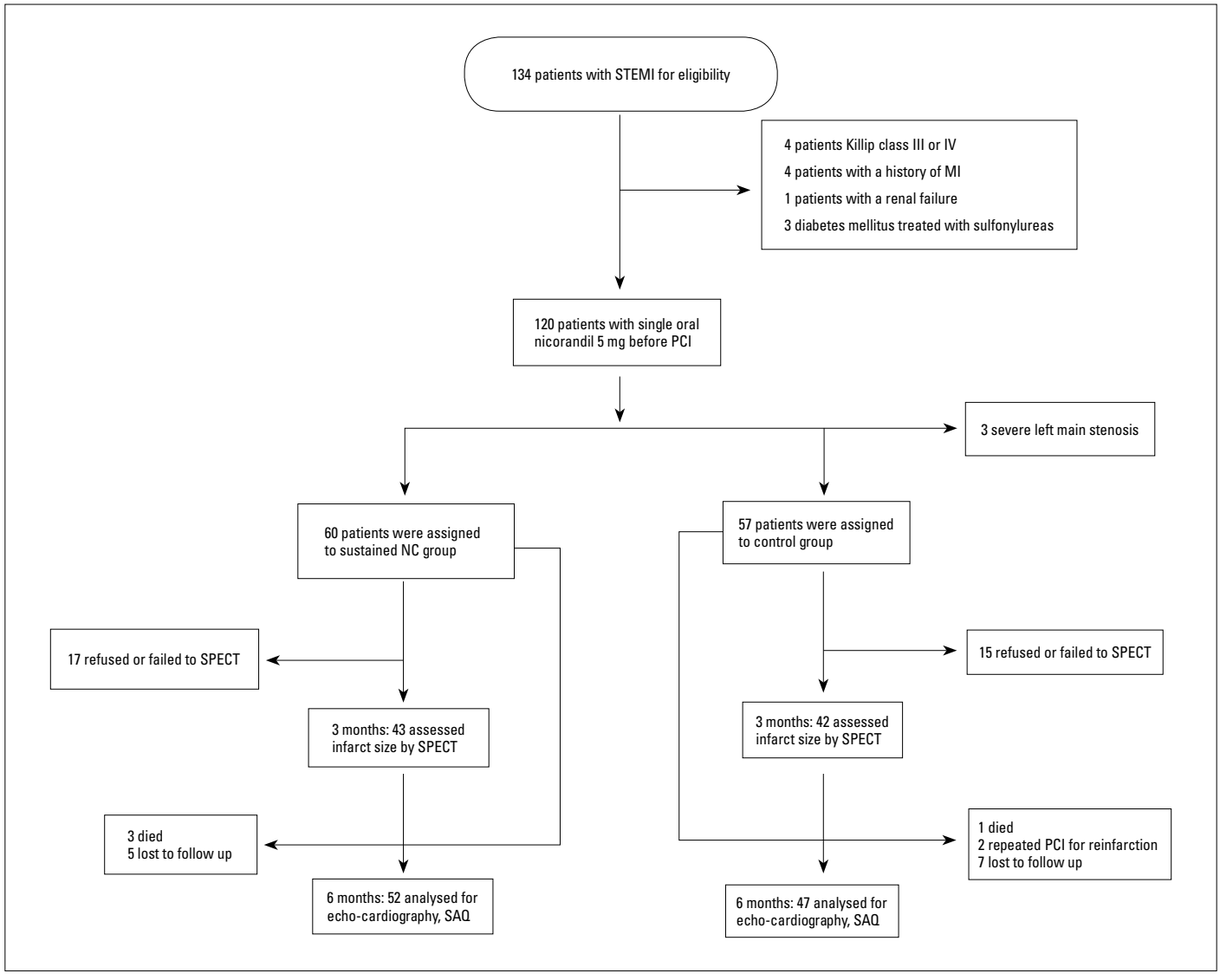

Figure 1. Diagram of study flow

NC - nicorandil; SPECT - single-photon emission computed tomography; SAQ - Seattle Angina Questionnaire scores; STEMI - ST- segment elevation myocardial infarction; PCI - percutaneous coronary intervention

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Table 1. Baseline characteristics, angiographic data, and treatments

	Nicorandil group (n=60)	Control group (n=57)	*P*-value
Age (years)	58.4±9.99	55.8±10.56	0.176
Gender (male)	54 (90%)	47 (82.5%)	0.235
BMI	26.0±2.72	25.1±2.52	0.060
SBP (mm Hg)	126.3±21.56	129.0±23.05	0.522
DBP (mm Hg)	77.4±13.17	78.9±12.81	0.540
Killip class (I)	46 (76.7%)	39 (68.4%)	0.317
Diabetes mellitus	12 (20.0%)	10 (17.5%)	0.734
Hypertension	28 (46.7%)	22 (38.6%)	0.378
Current smoking	35 (58.3%)	27 (47.4%)	0.235
Blood glucose (mmol/L)	6.5±1.55	6.6±2.04	0.761
TC (mmol/L)	3.8±0.82	3.6±0.72	0.187
TG (mmol/L)	1.64±0.90	1.61±1.01	0.851
HDL	1.03±0.25	1.07±0.30	0.438
LDL	2.26±0.84	2.31±0.87	0.769
TnI (ng/mL)	6.8 (2.17-24.76)	6.5 (1.21-27.72)	0.524
CK-MB (ng/mL)	55.1 (4.0-156.7)	46.9 (4.4-150.1)	0.579
LVEF (%)	49 (42-57.75)	50 (43.5-57)	0.851
Symptom-balloon time (hours)	6 (4-9)	5 (3.5-8)	0.170
IRA			0.483
LAD	31 (51.7%)	28 (49.1%)	
LCX	10 (16.7%)	6 (10.5 %)	
RCA	19 (31.7%)	23 (40.4%)	
Multivessel disease (%)	26 (43.3%)	21 (36.8%)	0.474
TIMI flow grade before PCI			0.329
0	41 (68.3%)	42 (73.3%)	
1	10 (16.7%)	4 (7.0%)	
2	4 (6.7%)	7 (12.3%)	
3	5 (8.3%)	4 (7.0%)	
Patients with stents (%)	56 (93.3%)	50 (87.7%)	0.298
Number of stents	1.32±0.62	1.26±0.75	0.637
Stent diameter (mm)	3.23±0.64	3.06±0.77	0.141
Final TIMI flow grade 3	53 (88.3%)	51 (89.5%)	0.844
Medications of perioperative period			
Aspirin	60 (100%)	57 (100%)	-
Clopidogrel	26 (43.3%)	30 (52.6%)	0.171
Ticagrelor	34 (56.7%)	27 (47.4%)	0.314
Statins	60 (100%)	57 (100%)	-
β-blockers	52 (86.7%)	46 (80.7%)	0.382
ACEI or ARB	41 (68.3%)	32 (56.1%)	0.174

Data are median (interquartile range), number (%) or mean (SD), unless otherwise stated.
ACEI - angiotensin-converting enzyme inhibitor; ARB - angiotensin receptor blocker; BMI - body mass index; CK-MB - creatinine kinase MB isoenzyme; HDL - high-density lipoprotein; LDL - low-density lipoprotein; TC - total cholesterol; TG - triglyceride; TnI - Troponin I; LVEF - left ventricular ejection fraction; IRA - infarct related artery; LAD - left anterior descending coronary artery; LCX - left circumşex artery; RCA - right coronary artery; TIMI - thrombolysis in Myocardial Infarction Score; PCI - percutaneous coronary intervention

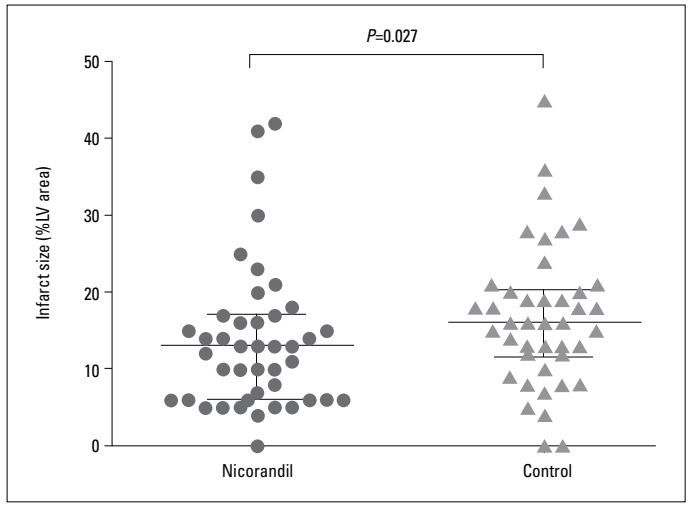

Figure 2. Effect of continual oral nicorandil administration on the infarct size assessed by single-photon emission computed tomography at 3 months after percutaneous coronary intervention
Lines represent median and interquartile range. Spots indicate individual data

several reasons (Killip III–IV class, previous MI, renal failure, and oral sulfonylureas), and 117 patients were eligible in our study. The baseline characteristics of the patients are presented in Table 1. Finally, 99 patients with a first STEMI diagnosis in both groups completed the follow-up at 6 months. No significant difference was observed with regard to LVEF, CK-MB, and TnI before pPCI and coronary angiography features, indicating that the cardiac injury level in both groups may be similar before reperfusion (Table 1).

The impact of nicorandil on IS was evaluated by SPECT 3 months after pPCI and expressed as a percentage of the left ventricle wall (Fig. 2 and Table 2). Actually, only 85 patients performed the SPECT scan and were suitable for an IS assessment. No statistically significant difference of population characteristics was observed in the subjects who received the SPECT examination

Table 2. Primary endpoint and other outcomes

	Nicorandil group	Control group	*P*-value
3 months	**n=43**	**n=42**	
Infarct size (LV area %)*	13 (8.0-17.0)	16 (12.0-20.3)	**0.027**
24 h	**n=60**	**n=57**	
TnI (ng/mL)	14.5 (3.58-46.55)	23.4 (5.01-67.25)	**0.042**
CK-MB (ng/mL)	75.1 (5.4-183.6)	80.6 (5.1-194.6)	0.325
1 month	**n=57**	**n=55**	
LVEF (%)	53 (47-58)	50 (46-57)	0.230
LVFS (%)	27 (23-30)	25 (22-30)	0.352
LVEDV (mL)	108 (93-125)	111 (91-131)	0.505
LVESV (mL)	52 (41-61)	52 (45-72)	0.302
3 months	**n=55**	**n=51**	
LVEF (%)	55 (51-58)	52 (47-56)	**0.039**
LVFS (%)	28 (25-30)	26 (23-30)	0.059
LVEDV (mL)	108 (93-118)	110 (92-125)	0.105
LVESV (mL)	48 (36-60)	53 (42-62)	0.043
6 months	**n=52**	**n=47**	
LVEF (%)	55 (51-60)	52 (48-59)	0.090
LVFS (%)	29 (25-31)	26 (24-30)	0.101
LVEDV (mL)	105 (93-113)	109 (99-124)	0.125
LVESV (mL)	48 (38-53)	53 (45-61)	0.053
SAQ			
Physical limitation	73.3±14.07	67.4±13.21	**0.034**
Angina stability	63.8±10.74	55.8±12.10	**0.001**
Angina frequency	79.3±12.07	77.3±14.09	0.445
Treatment satisfaction	86.5±8.32	88.2±6.87	0.282
Disease perception	70.1±6.79	71.3±6.65	0.369

*Primary endpoint
TnI - troponin I; CK-MB - creatinine kinase MB isoenzyme; LVEF - left ventricular ejection fraction; LVEDV - left ventricular end-diastolic volume; LVESV - left ventricular end-systolic volume; SV - stroke volume; SAQ - Seattle Angina Questionnaire scores

(Supplemental Table 1). The patients in the oral sustained nicorandil group had a statistically smaller IS than the control group [13% (IQR, 8–17) versus 16% (IQR, 12–20.3), p=0.027].

The cardiac biomarkers (TnI and CK-MB) at 24 h after PCI were higher than before treatment. However, TnI in the sustained nicorandil group was relatively low compared with the control group [14.5 (3.58–46.55) vs. 23.4 (5.01–67.25), p=0.042], indicating continual nicorandil tends to relieve myocardial injury. Echocardiography was applied to evaluate cardiac function at 1, 3, and 6 months after pPCI. Based on data analysis, sustained oral nicorandil treatment showed a significant improvement in LVEF [55 (51–58) vs. 52 (47–56), p=0.039] and LVESV [48 (36–60) vs. 53 (42–62), p=0.043] at 3 months. Additionally, there was still a

Supplemental Table 1. Baseline characteristics of patients with STEMI with IS assessment

	Nicorandil group (n=43)	Control group (n=42)	*P*-value
Age (years)	58.2±9.84	56.7±10.68	0.504
Gender (male)	41 (95.3%)	35 (83.3%)	0.148
BMI	26.3±2.60	25.3±2.38	0.064
Killip class (I)	33 (76.7%)	28 (66.7%)	0.302
Diabetes mellitus	6 (14%)	6 (14.3%)	0.965
Hypertension	21 (48.8%)	17 (40.5%)	0.438
Current smoking	26 (60.5%)	22 (52.4%)	0.452
Blood glucose (mmol/L)	6.7±2.15	7.3±2.88	0.291
TC (mmol/L)	3.8±0.86	4.0±0.88	0.570
TG (mmol/L)	1.5±0.81	1.7±1.33	0.496
TnI (ng/ml)	4.0 (1.93-20.85)	3.7 (1.2-27.8)	0.651
CK-MB (ng/mL)	50.8 (4.0-159.5)	41 (3.3-150.6)	0.276
LVEF (%)	49 (43-57)	48 (43.8-55.3)	0.937
Symptom-balloon time (hours)	5 (3-8)	5 (2.6-7.6)	0.381
IRA			0.790
LAD	21 (48.8%)	20 (47.6%)	
LCX	7 (16.3%)	5 (11.9 %)	
RCA	15 (34.9%)	17 (40.5%)	
Multivessel disease (%)	20 (46.5%)	15 (35.7%)	0.312
TIMI flow grade before PCI			0.508
0	29 (67.4%)	31 (73.8%)	
1	9 (20.9%)	4 (9.5%)	
2	3 (7.0%)	4 (9.5%)	
3	2 (4.7%)	3 (7.1%)	
Patients with stents (%)	39 (90.7%)	37 (88.1%)	0.697
Medications of perioperative period			
Aspirin	43 (100%)	42 (100%)	-
Clopidogrel	18 (41.9%)	22 (52.4%)	0.331
Ticagrelor	22 (51.2%)	22 (52.4%)	0.911
Statins	43 (100%)	42 (100%)	-
β-blockers	39 (90.7%)	37 (88.1%)	0.697
ACEI or ARB	30 (69.8%)	24 (57.1%)	0.227

Of 117 patients eligible in this trial, only 85 patients received the SPECT scan and were suitable for IS assessment. Their baseline characteristics are presented above and have no significant difference, indicating a possible comparability.
STEMI - ST-segment elevation myocardial infarction; IS - infarct size; BMI - body mass index; TC - total cholesterol; TG - triglyceride; TnI - troponin I; CK-MB - creatinine kinase MB isoenzyme; LVEF - left ventricular ejection fraction; IRA - infarct related artery; LAD - left anterior descending coronary artery; LCX - left circumşex artery; RCA - right coronary artery; TIMI - thrombolysis in Myocardial Infarction Score; PCI - percutaneous coronary intervention; ACEI - angiotensin-converting enzyme inhibitor; ARB - angiotensin receptor blocker

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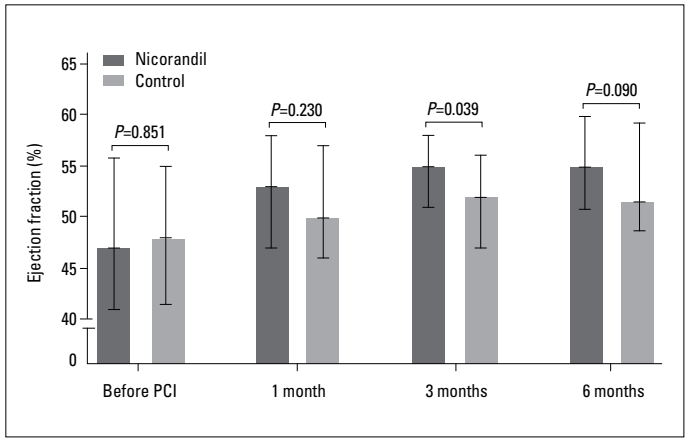
Supplemental Table 2. The incidence of MACE at 6 months after acute myocardial infarction

	Nicorandil group n=55	Control group n=50	*P*-value
MACE	10 (18.2%)	13 (26.0%)	0.333
All-cause death	3 (5.5%)	1 (2.0%)	0.679
Reinfarction	0	2 (4.0%)	0.434
Severe heart failure	4 (7.3%)	5 (10.0%)	0.881
Rehospitalization**	6 (9.1%)	8 (16.0%)	0.300

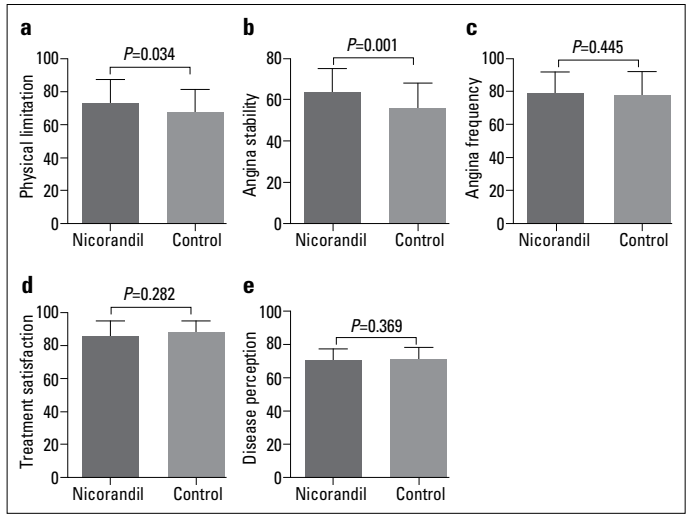
**Unplanned rehospitalization for cardiac cause
MACE includes all-cause death, myocardial reinfarction, severe heart failure, and unplanned rehospitalization from a cardiac cause. There was no significant difference in the incidence of adverse cardiac events. MACE - the major adverse cardiac events



Supplemental Figure 1. Effects of long-term nicorandil administration on cardiac function
Left ventricular ejection fraction (LVEF) assessed by echocardiography at admission to hospital, and 1, 3, and 6 months after PCI. Sustained oral nicorandil treatment led to a significant improvement in LVEF at 3 months. Additionally, there was still a tendency toward a higher LVEF at 6 months, although the difference between both groups was moderate. The columns and error bars represent the median and interquartile ranges

tendency toward a higher LVEF at 6 months, although the difference between both the groups was significant [55 (51–60) vs. 52 (48–59), p=0.090; Table 2 and Supplemental Fig. 1].

Maintained nicorandil also improved the quality of life for STEMI patients (Table 2 and Supplemental Fig. 2). The follow-up data of SAQ 6 months post-pPCI indicated that continual nicorandil treatment ameliorated physical limitations (73.3±14.07 vs. 67.4±13.21, p=0.034) and angina stability (63.8±10.74 vs. 55.8±12.10 p=0.001). A subgroup analysis did not reveal any statistical heterogeneity with regard to age, body mass index, diabetes mellitus, current smoking status, symptom onset-balloon time, and left anterior descending coronary artery (Fig. 3). No significant difference in the incidence of adverse cardiac events was observed (Supplemental Table 2).



Supplemental Figure 2. Effects of nicorandil on the quality of life at 6 months after percutaneous coronary intervention
Seattle Angina Questionnaire scores (SAQ) evaluate five aspects: physical limitation, angina stability, angina frequency, treatment satisfaction, and disease perception. Continuous nicorandil treatment ameliorated physical limitations and angina stability at 6 months after primary percutaneous coronary intervention. The columns and error bars represent the means and standard deviation (SD)

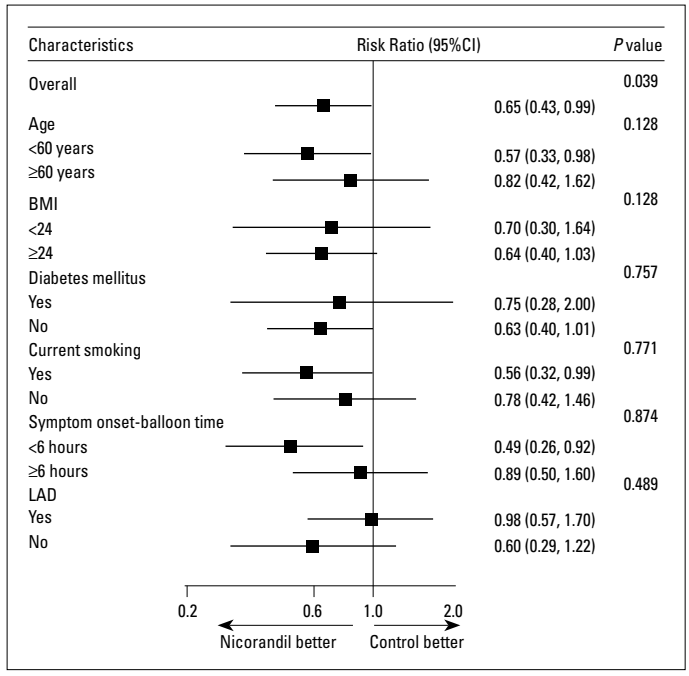


Figure 3. Subgroup analyses of the primary endpoint
Risk ratio, with 95% confidence intervals is applied to reflect the effect of nicorandil, with transforming continuous infarct size into a large infarct size (≥ median, 14%) and small.
BMI - body mass index; LAD - left anterior descending coronary artery

Discussion

This study shows that compared with a single oral nicorandil treatment, sustained administration of nicorandil reduced myo-

cardial infarction area [13%, (8–17) vs. 16% (12–20.3), p=0.027] and elevated LVEF (55% vs. 52%, p=0.039) and LVESV (48 mL vs. 53 mL, p=0.043) at 3 months and quality of life [physical limitation (73.3±14.07 vs. 67.4±13.21, p=0.034) and angina stability (63.8±10.74 vs. 55.8±12.10, p=0.001)] at 6 months in STEMI patients undergoing primary PCI. The IS is closely associated with clinical outcomes (21). The main purpose of our trial is to investigate the cardioprotective effects of continual nicorandil treatment on IS reduction in patients with STEMI and Killip I–II.

As it has a unique structure, nicorandil has a variety of cardiac protective mechanisms through the K_{ATP} channel agonism and NO pathways. Nicorandil effectively improves the symptoms and outcomes of ischemic heart disease (11, 22). In addition to relaxing large coronary vessels via NO, nicorandil dilates the microvasculature to improve cardiac perfusion by activating K_{ATP} channels specifically. Nicorandil also protects myocytes through opening K_{ATP} channels located in the sarcolemma and mitochondrion under ischemia-reperfusion conditions (9). Moreover, nicorandil has other cardioprotective mechanisms, such as inhibiting apoptosis and regulating cardiac sympathetic nerve activity and mediating autophagy (23-25).

According to the mechanisms described above, nicorandil may have a promising effect that can lessen the IS for AMI patients. As expected, animal experiments demonstrated that nicorandil reduced the infarct area by 52%–54.9% via activating the K_{ATP} channel (12, 13). Nevertheless, whether nicorandil limited the IS of patients with STEMI was still controversial. The J-WIND study aimed to assess whether nicorandil reduced the IS in patients with STEMI. Unexpectedly, nicorandil could not decrease the IS assessed by creatine kinase compared to the placebo. Another small study performed by Yamada et al. (16) enrolled 55 patients with AMI undergoing pPCI and administered intracoronary nicorandil or nitrate for 4 days. Their data revealed that nicorandil reduced IS by 18.9% compared with nitrate. In our study, the results exhibited that sustained oral nicorandil administration had the effect of reducing IS for patients STEMI undergoing pPCI.

Presumably, several reasons may explain this inconsistency. The J-WIND study employed continuous monitoring of CK to estimate IS indirectly. Although some studies indicated CK and CK-MB were associated with IS (correlation coefficient, 0.55–0.73). These biomarkers could only be thought as predictors of IS but not instead IS itself (21, 26, 27). Because reperfusion attached a rapid washout of CK in the ischemic band, it may affect the IS estimate (27). Second, the dosage impacted its effect. Previous studies also suggested that nicorandil improved exercise tolerance, cardiac function, and myocardial injury for CAD patients in a dose-dependent fashion. J-WIND study investigators also inferred the dosage of nicorandil is insufficient. Similarly, the primary endpoint in our trial was below expectations and may also be associated with dosage. Additionally, the time of medication may also be significant for nicorandil. In the J-WIND study, patients received intravenous nicorandil for 1 day, and no difference was observed. In Yamada et al. (16) study, nicorandil was given continuously for 4 days with a positive result. We evaluated IS at 3 months with continual oral nicorandil, and the above results may also support this point. In fact, there still remained persistent microvascular obstruction even at 6–10 days after MI (28, 29). Meanwhile, the stunned myocardium may need several weeks to recover contractile function (17, 30). Therefore, our trial, and previous studies, indicated that continuously alleviating CMVO and protecting cardiomyocytes were beneficial for saving variable myocadium.

In the present study, it was observed that the TnI level, rather than CK-MB, was statistically lower in the continual nicorandil group compared to the control group. The biomarker level was not measured successively, and those data only suggest that TnI at 24 h after PCI may be more sensitive than CK-MB to predict IS. Furthermore, other researchers observed early the CK-MB level at 4–12 h after PCI was a good predictor for IS, which may also support this point (26, 31). Consistent with previous reports, our results also indicated that sustained nicorandil administration elevated LVEF and the quality of life (15, 32). However, we did not observe a significant difference in LVEF at 6 months for both groups. Partly because the recovery of cardiac function existed in both groups as time passed, more patients were required to survey the effect. Additionally, numerous studies have demonstrated that nicorandil decreased the occurrence of MACE (11, 33). In this study, continuous nicorandil did not clearly affect the incidence of MACE, partly due to an insufficient sample size.

Study limitations

Several limitations existed in this study. First, the SPECT was chosen to assess IS in our study. Indeed, delayed enhancement CMR has a better spatial resolution to detect small myocardial infarcts than single-photon emission computed tomography (34). Second, we assessed IS at 3 months according to the equivalent myocardial injury of baseline. We did not collect the data about the area at risk at cute phases. Thus, the myocardial salvage index was not observed. Third, a follow-up for 6 months and a small sample size were insufficient to assess the long-term clinical outcomes and further subgroup analysis. Fourth, we just administered a routine dosage in this pilot study. The difference on IS was modest with 30% primary endpoint missing that resulted in possible selection bias. So it was not enough to be a clinical directive. Nicorandil plays a variety of biological roles in a dose-dependent manner (35-37), suggesting it may also reduce IS this way. Thus, the extent to which IS can be reduced by adjusting nicorandil administration still needs to be studied. Considering the distinct pathophysiology in the acute phase, we could further investigate the cardiac protective effect of nicorandil with sequential therapy, giving a large dose in the first week and continual standard doses thereafter.

Conclusion

A single administration of nicorandil before PCI may be insufficient to exert its protective effects. Our results suggest that

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sustained nicorandil administration has a more beneficial effects on reducing IS and improving clinical outcomes for patients with STEMI undergoing pPCI. Furthermore, continual pharmaceutical administration seems to be a promising strategy to reduce the necrosis area compared with short-term intervention after the onset that needs further validation.

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