Effects of Nicorandil Administration on Infarct Size in Patients With ST-Segment–Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention: The CHANGE Trial

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BACKGROUND: Nicorandil was reported to improve microvascular dysfunction and reduce reperfusion injury when administered before primary percutaneous coronary intervention. In this multicenter, prospective, randomized, double-blind clinical trial (CHANGE [Effects of Nicorandil Administration on Infarct Size in Patients With ST-Segment–Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention]), we investigated the effects of nicorandil administration on infarct size in patients with ST-segment–elevation myocardial infarction treated with primary percutaneous coronary intervention.

METHODS AND RESULTS: A total of 238 patients with ST-segment–elevation myocardial infarction were randomized to receive intravenous nicorandil (n=120) or placebo (n=118) before reperfusion. Patients in the nicorandil group received a 6-mg intravenous bolus of nicorandil followed by continuous infusion at a rate of 6 mg/h. Patients in the placebo group received the same dose of placebo. The predefined primary end point was infarct size on cardiac magnetic resonance (CMR) imaging performed at 5 to 7 days and 6 months after reperfusion. CMR imaging was performed in 201 patients (84%). Infarct size on CMR imaging at 5 to 7 days after reperfusion was significantly smaller in the nicorandil group compared with the placebo (control) group (26.5±17.1 g versus 32.4±19.3 g; P=0.022), and the effect remained significant on long-term CMR imaging at 6 months after reperfusion (19.5±14.4 g versus 25.7±15.4 g; P=0.008). The incidence of no-reflow/slow-flow phenomenon during primary percutaneous coronary intervention was much lower in the nicorandil group (9.2% [11/120] versus 26.3% [31/118]; P=0.001), and thus, complete ST-segment resolution was more frequently observed in the nicorandil group (90.8% [109/120] versus 78.0% [92/118]; P=0.006). Left ventricular ejection fraction on CMR imaging was significantly higher in the nicorandil group than in the placebo group at both 5 to 7 days (47.0±10.2% versus 43.3±10.0%; P=0.011) and 6 months (50.1±9.7% versus 46.4±8.5%; P=0.009) after reperfusion.

CONCLUSIONS: In the present trial, administration of nicorandil before primary percutaneous coronary intervention led to improved myocardial perfusion grade, increased left ventricular ejection fraction, and reduced myocardial infarct size in patients with ST-segment–elevation myocardial infarction.

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Key Words: cardiac catheterization ■ cardiac imaging techniques ■ nicorandil ■ prospective studies ■ ST elevation myocardial infarction
Primary percutaneous coronary intervention (PPCI) is considered the most effective treatment for reperfusion in patients with ST-segment–elevation myocardial infarction (STEMI), because it can reduce infarct size and improve prognosis for STEMI. However, even if successful revascularization is achieved, reperfusion injury may impair myocardial microvascular function, resulting in the occurrence of the no-reflow phenomenon, increased infarct size, and major adverse cardiovascular events (MACEs). Recent clinical trials found that nicorandil, a hybrid ATP-sensitive potassium channel opening agent, improved microvascular function, prevented no-reflow phenomenon, and had beneficial cardioprotective effects in patients receiving PPCI. However, some clinical studies produced controversial results on whether nicorandil exerted beneficial effects on infarct size and clinical outcomes. Most of the trials on nicorandil in patients with STEMI used myocardial enzyme levels, thrombolyis in myocardial infarction (TIMI) flow, or myocardial perfusion tomographic imaging as primary end points for reduction in myocardial damage. A major determinant of outcomes after STEMI is the extent of myocardial necrosis, which can be assessed by cardiac magnetic resonance (CMR) imaging. In addition, the infarct size changes dynamically during the acute phase of STEMI, and the effects of nicorandil before reperfusion on the final infarct size on CMR imaging remain unclear. The present multicenter, randomized, parallel-controlled, double-blind clinical trial was conducted to assess the infarct sizes after intravenous administration of nicorandil before reperfusion in patients with STEMI undergoing PPCI.

METHODS

The CHANGE (Effects of Nicorandil Administration on Infarct Size in Patients With ST-Segment–Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention) trial was a multicenter, prospective, randomized, double-blind, parallel-controlled clinical trial that compared administration of intravenous nicorandil and placebo before PPCI. The data that support the findings of this study are available from the corresponding author upon reasonable request. The design of the trial was described in a previous report. Briefly, the recruitment for research was conducted between April 2018 and July 2019 in 9 centers in China. All of the eligible patients provided written informed consent to participate in the study. The trial was registered on ClinicalTrials.gov (NCT03445728). The study was approved by the ethics committee and institutional review board at each participating center. The primary hypothesis of the trial was that patients with STEMI receiving early intravenous nicorandil before reperfusion would have reduced infarct size compared with placebo subjects.

Patients

Patients with STEMI eligible for enrollment were 18 to 80 years of age, showed symptoms and electrocardiographic findings consistent with STEMI as indications for PPCI, and provided an informed consent form. The diagnosis of STEMI was based on episodes of chest pain persisting for at least 30 minutes, but no longer than 12 hours, and ST-segment elevation of >0.1 mV in ≥2 electrocardiographic leads. Patients who met the following criteria were excluded: (1) systolic blood pressure <80 mm Hg, (2) left main artery as culprit artery, (3) acute aortic dissection, (4) previous myocardial infarction within 6 months, (5) previous percutaneous coronary intervention or coronary artery bypass grafting within 6 months, (6) active treatment with nicorandil, (7) any known allergic reaction or contraindication for

Nonstandard Abbreviations and Acronyms

- AAR: area at risk
- LGE: late gadolinium enhancement
- MVO: microvascular obstruction
- PPCI: primary percutaneous coronary intervention
- TIMI: thrombolysis in myocardial infarction
nicorandil, (9) intolerance of CMR imaging, (9) participation in other research projects, (10) pregnancy or lactation, (11) other clinical disorders not suitable for clinical trial. All screening-qualified study patients provided informed consent in the emergency room before the PPCI procedure. All patients were informed of the potential risks associated with nicorandil before they signed the informed consent form. Patients were identified and randomized at any of the 9 participating centers. Randomization was stratified by grouping center. Patients were randomized 1:1 with a block size of 4 within strata. A drug code was assigned to each participant in chronological order of entry into the cohort, and the drug and placebo bottles were labeled with the corresponding code generated by computer. The physicians in the emergency room opened the envelope for the random assignment. The appearances of drug and placebo were completely the same, and the same vials of 0.9% saline were used in both groups. Both code-related grouping and treatment allocation were blinded to the investigators and study patients. The investigators, participants, and the other study personnel were blinded to the assigned treatment allocation for the duration of the trial.

**Experimental Treatment Protocol**

All enrolled patients were equally randomized at 1:1 to receive either intravenous nicorandil or intravenous placebo before PPCI. All enrolled patients took loading dose of aspirin and ticagrelor in the emergency department. Thrombus aspiration during PPCI was recommended in cases of high thrombus load. Medications including statins, β-blockers, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, and other treatments during follow-up were given in accordance with the clinical guideline.1 The appearances of nicorandil and placebo were identical and were provided by Beijing Sihuan Kebao Pharmaceutical (Beijing, China). A total of 12 mg nicorandil or placebo was dissolved in 20 mL of saline and injected as a 10-mL intravenous bolus within 20 seconds before the procedure, followed by intravenous administration of 144 mg nicorandil or placebo at a rate of 6 mg/h for 24 hours.10 Blood samples were taken for evaluation of cardiac enzymes and other biochemical indexes before and after PPCI. CMR imaging was scheduled for 5 to 7 days and 6 months after reperfusion.

**End Points**

The primary end point was infarct size on CMR imaging based on the extent of myocardial necrosis quantified by late gadolinium enhancement (LGE) at 5 to 7 days and 6 months after PPCI. Prespecified secondary end points were corrected TIMI frame count, slow-flow/no-reflow phenomenon defined as TIMI flow grade after PPCI ≤2, complete ST-segment resolution (ST-segment resolution ≥70% within 2 hours after PPCI in the lead with maximal ST-segment elevation on baseline electrocardiogram), infarct size estimated by cardiac enzyme levels, microvascular obstruction (MVO) and myocardial edema (area at risk) on CMR imaging at 5 to 7 days after reperfusion, left ventricular ejection fraction (LVEF) on baseline electrocardiogram, infarct size estimated by cardiac enzyme levels, microvascular obstruction (MVO) and myocardial edema (area at risk) on CMR imaging at 5 to 7 days and 6 months after reperfusion, and MACEs during follow-up. MACEs were defined as cardiac death, or noncardiac death, or rehospitalization for heart failure, or unplanned revascularization after PPCI. CMR imaging and angiography were evaluated by independent cardiologists, and MACEs were evaluated by an independent clinical events committee, all of whom were blinded to the group assignment. The major prespecified safety secondary end points were blood pressure during study drug administration and other adverse drug events. Intraoperative hypotension was defined as a blood pressure <90/60 mm Hg or as a significant drop from baseline blood pressure of >30 mm Hg during PPCI.

**Clinical Follow-Up**

The patients with STEMI underwent follow-up by routine outpatient clinic visits or telephone interviews until 12 months after reperfusion, and the occurrence of any MACEs was recorded. The follow-up data were collected by physicians in the participating hospitals who received training organized by the researchers. No patients were lost to follow-up in either the nicorandil group or the placebo group during the follow-up period.

**CMR Analysis and Coronary Angiographic Analysis**

Detailed descriptions of the CMR imaging protocol and analysis methods were provided in a previous report.10 CMR was performed at 5 to 7 days and 6 months after PPCI on a 1.5T CMR scanner (Achieva; Philips Medical Systems, Best, the Netherlands) to assess the infarction size, MVO, area at risk (AAR), LVEF, and left ventricular mass. CMR data were judged and analyzed by 2 experienced CMR readers through cardiovascular image analysis software CVI42 (version 5.10.3; Circle Cardiovascular Imaging, Calgary, Canada). All of the CMR image data including infarction size, MVO, AAR, and LVEF were validated by analysis of the interobserver and intraobserver reproducibility. The myocardial infarct size was derived from the program’s semiautomatic analysis of LGE, by the method of mean±SD reference region of interest with our manual correction. The myocardial infarct size is expressed as grams of left ventricle (LV) tissue or
percentage of LV mass (myocardial infarct size/total LV size), and the papillary muscle was considered part of the left ventricular cavity. We removed artifacts in the remote myocardium that may have affected the final result of myocardial infarction size. MVO was identified on LGE images, and MVO was defined as the central core of infarct myocardium as a region with lower enhancement (dark area) than surrounding area. AAR was defined by the extent of myocardial edema (high signal intensity on T2-weighted images), and AARs were auto-identified by density values higher than 2 SD of normal myocardial tissue. To provide an additional measure of the AAR, coronary angiographies were analyzed by 2 independent investigators blinded to the treatment allocation using the APPROACH (Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in Diabetes Patients With Cardiovascular History) scores and BARI (Bypass Angioplasty Revascularization Investigation) scores.11,12 Coronary angiography, including coronary collateralization to the AAR (Rentrop grade) and coronary thrombus burden (TIMI thrombus grade), was estimated by 2 independent investigators.13,14

Statistical Analysis

We performed a sample size calculation. The study was designed to have approximately 80% power to detect a relative reduction in infarct size of about 20% in patients with nicorandil administration. The sample size calculation was based on a previous report for experimental CMR imaging of infarct size in patients with STEMI with nicorandil pretreatment.15 The calculation indicated that approximately 100 evaluable patients were required in each group to provide 80% power. To compensate for about 15% patients not undergoing CMR imaging, we planned to recruit approximately 240 patients in total. For quantitative variables, data were expressed as mean±SD and compared between the 2 groups using an χ² test, if appropriate. We performed multivariable regression after adjusting for baseline clinical variables to further explore the relationship between the infarct size and the nicorandil administration. We used the Pearson correlation analysis to explore the relationship between infarct size and AAR on CMR. All statistical analyses were performed by SPSS statistical software version 18.0 (IBM, Armonk, NY). All statistical tests were 2-sided, and P<0.05 was considered statistically significant.

RESULTS

Between April 2018 and July 2019, a total of 613 patients with STEMI were screened for study eligibility. Of these, 238 patients were randomized to receive intravenous nicorandil (n=120) or placebo (n=118) before reperfusion. Patients who did not undergo CMR imaging comprised 21 patients in the nicorandil group and 16 patients in the placebo group. Thus, 201 patients (99 in the nicorandil group and 102 in the placebo group) underwent the first CMR imaging examination and had available data for the primary analysis. Subsequently, 171 patients underwent the second CMR imaging examination to determine the final infarct size (60 in the nicorandil group and 91 in the placebo group). A consolidated standard of reporting trials flow diagram is shown in Figure 1.

Baseline Characteristics

The baseline characteristics of the total study patients (n=238) and the patients who underwent the first CMR imaging (n=201) are presented in Table 1. There were no significant differences in time from symptom onset to hospital arrival and door to balloon time between the nicorandil group and placebo group (all P>0.05). There were no significant differences in sex, age, anterior infarction, hemoglobin, white blood cell count, serum creatinine, Killip class at recruitment, and treatment at time of PPCI between the 2 groups, and the baseline clinical characteristics were well balanced in both groups with or without CMR imaging (all P>0.05). There were no significant differences in baseline TIMI flow, location of culprit vessel lesion, thrombus burden, AAR by angiographic score, and coronary collateral circulation between the nicorandil group and the placebo group, which are presented in Table 2. Moreover, performance of thrombus aspiration was similar between the 2 groups.

Effects on Infarct Size

The actual first CMR timing was 5.9±1.6 days in the nicorandil group and 5.8±1.6 days in the placebo group, with no significant difference (P=0.488). Infarct size (primary end point) evaluated by CMR imaging at 5 to 7 days after PPCI was significantly smaller in the nicorandil group compared with the placebo group (26.5±17.1 g versus 32.4±19.3 g; adjusted treatment effect, −6.0 [95% CI, −11.0 to −0.9]; P=0.022), and the effect remained significant for the final infarct size evaluated by CMR imaging at 6 months after PPCI (19.5±14.4 g versus 25.7±15.4 g; adjusted treatment effect, −6.1 [95% CI, −10.7 to −1.6]; P=0.008, Figure 2), as well as infarct size expressed as a percentage of the LV (all P<0.05; Table 3). In the multivariable regression analysis, nicorandil remained significantly associated with reduction in infarction size after adjustment for effects of baseline variables including age, sex,
total ischemia time, diabetes, baseline heart rate, infarction location, location of culprit vessel lesion and TIMI grade before percutaneous coronary intervention (P=0.018). Infarct size expressed as percentage of the LV was significantly and positively correlated with AAR (extension of myocardium edema) expressed as percentage of the LV (r=0.679, P<0.001). The nicorandil group had significantly increased LVEF on CMR imaging compared with the placebo group at both 5 to 7 days (47.0±10.2% versus 43.3±10.0%; P=0.011) and 6 months (50.1±9.7% versus 46.4±8.5%; P=0.009) after reperfusion. The incidence of MVO evaluated by CMR imaging was significantly less in the nicorandil group compared with the placebo group (32.3% [32/99] versus 46.1% [47/102]; P=0.046, Table 3). Finally, the nicorandil group had significantly reduced plasma levels of creatine kinase (CK) compared with the placebo group at 12, 18, and 24 hours (all P<0.05), resulting in a significant reduction in total 24 hours area under the curve (AUC) for CK. The AUC of CK release in the intravenous nicorandil group was 39 981 U/L (95% CI, 14952–65 010 U/L), whereas AUC of CK release in the placebo group was 50 886 U/L (95% CI, 21040–80 732 U/L) (P<0.05). Figure 3 shows the AUC of CK release in the nicorandil group and placebo group. All of these results supported evidence of a significant reduction in infarct size following intravenous nicorandil administration before reperfusion.

**Other Secondary End Points**

TIMI flow grade at the end of the PPCI procedure was significantly better in the nicorandil group compared with the placebo group (P=0.004; Table 2). Occurrence of no-reflow/slow-flow phenomenon during PPCI was significantly less frequent in the nicorandil group (9.2% [11/120] versus 26.3% [31/118]; P=0.001), and corrected TIMI frame count after PPCI was significantly lower in the nicorandil group (18±6 versus 22±13; P=0.001), which is shown in Table 2 and Figure 4. Complete ST-segment resolution at 2 hours after PPCI was significantly more frequent in the nicorandil group (90.8% [109/120] versus 78.0% [92/118]; P=0.006). Taken together, these data show that administration of intravenous nicorandil before PPCI improved epicardial flow and accelerated ST-segment resolution in the patients with STEMI in our trial (Table 2).

**Main Safety Data and Clinical Follow-Up**

There were no significant differences in blood pressure between the 2 groups before and after PPCI (all P>0.05; Table 1). The rates of intraoperative hypotension during PPCI in the nicorandil group and the placebo group were 17.5% (21/120) and 16.1% (19/118), respectively (P=0.773). Prereperfusion administration of intravenous nicorandil did not increase the incidence of...
hypotension during PPCI. At the 12-month follow-up, there were 2 deaths (1.7%) in the nicorandil group and 3 deaths (2.5%) in the placebo group. Although there was no significant difference between the groups in the incidence of MACEs (\(P\) for log rank=0.456), both all-cause death and unplanned revascularization after PPCI were lower in the nicorandil group compared with the placebo group without significance (all \(P\) >0.05; Table 4).

**DISCUSSION**

The main findings of the trial were that administration of intravenous nicorandil before reperfusion in patients with STEMI not only improved epicardial flow during PPCI but also reduced infarct size on CMR imaging at both 5 to 7 days and 6 months after reperfusion. Furthermore, intravenous administration of nicorandil before reperfusion significantly increased LVEF evaluated by CMR imaging. Given the dynamic changes to the myocardium in patients with STEMI after reperfusion,8,9 we performed CMR imaging at 5 to 7 days and 6 months after reperfusion to determine the infarct size, as a more powerful and convincing strategy than single CMR imaging. The CMR imaging examinations at different times in our trial provided solid evidence of a significant and consistent reduction in infarct size resulting from intravenous nicorandil administration before reperfusion.

Some previous studies found that nicorandil administration before PPCI preserved microvascular integrity, improved cardiac systolic function, and led to better long-term prognosis in patients with STEMI,3,4,16,17 However, the J-WIND (acute myocardial infarction for
the reduction of necrotic damage by nicorandil) trial, a large-scale multicenter clinical research undertaken in Japan, found that intravenous nicorandil did not affect infarct size estimated by CK levels. Myocardial necrosis evaluated by LGE on CMR imaging, as a surrogate end point in clinical trials, was reported to have important prognostic value for MACEs. LGE on CMR imaging is the gold standard for powerful assessment of myocardial infarct size compared with other methods such as myocardial enzyme levels or myocardial perfusion radionuclide imaging. A prior study on patients with STEMI demonstrated that infarct size on CMR imaging was significantly smaller in patients administered nicorandil than in patients administered nitrate. The incidence of the no-reflow/slow-flow phenomenon in our present trial was much higher than that in the J-WIND trial (17.6% [42/238] versus 10.6% [58/545]), and many researchers reported that administration of nicorandil reduced the incidence of the no-reflow/slow-flow phenomenon during PPCI. Compared with the J-WIND trial, the patients enrolled in the present trial presented with longer ischemia duration, and longer ischemia duration was often associated with more risk of the no-reflow/slow-flow phenomenon and larger infarction size. In our trial, we have found that nicorandil administration before reperfusion reduced the occurrence of the no-reflow/slow-flow phenomenon. Current guidelines do not emphasize early nicorandil administration before reperfusion to prevent the no-reflow/slow-flow phenomenon. We obtained solid evidence that administration of nicorandil before reperfusion improved coronary TIMI flow resulting in reduced infarct size and improved LVEF. For patients with STEMI, especially patients at high risk of no-reflow/slow-flow, early intravenous administration of nicorandil before reperfusion should be considered to limit myocardial damage in clinical practice. Although we did not observe significant differences in MACEs between the 2 groups because of the limited sample size in the present trial, the clinical benefits observed in the IONA (impact of nicorandil in angina) trial, and other clinical trials indicated that nicorandil administration reduced MACEs in both short-term and long-term follow-up.

### Table 2. Angiographical Finding and Electrocardiogram Characteristics Analysis

| Variables                                      | All patients, n=238 | Nicorandil group, n=120 | Placebo group, n=118 | P value | Nicorandil group, n=99 | Placebo group, n=102 | P value |
|------------------------------------------------|---------------------|--------------------------|----------------------|---------|------------------------|----------------------|---------|
| Location of culprit vessel lesion, n (%)      |                     |                          |                      |         |                        |                      |         |
| Proximal lesion                               | 67 (55.8)           | 65 (55.1)                | 0.908                |         | 58 (55.6)              | 57 (55.9)            | 0.699   |
| Middle lesion                                 | 42 (35.0)           | 43 (36.4)                | 0.817                |         | 32 (32.3)              | 35 (34.3)            | 0.765   |
| Distal lesion                                 | 11 (9.2)            | 10 (8.5)                 | 0.851                |         | 9 (9.1)                | 10 (9.8)             | 0.863   |
| TIMI grade flow before PPCI, n (%)            |                     |                          |                      |         |                        |                      |         |
| 0                                             | 83 (69.2)           | 77 (65.3)                | 0.770                |         | 67 (67.7)              | 68 (66.7)            | 0.809   |
| 1                                             | 3 (2.5)             | 2 (1.7)                  |                      |         | 3 (3.0)                | 2 (2.0)              |         |
| 2                                             | 10 (8.3)            | 9 (7.6)                  |                      |         | 9 (9.1)                | 7 (6.9)              |         |
| 3                                             | 24 (20.0)           | 30 (25.4)                |                      |         | 20 (20.2)              | 25 (24.5)            |         |
| AAR by angiographic score, % LV               |                     |                          |                      |         |                        |                      |         |
| APPROACH score                                | 33.2±12.9           | 34.4±13.8                | 0.467                |         | 32.6±12.6              | 33.9±13.5            | 0.462   |
| BARI score                                    | 34.5±14.1           | 35.4±13.0                | 0.602                |         | 34.1±14.3              | 34.9±12.9            | 0.684   |
| Collateralization to the AAR (Rentrop grade ≥2), n (%) | 5 (4.2) | 8 (6.8) | 0.375 |         | 4 (4.0) | 7 (6.9) | 0.379 |
| No. of stents per patients, n                 | 1.2±0.6             | 1.3±0.6                  | 0.393                |         | 1.2±0.6                | 1.3±0.6              | 0.428   |
| High thrombus burden, TIMI thrombus grade ≥3, n (%) | 74 (61.7) | 66 (55.9) | 0.369 |         | 62 (62.6) | 57 (55.9) | 0.331 |
| TIMI grade flow after PPCI, n (%)             |                     |                          |                      |         |                        |                      |         |
| 3                                             | 109 (90.8)          | 87 (73.7)                | 0.004                |         | 91 (91.9)              | 73 (71.6)            | 0.002   |
| 2                                             | 11 (9.2)            | 27 (22.9)                |                      |         | 8 (8.1)                | 25 (24.5)            |         |
| 1                                             | 0 (0.0)             | 1 (0.8)                  |                      |         | 0 (0.0)                | 1 (1.0)              |         |
| 0                                             | 0 (0.0)             | 3 (2.5)                  |                      |         | 0 (0.0)                | 3 (2.9)              |         |
| cTFC after PPCI                               | 18±6                | 22±13                    | 0.001                |         | 17±6                   | 23±14                | 0.001   |
| ST-segment resolution within the first 2 h after PPCI, n (%) | 109 (90.8) | 92 (78.0) | 0.006 |         | 89 (89.9) | 78 (76.5) | 0.011 |

AAR indicates area at risk; APPROACH, Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in Diabetes Patients With Cardiovascular History; BARI, Bypass Angioplasty Revascularization Investigation; CMR, cardiac magnetic resonance; cTFC, corrected TIMI frame count; LV, left ventricle; PPCI, primary percutaneous coronary intervention; and TIMI, thrombolyis in myocardial infarction.
Previous studies showed nicorandil dilated coronary microvessels (<100 μm), increased coronary blood flow, and improved microcirculation. Reperfusion-induced impairment of microcirculation in patients with STEMI remained a challenge for cardiologist, and nicorandil had cardioprotective effects against myocardial reperfusion injury, possibly through reducing area of microcirculatory occlusion, improving myocardial ischemic preconditioning, reducing microvascular spasm, inhibition of oxidative stress and microembolization. It is our hypothesis that nicorandil administration before PPCI reduces infarct size by improving coronary microvascular function and ameliorating reperfusion injury. In agreement with this hypothesis, intravenous administration of nicorandil significantly reduced the incidence of MVO and AUC of cardiac enzyme release, which was consistent with the findings in previous studies. Compared with intracoronary injection, intravenous nicorandil infusion is easy and convenient in clinical practice, and does not affect the reperfusion time. Nicorandil administration before PPCI exerted cardioprotective effects, similar to the reported effects of ischemic preconditioning in patients with STEMI, and preconditioning with nicorandil

Figure 2. Primary end point analyses. Infarct size evaluated by cardiac magnetic resonance (CMR) imaging at 5 to 7 days (left) after reperfusion was significantly smaller in the nicorandil group compared with the placebo group (26.5±17.1 g vs 32.4±19.3 g; *P* = 0.022). The nicorandil group also had significantly smaller final myocardial infarct size evaluated by CMR imaging at 6 months (right) after reperfusion compared with the placebo group (19.5±14.4 g vs 25.7±15.4 g; *P* = 0.008). Red lines represent mean±SEM. Individual values are plotted for all study patients who underwent the first or the second CMR.

Table 3. Magnetic Resonance Imaging Data of the Study Patients

| Variables                              | Nicorandil group | Placebo group | Difference (95% CI)       | *P* value |
|---------------------------------------|------------------|---------------|--------------------------|-----------|
| Infarcted myocardium, first CMR, g    | 26.5±17.1, n=99  | 32.4±19.3, n=102 | −6.0 (−11.0 to −0.9)     | 0.022     |
| Infarcted myocardium, first CMR, % LV | 22.1±11.4, n=99  | 27.1±13.4, n=102 | −4.9 (−8.4 to −1.5)      | 0.005     |
| Left ventricle ejection fraction, first CMR, % | 47.0±10.2, n=99 | 43.3±10.0, n=102 | 3.7 (0.8 to 6.5)        | 0.011     |
| Extension of edema, first CMR, g      | 44.7±18.1, n=99  | 49.6±24.5, n=102 | −4.9 (−10.9 to 1.1)     | 0.110     |
| Microvascular obstruction, first CMR, g | 0.00 (0.00, 1.17), n=99 | 0.00 (0.00, 2.21), n=102 | −0.8 (−1.7 to −0.0)     | 0.047*    |
| Microvascular obstruction incidence, first CMR, n (%) | 32 (32.3), n=99 | 47 (46.1), n=102 | −13.8 (−27.3 to −0.2)   | 0.046     |
| Final left ventricle ejection fraction, second CMR, % | 50.1±9.7, n=80 | 46.4±8.5, n=91 | 3.7 (0.9 to 6.4)        | 0.009     |
| Final infarcted myocardium, second CMR, g | 19.5±14.4, n=80 | 25.7±15.4, n=91 | −6.1 (−10.7 to −1.6)    | 0.008     |
| Final infarcted myocardium, second CMR, % LV | 18.8±13.6, n=80 | 23.1±11.7, n=91 | −4.4 (−8.2 to −0.5)     | 0.026     |

CMR indicates cardiac magnetic resonance; and LV, left ventricle.

*Nonparameter tests.
attenuated myocardial ischemia/reperfusion injury. Based on these points, pre-PPCI administration of intravenous nicorandil has some advantages over intracoronary administration during PPCI.

Limitations
The first limitation of the present study is that 16% of the recruited patients did not receive CMR imaging for different reasons, which may have affected the results. This attrition rate was consistent with our prediction and was similar to the rates in other studies on patients with STEMI that used CMR imaging for the primary end point. Second, not all of the CMR imaging examinations were performed at exactly the seventh day after PPCI, which may have affected the results because of the rapidly changing pathophysiological processes in the infarct myocardial tissue. Actual CMR imaging timings in both the nicorandil and placebo groups were not significant statistical differences in our trial. Finally, because of the limitations of the sample size and follow-up time, we did not observe significant differences in MACEs, and further evidence is needed to assess longer-term clinical benefits of early intravenous nicorandil administration for STEMI.

CONCLUSIONS
This multicenter, prospective, randomized, double-blind, parallel-controlled clinical trial demonstrated that early intravenous nicorandil initiated before PPCI

Table 4. Main Adverse Cardiac Events for 12 Months Follow-Up

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| Main adverse cardiac event                  | Nicorandil group, n=120 | Placebo group, n=118 | P value |
|---------------------------------------------|--------------------------|---------------------|---------|
| Unplanned revascularization after PPCI, n (%) | 5 (4.2)                 | 7 (5.9)             | 0.569*  |
| Rehospitalization for heart failure, n (%)  | 2 (1.7)                 | 2 (1.7)             | 1.000*  |
| Cardiovascular death, n (%)                 | 1 (0.8)                 | 2 (1.7)             | 0.620*  |
| All-cause death, n (%)                      | 2 (1.7)                 | 3 (2.5)             | 0.682*  |
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PPCI indicates primary percutaneous coronary intervention. *Fisher exact test.

Figure 3. Effects of early intravenous nicorandil administration on peak and area under the curve (AUC) of creatine kinase (CK) release after primary percutaneous coronary intervention.

The CK levels in the nicorandil group were significantly lower than those in the placebo group at 12, 18, and 24 hours after reperfusion (*P<0.05, Wilcoxon rank sum test), and AUC for CK release was significantly reduced in the nicorandil group than in the placebo group (P<0.05). Data are presented as mean±SEM for each time point of CK.

Figure 4. Comparisons of corrected thrombolysis in myocardial infarction (TIMI) frame count and frequency of no-reflow/slow-flow phenomenon between the nicorandil group and the placebo group.

The incidence of no-reflow/slow-flow phenomenon was significantly lower in the nicorandil group compared with the placebo group, as well as the corrected TIMI frame count (all P<0.001).
improved myocardial perfusion grade, increased LVEF, and reduced myocardial infarct size in patients with STEMI.

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