Effect of nicorandil treatment adjunctive to percutaneous coronary intervention in patients with acute myocardial infarction: a systematic review and meta-analysis

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Abstract

Objective: There is controversy whether nicorandil treatment has cardioprotective effects in patients with acute myocardial infarction (AMI) following percutaneous coronary intervention (PCI). This meta-analysis was conducted to assess the efficacy of nicorandil on functional and clinical outcomes after PCI.

Methods: Systematic databases were searched to retrieve studies that compared the effect of nicorandil with a control group in patients with AMI who underwent PCI. Outcomes related to coronary blood flow, and functional and clinical outcomes were extracted and a meta-analysis was performed. Trial sequential analysis was conducted to estimate the required sample size for statistical power.

Results: Twenty-four trials involving 2965 patients with AMI were enrolled. Pooled results showed that nicorandil treatment significantly suppressed the incidence of no-reflow phenomenon and reperfusion arrhythmia after reperfusion, improved the left ventricular ejection fraction and left ventricular end-systolic volume index, and reduced major adverse cardiovascular events and cardiovascular death. Trial sequential analysis confirmed the effect of nicorandil in reducing the incidence of no-reflow phenomenon and follow-up major adverse cardiovascular events in patients with AMI after PCI.

Conclusion: Our findings suggest that nicorandil treatment adjunctive to reperfusion therapy improves myocardial reperfusion, cardiac function, and clinical outcomes in patients with AMI.

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Introduction
Percutaneous coronary intervention (PCI) is considered the most effective and important treatment for urgent reperfusion in patients with acute myocardial infarction (AMI). However, the clinical efficacy of PCI is sometimes limited by occurrence of reperfusion injury, including the no-reflow phenomenon (NRP) or slow-reflow phenomenon.1 The mechanisms of the NRP may be related to microvascular endothelial damage, microvascular spasm, thromboembolism, oxidative stress, and inflammation.2,3 The NRP has an incidence rate of 5% to 25%,4 and is associated with increased persistent contractile dysfunction of the left ventricle, malignant arrhythmia, cardiac death, and other major adverse cardiovascular events (MACEs).5 Currently, several pharmacological treatments have been reported to be effective in attenuating coronary microvascular dysfunction and obstruction, and preventing the NRP and MACEs. Nicorandil is one of the most selective and important drugs for treating reperfusion injury.

Nicorandil, which is a hybrid of an adenosine triphosphate (ATP)-sensitive channel opener and nitrate, improves coronary microvascular dysfunction and obstruction through its vasodilatory effect on small coronary arteries.7 Several mechanisms for the cardioprotective effect of nicorandil have been postulated, including anti-free radical and neutrophil-modulating properties, vasodilatation of small coronary and peripheral arteries, an opener of the ATP-sensitive potassium channel, and mimicking ischemic preconditioning.8 However, relevant clinical studies have shown controversial results on whether nicorandil has beneficial effects on coronary artery reflow, ventricular function, and clinical outcomes. Although some trials showed beneficial actions of nicorandil on infarct size, ventricular functional recovery, MACEs, and cardiac death,9–11 other studies failed to find the same conclusions.12,13 Many factors, including patients’ baseline characteristics, route of drug administration, and doses of injection, affect the therapeutic effect of nicorandil. Additionally, many previous studies on this issue were single-center and small-scale trials.14,15 Consequently, these trials were insufficient for defining the actual effect of nicorandil. Therefore, this meta-analysis aimed to quantitatively and comprehensively assess the efficacy of nicorandil as an adjunctive treatment to PCI on cardioprotection, functional recovery, left ventricular remodeling, and clinical outcomes in patients with AMI.

Materials and methods
This meta-analysis was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).16 Study registration with PROSPERO was absent in the current meta-analysis, but we intend to perform this registration in future studies.
Search strategy

Electronic databases, including PubMed, EMBASE, Scopus, and the Cochrane Library, were searched to retrieve relevant publications from inception of the databases to 1 June 2020, without restriction on language and publication status. Studies that compared the effect of intracoronary and/or intravenous and/or oral administration of nicorandil with placebo or no nicorandil control before and/or at the time of and/or after PCI in patients with AMI were potentially eligible. The search terms used were “nicorandil”, “acute myocardial infarction”, “reperfusion”, and “percutaneous coronary intervention”. A manual search on relevant meta-analyses and reference lists of all eligible articles was also conducted to find additional studies. Any disagreement was resolved by discussion.

Selection criteria

Study selection was performed by two reviewers independently, and disagreements were resolved through discussion or the opinion of the third reviewer. Studies were eligible for inclusion if they met the following criteria: 1) randomized, controlled trials (RCTs) on nicorandil treatment as an adjunctive therapy to PCI in patients with AMI; 2) studies involved a control group in which patients did not receive nicorandil treatment; and 3) nicorandil was injected before or during or after PCI by the intracoronary route, intravenously, orally, or a combination of these. There was no restriction on subsequent oral nicorandil treatment after intracoronary or intravenous administration. Studies were also eligible for inclusion if they provided at least one of the following outcomes: incidence of the NRP after PCI, Thrombolysis in Myocardial Infarction (TIMI) myocardial perfusion grade (TMPG) ≤2 after PCI, corrected TIMI frame count (cTFC), complete ST-segment resolution (STR), peak creatine kinase (CK) values, peak cardiac troponin I (cTnI) levels, left ventricular ejection fraction (LVEF), left ventricular end-systolic volume index (LVESVI), left ventricular end-diastolic index (LVEDVI), wall motion score (WMS), reperfusion arrhythmia, and clinical outcomes regarding MACEs and mortality. Studies that did not fulfill the above-mentioned conditions, duplicated publications, case reports, reviews, and articles that only published in abstract form were excluded. For studies that included the same cohort of patients, only the latest publication with the most robust study design and the most specific outcomes was enrolled.

Data extraction

Two independent investigators reviewed all of the eligible articles in full-text and extracted data on the basis of a pre-specified form. The following information were included: basic information on the trial (authors’ names, publication year, region of experiment, and study design), patients’ characteristics (age, sex distribution, time from onset to reperfusion, and proportions of hypertension, diabetes, dyslipidemia, and current smokers), intervention (timing, route, and doses of administration), and functional and clinical outcomes as stated above. Data on the same functional outcome expressed in different units of measure were collected. Parameters were converted to the same units if available, but otherwise, data were pooled using the standardized mean difference (SMD) model. In case of discrepancy, consensus was reached by discussion or by the opinion of a third reviewer.

The quality of the included RCTs was evaluated using the seven-point Jadad scale. Each study was judged on four aspects, including randomization, allocation concealment, double blinding, and
withdrawals and dropouts. Each study was scored from 0 to 7. Studies with scores of 4 to 7 were considered as high quality, whereas scores of 0 to 3 represented poor or low quality.

**Statistical analysis**

The meta-analysis was processed with Stata software version 15.0 (Stata Corporation, College Station, TX, USA). Dichotomous variables were generated as the risk ratio (RR) with its 95% confidence interval (CI) without continuity correction. Because using a RR automatically removed studies with no events in both groups, the subsequent risk difference (RD) with the 95% CI was also calculated to ensure all studies reporting data on the outcomes of interest were included. Continuous variables were determined as the weighted mean difference (WMD) or SMD with 95% CI. Heterogeneity among the included studies was examined using the chi-square Q test and I² statistics. If the P value of the Q test was < 0.05 or I² was > 50%, a random effects model was used for data calculation. Data were pooled by a fixed effect model if the P value of the Q test was > 0.05 or I² was < 50%. Sensitivity analysis was performed by removing the study outcome one by one to test the stability of the overall effect size. For analysis of overall functional outcomes, the data at the final follow-up were used. Subgroup analysis was based on the follow-up duration and the route of nicorandil administration was performed to investigate the effect of these factors on the overall results and heterogeneity. For analysis of overall clinical outcomes, in-hospital and follow-up data were pooled separately. A P value < 0.05 was considered statistically significant. Additionally, trial sequential analysis (TSA) was conducted to control for random errors by calculating the required sample size for the statistical power. Publication bias (number of studies > 10) was estimated by Deeks funnel plot and Egger’s asymmetry testing. P < 0.05 indicated the presence of publication bias.

**Results**

**Study selection**

Using four databases, PubMed, EMBASE, Scopus and Cochrane Library, we initially identified 923 articles for inclusion after removal of 592 duplicate reports. Three studies were further found by a manual search. Sixty-five full-text studies were retrieved and reviewed after screening of titles and abstracts. Eventually, 24 trials that satisfied all of the inclusion criteria were enrolled in the meta-analysis. The process of literature search and study selection is shown in Figure 1.

**Study characteristics**

The 24 selected trials comprised 2965 patients with AMI, including 1554 patients who received nicorandil treatment and 1411 control subjects. Male patients comprised 78% of the whole population. The patient cohort sizes ranged from 13 to 276 in the nicorandil group and from 10 to 269 in the control group. The time from onset of AMI to reperfusion ranged from 3.6 to 9.3 hours in the nicorandil group and from 3.7 to 7.8 hours in the control group. Nicorandil was administered by intravenous infusion in eight studies and by intracoronary injection in nine studies. Another nine trials applied intravenous and intracoronary injection. Four studies used subsequent oral administration. For a three-arm trial that consisted of a control and two nicorandil arms with intracoronary and combined intravenous and intracoronary injection, or with and without subsequent oral nicorandil, data between the (same) control group versus one of two
nicorandil groups were compared. For four-arm studies in which the study patients were divided into two groups before randomization, based on coronary flow grade before PCI or on pre-existing angina, the comparisons were considered as two separate comparisons between the control and the corresponding nicorandil arm within a group. More detailed information about the patients’ characteristics and intervention regimens are shown in Tables 1 and 2.

According to the Jadad scale assessment, only seven trials were considered as high quality. The rest of the included studies were ranked as low quality because they did not describe the specific method of randomization, or provide information regarding allocation concealment or the double blinding method.

Figure 1. Flow diagram of the literature search and study selection.
| First author | Year | Country | Group | Sample size (n) | Age (years) | Men (n) | Time to reperfusion (hours) | Disease | Hypertension (n) | Diabetes (n) | Dyslipidemia (n) | Smoker (n) | Follow-up |
|--------------|------|---------|-------|---------------|------------|--------|----------------------------|---------|----------------|---------------|----------------|-----------|-----------|
| Akagi | 2006 | Japan | NIC | 20 | 68 ± 9 | 11 | 4 | AMI | – | – | – | – | 3 mo |
| Control | 10 | 61 ± 9 | 9 | 3.7 | – | – | – | – | – | – | – | – |
| An | 2008 | Korea | NIC | 37 | 56.4 ± 13 | 31 | – | STEMI | 10 | 10 | – | – | 32 | 1 mo |
| Control | 36 | 60.2 ± 12 | 30 | – | 12 | 13 | – | – | – | – | – | 25 |
| Chen | 2015 | China | NIC | 26 | 57.6 ± 4.7 | 18 | 7.5 | STEMI | 19 | 5 | 5 | 15 | 1 mo |
| Control | 26 | 59.8 ± 4.8 | 19 | 6.8 | 24 | 8 | 6 | 17 | – | – | – | – |
| Ezhilan | 2007 | India | NIC | 29 | 52.3 ± 11 | 26 | – | STEMI | 8 | 14 | 23 | 17 | 12 mo |
| Control | 34 | 57.3 ± 10.7 | 30 | – | 23 | 15 | 22 | 18 | – | – | – | – |
| Feng | 2018 | China | NIC | 84 | 69.2 ± 4.2 | 59 | 4.7 | STEMI | 47 | 35 | 28 | 38 | 6 mo |
| Control | 86 | 68.5 ± 5.1 | 62 | 4.8 | 51 | 31 | 26 | 42 | – | – | – | – |
| Fujiwara | 2007 | Japan | NIC | 31 | 62 ± 2 | 26 | 5.8 | STEMI | 18 | 12 | 14 | 22 | 6 mo |
| Control | 31 | 62 ± 2 | 25 | 5.9 | 16 | 12 | 11 | 25 | – | – | – | – |
| Fukuzawa | 2000 | Japan | NIC | 15 | 60 ± 14 | 11 | 4.4 | STEMI | 10 | 6 | 7 | 10 | 1 mo |
| Control | 17 | 64 ± 11 | 12 | 4.8 | 12 | 5 | 7 | 10 | – | – | – | – |
| Hwang | 2013 | Korea | NIC | 41 | 66.2 ± 9 | 20 | – | STEMI | 27 | 15 | – | 14 | 6 mo |
| Control | 40 | 65.3 ± 10 | 25 | – | 27 | 14 | – | 14 | – | – | – | – |
| Ishii | 2005 | Japan | NIC | 185 | 63 ± 9.4 | 114 | 4.8 | STEMI | 52 | 61 | 48 | 66 | 2.4 ± 1.4 y |
| Control | 183 | 64 ± 10.1 | 154 | 4.5 | 57 | 58 | 52 | 77 | – | – | – | – |
| Ishii | 2006 | Japan | NIC | 77 | 64 ± 9.3 | 62 | 4.4 | STEMI | 27 | 45 | 20 | 26 | 5 y |
| Control | 81 | 63 ± 9.3 | 61 | 5 | 27 | 48 | 26 | 27 | – | – | – | – |
| Ishii | 2007 | Japan | NIC | 129 | 63 ± 9.7 | 102 | 4.6 | STEMI | 33 | 39 | 32 | 40 | – |
| Control | 131 | 64 ± 10 | 111 | 4.6 | 40 | 41 | 35 | 54 | – | – | – | – |
| Ito | 1999 | Japan | NIC | 40 | 60 ± 10 | 32 | 4.8 | STEMI | 21 | 10 | 11 | 24 | 1 mo |
| Control | 41 | 60 ± 10 | 32 | 5.3 | 21 | 12 | 14 | 21 | – | – | – | – |
| Kasama | 2007 | Japan | NIC | 20 | 63 ± 11 | 14 | 3.6 | STEMI | 11 | 0 | 9 | 14 | 6 mo |
| Control | 20 | 65 ± 10 | 15 | 3.7 | 12 | 0 | 10 | 15 | – | – | – | – |
| Kitakaze | 2007 | Japan | NIC | 276 | 61.1 ± 11.4 | 246 | – | STEMI | 127 | 104 | 121 | 178 | 6–12 mo |
| Control | 269 | 63.7 ± 10.2 | 220 | – | 137 | 82 | 114 | 170 | – | – | – | – | (continued)
| First author | Year | Country | Group | Sample size (n) | Age (years) | Men (n) | Time to reperfusion (hours) | Disease | Hypertension (n) | Diabetes (n) | Dyslipidemia (n) | Smoker (n) | Follow-up |
|--------------|------|---------|-------|----------------|-------------|---------|----------------------------|----------|----------------|--------------|----------------|------------|-----------|
| Kobayashi    | 1998 | Japan   | NIC   | 19             | 65 ± 8      | 17      | 4.4                        | STEMI    | 13             | 7            | 7              | 12         | 1 mo      |
|              |      |         | Control | 17             | 66 ± 11     | 15      | 5.2                        |          | 12             | 9            | 8              | 8          |           |
| Lee          | 2008 | Korea   | NIC   | 37             | 56.4 ± 13   | 31      | 5.9                        | STEMI    | 19             | 10           | —              | 32         | 1 mo      |
|              |      |         | Control | 36             | 60.2 ± 12   | 30      | 5.8                        |          | 24             | 13           | —              | 25         |           |
| Nameki       | 2004 | Japan   | NIC   | 13             | 64 ± 10     | 11      | 5.9                        | STEMI    | 6              | 4            | 3              | 10         | 3 mo      |
|              |      |         | Control | 14             | 62 ± 11     | 11      | 6.7                        |          | 8              | 3            | 6              | 12         |           |
| Ono          | 2004 | Japan   | NIC   | 33             | 64 ± 13     | 22      | 5.6                        | STEMI    | 18             | 11           | 14             | 15         | 6 mo      |
|              |      |         | Control | 25             | 66 ± 12     | 16      | 5.1                        |          | 14             | 8            | 9              | 9          |           |
| Ota          | 2006 | Japan   | NIC   | 63             | 63.5 ± 10   | 52      | 4.13                       | STEMI    | 13             | 18           | 38             | 34         | 3 mo      |
|              |      |         | Control | 27             | 64.2 ± 11   | 20      | 3.86                       |          | 11             | 18           | 24             | 28         |           |
| Pi           | 2019 | China   | NIC   | 95             | 68.3 ± 10.6 | 69      | 6.86                       | STEMI    | 59             | 60           | 58             | 68         | 48 hours  |
|              |      |         | Control | 45             | 68.7 ± 10.9 | 32      | 6.86                       |          | 30             | 56           | 52             | 64         |           |
| Qi           | 2018 | China   | NIC   | 40             | 59 ± 9      | 26      | 5.9                        | STEMI    | 19             | 13           | 13             | 14         | 3 mo      |
|              |      |         | Control | 40             | 56 ± 7      | 29      | 5.7                        |          | 22             | 17           | 16             | 16         |           |
| Sugimoto     | 2003 | Japan   | NIC   | 158            | 60 ± 11     | 125     | 9.3                        | STEMI    | 62             | 53           | 65             | 91         | 3 mo      |
|              |      |         | Control | 114            | 63 ± 10     | 91      | 7.8                        |          | 48             | 34           | 40             | 75         |           |
| Toyama       | 2006 | Japan   | NIC   | 33             | 67 ± 11     | 23      | 5.2                        | AMI      | 12             | 8            | 12             | 23         | 6 mo      |
|              |      |         | Control | 35             | 63 ± 12     | 21      | 4.7                        |          | 13             | 12           | 8              | 27         |           |
| Wang         | 2015 | China   | NIC   | 53             | 61.6 ± 11.6 | 43      | 4.8                        | STEMI    | 29             | 13           | 16             | 30         | 3 mo      |
|              |      |         | Control | 53             | 63.9 ± 10.8 | 45      | 4.5                        |          | 33             | 13           | 20             | 28         |           |

Data are mean ± standard deviation or number.
NIC, nicorandil; AMI, acute myocardial infarction; STEMI, acute ST-segment elevation myocardial infarction; mo, months; y, years.
| First author | Year | Route of administration | Dosage | Subsequent oral administration | Intervention of controls |
|--------------|------|--------------------------|--------|-------------------------------|-------------------------|
| Akagi        | 2006 | iv and ic                | 4 mg/hour iv for 48 hours + 2 mg ic | No               | PCI only                   |
| An           | 2008 | iv and ic                | 4 mg/hour iv for 48 hours + 2 mg ic | Yes              | PCI only                   |
| Chen         | 2015 | ic                       | 4-mg ic bolus                      | No               | PCI only                   |
| Ezhilan      | 2007 | iv and ic                | 1-mg ic bolus + 2-mg ic bolus + 8 mg/hour iv for 24–48 hours | No               | PCI only                   |
| Feng         | 2018 | ic                       | 2 mg                               | No               | Saline                     |
| Fujiwara     | 2007 | iv                       | 4-mg bolus + 8 mg/hour iv for 24 hours | No               | PCI only                   |
| Fukuzawa     | 2000 | iv and ic                | 4-mg ic bolus + 6 mg/hour iv for 24 hours | No               | Placebo                    |
| Hwang        | 2013 | ic                       | 2-mg ic bolus previously + 2-mg ic bolus before stent | No               | PCI only                   |
| Ishii        | 2005 | iv                       | 12 mg in 100 mL of 0.9% saline iv for 20–30 minutes | No               | Saline                     |
| Ishii        | 2006 | iv                       | 12 mg in 100 mL of 0.9% saline iv for 20–30 minutes | No               | Saline                     |
| Ishii        | 2007 | iv                       | 12 mg in 100 mL of 0.9% saline iv for 20–30 minutes | No               | Saline                     |
| Ito          | 1999 | iv                       | 4-mg iv bolus + 6 mg/hour iv for 24 hours | Yes (15 mg/day; mean, 28 days) | PCI only |
| Kasama       | 2007 | iv                       | 4 mg/hour iv for 24 hours           | Yes (15 mg/day)  | Placebo                    |
| Kitakaze     | 2007 | iv                       | 0.067 mg/kg bolus + 1.67 mg/kg per minute iv for 24 hours | No               | Saline                     |
| Kobayashi    | 1998 | iv and ic                | 2-mg ic bolus + 6 mg/hour iv for 3 hours | No               | PCI only                   |
| Lee          | 2008 | ic                       | 2-mg ic bolus previously + 2-mg ic bolus before stent | No               | PCI only                   |
| Nameki       | 2004 | iv and ic                | 4 mg iv, 4-mg ic bolus + 8 mg/hour iv for 24 hours | No               | PCI only                   |
| Ono          | 2004 | iv                       | 4-mg iv bolus + 8 mg/hour iv for 24 hours | No               | PCI only                   |
| Ota          | 2006 | ic                       | 1–2-mg ic bolus                     | No               | PCI only                   |
| Pi           | 2019 | iv and ic                | 1–2-mg iv bolus + 6 mg/hour iv for 24 hours | No               | PCI only                   |
| Qi           | 2018 | ic                       | 2-mg ic bolus                       | No               | PCI only                   |
| Sugimoto     | 2003 | iv and ic                | 4-mg ic bolus + 6 mg/hour iv for 24 hours | Yes (15 mg/day; mean, 28 days) | PCI only |
| Toyama       | 2006 | iv and ic                | 4 mg/hour iv for 24 hours + 2-mg ic bolus | No               | PCI only                   |
| Wang         | 2015 | ic                       | 6-mg ic bolus                       | No               | PCI only                   |

iv, intravenous; ic, intracoronary; PCI, percutaneous coronary intervention.
Overall outcomes related to coronary flow and subgroup analysis of the administration route

The incidence of the NRP after PCI was assessed in 13 studies. After coronary reperfusion, the NRP was observed in 80 of 1027 patients in the nicorandil treatment group and in 136 of 929 patients in the control group. Nicorandil treatment significantly reduced the incidence of the NRP after PCI (RR, 0.53; 95% CI, 0.41–0.68; I² = 0%; P < 0.001) (Figure 2). Subgroup analysis was conducted on the basis of the nicorandil administration route (intracoronary, intravenous, or combined intracoronary and intravenous). This analysis also showed a significantly lower incidence of the NRP in the nicorandil treatment group compared with the control group (all P < 0.05, Table 3).

Four enrolled studies reported the incidence of a TMPG ≤ 2. The nicorandil treatment group had a significantly lower incidence rate of a TMPG ≤ 2 compared with the control group (RR, 0.50; 95% CI, 0.33–0.75; I² = 6.4%; P = 0.001) (Table 3).

The number of patients who achieved complete STR was measured in five trials with seven comparisons. In all of the included studies, complete STR was defined as a decrease in the sum ST-segment elevation by ≥70%. The nicorandil treatment group had a significantly lower incidence rate of complete STR compared with the control group (RR, 0.50; 95% CI, 0.33–0.75; I² = 6.4%; P = 0.001).

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**Figure 2.** Forest plot of the incidence of the no-reflow phenomenon after percutaneous coronary intervention between the nicorandil treatment and control groups.

RR, risk ratio; CI, confidence interval.
Figure 3. Trial sequential analysis of nicorandil versus controls for (a) the no-reflow phenomenon and (b) follow-up MACEs. Trial sequential analysis showed that the Z-curve (blue line) crossed the upper trial sequential monitoring boundary for benefit (upper red line). Therefore, there was sufficient information to confirm that nicorandil was superior compared with controls in reducing the incidence of the no-reflow phenomenon and follow-up MACEs in patients with AMI who underwent PCI.

DAIRS, diversity-adjusted required information size; MACEs, major adverse cardiovascular events.
higher complete STR rate after PCI compared with the control group (RR, 1.55; 95% CI, 1.23–1.95; $I^2 = 59.2%$; $P < 0.001$). Results of subgroup analysis based on the administration route (intracoronary, intravenous, or combined) were consistent with the overall outcome (Table 3).

The outcome of cTFC was provided in 10 studies with a total of 12 comparisons. Pooled statistics showed that the nicorandil treatment group had a significantly reduced cTFC compared with the control group (WMD: $-4.62$; 95% CI, $-5.60$ to $-3.64$; $I^2 = 0%$; $P < 0.0001$), which suggested a better treatment effect in the nicorandil group. All subgroup analyses showed a beneficial effect of nicorandil treatment on cTFC for patients with AMI undergoing PCI (Table 3).

The incidence of reperfusion arrhythmia was estimated in nine trials. $I_{15,21,26,27,30–32,34,37}$ The nicorandil treatment group had a significantly reduced occurrence of reperfusion arrhythmia after PCI compared with the control group (RR, 0.60; 95% CI, 0.48–0.74; $I^2 = 0%$; $P < 0.001$). Results of

### Table 3. Overall results and subgroup analysis of outcomes related to coronary blood flow.

| Outcome                  | Number of studies | Number of comparisons | RR/WMD/SMD | 95% CI        | P             | $I^2$, % |
|--------------------------|-------------------|-----------------------|------------|---------------|---------------|---------|
| NRP                      | Overall           | 12                    | 13         | 0.53          | 0.41–0.68     | $<0.0001$| 0       |
|                          | ic                | 6                     | 6          | 0.40          | 0.23–0.69     | 0.001   | 0       |
|                          | iv                | 4                     | 4          | 0.58          | 0.40–0.83     | 0.003   | 0       |
|                          | ic + iv           | 4                     | 4          | 0.56          | 0.34–0.90     | 0.016   | 0       |
| TMPG ≤ 2                 | Overall           | 4                     | 4          | 0.50          | 0.33–0.75     | 0.001   | 6.4     |
| Complete STR             | Overall           | 5                     | 7          | 1.55          | 1.23–1.95     | $<0.0001$| 59.2    |
|                          | ic                | 5                     | 5          | 1.31          | 1.16–1.49     | $<0.0001$| 0       |
|                          | ic + iv           | 2                     | 2          | 2.36          | 1.63–3.43     | $<0.0001$| 0       |
| cTFC                     | Overall           | 10                    | 12         | $-4.62$       | $-5.60$ to $-3.64$ | $<0.0001$| 0       |
|                          | ic                | 4                     | 4          | $-4.50$       | $-6.02$ to $-2.98$ | $<0.0001$| 0       |
|                          | iv                | 4                     | 4          | $-5.14$       | $-6.78$ to $-3.51$ | $<0.0001$| 9.8     |
|                          | ic + iv           | 4                     | 4          | $-3.99$       | $-6.06$ to $-1.92$ | $<0.0001$| 0       |
| Reperfusion arrhythmia   | Overall           | 8                     | 9          | 0.60          | 0.48–0.74     | $<0.0001$| 0       |
|                          | ic                | 4                     | 4          | 0.59          | 0.39–0.89     | 0.011   | 6.3     |
|                          | iv                | 3                     | 3          | 0.60          | 0.44–0.82     | 0.018   | 0       |
|                          | ic + iv           | 3                     | 3          | 0.58          | 0.37–0.91     | $<0.0001$| 0       |
| Peak CK value            | Overall           | 5                     | 6          | $-0.30$       | $-0.62$ to $0.01$ | 0.059   | 68.2    |
| Peak cTnI value          | Overall           | 4                     | 4          | $-0.66$       | $-1.82$ to $0.51$ | 0.270   | 97.2    |

iv, intravenous; ic, intracoronary; RR, risk ratio; WMD, weighted mean difference; SMD, standardized mean difference; CI, confidence interval; NRP, no-reflow phenomenon; TMPG, Thrombolysis in Myocardial Infarction Myocardial Perfusion Grade; STR, ST-segment resolution; cTFC, corrected Thrombolysis in Myocardial Infarction frame count; CK, creatine kinase; cTnI, cardiac troponin I.
subgroup analysis based on the administration route were consistent with the overall effect (Table 3).

Analysis of peak CK values involved five studies with six comparisons, while peak cTnI values involved four trials. There was no significant difference in the peak CK value (SMD: \(-0.30\); 95% CI, \(-0.62\) to 0.01; \(I^2 = 68.2\%\)) or the peak cTnI value (SMD: \(-0.66\); 95% CI, \(-1.82\) to 0.51; \(I^2 = 97.2\%\)) between the nicorandil treatment and control groups (Table 3).

**Cardiac function**

Effects of nicorandil on LVEF (11 trials), LVEDVI (7 trials), LVESVI (5 trials), and WMS (6 trials) were meta-analyzed. Overall results showed that the LVEF was significantly greater by 2.57 (95% CI, 1.37–3.75; \(I^2 = 63.2\%\); \(P < 0.001\)) and the LVEDVI was significantly lower by \(-4.68\) (95% CI, \(-9.01\) to \(-0.34\); \(I^2 = 97.7\%\); \(P = 0.034\)) in the nicorandil arm than in the control arm. No significant differences in the LVESVI (WMD: \(-1.68\); 95% CI, \(-8.05\) to 4.70; \(I^2 = 98\%\)) and WMS (WMD: \(-0.06\); 95% CI, \(-0.64\) to 0.51; \(I^2 = 70.9\%\)) were found between patients treated with nicorandil and control therapy (Table 4).

For the four functional outcomes, subgroup analyses based on the follow-up duration (1, 3, and 6 months) and administration route (intracoronary, intravenous, and combined intracoronary and intravenous, with subsequent oral nicorandil treatment) were performed. Nicorandil had a beneficial effect on the LVEF, LVEDVI, and LVESVI at the 6-month follow-up (all \(P < 0.01\)). Additional oral nicorandil treatment accompanied by intracoronary or intravenous administration of nicorandil did not show a significant effect on the LVEF and LVEDVI (Table 4).

**Clinical outcomes**

The incidence of MACE was assessed with data provided from 14 trials. A significantly lower incidence rate of in-hospital (RR: 0.45; 95% CI, 0.30–0.68; \(I^2 = 61.3\%\); \(P < 0.0001\); RD: \(-0.22\); 95% CI, \(-0.39\) to \(-0.05\); \(I^2 = 94.5\%\); \(P = 0.011\)) and follow-up (RR: 0.52; 95% CI, 0.41–0.67; \(I^2 = 0\%\); \(P < 0.0001\); RD: \(-0.09\); 95% CI, \(-0.14\) to \(-0.04\); \(I^2 = 59.7\%\); \(P = 0.001\)) MACEs was observed in the nicorandil treatment group compared with the control group. Patients in the nicorandil treatment group had a significantly lower incidence rate of follow-up new myocardial infarction, in-hospital/tachycardia/ventricular fibrillation, and in-hospital/follow-up congestive heart failure than those in the control group (all \(P < 0.05\)). Use of nicorandil was associated with a significant reduction in the incidence of cardiovascular death (\(P = 0.001\)). However, no significant difference was observed in all-cause death between the nicorandil treatment and control groups (Table 5).

**Sensitivity analysis**

Sensitivity analysis was performed in all assessed outcomes. In almost all of the parameters, excluding each included study at one time showed that individual studies were consistent with the direction and size of the overall effect size. In the analysis of the LVEDVI, excluding each study outcome (except for that for Akagi et al.,\(^{18}\)) changed the direction and size of the overall effect.

**Trial sequential analysis**

For TSA of the NRP and follow-up MACEs, the adjusted optimal information sizes were 4165 and 2532, respectively. TSA of nicorandil versus controls for the incidence of the NRP and follow-up MACEs...
after PCI in patients with AMI showed that the Z-curve crossed the upper trial sequential monitoring boundary for benefit. Therefore, there was sufficient information to confirm that nicorandil was superior compared with controls in suppressing the NRP and follow-up MACEs after PCI (Figure 3). For in-hospital MACEs and follow-up cardiovascular death, the adjusted optimal information sizes were 4521 and 11,119, respectively. TSA showed that the cumulative Z-curve crossed the conventional threshold for statistical significance, but did not cross the monitoring boundary curve for benefit or reach the required information size, which suggested that the available evidence was insufficient to reach a conclusion (Figure 4).

Table 4. Overall results and subgroup analysis of functional outcomes.

| Outcome | Number of studies | Number of comparisons | WMD   | 95% CI   | P    | I², % |
|---------|-------------------|-----------------------|-------|---------|------|-------|
| LVEF    |                   |                       |       |         |      |       |
| Overall | 11                | 13                    | 2.57  | 1.39–3.75 | <0.001 | 63.2  |
| 1 month | 5                 | 6                     | 1.79  | 0.50–3.08 | 0.006  | 0     |
| 3 months| 4                 | 5                     | −0.27 | −2.08 to 1.53 | 0.765 | 0    |
| 6 months| 4                 | 5                     | 3.37  | 2.16–4.59 | <0.0001 | 67.3  |
| ic      | 2                 | 2                     | 3.22  | 2.26–4.17 | <0.0001 | 0 |
| iv      | 5                 | 5                     | 2.77  | 0.61–4.92 | 0.012  | 84.9  |
| ic + iv | 4                 | 5                     | 0.93  | −1.44 to 3.31 | 0.442 | 0 |
| Oral    | 3                 | 3                     | 2.59  | −0.61 to 5.79 | 0.112 | 0 |
| LVEDVI  |                   |                       |       |         |      |       |
| Overall | 7                 | 8                     | −4.68 | −9.01 to −0.34 | 0.034 | 97.7  |
| 1 month | 2                 | 3                     | 1.57  | −2.42 to 5.57 | 0.441 | 42.9  |
| 3 months| 3                 | 4                     | 1.52  | −3.64 to 6.68 | 0.564 | 87 |
| 6 months| 3                 | 3                     | −10.56 | −18.38 to −2.75 | 0.008 | 98.3  |
| ic      | 4                 | 4                     | −8.92 | −17.93 to 0.10 | 0.053 | 98.9  |
| iv      | 2                 | 3                     | 3.51  | −1.82 to 8.85 | 0.197 | 60.6  |
| Oral    | 2                 | 2                     | −0.22 | −9.90 to 9.46 | 0.965 | 73.9  |
| LVESVI  |                   |                       |       |         |      |       |
| Overall | 5                 | 6                     | −1.68 | −8.05 to 4.70 | 0.606 | 98 |
| 1 month | 1                 | 2                     | 4.42  | 1.53–7.30 | 0.003 | 0 |
| 3 months| 3                 | 4                     | 3.00  | −1.45 to 7.45 | 0.186 | 71.9  |
| 6 months| 2                 | 2                     | −8.17 | −14.04 to −2.30 | 0.006 | 91.0  |
| iv      | 3                 | 3                     | −5.05 | −13.84 to 3.75 | 0.260 | 99.2  |
| ic + iv | 2                 | 3                     | 4.69  | −0.85 to 10.22 | 0.097 | 45.7  |
| WMS     |                   |                       |       |         |      |       |
| Overall | 6                 | 7                     | −0.06 | −0.64 to 0.51 | 0.825 | 70.9  |
| 1 month | 3                 | 3                     | −1.13 | −3.39 to 1.12 | 0.325 | 75.5  |
| 3 months| 2                 | 2                     | −0.19 | −2.57 to 2.18 | 0.874 | 85.4  |
| 6 months| 1                 | 2                     | 0.37  | −0.11 to 0.85 | 0.135 | 0 |
| iv      | 2                 | 2                     | −2.36 | −4.77 to 0.05 | 0.270 | 20.2  |
| ic + iv | 3                 | 4                     | 0.26  | −0.42 to 0.94 | 0.059 | 58.4  |

WMD, weighted mean difference; CI, confidence interval; LVEF, left ventricular ejection fraction; LVEDVI, left ventricular end-diastolic index; LVESVI, left ventricular end-systolic volume index; WMS, wall motion score.
Publication bias

Begg’s funnel plot and Egger’s test showed no evidence of publication bias for the NRP (P = 0.14), in-hospital MACEs (P = 0.53), LVEF (P = 0.17), and cTFC (P = 0.15). However, publication bias was detected in the outcomes of reperfusion arrhythmia (P = 0.01), follow-up MACEs (P = 0.03), and follow-up cardiovascular death (P = 0.02). For outcomes in which publication bias was present, trim and fill analysis was conducted. The nicorandil treatment group still showed a significantly lower incidence rate of reperfusion arrhythmia (P < 0.001), follow-up MACEs (P < 0.001), and follow-up cardiovascular death (P < 0.001) compared with the control group. This finding suggested little effect of publication bias on the overall RR for the three analyses.

Discussion

The complex pathophysiological mechanism of AMI, individual comorbidities, and complications, such as the NRP and myocardial reperfusion injury, may attenuate the treatment effect of PCI. Therefore, additional pharmacotherapy is encouraged to improve the patient’s prognosis. The present meta-analysis, which included 2965 patients in 24 studies, showed that the use of nicorandil treatment in patients with AMI who underwent PCI significantly reduced the incidence of the NRP, TMPG ≤2, reperfusion arrhythmia, and cTFC, increased complete STR, improved the

Table 5. Overall results and subgroup analysis of clinical outcomes.

| Outcome                      | Number of studies | Number of comparisons | RR   | 95% CI         | P      | I² (%) | RD   | 95% CI         | P      | I² (%) |
|------------------------------|-------------------|-----------------------|------|----------------|--------|--------|------|----------------|--------|--------|
| MACEs                        |                   |                       |      |                |        |        |      |                |        |        |
| In-hospital                  | 9                 | 10                    | 0.45 | 0.30–0.68      | <0.0001| 61.3   | −0.22| −0.39 to −0.05 | 0.011  | 94.5   |
| Follow-up                    | 10                | 10                    | 0.52 | 0.41–0.67      | <0.0001| 0      | −0.09| −0.14 to −0.04 | 0.001  | 59.7   |
| All-cause death              |                   |                       |      |                |        |        |      |                |        |        |
| In-hospital                  | 8                 | 9                     | 0.55 | 0.19–1.63      | 0.279  | 0      | −0.01| −0.03 to 0.01  | 0.344  | 0      |
| Follow-up                    | 8                 | 8                     | 0.77 | 0.49–1.20      | 0.25   | 15.3   | −0.01| −0.04 to 0.01  | 0.268  | 0      |
| Cardiovascular death         |                   |                       |      |                |        |        |      |                |        |        |
| Follow-up                    | 11                | 11                    | 0.39 | 0.22–0.68      | 0.001  | 0      | −0.04| −0.06 to −0.02 | 0.001  | 11.8   |
| Congestive heart failure     |                   |                       |      |                |        |        |      |                |        |        |
| In-hospital                  | 4                 | 4                     | 0.38 | 0.23–0.66      | <0.0001| 0      | −0.12| −0.23 to −0.01 | 0.029  | 66.2   |
| Follow-up                    | 4                 | 4                     | 0.54 | 0.33–0.88      | 0.014  | 32.1   | −0.03| −0.08 to 0.02  | 0.259  | 55.7   |
| New MI                       |                   |                       |      |                |        |        |      |                |        |        |
| In-hospital                  | 5                 | 5                     | 1.25 | 0.26–5.96      | 0.778  | 0      | −0.01| −0.03 to 0.04  | 0.767  | 0      |
| Follow-up                    | 8                 | 8                     | 0.42 | 0.22–0.80      | 0.008  | 0      | −0.03| −0.05 to 0.01  | 0.009  | 27     |
| VT/VF                        |                   |                       |      |                |        |        |      |                |        |        |
| In-hospital                  | 6                 | 6                     | 0.32 | 0.15–0.67      | 0.003  | 0      | −0.06| −0.13 to 0.01  | 0.113  | 71.4   |
| Follow-up                    | 4                 | 4                     | 0.40 | 0.08–2.00      | 0.263  | 0      | −0.02| −0.06 to −0.02 | 0.279  | 0      |
| TLR                          |                   |                       |      |                |        |        |      |                |        |        |
| In-hospital                  | 3                 | 3                     | 2.92 | 0.47–18.22     | 0.251  | 0      | 0.03 | −0.02 to 0.07  | 0.216  | 0      |
| Follow-up                    | 4                 | 4                     | 0.52 | 0.13–2.03      | 0.35   | 0      | −0.02| −0.06 to 0.02  | 0.362  | 0      |
| TVR                          |                   |                       |      |                |        |        |      |                |        |        |
| In-hospital                  | 3                 | 3                     | 3.00 | 0.12–72.02     | 0.498  | –      | 0.01 | −0.02 to 0.04  | 0.614  | 0      |
| Follow-up                    | 5                 | 5                     | 0.93 | 0.59–1.46      | 0.754  | 0      | −0.01| −0.05 to 0.04  | 0.758  | 0      |

RR, risk ratio; CI, confidence interval; RD, risk difference; MACEs, major adverse cardiovascular events; MI, myocardial infarction; VT/VF, ventricular tachycardia/ventricular fibrillation; TLR, target lesion revascularization; TVR, target vessel revascularization.
Figure 4. Trial sequential analysis of nicorandil versus controls for (a) in-hospital MACEs and (b) follow-up cardiovascular death. Trial sequential analysis showed that the Z-curve (blue line) crossed the conventional threshold for statistical significance (green line), but did not cross the upper trial sequential monitoring boundary for benefit (upper red line) or reach the required information size. Therefore, the available evidence was insufficient for reaching a definite conclusion.

DAIRS, diversity-adjusted required information size; MACEs, major adverse cardiovascular events.
LVEF and LVEDVI, and eventually decreased the occurrence of MACEs and cardiovascular death. Taken together, our findings suggest that the use of periprocedural nicorandil improves coronary blood flow, cardiac systolic function, and clinical outcomes in patients with AMI receiving PCI.

To date, the long-term effects of nicorandil treatment adjunctive to PCI for patients with AMI remain unclear. In this meta-analysis, our results of the NRP, TMPG ≤ 2, reperfusion arrhythmia, cTFC, complete STR, and in-hospital MACEs may reflect the short-term beneficial effect of nicorandil. Additionally, subgroup analysis of functional outcomes based on the follow-up time showed significantly better LVEF, LVEDVI, and LVESVI in the nicorandil treatment group than in the control group at the 6-month follow-up. Although 6 months may not be considered as long-term, these results at least showed that the beneficial effect of nicorandil combined with PCI in patients with AMI on cardiac function might continue. Follow-up clinical outcomes were also estimated in our analysis. Although follow-up time widely varied among the studies (range: 1 month to 5 years), the results of the follow-up clinical outcomes still reflected some of the long-term beneficial effect of nicorandil. Nevertheless, by collating often inconsistent data from widely heterogeneous studies, the current study indicated some of the short- and long-term potential benefits of nicorandil for patients with AMI receiving PCI. This could increase the choices of treatment decisions, as well as encourage further experiments to verify our findings.

Intracoronary and intravenous administration is well-established for nicorandil infusion in patients with AMI. There is controversy whether intracoronary administration, which delivers the drug directly to the target vessel at higher concentrations, is more effective for prevention and treatment of the NRP in patients with AMI undergoing PCI than other types of administration. However, subgroup analysis showed that intracoronary, intravenous, and combined intracoronary and intravenous administration were equally effective in reducing the NRP, TMPG ≤ 2, reperfusion arrhythmia and cTFC, as well as increasing complete STR. In some functional (LVEF and LVEDVI) and clinical (MACEs and new MI) outcomes, discrepant results were found with different administration routes. However, this discrepancy might be attributed to the small sample size in each subgroup. Subsequent oral nicorandil treatment after initial nicorandil treatment might provide a better outcome. The J-Wind trail, which was a multicenter study that involved 545 patients, only reported a significant increase in the LVEF in patients who received subsequent oral nicorandil after intravenous administration. Subsequent oral nicorandil treatment could also help to maintain lower QT dispersion during the chronic phase of AMI and reduced left ventricular size. However, in the present study, no significant differences in the LVEF and LVEDVI were found between the nicorandil treatment and control groups when combining studies with subsequent oral nicorandil treatment. These findings appear to deny the extra effect of additional oral nicorandil treatment. Nevertheless, only three studies were included in this analysis, which was insufficient to draw a definite conclusion. Therefore, future studies are required to verify our findings.

Several studies have indicated that the beneficial effect of nicorandil might be dose-dependent as follows. One study showed that a higher dose nicorandil (a bolus injection of 0.2 mg/kg followed by continuous infusion at 0.2 mg/kg/hour) improved the coronary microcirculation compared with a lower dose (nicorandil 0.06 mg/kg/hour for 24 hours) in patients.
with AMI. The trials included in our meta-analysis infused a 2- to 6-mg bolus or 1.67 to 8 mg/hour of nicorandil continually in patients with AMI, and the authors of all 24 studies concluded that nicorandil treatment achieved some improvement in myocardial perfusion, and functional and clinical outcomes. This result suggests that administration of nicorandil at doses of a 2- to 6-mg bolus or 1.67 to 8 mg/hour continually for 3 to 24 hours is safe and does not lead to adverse complications. However, the available data were limited and subgroup analysis could not be performed to determine the optimal dose of nicorandil.

The present study expanded on previous meta-analyses. While some analyses assessed only functional or clinical outcomes, we provided data on coronary blood flow, and functional and clinical outcomes associated with the efficacy of nicorandil treatment. Several studies only assessed the incidence of TIMI flow grade ≤2 to represent the effect of nicorandil on coronary blood flow, which might have underestimated the incidence of NRP. The current study directly assessed the incidence of the NRP, as well as the TMPG, complete STR, and cTFC, which might be better approaches to reflect myocardial perfusion after revascularization and long-term outcomes. The beneficial effects of nicorandil combined with PCI in patients with AMI in reducing the NRP, cTFC, and MACEs, and improving the LEVF have been demonstrated in several meta-analyses. The present study, which included more recent clinical trials, further proved these effects of nicorandil. As an update to other studies, we also conducted TSA to assess the possibility of the effect size of the present meta-analysis to change according to potential future data and the requirement for future data. TSA confirmed the effect of nicorandil in reducing the incidence of the NRP and follow-up MACEs in patients with AMI after PCI. With regard to in-hospital MACES, cardiovascular death, and other clinical outcomes, further trials need to be conducted before the effect of nicorandil can be verified or rejected. Several clinical trials investigating the efficacy of nicorandil in patients with AMI undergoing PCI are still ongoing (trial registry numbers: NCT03445728, NCT02435797, NCT02449070, ChiCTR1800015932, and IRCT20140512017666N1). Therefore, with enlarged sample sizes, an update of the present meta-analysis is expected in the future.

There are some limitations in the present study. First and most importantly, the relatively small sample size in each included study might have affected the statistical power of the analysis. In some small population trials, nicorandil treatment was suggested to be effective, whereas in a study with a larger sample size, the effects of nicorandil on infarct size, the LVEF, and the LVEDVI were insignificant. Moreover, our analysis included trials with different timing of intervention, administration routes, doses of nicorandil, and duration of follow-up, which might have caused heterogeneity. The collected data only allowed us to conduct subgroup analysis on the basis of administration routes or duration of follow-up, and biases induced by other factors are yet to be established. Furthermore, analysis could not be performed to determine the effect of angina in patients before nicorandil treatment, which might mimic ischemic precondition to abolish the effect of nicorandil. Finally, all 24 included studies were on the Asian population. Whether nicorandil is feasible and effective in other populations needs further validation.

**Conclusion**

The results of this meta-analysis provide further evidence that nicorandil as additional therapy to PCI in patients with AMI
can improve myocardial reperfusion, left ventricular function, and clinical outcomes. Nicorandil treatment plays a positive role in preventing the NRP and reperfusion arrhythmia, improving the LVEF and LVEDVI, and reducing MACEs. However, despite the promising results in this meta-analysis, there are other factors that may affect the performance of nicorandil. Therefore, future larger-scale research with a more rigorous RCT design is required to verify our findings.

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