Clinical Outcomes of Nicorandil Administration In Patients With Acute ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention: A Systematic Review And Meta-Analysis of Randomized Controlled Trials

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Research Article

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Abstract

Background: Primary percutaneous coronary intervention is the treatment of choice in ST-segment elevation myocardial infarction and no-reflow phenomenon is still an unsolved problem.

Methods: We searched PubMed, EmBase, and Cochrane Central Register of Controlled Trials for relevant randomized controlled trials. The primary endpoint was the incidence of major adverse cardiac events and the secondary endpoint was the incidences of no-reflow phenomenon and complete resolution of ST-segment elevation.

Results: Eighteen randomized controlled trials were enrolled. Nicorandil significantly reduced the incidence of no-reflow phenomenon (OR, 0.46; 95% CI, 0.36 to 0.59; \( P \leq 0.001; I^2 = 0\% \)) and major adverse cardiac events (OR, 0.42; 95% CI, 0.27 to 0.64; \( P \leq 0.001; I^2 = 52\% \)). For every single outcome of major adverse cardiac events, only heart failure and ventricular arrhythmia were significantly improved with no heterogeneity (OR, 0.36; 95% CI, 0.23 to 0.57, \( P \leq 0.001; OR, 0.43; 95\% CI, 0.31 \text{ to } 0.60, P \leq 0.001 \) respectively). A combination of intracoronary and intravenous nicorandil administration significantly reduced the incidence of major adverse cardiac events with no heterogeneity (OR, 0.24; 95% CI, 0.13 to 0.43, \( P \leq 0.001 \)), while a single intravenous administration could not (OR, 0.66; 95% CI, 0.40 to 1.06, \( p = 0.09; I^2 = 52\% \)).

Conclusions: Nicorandil can significantly improve no-reflow phenomenon and major adverse cardiac events in patients undergoing primary percutaneous coronary intervention. The beneficial effects on major adverse cardiac events might be driven by the improvements of heart failure and ventricular arrhythmia. A combination of intracoronary and intravenous administration might be an optimal usage of nicorandil.

Background

Primary percutaneous coronary intervention (PCI) has been the treatment of choice for ST-segment elevation myocardial infarction (STEMI) in the era of reperfusion. Although door-to-balloon times improve significantly, in-hospital mortality has remained virtually unchanged [1]. Re-opening of an infarct-related coronary artery by primary PCI does not always restore myocardial perfusion, due to the no-reflow phenomenon (NRP) in up to 30% of patients, which is associated with larger infarct size and worse outcomes [2]. Distal microthrombus embolization after balloon dilation or stent implantation and microvascular damages caused by ischemia-reperfusion injury play important roles in the genesis of NRP [3].

Nicorandil, a hybrid of the adenosine triphosphate-sensitive potassium (K\(_{\text{ATP}}\)) channel opener and nitrate, can not only cause vasodilation of both the epicardial coronary arteries and coronary resistance arterioles, but also exert pharmacological preconditioning effects by opening mitochondrial K\(_{\text{ATP}}\) channel [4]. So nicorandil might improve NRP and clinical outcomes after primary PCI in patients with STEMI by ameliorating ischemia-reperfusion injury and improving microvascular function. Several randomized controlled trials (RCTs) have been conducted to evaluate the clinical efficacy of nicorandil in patients treated by primary PCI and significantly heterogeneous clinical outcomes have been achieved, though improved microvascular function was guaranteed. The trial conducted by Feng et al. had shown that nicorandil could reduce the rate of NRP after primary PCI and improve the clinical outcomes at 6 months follow-up [5]. However, these better effects were not demonstrated in some other trials. Chen et al. investigated the effects of intracoronary nicorandil in individuals undergoing primary PCI for acute inferior myocardial infarction [6]. No significantly reduced no-reflow rate (OR: 0.57; 95% CI: 0.22 to 1.46)
and major adverse cardiac events (MACE) (OR: 0.48, 95% CI: 0.08 to 2.74) were found in patients with the use of nicorandil. There were also great heterogeneities in the usage of nicorandil (intracoronary, intravenous or both during primary PCI, with/without following intravenous nicorandil after primary PCI). To clarify the effects of nicorandil administration on NRP, clinical outcomes and explore the optimal usage of nicorandil in patients undergoing primary PCI, we performed this systematic review and meta-analysis.

Methods

We conducted this study in accordance with the preferred reporting items for systematic reviews and meta-analysis (PRISMA) checklist [7]. This study is a meta-analysis of RCTs and all data were collected from published trials, so an additional ethical approval is not necessary.

Literature search

We searched PubMed, Embase, and Cochrane Central Register of Controlled Trials with no language restriction for relevant articles till May 8, 2021 by the PICOS search strategy. Combinations of MeSH terms, entry terms, and text words were used for the search of every theme. For the theme ‘nicorandil’, we used the following key words Nicorandil OR 2-Nicotinamidoethyl Nitrate OR SG 75 OR Ikorel OR Adancor OR Dancor. For the theme ‘ST elevation myocardial infarction’, we used: ST Elevation Myocardial Infarction OR ST Segment Elevation Myocardial Infarction OR ST Elevated Myocardial Infarction OR STEMI. Randomized controlled trial OR controlled clinical trial OR randomized OR randomly were used for the theme ‘randomized controlled trial’. For the final search results, we combined the search results of each theme by the Boolean operator ‘AND’. We also performed manual search for potential eligible studies. Authors of published studies were also contacted for more data as needed. For studies of overlapping patient populations, data from the most informative or most recent publications were included in our meta-analysis.

Eligibility criteria

The inclusion criteria were as follows: RCTs; adult patients with STEMI undergoing primary PCI; nicorandil with/without other positive drugs were administrated intravenously or via intracoronary in experimental groups, while placebo with/without other positive drugs were given in control groups; the clinical outcomes and/or myocardial reperfusion measurements such as thrombolysis in myocardial infarction (TIMI) flow grade; TIMI myocardial perfusion grade (TMPG); complete resolution of ST-segment elevation (STR) on ECG after primary PCI were reported in both experimental and control arms. The followings were excluded: conference abstracts without needed data; no clinical outcomes and incidences of NRP were reported; only oral nicorandil was administrated.

Data extraction

Two reviewers (NG and DLZ) independently extracted data from all eligible studies. Disagreements were resolved through discussion with all the reviewers. The extracted information included: first author; year of publication; sample size; patient characteristics; procedure; interventions in treatment and control groups; dosage and administration method of nicorandil; incidences of MACEs, NRP and complete STR. If enrolled studies included more than 2 arms, we combined the arms in which nicorandil was administrated as experimental groups; arms with no nicorandil administration as control groups. For a binary outcome (incidences of MACEs, NRP or complete STR), combining the arms simply means adding the numbers of events and total participants over all arms. The
clinical results at the longest follow-up durations were employed for the pooled analyses to maximize the effects of nicorandil if clinical results were reported at different follow-up durations.

**Assessment of risk of bias**

Two reviewers (NG and LR) independently assessed risk of bias for each eligible study by creating risk of bias graph and risk of bias summary graph, using the Cochrane Collaboration's tool for assessing risk of bias. This tool evaluated each trial by considering the following sources of bias: selection bias; performance bias; attrition bias; detection bias; reporting bias; and other potential sources of bias. The risk of each bias was evaluated and rated as “low,” “unclear,” or “high”. Any discrepancy was solved by discussion.

**Statistical analyses**

The primary endpoint of our meta-analysis was the incidence of MACE and the secondary endpoint was the incidences of NRP and complete STR. All statistical analyses were performed by Review Manager 5.3 (The Cochrane Collaboration, Copenhagen, DK). Odds ratio (OR) and 95% confidence interval (CI) were used to describe dichotomous data (incidences of MACE, NRP, complete STR) for each study. The heterogeneity across trials was quantified using the $I^2$ statistic, which indicates the percentage of total variation attributed to statistical heterogeneity rather than chance, with $I^2<25\%$, 25% to 50%, and >50% representing mild, moderate, and severe heterogeneity respectively [8]. Subgroup analyses were also conducted to explore the origin of heterogeneity; optimal usage of nicorandil; efficacy of nicorandil with/without following intravenous administration after primary PCI procedure; efficacy of nicorandil at different follow-up durations. We pooled the trials using random-effects model and estimated the absolute between-study variance using the DerSimonian and Laird estimator, considering the potential heterogeneities across included trials due to expected clinical and methodological heterogeneities that might manifest as statistical heterogeneity.

Sensitivity analysis was performed to assess the stability of the results by removing a single trial in turn and pooling the remaining ones. For all of the results, intention-to-treat analyses were utilized. $P<0.05$ in 2-tailed tests was considered statistically significant.

**Results**

**Study selection**

We identified 256 potentially relevant citations from the initial search. After removing the duplicates and screening the titles and abstracts, 27 full-text articles were deemed to be assessed for eligibility. No clinical outcomes and NRP were reported in 6 trials and only oral nicorandil was administrated in 3 trials. Therefore, 18 RCTs [5,6,9-24] involving 2398 patients with STEMI undergoing primary PCI were identified and analyzed. Our search strategy and results were outlined in Supplementary Fig. 1.

**Characteristics of included studies**

Characteristics of included studies are presented in Table 1. Only intravenous nicorandil was administrated in 6 trials [9,11-13,17,24]; only intracoronary nicorandil in 5 trials [5,6,14,20,21]; both intravenous and intracoronary nicorandil in 7 trials [10,15,16,18,19,22,23] during primary PCI. Oral nicorandil was administrated during follow-up in 2 trials [12,15]. Six studies had more than 2 groups (5 studies: 3 groups [16,18-21]; 1 study: 4 groups [6]).
Patient characteristics

The major characteristics of the patients in every enrolled trial are shown in Supplementary Table 1. All the baseline characteristics (age, gender, diabetes, hypertension) were statistically similar between the experimental groups and control groups in each trial.

Risks of bias within studies

Risk of bias graph and risk of bias summary graph are presented in Supplementary Fig. 2 and Supplementary Fig. 3 separately, which evaluated the relevant study characteristics according to Cochrane Handbook for Systematic Reviews of Interventions. Only 6 trials [5,13,19,21,23,24] reported methods of random sequence generation and 4 trials [11,13,17,18] described the concealments of allocation.

Major adverse cardiac events

MACEs were defined as a combination of mortality, new onset of acute myocardial infarction (AMI), target vessel revascularization (TVR), re-hospitalization for congestive heart failure (CHF) and ventricular arrhythmia (ventricular tachycardia or fibrillation). The MACEs were predefined and reported in 9 studies [5,6,13,14,17-20, 23]. In study by Ishii et al [11] and Wang et al [24], the MACEs were not pre-defined, but composite end points of all-cause mortality, all-cause re-admission (Re-PCI; CABG) were reported in study by Ishii et al; all-cause death, cardiovascular death, unplanned hospitalization for CHF, TVR in study by Wang et al. We defined these composite end points as MACEs in these 2 studies respectively. So, 11 studies were used for the pooled analysis of MACEs. Nicorandil was administrated in 969 patients, whereas 906 patients were in control groups. The overall incidence of MACEs in nicorandil groups was 18.3% compared with 25.2% in the control groups. Nicorandil did significantly reduce the incidence of MACEs, but a severe heterogeneity existed (OR, 0.42; 95% CI, 0.27 to 0.64; P<0.001; I²=52%; Fig. 1).

To detect the origin of the severe heterogeneity and clinical effects produced by different methods of nicorandil administration, we performed a subgroup analysis based on the administering methods of nicorandil (intracoronary plus intravenous vs. intracoronary vs. intravenous). The results were shown in Fig. 1. A combination of intracoronary and intravenous nicorandil was administrated in 3 studies [18,19,23]; intracoronary nicorandil in 4 studies [5,6,14,20] and intravenous nicorandil in 4 studies [11,13,17,24]. No heterogeneities were present in the combination and the intracoronary subgroups (combination subgroup: Tau²=0.00; Chi²=1.07, P=0.59; I²=0%; intracoronary subgroup: Tau²=0.00; Chi²=1.83, P=0.61; I²=0%). There was a still severe heterogeneity in intravenous subgroup (Tau²=0.09; Chi²=4.19, P=0.12; I²=52%). So, the different methods of nicorandil usage might act as a partial origin of heterogeneity. We found a trend of less risk of MACEs across the intravenous, intracoronary and intracoronary plus intravenous subgroups (OR: 0.66; 0.37; 0.24 respectively). Interestingly a single intracoronary administration or combined with intravenous administration could significantly reduce the incidence of MACEs (intracoronary subgroup: OR, 0.37; 95% CI, 0.18 to 0.77; P=0.008; combination subgroup: OR, 0.24; 95% CI, 0.13 to 0.43; P<0.001), but a single intravenous administration could not (OR, 0.66; 95% CI, 0.40 to 1.06; P=0.09). Combination of intracoronary and intravenous nicorandil had a significantly lower incidence of MACEs compared with a single intravenous nicorandil (Chi², 6.76; I², 85.2%; PInteraction=0.009, data not shown). So, a single intravenous administration might not be an optimal usage of nicorandil, while a combination of intracoronary and intravenous nicorandil might be.
In 7 studies [5,6,11,14,18-20], intracoronary and/or intravenous nicorandil were administrated only during the primary PCI procedures in the experimental groups or one arm of the experimental groups (we defined these studies as ‘no nicorandil after PPCI’ subgroup). While in 5 studies [13,17-19,23], intracoronary and/or intravenous nicorandil were followed by a continuous intravenous nicorandil infusion after the procedure in the experimental groups or one arm of the experimental groups (we defined these studies as ‘maintaining nicorandil after PPCI’ subgroup). In order to explore the effects of continuous maintaining nicorandil after primary PCI on clinical outcomes, we performed a subgroup analysis comparing the clinical outcomes between the 2 subgroups. Nicorandil can significantly reduce the incidence of MACEs in both subgroups. We found a trend of less risk of MACEs in ‘maintaining nicorandil after PPCI’ subgroup (OR, 0.30; 95% CI, 0.12 to 0.79) compared with ‘no nicorandil after PPCI’ subgroup (OR, 0.47; 95% CI, 0.33 to 0.67) (Supplementary Fig. 4). But the difference was not statistically significant ($I^2=0\%$, $P_{\text{interaction}}=0.40$). The additional continuous intravenous nicorandil infusion did not further reduce the incidence of MACEs significantly, which further suggested that intravenous nicorandil administration might not be an optimal usage.

Some of the included studies only reported the MACEs during in-hospital stay [17-19], while some others followed patients for more than two years [11,13]. We performed a subgroup meta-analysis to evaluate the MACEs during in-hospital stay and during follow-up after hospital discharge. In-hospital or follow-up MACEs were reported in 6 [6,14,17-20] and 7 [5,6,11,13,14,20,23] studies (range from 1 month to 2.5 years) respectively. We found that the risk of MACEs could be significantly reduced during in-hospital (OR, 0.23; 95% CI, 0.13 to 0.41; $P<0.001$) and the beneficial effect could be maintained during the follow-up (OR, 0.60; 95% CI, 0.42 to 0.86; $P=0.006$), (Supplementary Fig. 5). There were no and mild heterogeneities in these 2 subgroups respectively (in-hospital subgroup: $I^2=0\%$; follow-up subgroup: $I^2=23\%$). So, the different follow-up durations might also be an origin of heterogeneity.

**Meta-analyses on every single outcome of MACEs**

In order to explore the effects of nicorandil on every single outcome of MACEs, we also performed pooled analyses on mortality [5,6,11-16,19-21,23,24]; new-onset AMI [6,14,15,17,20]; TVR [6,11,14,15,19-21,24]; re-hospitalization for CHF [5,11,12,15,17,19-21,23,24]; arrhythmia (ventricular tachycardia or fibrillation) [10-12,16-21,24] separately. The results were presented in Table 2. The nicorandil administration did reduce the incidences of re-hospitalization for CHF (OR, 0.36; 95% CI, 0.23 to 0.57; $P<0.001$) and ventricular arrhythmia (OR, 0.43; 95% CI, 0.31 to 0.60; $P<0.001$) with no heterogeneity (CHF: $\text{Tau}^2=0\%$; $P=0.55$; $I^2=0\%$; ventricular arrhythmia: $\text{Tau}^2=0\%$; $P=0.91$; $I^2=0\%$), but not the mortality (OR, 0.68; 95% CI, 0.41 to 1.11; $P=0.12$; $I^2=0\%$), new AMI (OR, 0.56; 95% CI, 0.19 to 1.67; $P=0.30$; $I^2=0\%$), TVR (OR, 1.01; 95% CI, 0.64 to 1.59; $P=0.95$; $I^2=0\%$). So, the improvement of MACEs was mainly driven by the favorable effects on CHF and ventricular arrhythmia. Severe heterogeneity existed in the pooled analysis of MACEs but disappeared when every single outcome was pool-analyzed. The different predefinitions of MACEs among the included studies might be an important origin of the severe heterogeneity.

**No-reflow phenomenon**

A total of 17 studies [5,6,9-15,17-24] reported NRP and were used for pooled analysis. Several measurements were applied for the evaluation of NRP. We chose TMPG as the measurement of choice. TIMI flow grade would be used if TMPG was not reported. Other measurements would be employed depending on the author’s choice if neither TMPG nor TIMI flow grade were reported. TMPG, TIMI grade, corrected TIMI frame count (cTFC) and myocardial
contrast echocardiography (MCE) were used for pooled analysis in 5 [5,6,15,20,23], 10 [9-11,13,14,17-19,22,24], 1 [21], and 1 [12] studies respectively. The pooled analysis showed that nicorandil administration significantly reduced incidence of NRP with no heterogeneity (OR, 0.46; 95% CI, 0.36 to 0.59; P<0.001; I²=0%; Fig. 2).

**Resolution of ST-segment elevation**

Complete STR can serve as a simple and practical index of microvascular function and myocardial reperfusion after primary PCI. So, we performed a meta-analysis on complete STR to evaluate nicorandil’s effect on microvascular function. Ten studies [5,6,10,11,18-21,23,24] reported complete STR and were used for the pooled analysis. The pooled result showed a beneficial effect of nicorandil on complete STR with no heterogeneity (OR, 2.86; 95% CI, 2.19 to 3.73; p<0.001; I²=0%, Supplementary Fig. 6).

**Sensitivity analysis**

Sensitivity analysis of MACEs demonstrated effect sizes of nicorandil were similar in magnitude and direction to the overall estimate after 1-by-1 exclusion of each individual study (Table 3). Removal of study Kitakaze 2007 [13] or study Pi 2019 [19] could lower the heterogeneity from severe heterogeneity to mild and moderate heterogeneities (Kitakaze 2007: Tau²=0.05; P=0.30; I²=16%; Pi 2019: Tau²=0.10; P=0.15; I²=34%). If both studies were removed, the heterogeneity disappeared (Tau²=0.00; Chi²=5.61, P=0.59; I²=0%; data not shown), which meant these two studies might be the origin of severe heterogeneity. This result was consistent with the subgroup analysis based on the administration methods of nicorandil, because study Pi 2019 [19] and Kitakaze 2007 [13] had the greatest sample sizes in the intracoronary plus intravenous and the intravenous subgroup respectively.

**Discussion**

Our meta-analysis showed that nicorandil administrations could improve the NRP and complete STR after primary PCI, reduce the incidence of MACEs during in-hospital stay and this improvement could maintain at follow-up. The improved effects on MACEs were mainly driven by reduced incidences of CHF and ventricular arrhythmia (ventricular tachycardia or ventricular fibrillation). Continuous intravenous nicorandil after primary PCI cannot further improve incidence of MACEs. Interestingly the improvement of MACEs could only be detected in studies with intracoronary combined/not combined with intravenous nicorandil administrations, not in studies with only intravenous nicorandil being administrated. Intravenous administration might not be an optimal usage of nicorandil to improve MACEs in patients treated with primary PCI.

The aim of primary PCI is to open the infarct-related artery and salvage more myocardium as soon as possible in patients with STEMI. But restoration of anterograde coronary flow and complete myocardial reperfusion are not always achieved even though there is no residual stenosis, which is known as coronary NRP and is associated with MACEs and poor prognosis. Impaired microvasculature function caused by ischemia or ischemia-reperfusion injury is the main pathophysiology underlying NRP. Nicorandil, as a nicotinamide derivative, can improve both the epicardial coronary artery and microvasculature function via nitrate-like and K⁺ATP agonist effects respectively. Our study convinced the beneficial effects of nicorandil on improvement of NRP (OR, 0.46; 95% CI, 0.36 to 0.59; P<0.001) and STR (OR, 2.86; 95% CI, 2.19 to 3.73; p<0.001).

There are several methods used for assessing clinical NRP and it is important to be aware of the limitations of these measurements. TIMI flow grade and cTFC are widely used to evaluate the prognosis of NRP after primary
Higher TIMI flow grades are associated with improved clinical outcomes and lower mortality [25], but TIMI flow grades cannot reflect tissue perfusion accurately and distal tissue perfusion may vary considerably despite TIMI grade 3 flow is achieved [26]. CTFC attempts to assess the coronary reperfusion more objectively compared with TIMI flow grades. Though cTFC reflects epicardial coronary blood flow velocity accurately, it is not accurate enough to assess the degree of microvasculature injury after primary PCI [27]. While myocardial blush grade (MBG) is used to assess myocardial staining after primary PCI, TMPG assesses myocardial perfusion, based on the evolution (i.e., entry, endurance, and clearance) of contrast media at the myocardial level. In a study by Wong DTL, TMPG had the strongest relationship with coronary microvasculature obstruction (MVO) assessed by cardiac magnetic resonance (CMR) on day 3 post-STEMI, while MBG did not correlate with MVO in patients undergoing primary PCI [28]. So, we chose TMPG as the measurement of choice to accurately evaluate the NRP in our pooled analysis.

The predominant electrophysiology effect of high-concentration nicorandil is shortening of the action potential and refractory period [29], which may yield proarrhythmic effects. However, our study showed nicorandil could significantly reduce the incidence of ventricular fibrillation and tachycardia in patients undergoing primary PCI, which is in agreement with some other animal and clinical studies. Study by Hirose et al [30] demonstrated that nicorandil shortened action potential without increasing dispersion of action potential durations; suppressed the increased dispersion of local conduction velocity during ischemia; increased the size of non-excited area in the epicardial region of the transmural wall (the origin of reentry) by activating sarcolemma K$^{+}$<sub>ATP</sub> channels, thus preventing ventricular tachycardia during acute global ischemia in arterially perfused canine left ventricular wedges. A historical cohort study by Ueda et al [31] showed that intravenous nicorandil could reduce the occurrences of ventricular fibrillation and QT dispersion in 83 patients with AMI who underwent successful PCI. QT dispersions in the nicorandil group were shorter than those in the control group 48 hours after percutaneous transluminal coronary angioplasty (nicorandil group: 23.2+/−16.1ms; control group: 33.4+/−24.0ms, P<0.05). Ventricular fibrillation was observed in 3 patients in the control group, but none in the nicorandil group.

Our study showed that nicorandil could reduce the incidence of heart failure compared with controls in STEMI patients undergoing primary PCI (OR:0.36, 95% CI:0.23-0.57, P<0.001). Cardiomyocyte apoptosis are crucial events underlying the development of cardiac abnormalities and dysfunction after AMI. Wang S et al. found nicorandil alleviated post-MI cardiac dysfunction and remodeling in left anterior descending coronary artery ligated mice [32]. The mechanisms were associated with enhancing autophagy and inhibiting apoptosis through Mst1 inhibition. Nicorandil can exert cardiac protections not only by improving the vasculature function but also by enhancing pharmacological preconditioning in cardiac cells and arterioles during ischemic reperfusion. Mitochondrial permeability transition pore (mPTP) opening plays an important role in the myocardial injury during the first minutes after restoration of blood flow [33]. Nicorandil, not only directly but also indirectly via activation of the NO-PKG pathway, opens mitochondrial K$^{+}$<sub>ATP</sub> channels [34], which is believed to inhibit mPTP opening [35], thus alleviate myocardial injury during reperfusion and enable greater salvage of myocardium.

Yamada et al [22] used CMR imaging to compare the infarct and edema size in 52 patients with AMI treated by nicorandil with those treated by nitrate. All these patients underwent emergency PCI. The results showed both the edema size on T$_2$-weight CMR and the infarct size on delayed enhancement CMR were significantly smaller in patients treated by nicorandil than nitrate (17.7±9.9% vs. 21.9±13.7%, P=0.03; 10.3±6.0% vs. 12.7±6.9%, P=0.03,
respectively); the presence and amount of microvasculature obstruction were significantly smaller in patients treated by nicorandil than nitrate (39.2% vs. 64.7%, P=0.03; 2.2±1.3 cm$^2$ vs. 3.4±1.5 cm$^2$, P=0.02, respectively).

There are several limitations in our study.

First, the oral administrations of nicorandil following intravenous or intracoronary nicorandil were reported in only 2 of the included RCTs [12,15]. Kang et al reported that 4 weeks oral nicorandil could attenuate sympathetic hyperinnervation after infarction by activating mitochondrial K$_{ATP}$ channels in postinfarcted rat hearts [36]. Whether this beneficial effect can be translated into improvement of clinical prognoses in STEMI patients needs to be further investigated.

Second, there are great heterogeneity in the administration methods of nicorandil, measurements for evaluating NRP, follow-up durations in the studies enrolled. Future large RCTs designed to evaluate the efficacy of nicorandil in different conditions are needed.

Third, subgroup analyses are observational by nature and the possibility of our subgroup analyses being biased by some confounding factors couldn't be ruled out. So, the results of our subgroup analyses need to be confirmed by future large scale RCTs.

Last, racial differences and genetic polymorphisms may affect efficacy of certain disease processes and medications [37]. All the 18 included trials were performed in Asia (10 in Japan; 7 in China; 1 in Korea). More studies on the cardioprotective effects of nicorandil are expected in countries out of Asia.

**Conclusions**

Nicorandil can significantly improve NRP, STR and MACEs in patients with STEMI undergoing primary PCI. The beneficial effects of nicorandil on MACEs might be driven by the improvements of heart failure and ventricular arrhythmia after primary PCI. A combination of intracoronary and intravenous administration might be an optimal usage of nicorandil.

**Abbreviations**

AMI: acute myocardial infarction; CHF: congestive heart failure; CMR: cardiac magnetic resonance; cTFC: corrected TIMI frame count; MACE: major adverse cardiac events; MCE: myocardial contrast echocardiography; mPTP: Mitochondrial permeability transition pore; MVO: microvasculature obstruction; NRP: no-reflow phenomenon; PCI: percutaneous coronary intervention; RCTs: randomized controlled trials; STEMI: ST-segment elevation myocardial infarction; STR: resolution of ST-segment elevation; TIMI: thrombolysis in myocardial infarction; TMPG: TIMI myocardial perfusion grade; TVR: target vessel revascularization

**Declarations**

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Not applicable.

**Author Contributions**
NG, WYP designed the study. NG, DLZ performed literature searches, data extraction, assessment of risk of bias. NG, LR and LSX performed the analysis of the data. NG, LR wrote the first draft of the article.

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**Availability of data and materials**

The data and material that support the findings of this study are from published trials available in online database (PubMed, EMBase, and Cochrane Central Register of Controlled Trials).

**Ethics approval and consent to participate**

This study is a meta-analysis of RCTs and all data were collected from published trials, so an additional ethical approval and consent to participate is not necessary.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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**References**

1. Menees DS, Peterson ED, Wang Y, Curtis JP, Messenger JC, Rumsfeld JS, et al. Door-to-balloon time and mortality among patients undergoing primary PCI. N Engl J Med 2013;369:901–9.
2. Abbate A, Kontos MC, Biondi-Zoccai GG. No-reflow: the next challenge in treatment of ST-elevation acute myocardial infarction. Eur Heart J 2008; 29:1795-7.
3. Jaffe R, Charron T, Puley G, Dick A, Strauss BH. Microvascular obstruction and the no-reflow phenomenon after percutaneous coronary intervention. Circulation 2008;117:3152-6.
4. Sato T, Sasaki N, O Rourke B, Marbán E. Nicorandil, a potent cardioprotective agent, acts by opening mitochondrial ATP-dependent potassium channels. J Am Coll Cardiol 2000;35:514-8.
5. Feng C, Liu Y, Wang L, Niu D, Han B. Effects of early intracoronary administration of nicorandil during percutaneous coronary intervention in patients with acute myocardial infarction. Heart Lung Circ
6. Chen C, Fu X, Li W, Jia X, Bai S, Geng W, et al. Intracoronary administration of anisodamine and nicorandil in individuals undergoing primary percutaneous coronary intervention for acute inferior myocardial infarction: a randomized factorial trial. Exp Ther Med 2015;10:1059–65.

7. Moher D, Liberati A, Tetzlafl J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009;62:1006–12.

8. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.

9. Fukuzawa S, Ozawa S, Inagaki M, Shimada K, Sugio A, Tateno K, et al. Nicorandil affords cardioprotection in patients with acute myocardial infarction treated with primary percutaneous transluminal coronary angioplasty: assessment with thallium-201/iodine-123 BMIPP dual SPECT. J Nucl Cardiol 2000;7:447–53.

10. Ikeda N, Yasu T, Kubo N, Hashimoto S, Tsuruya Y, Fujii M, et al. Nicorandil versus isosorbide dinitrate as adjunctive treatment to direct balloon angioplasty in acute myocardial infarction. Heart 2004;90:181–5.

11. Ishii H, Ichimiya S, Kanashiro M, Amano T, Imai K, Murohara T, et al. Impact of a single intravenous administration of nicorandil before reperfusion in patients with ST-segment-elevation myocardial infarction. Circulation 2005;112:1284–8.

12. Ito H, Taniyama Y, Iwakura K, Nishikawa N, Masuyama T, Kuzuya T, et al. Intravenous nicorandil can preserve microvascular integrity and myocardial viability in patients with reperfused anterior wall myocardial infarction. J Am Coll Cardiol 1999;33:654–60.

13. Kitakaze M, Asakura M, Kim J, Shintani Y, Asanuma H, Hamasaki T, et al. Human atrial natriuretic peptide and nicorandil as adjuncts to reperfusion treatment for acute myocardial infarction (J-WIND): two randomised trials. Lancet 2007;370:1483–93.

14. Lee HC, An SG, Choi JH, Lee TK, Kim J, Kim JH, et al. Effect of intra-coronary nicorandil administration prior to reperfusion in acute ST segment elevation myocardial infarction. Circ J 2008;72:1425–9.

15. Miyazawa A, Ikari Y, Tanabe K, Nakajima H, Aoki J, Iijima R, et al. Intracoronary nicorandil prior to reperfusion in acute myocardial infarction. EuroIntervention 2006;2:211-7.

16. Nameki M, Ishibashi I, Miyazaki Y, Sakai Y, Namikawa S, Kuriyama N, et al. Comparison between nicorandil and magnesium as an adjunct cardioprotective agent to percutaneous coronary intervention in acute anterior myocardial infarction. Circ J 2004;68:192–7.

17. Ono H, Osanai T, Ishizaka H, Hanada H, Kamada T, Onodera H, et al. Nicorandil improves cardiac function and clinical outcome in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention: role of inhibitory effect on reactive oxygen species formation. Am Heart J 2004;148:e15.

18. Ota S, Nishikawa H, Takeuchi M, Nakajima K, Nakamura T, Okamoto S, et al. Impact of nicorandil to prevent reperfusion injury in patients with acute myocardial infarction: Sigmart Multicenter Angioplasty Revascularization Trial (SMART). Circ J 2006;70:1099–104.

19. Pi SF, Liu YW, Li T, Wang Y, Zhou Q, Liu BJ, et al. Effect of sequential nicorandil on myocardial microcirculation and short-term prognosis in acute myocardial infarction patients undergoing coronary intervention. J Thorac Dis 2019;11:744-52.

20. Qi Q, Niu J, Chen T, Yin H, Wang T, Jiang Z. Intracoronary nicorandil and the prevention of the no-reflow phenomenon during primary percutaneous coronary intervention in patients with acute ST-segment elevation myocardial infarction. Med Sci Monit 2018;24:2767–76.
21. Wang ZQ, Chen MX, Liu DL, Zheng WX, Cao XZ, Chen H, et al. The effect on myocardial perfusion and clinical outcome of intracoronary nicorandil injection prior to percutaneous coronary intervention in ST-segment elevation myocardial infarction. Chin J Cardiol 2017;45:26–33.

22. Yamada K, Isobe S, Ishii H, Yokouchi K, Iwata H, Sawada K, et al. Impacts of nicorandil on infarct myocardium in comparison with nitrate: assessed by cardiac magnetic resonance imaging. Heart and Vessels 2016;31:1430-7.

23. Chen GX, Wang HN, Zou JL, Yuan XX. Effects of intracoronary injection of nicorandil and tirofiban on myocardial perfusion and short-term prognosis in elderly patients with acute ST-segment elevation myocardial infarction after emergency PCI. World J Emerg Med 2020;11:157–63.

24. Wang ZD, Li H, Liu M, Li P, Chen J, Liang XW, et al. Effect of intravenous application of nicorandil on area of myocardial infarction in patients with STEMI during the perioperative stage of PCI. Clin Hemorheol Microcirc 2021;77:411-23.

25. Vogt A, von Essen R, Tebbe U, Feuerer W, Appel KF, Neuhaus KL. Impact of early perfusion status of the infarct-related artery on short-term mortality after thrombolysis for acute myocardial infarction: retrospective analysis of four German multicenter studies. J Am Coll Cardiol 1993;21:1391–5.

26. Roe MT, Ohman EM, Maas AC, Christenson RH, Mahaffey KW, Granger CB, et al. Shifting the open-artery hypothesis downstream: the quest for optimal reperfusion. J Am Coll Cardiol 2001;37:9–18.

27. Ohara Y, Hiasa Y, Takahashi T, Yamaguchi K, Ogura R, Ogata T, et al. Relation between the TIMI frame count and the degree of microvascular injury after primary coronary angioplasty in patients with acute anterior myocardial infarction. Heart 2005;91:64–7.

28. Wong DTL, Leung MCH, Richardson JD, Puri R, Bertaso AG, Williams K, et al. Cardiac magnetic resonance derived late microvascular obstruction assessment post ST-segment elevation myocardial infarction is the best predictor of left ventricular function: a comparison of angiographic and cardiac magnetic resonance derived measurements. Int J Cardiovasc Imaging 2012;28:1971–81.

29. Kojima M, Ban T. Nicorandil shortens action potential duration and antagonises the reduction of Vmax by lidocaine but not by disopyramide in guinea-pig papillary muscles. Naunyn Schmiedebergs Arch Pharmacol 1988;337:203-12.

30. Hirose M, Tsujino N, Nakada T, Yano S, Imamura H, Yamada M. Mechanisms of preventive effect of nicorandil on ischaemia-induced ventricular tachyarrhythmia in isolated arterially perfused canine left ventricular wedges. Basic Clin Pharmacol Toxicol 2008;102:504-14.

31. Ueda H, Nakayama Y, Tsumura K, Yoshimaru K, Hayashi T, Yoshikawa J. Intravenous nicorandil can reduce the occurrence of ventricular fibrillation and QT dispersion in patients with successful coronary angioplasty in acute myocardial infarction. Can J Cardiol 2004;20:625-9.

32. Wang S, Fan Y, Feng X, Sun C, Shi Z, Li T, et al. Nicorandil alleviates myocardial injury and post-infarction cardiac remodeling by inhibiting Mst1. Biochem Biophys Res Commun 2018;495:292-9.

33. Di Lisa F, Menabò R, Canton M, Barile M, Bernardi P. Opening of the mitochondrial permeability transition pore causes depletion of mitochondrial and cytosolic NAD+ and is a causative event in the death of myocytes in postischemic reperfusion of the heart. J Biol Chem 2001;276:2571-5.

34. Kuno A, Critz SD, Cohen MV, Downey JM. Nicorandil opens mitochondrial K(ATP) channels not only directly but also through a NO-PKG-dependent pathway. Basic Res Cardiol 2007;102:73-9.
35. Costa AD, Jakob R, Costa CL, Andrukhiv K, West IC, Garlid KD. The mechanism by which the mitochondrial ATP-sensitive K\(^+\) channel opening and H\(_2\)O\(_2\) inhibit the mitochondrial permeability transition. J Biol Chem 2006;281:20801-8.

36. Kang CS, Chen CC, Lin CC, Chang NC, Lee TM. Effect of ATP-sensitive potassium channel agonists on sympathetic hyperinnervation in postinfarcted rat hearts. Am J Physiol Heart Circ Physiol 2009;296:H1949-59.

37. Hasan MS, Basri HB, Hin LP, Stanslas J. Genetic polymorphisms and drug interactions leading to clopidogrel resistance: why the Asian population requires special attention. Int J Neurosci 2013;123:143-54.

Tables

Table 1 Characteristics of included studies
| Study                  | Year | Onset to reperfusion time, (hours) | Sample size(N/C) (N/C) | Interventions                                                                 | Followup |
|-----------------------|------|----------------------------------|------------------------|-------------------------------------------------------------------------------|----------|
| Chen CH et al\(^6\)   | 2015 | 7.1/7.0                          | 52/52                  | 2mg ic or 2mg+anisodamine 2mg ic                                               | IH, 30d  |
| Chen GX et al [23]    | 2020 | NA                               | 39/39                  | 0.06 mg/kg ic; 2 mg/h iv for 36 h tirofiban 10 μg/kg ic; 0.1 μg/kg·m iv for 36 h | IH, 30d  |
| Feng et al [5]        | 2019 | 4.7/4.8                          | 90/90                  | 2-6 mg ic; thrombectomy; Tirofiban 10 mg/kg ic                                 | 1,3,6m  |
| Fukuzawa et al [9]    | 2000 | 4.6/4.5                          | 31/31                  | 4mg bolus iv, 6 mg/h iv for 24h no agent                                       | IH       |
| Ikeda et al [10]      | 2004 | 5.2/5.7                          | 30/30                  | 6mg/h iv for 72h, 2mg ic isosorbide dinitrate 6mg/h iv for 72h,2mg ic          | IH       |
| Ishii et al [11]      | 2005 | 4.8/4.5                          | 185/183                | 12mg+saline 100ml iv; isosorbide 2.5-5mg ic                                   | 2.4y*    |
| Ito et al [12]        | 1999 | 4.8/5.3                          | 40/41                  | 4mg bolus iv; 6 mg/h for 24 h; 15 mg/day po (a mean of 28 days) no agent       | IH       |
| Kitakaze et al [13]   | 2007 | 4.20/4.25                        | 276/269                | 0.067mg/kg bolus iv; 1•67μg/kg.min iv for 24 h saline by the same method       | 2.5y*    |
| Lee et al [14]        | 2008 | 5.9/5.8                          | 37/36                  | 2mg ic before CAG; 2mg ic before stenting no agent                             | IH;30d   |
| Miyazawa et al [15]   | 2006 | 6.1/8.0                          | 35/35                  | 2mg ic distal to lesion; 2mg/h for 24h; 15mg/d po no agent                    | 8m       |
| Study                  | Year | Mortality | MI Rate | Treatments                                                                 | Follow-up |
|-----------------------|------|-----------|---------|-----------------------------------------------------------------------------|-----------|
| Nameki et al [16]     | 2004 | 5.85/6.17 | 13/27   | 4 mg iv 4 mg ic before reperfusion, 4 mg/h iv for 24 h                      | IH;3m     |
|                       |      |           |         | Magnesium: 10 mmol iv before reperfusion, 0.4 mmol/h iv for 24 h or no agent |           |
| Ono et al [17]        | 2004 | 5.6/5.1   | 33/25   | 4 mg bolus iv, 8 mg/h iv for 24 h after PCI                                | IH;6m     |
|                       |      |           |         | no agent                                                                   |           |
| Ota et al [18]        | 2006 | 4.05/3.86 | 63/27   | 1–2 mg ic or 1–2 mg ic+4 mg bolus iv, 6 mg/h iv (total: 96 mg)              | IH        |
|                       |      |           |         | no agent                                                                   |           |
| Pi et al [19]         | 2019 | 6.51/6.86 | 95/45   | a: 4 mg ic, 4 mg/h iv for 24h; b: 4 mg ic, saline 4 ml/h iv for 24 h        | IH        |
|                       |      |           |         | saline: 8 ml ic, 4 ml/h iv for 24 h                                        |           |
| Qi et al [20]         | 2018 | 5.7/6.1   | 40/80   | 2 mg ic                                                                     | IH;3m     |
|                       |      |           |         | nitroprusside: 200 μg ic or saline only                                      |           |
| Wang ZQ et al [21]    | 2017 | 4.8/4.5/3.8* | 53/105 | 6 mg ic                                                                     | IH;3m     |
|                       |      |           |         | NG 300 μg ic or no agent                                                     |           |
| Wang ZD et al [24]    | 2020 | 5.9/5.7   | 59/60   | iv, dosage not mentioned                                                   | 6m        |
|                       |      |           |         | no agent                                                                   |           |
| Yamada et al [22]     | 2015 | 6.4/6.8   | 28/24   | 0.2 mg/kg ic before the initial and final angiograms; 2.0 mg/h iv for 4 days| IH        |
|                       |      |           |         | nitroglycerin 0.2 mg/kg ic before the initial and final angiograms; 2.0 mg/h iv for 4 days |           |

*: median

Ic, intracoronary; IH, in hospital; iv, intravenous; N/C, nicorandil/control groups; po, per oral.

Table 2 Meta-analyses of mortality, new AMI, TVR, heart Failure, arrhythmia
| Clinical outcomes | Studies included | Effect sizes | Heterogeneity |
|-------------------|-----------------|--------------|---------------|
|                   |                 | OR  | 95% CI     | P value | Tau² | I², % | P value |
| Mortality         | 13              | 0.68| 0.41–1.11  | 0.12    | 0.00 | 0     | 0.83    |
| New AMI           | 5               | 0.56| 0.19–1.67  | 0.30    | 0.00 | 0     | 0.90    |
| TVR               | 8               | 1.01| 0.64–1.59  | 0.95    | 0.00 | 0     | 0.77    |
| Heart failure     | 10              | 0.36| 0.23–0.57  | 0.00    | 0.00 | 0     | 0.55    |
| Arrhythmia        | 10              | 0.43| 0.31–0.60  | 0.00    | 0.00 | 0     | 0.91    |

Arrhythmia refers to ventricular tachycardia and ventricular fibrillation.

AMI, acute myocardial infarction; CI, confidence interval; OR, odds ratio; TVR, target vessel revascularization.

Table 3 Sensitivity analysis of the incidences of MACEs after 1-by-1 exclusion of each individual study

| Study removed each time | Statistics after one study removed | Heterogeneity |
|-------------------------|-----------------------------------|---------------|
|                         | OR      | 95% CI     | P        | Tau² | I², % | P |
| No study removed        | 0.42    | 0.27-0.64  | 0.001   | 0.21 | 52    | 0.03 |
| Chen 2015 [6]           | 0.41    | 0.26-0.65  | 0.001   | 0.24 | 57    | 0.02 |
| Chen 2020 [23]          | 0.42    | 0.26-0.67  | 0.001   | 0.24 | 56    | 0.02 |
| Feng 2019 [5]           | 0.42    | 0.26-0.68  | 0.001   | 0.23 | 55    | 0.02 |
| Ishii 2005 [11]         | 0.37    | 0.21-0.64  | 0.001   | 0.35 | 57    | 0.02 |
| Kitakaze 2007 [13]      | 0.37    | 0.25-0.54  | 0.001   | 0.05 | 16    | 0.30 |
| Lee 2008 [14]           | 0.40    | 0.25-0.63  | 0.001   | 0.23 | 57    | 0.02 |
| Ono 2004 [17]           | 0.43    | 0.27-0.68  | 0.001   | 0.22 | 54    | 0.03 |
| Ota 2006 [18]           | 0.44    | 0.28-0.69  | 0.001   | 0.21 | 53    | 0.03 |
| Pi 2019 [19]            | 0.50    | 0.34-0.74  | 0.001   | 0.10 | 34    | 0.15 |
| Qi 2018 [20]            | 0.43    | 0.28-0.67  | 0.001   | 0.20 | 53    | 0.03 |
| Wang 2020 [24]          | 0.42    | 0.27-0.64  | 0.001   | 0.21 | 52    | 0.03 |

CI: confidence interval; MACE: major adverse cardiovascular events; OR: odds ratio

Figures
### Figure 1

Subgroup analysis of major adverse cardiovascular events based on different methods of nicorandil administration.

| Study or Subgroup | Nicorandil | Control | Odds Ratio | Odds Ratio |
|-------------------|------------|---------|------------|------------|
|                   | Events     | Total   | Weight     | M-H, Random, 95% CI | M-H, Random, 95% CI |
| **1.1.1 intracoronary and intravenous** |            |         |            |            |            |
| Chen 2020         | 6          | 39      | 13         | 39 9.5% 0.36 [0.12, 1.09] |            |
| Ota 2006          | 7          | 65      | 9          | 27 9.2% 0.25 [0.09, 0.77] |            |
| Pi 2019           | 46         | 95      | 38         | 45 11.7% 0.17 [0.07, 0.43] |            |
| Subtotal (95% CI) | 197        | 60      |            | 111 30.4% 0.24 [0.13, 0.43] |            |
| Total events      | 59         | 60      |            |            |            |

Heterogeneity: Tau² = 0.00; Chi² = 1.07, df = 2 (P = 0.59); I² = 0%
Test for overall effect: Z = 4.76 (P < 0.00001)

| **1.1.2 intracoronary** |            |         |            |            |            |
| Chen 2015             | 2          | 52      | 4          | 52 4.9% 0.48 [0.08, 2.74] |            |
| Feng 2019             | 6          | 90      | 16         | 90 10.6% 0.33 [0.12, 0.89] |            |
| Lee 2008              | 2          | 37      | 2          | 36 3.9% 0.97 [0.13, 7.29] |            |
| Qi 2018               | 1          | 40      | 12         | 80 3.7% 0.15 [0.02, 1.16] |            |
| Subtotal (95% CI)     | 219        | 258     |            | 238 23.2% 0.37 [0.18, 0.77] |            |
| Total events          | 11         | 34      |            |            |            |

Heterogeneity: Tau² = 0.00; Chi² = 1.83, df = 3 (P = 0.61); I² = 0%
Test for overall effect: Z = 2.65 (P = 0.008)

| **1.1.3 intravenous** |            |         |            |            |            |
| Ishii 2005            | 47         | 185     | 66         | 183 18.9% 0.60 [0.33, 0.94] |            |
| Kitakaze 2007         | 55         | 276     | 58         | 269 19.5% 0.91 [0.60, 1.37] |            |
| Ono 2004              | 5          | 33      | 10         | 25 8.4% 0.27 [0.08, 0.93] |            |
| Wang 2020             | 0          | 59      | 0          | 50   | Not estimable |
| Subtotal (95% CI)     | 553        | 537     |            | 464 46.4% 0.66 [0.40, 1.06] |            |
| Total events          | 107        | 134     |            |            |            |

Heterogeneity: Tau² = 0.03; Chi² = 4.19, df = 2 (P = 0.12); I² = 52%
Test for overall effect: Z = 1.71 (P = 0.09)

Total (95% CI)          969 906 100.0% 0.42 [0.27, 0.64]
Total events            177 228

Heterogeneity: Tau² = 0.21; Chi² = 18.78, df = 9 (P = 0.03); I² = 52%
Test for overall effect: Z = 3.95 (P < 0.0001)
Test for subgroup differences: Chi² = 6.92, df = 2 (P = 0.03), I² = 71.1%
Figure 2

Forest plot of no-reflow phenomena.

**Supplementary Files**

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