Effects of Nicorandil on All-Cause Mortality and Cardiac Events in CAD Patients Receiving PCI
A Systematic Review and Meta-Analysis

Xin Zhang, MD, Qian Yu, MD, Xun Yao, MD, Guanjian Liu, MD, Jing Li, PhD and Liang Du, PhD

Summary
Current studies demonstrating the effects of nicorandil in the prognosis of coronary artery disease (CAD) patients who received percutaneous coronary intervention (PCI) are inconclusive due to the small sample size and small events rate.

PubMed, OVID, CBM and CNKI databases were searched using a pre-specified search string to collect randomized controlled trials (RCTs) studying the effects of nicorandil on CAD patients receiving PCI. Data on all-cause mortality and cardiovascular events were collected. RevMan 5.3 software was used for meta-analysis. Subgroup analysis was conducted in patients receiving primary PCI (PPCI) and elective PCI (EPCI).

A total of 18 RCTs were included in our final analysis. Nicorandil treatment significantly reduced total mortality in PPCI (Peto OR = 0.44, 95%CI 0.25-0.79, \( P = 0.006 \)) and EPCI (Peto OR = 0.41, 95%CI 0.25-0.67, \( P = 0.0004 \)), cardiovascular death in both PPCI (Peto OR = 0.41, 95%CI 0.20-0.84, \( P = 0.01 \)) and EPCI (Peto OR = 0.40, 95%CI 0.20-0.80, \( P = 0.009 \)), and heart failure in PPCI (RR = 0.36, 95%CI 0.22-0.59, \( P < 0.0001 \)). When compared with placebo plus standard treatment or standard treatment alone, nicorandil plus standard treatment was associated with reduced total mortality in both PPCI and EPCI, CV death in EPCI, and heart failure in PPCI. Nicorandil is associated with lower risks of total mortality and CV death in PPCI and EPCI in those who received nicorandil > 28 days.

Nicorandil as an adjunct therapy along with PCI is associated with reduced total mortality and cardiovascular death in PPCI and EPCI patients, and reduced heart failure in PPCI patients.

(Key words: Prognosis, PPCI, EPCI, Adjunctive therapy, Cardiovascular events)

Coronary heart disease, characterized by narrowing of arterial lumen and reduced blood flow to the heart, is a leading cause of morbidity and mortality globally.\(^1\,2\) Percutaneous coronary intervention (PCI) is an efficient method widely used in coronary artery disease (CAD) for relieving myocardial ischemia and preserving ventricular function.\(^3\,4\) However, PCI in CAD patients can cause coronary microvascular dysfunction which leads to myocardial damage and a poor long-term prognosis.\(^5\,6\) PCI can also lead to abnormal microvascular vasomotility and distal coronary microembolization of atheromatous and thrombotic debris and may cause aggravation of microcirculatory disturbance, abnormal myocardial metabolism, and myocardial necrosis.\(^7\) The serious complications of PCI that lead to a poor prognosis are no-reflow and myocardial injury.\(^7\,11\)

Nicorandil, a potent coronary vasodilator, is a hybrid of adenosine triphosphate-sensitive potassium (KATP) channel opener and nitrates are commonly prescribed for the treatment of coronary heart disease.\(^3\,12\) A large-scale study on stable angina, the IONA study (Impact of Nicorandil in Angina) reported that nicorandil administration not only reduced death but also decreased hospitalizations for myocardial infarction and chest pain.\(^15\) Nicorandil has cardio-protection effects in coronary heart disease patients undergoing PCI by mimicking preconditioning in the absence of ischemia through the mechanism of activation of myocardial KATP channels. Nicorandil has cardioprotective effects in coronary heart disease patients undergoing PCI.\(^16\,17\) Nicorandil could prevent the slow reflow/no flow phenomenon and reduce the elevation of creatine kinase-MB and cardiac troponin, indicators of myocardial damage in CAD patients undergoing primary PCI.\(^18\,19\) Its efficacy is also observed as an adjuvant therapy with PCI on
myocardial protection as measured by reduced ST segment elevation and angina in unstable angina.\(^\text{19}\)

Currently, there is only one meta-analysis on nicorandil in patients with acute myocardial infarction undergoing primary PCI demonstrating that nicorandil is associated with improvement of coronary reflow and left ventricular function, and furthermore, it is also associated with suppression of ventricular arrhythmia.\(^\text{20}\) Another meta-analysis on the clinical effect of nicorandil on perioperative myocardial protection indicated that nicorandil could reduce myocardial injury and also reduce the frequency of adverse reaction caused by PCI in Chinese population;\(^\text{21}\) however, no study thus far has demonstrated that nicorandil could improve the prognosis of CAD patients who receive PCI.

### Methods

**Data collection and screening:** This systematic review and meta-analysis was conducted by adhering to the “Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)” guidelines\(^\text{22}\) and is registered in PROSPERO (PROSPERO 2017:CRD42017082564). Clinical trials, studies pertaining to the evaluation of the efficacy of nicorandil on all-cause mortality and cardiac events in CAD patients receiving PCI, were retrieved for analysis for total mortality (all-cause mortality) and other pre-specified outcomes included cardiac death, myocardial infection and heart failure. Comparison was also made between patients receiving primary PCI (PPCI group) and patients receiving elective PCI (EPCI group). We searched PubMed, EMBASE via OVID, CENTRAL via the cochranelibrary.com, CBM (Chinese BioMedical Database), CNKI (China National Knowledge Infrastructure database), VIP database, and WAFANG database until April 2017, with no language restrictions. For some uncertain or incomplete data, original investigators were contacted. The search strategies are presented in Table 1.

Two reviewers independently screened the abstracts and full-texts for eligibility of inclusion. Inclusion criteria consisted of (1) randomized clinical trials studies (2) patients receiving PCI randomized to nicorandil or control, (3) nicorandil administered either orally, intravenously, or intracoronary for short or long-term, and (4) with outcomes of all-cause mortality, cardiac death, non-fatal MI and heart failure reported irrespective of the follow-up period. Excluded articles were studies that were (1) cross-sectional designed studies, (2) follow-up period less than 28 days, and (3) total mortality was zero in both groups.

During the screening process, duplicates and articles which did not meet the eligibility criteria were removed. The remaining articles were screened by two independent reviewers in order to ensure that they met the pre-specified study inclusion criteria. Any disagreement was resolved by a third reviewer. In addition, we searched the bibliographies of original trials, meta-analyses, and review articles identified to find other eligible trials, and kept up to date with the search by weekly reminders from Pub-

### Table 1. Search Strategy Used in the Meta-Analysis for Procurung Relevant Articles

| Database          | Search strategy                                                                                                                                 |
|-------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| PubMed            | (“Nicorandil”[Mesh] OR SG75[tw] OR “SG-75”[tw] OR “sigma-75”[tw] OR Ikorel*[tw] OR Adancor*[tw] OR dancor*[tw] OR SIGMART*[tw] OR nicorandil*[tw] OR Aprior*[tw] OR Angedi*[tw] OR nikoran*[tw] OR nitorubin*[tw] OR siomart*[tw] OR perisalol*[tw] OR (Nicotinamidioethyl*[tw] AND (“nitrates”[MeSH Terms] OR nitrate*[tw])) AND (“Percutaneous Coronary Intervention”[Mesh] OR (percutaneous*[tw] AND coronar*[tw] AND (intervent*[tw] OR revascular*[tw] OR angioplast*)) OR PTCA OR ((Transluminal*[tw] OR Angioplast*[tw] OR Dilation*[tw]) AND Balloon*[tw] AND Coronar*[tw]) OR ((rotational*[tw] OR directional*[tw] OR coronar*[tw]) AND atherectomy*[tw])) AND (randomized controlled trial[Publication Type] OR random*[Title/Abstract] OR placebo[Title/Abstract]) |
| EMBASE via OVID   | 1 exp nicorandil/                                                                                                                                  |
|                   | 2 (nicorandil* or sg75 or sg-75 or sigma-75 or Ikorel* or Adancor* or dancor* or SIGMART* or Aprior* or Angedi* or nikoran* or nitorubin* or siomart* or perisalol*).mp. |
|                   | 3 Nicotinamidioethyl*.mp. and (exp nitrates/ or nitrate*.mp.)                                                                                     |
|                   | 4 exp percutaneous coronary intervention/                                                                                                           |
|                   | 5 (coronar* and percutaneous* and (intervent* or revascular* or angioplast*)).mp.                                                               |
|                   | 6 ((Transluminal* or Angioplast* or Dilation*) and Balloon* and Coronar*).mp.                                                                  |
|                   | 7 ((rotational* or directional* or coronar*) and atherectomy*).mp.                                                                              |
|                   | 8 PTCA.mp.                                                                                                                                       |
|                   | 9 randomized controlled trial.pt. or random*.mp. or placebo.mp.                                                                                  |
|                   | 10 1 or 2 or 3                                                                                                                                     |
|                   | 11 4 or 5 or 6 or 7 or 8                                                                                                                        |
|                   | 12 10 and 11 and 9                                                                                                                                |
| CENTRAL via thecochranelibrary.com | #1 “SG75” or “SG-75” or “sigma-75” or (Nicotinamidioethyl* and nitrate*) or Ikorel* or Adancor* or dancor* or SIGMART* or nicorandil* or Aprior* or Angedi* or nikoran* or nitorubin* or siomart* or perisalol* \#2 MeSH descriptor: [Nicorandil] explode all trees \#3 coronar* and percutaneous* and (intervent* or revascular* or angioplast*) \#4 (Transluminal* or Angioplast* or Dilation*) and Balloon* and Coronar* \#5 (rotational* or directional* or coronar*) and atherectomy* \#6 PTCA \#7 MeSH descriptor: [Percutaneous Coronary Intervention] explode all trees \#8 (#1 or #2) and (#3 or #4 or #5 or #6 or #7) |
Med.

Data extraction and quality assessment: Data extraction was performed and patient baseline characteristics such as age, risk factors for cardiac events including comorbidities, receiving PCI or primary PCI, method of CAD diagnosis, type of intervention, including dose, route of administration, duration and frequency of the nicorandil, versus placebo or any other comparator dose, route of administration, duration and frequency of active drug or versus no treatment and type of outcome measured including the frequency of all-cause mortality, cardiac death, myocardial infarction and heart failure were extracted into a pre-specified template into a Microsoft Excel spreadsheet. Cochrane tools for randomized trials were used to assess bias risk in individual studies by two authors independently. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment was used to evaluate the quality of evidence. Trials were assessed as being at low or unclear risk of bias for 30-80% of evaluated trial quality parameters, with moderate to high quality evidence according to the GRADE assessment.23)

Data analysis: RevMan5.3 software was used to conduct the meta-analysis. The meta-analyses were performed by computing Peto OR using fixed-effects model and RRs using random-effects model. Quantitative analyses were performed on an intention-to-treat basis. Peto OR (and RR) and 95% confidence intervals for each side effect (and all side effects) were calculated. Peto’s method was used for calculating Peto ORs of all-cause mortality and cardiac death between the nicorandil group and control group.

The Mantel-Haenszel method was used for calculating RRs of myocardial infarction and heart failure between the Mantel-Haenszel nicorandil group and control group. The chi-square test and $I^2$ statistic were used as the statistical tests for heterogeneity.

To investigate the effects of different follow-up periods on outcome, we analyzed the effects of nicorandil on total mortality according to different follow-up periods of more than 1 year, more than 30 days to no more than 1 year, and no more than 30 days in PPCI and EPCL. Subgroup analyses were performed with placebo/no treatment control versus active control; subgroups with long-term oral nicorandil versus without. Long-term oral nicorandil was defined as oral administration of nicorandil daily for no less than 28 days. We assessed the possibility of publi-
Table II. Characteristics of Included Studies

| Study          | Year | Population (n) | Mean age | Intervention (n /dose) | Comparison (n /dose) | Follow-up period | Outcomes                                    |
|----------------|------|----------------|----------|-----------------------|---------------------|------------------|--------------------------------------------|
| Qingqing, et al. 2015 | Elderly acute myocardial infarction patients receiving PCI in 12 hours (n = 115) | 68.51 ± 3.35 nicorandil 69.07 ± 2.75 control | Nicorandil (n = 57) 15 mg nicorandil administered orally after hospital admission and before PCI. Nicorandil 5 mg, tid after PCI until 30 days after PCI. | Isosorbide mononitrates (n = 58) Oral 20 mg, tid until 30 days after PCI. | 30 days | Total mortality, CV death, myocardial infarction, heart failure |
| Hongjun, et al. 2016 | Elderly acute myocardial infarction patients receiving PCI in 12 hours (n = 80) | 63.1 ± 10 | Nicorandil (n = 40) 12 mg nicorandil administered intravenously before PCI | Placebo (n = 40) Saline 100 mL administered intravenously | 3 months | Total mortality, Myocardial infarction, heart failure |
| Xiaoeng, et al. 2015 | Acute coronary syndrome patients receiving PCI (n = 150) | 45.12 ± 5.7 | Nicorandil (n = 75) 10 mg nicorandil administered orally before PCI | No treatment (n = 75) | 6 months | Total mortality, Myocardial infarction |
| Miyazawa, et al. 2006 | Patients with first ST-elevation AMI (STEMI) who underwent coronary intervention (n = 70) | 64 ± 10 Nicorandil 60 ± 9 control | Nicorandil (n = 35) 2 mg dose of nicorandil administered intravenously before PCI. After successful PCI, nicorandil was administered intravenously at 2 mg/hour for 24 hours, followed by oral nicorandil at 15 mg/day | No treatment (n = 35) | 8 months | Total mortality, myocardial infarction, heart failure, CV death |
| Chen, et al. 2015 | First anterior acute myocardial infarction patients receiving PCI (n = 115) | 59.8 ± 4.8 control; 58.9 ± 5.1 anisodamine; 57.6 ± 4.7 nicorandil | Nicorandil (n = 26) 2 mg, intracoronary administration | No treatment (n = 26) Anisodamine (n = 26) 2 mg Intracoronary administration Anisodamine and nicorandil (n = 26) Intracoronary administration | 30 days | Total mortality, CV death, myocardial infarction |
| Ishii, et al. 2005 | STEMI patients receiving PCI (n = 368) | 63 ± 9.4 nicorandil 64 ± 10.1 placebo | Nicorandil (n = 185) 12 mg, administered intravenously before PCI | Placebo (n = 183) 100 ml of 0.9% saline administered intravenously | 2.4 years | Total mortality, CV death, heart failure |
| Ito, et al. 1999 | First anterior AMI patients receiving PCI (n = 90) | 60 ± 10 Nicorandil 60 ± 10 no treatment | Nicorandil (n = 40) After the bolus injection of nicorandil (4 mg), it was injected at 6 mg/hour for 24 hours followed by oral nicorandil 15 mg/day until discharge (mean of 28 days) | No treatment (n = 41) | 28 days | Total mortality, CV death, myocardial infarction, heart failure |
| Nameki, et al. 2004 | Patients with AMI who underwent emergency coronary angiography (CAG) with stand-by PCI (n = 40) | 64 ± 10 nicorandil 62 ± 11 no treatment 62 ± 11 magnesium sulfate | Nicorandil (n = 13) 4 mg intravenously and 4 mg intracoronarily before reperfusion, followed by continuous intravenous infusion at 4 mg/hour for the subsequent 24 hours | No treatment (n = 14) Magnesium sulfate (n = 13) 10 mmol administered intravenously before reperfusion, followed by continuous infusion at 0.4 mmol/hour for the subsequent 24 hours | 3 months | Total mortality, CV death, myocardial infarction, heart failure |
| Kawai, et al. 2009 | ACS and non-ACS patients (n = 450) | ACS: 69 ± 11.1 nicorandil 71 ± 11.5 control Non-ACS: 72 ± 8.5 nicorandil 73 ± 9.6 control | Nicorandil (n = 225) Initially 6 mg of nicorandil administered intravenously and after the guidewire had crossed the stenotic lesion, 6 mg of nicorandil was administered by intravenous hand-injection over a 20 second period for patients in the nicorandil group 1 minute before stent implantation | Placebo (n = 225) 20 mL saline administered intravenously | 12 months | Total mortality, CV death, heart failure |
| Study          | Year | Population (n) | Mean age | Intervention (n) /dose | Comparison (n) /dose | Follow-up period | Outcomes                                      |
|---------------|------|----------------|----------|------------------------|---------------------|------------------|-----------------------------------------------|
| Chen, et al.  | 2015 | CAD patients receiving PCI (n = 62) | 62.6 ± 4.6 nicorandil (n = 30) Mean age 63.3 ± 5.2 control | Nicorandil (n = 30) 5 mg orally three times a day for post-operation (6 months) | Blank Control (n = 32) | 6 months | Total mortality, cardiac death, myocardial infarction, heart failure |
| Zhou, et al.  | 2015 | CAD patients receiving PCI (n = 48) | 65.2 ± 2.6 nicorandil (n = 26) Mean age 65.4 ± 2.2 control | Nicorandil (n = 26) 10 mg orally for pre-operation (30 minutes before operation), 10 mg a day orally for post-operation (6 months) | Rosuvastatin (n = 22) 10 mg orally for pre-operation (30 minutes before operation), 10 mg a day orally for post-operation (6 months) | 6 months | Total mortality |
| Gao, et al.   | 2016 | CAD patients receiving PCI (n = 64) | 65.6 ± 2.5 nicorandil (n = 32) Mean age 64.6 ± 2.7 control | Nicorandil (n = 32) 5 mg orally for pre-operation (30 minutes before operation), 5 mg three times a day orally for post-operation (18 months) | Control (n = 32) | 12 months | Total mortality |
| Feng, et al.  | 2016 | CAD patients receiving PCI (n = 79) | 63.1 ± 2.4 Mean age 63.6 ± 2.0 nicorandil | Nicorandil (n = 42) 10 mg/day orally for pre-operation (3 days), 10 mg/day orally for post-operation (6 months) | Oral Tirofiban (n = 37) 5 mg/day orally for pre-operation (3 days), 5 mg/day orally for post-operation (6 months) | 6 months | Total mortality |
| Kim, et al.   | 2005 | CAD patients receiving PCI (n = 200) | 61.7 ± 8.2 ISDN (n = 42) Mean age 60.4 ± 11.7 nicorandil | Nicorandil (n = 42) Initially 4 mg injection, and then infusion at a rate of 4 mg/hour, up to 6 mg/hour or less depending on symptoms, nicorandil infusions were given for 12-48 hours before PCI and for 48 hours after PCI, then replaced with oral nicorandil in group II for the next 6 months. | Isosorbide dinitrate (ISDN) Administered intravenously 2 mg/hour and gradually increased to 4 mg/hour, with a further increase up to 8 mg/hour or decrease depending on the symptoms. ISDN was given for 12-48 hours before PCI and for 48 hours after PCI, then replaced with oral medication of 80-160 mg/day ISDN for 6 months | 6 months | Total mortality, cardiac death, myocardial infarction, heart failure |
| Murakami, et al. | 2006 | CAD patients receiving PCI (n = 200) | 65 ± 9.7 nicorandil (n = 91) Mean age 66.1 ± 10.3 control | Nicorandil (n = 91) Intravenous administration of nicorandil, 2 mg/kg/minute, was started immediately after the patients were transferred into the catheterization laboratory and continued until 6 hours after the procedure. | Control (n = 101) Intravenous administration of 0.9% saline was started immediately after the patients were transferred into the catheterization laboratory and continued until 6 hours after the procedure. | 3 months -3.1 years | Total mortality, CV death, myocardial infarction |
| Nishimura, et al. | 2004 | CAD patients receiving PCI (n = 129) | 65.0 ± 9.5 nicorandil (n = 64) Mean age 64.0 ± 8.0 control | Nicorandil (n = 64) 5 mg tid orally | Blank control (n = 65) | 2.7 years | Total mortality, CV death |
| Shehata, et al. | 2014 | CAD patients receiving PCI (n = 100) | 59.4 ± 7.4 nicorandil (n = 50) Mean age 60.2 ± 4.3 control | Nicorandil (n = 50) Oral nicorandil (20 mg once daily) starting 1 week before PCI continued to receive the prescribed agent for 6 months after PCI | Blank control (n = 50) | 6 months | Total mortality, CV death, myocardial infarction |
| Miyoshi, et al. | 2017 | CAD patients receiving PCI (n = 396) | 70.0 ± 9.2 nicorandil (n = 132) Mean age 70.3 ± 10.1 control | Nicorandil (n = 132) 4 mg of nicorandil was intravenously administered for 5 minutes at least 1 hour before PCI, followed by continuous infusion of nicorandil (6 mg/hour) for at least 8 hours | Blank control (n = 133) | 8 months | Total mortality, heart failure |
culation bias by evaluating a funnel plot of the trial Peto ORs (or RRs) for asymmetry. Sensitivity analyses were performed to assess the robustness of our results by removing each included study at one time to obtain and evaluate the remaining overall estimates of total mortality.

**Results**

The database search yielded 361 results, of which 243 articles were excluded after removing duplicates based on title, abstracts and full-texts that did not meet the inclusion criteria. Screening of the abstracts and full-texts of the remaining original articles yielded 18 RCTs which were included in the final analysis (Figure 1).

Overview of the studies included in the analysis (Baseline and intervention characteristics of included studies) is represented in Table II. Included studies consisted of a total of 2360 patients with a mean age ranging from 45.12 ± 5.7 to 73 ± 6.9 years. All of the studies reported total mortality and many of the studies reported myocardial infarction, CV death and heart failure.

**Overall quality of evidence:** A GRADE assessment was performed for primary and secondary endpoints for overall quality of evidence. The GRADE evidence profile and the summary of findings are presented in Table III. The overall quality of evidence was moderate for outcomes of total mortality, CV death, MI and heart failure in the PPCI group. The outcomes of total mortality, CV death, MI and heart failure had low quality of evidence in the EPC group.

**Primary outcomes:** Nicorandil treatment significantly reduced total mortality among patients who received PPCI (Peto OR 0.44, (95% CI 0.25-0.79; \( I^2 = 3\% \)), or EPCI (Peto OR 0.41, (95% CI 0.25-0.67; \( I^2 = 0\% \)), cardiovascular death in both PPCI (Peto OR 0.41 (95% CI 0.20-0.84; \( I^2 = 23\% \)), and EPCI, Peto OR 0.40, (95% CI 0.20-0.80; \( I^2 = 13\% \)), and heart failure in PPCI (RR, 0.36, (95% CI 0.22-0.59; \( I^2 = 0\% \), \( P < 0.0001\)), but not in EPCI (RR, 0.55, (95% CI 0.32-1.73; \( I^2 = 41\% \), \( P = 0.49\))) were observed (Figure 5). The results of the analysis are represented in forest plots for total mortality (Figure 2), cardiovascular death (Figure 3) and heart failure (Figure 4). No differences in myocardial infarction in either PPCI (RR: 0.49 (95% CI 0.22-1.12; \( I^2 = 0\% \), \( P = 0.09\))) or EPCI (RR: 0.75 (95% CI 0.32-1.73; \( I^2 = 0\% \), \( P = 0.49\))) were observed (Figure 5).

**Risk of bias across studies:** Funnel plots were used to evaluate the publication bias. As the funnel plot was not completely symmetrical, publication bias on total mortality for patients receiving PPCI or EPCI cannot be ruled out (Figure 6). The risk of bias of RCTs is shown as assessed using the Cochrane tool (Figure 7). All of the studies were scored as having a generally low to unclear risk of bias. In 5 of the studies, it was unlikely that the participants were blinded to intervention. Incomplete outcome data was reported in only one study.

**Subgroup outcomes:** When we looked at the effects of nicorandil on total mortality with different follow-up perio-

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**Table III. Summary of Findings and GRADE Assessment**

| Outcomes/ Assumed risk | Summary of findings | Quality assessment | Overall quality of the evidence (GRADE) |
|------------------------|---------------------|--------------------|-----------------------------------------|
| **Total mortality**    |                     |                    |                                         |
| PPCI                   | 62 per (95% CI 0.25-0.79; I\(^2\) = 3% , P = 0.006) | No serious limitation | None (GRADE) |
| EPCI                   | 72 per (95% CI 0.25-0.67; I\(^2\) = 13% , P = 0.0004) | No serious limitation | None (GRADE) |

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**CV death**

| Outcomes/ Assumed risk | Summary of findings | Quality assessment | Overall quality of the evidence (GRADE) |
|------------------------|---------------------|--------------------|-----------------------------------------|
| PPCI                   | 60 per (95% CI 0.22-1.12; I\(^2\) = 23% , P < 0.0001) | No serious limitation | None (GRADE) |
| EPCI                   | 68 per (95% CI 0.32-1.73; I\(^2\) = 41% , P = 0.49) | No serious limitation | None (GRADE) |

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**MI**

| Outcomes/ Assumed risk | Summary of findings | Quality assessment | Overall quality of the evidence (GRADE) |
|------------------------|---------------------|--------------------|-----------------------------------------|
| PPCI                   | 65 per (95% CI 0.20-0.84; I\(^2\) = 0% , P = 0.01) | No serious limitation | None (GRADE) |
| EPCI                   | 39 per (95% CI 0.20-0.80; I\(^2\) = 13% , P = 0.009) | No serious limitation | None (GRADE) |

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**Heart failure**

| Outcomes/ Assumed risk | Summary of findings | Quality assessment | Overall quality of the evidence (GRADE) |
|------------------------|---------------------|--------------------|-----------------------------------------|
| PPCI                   | 139 per (95% CI 0.22-0.59; I\(^2\) = 23% , P = 0.28) | No serious limitation | None (GRADE) |
| EPCI                   | 61 per (95% CI 0.18-1.62; I\(^2\) = 41% , P = 0.49) | No serious limitation | None (GRADE) |

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**GRADE scoring:** High: Further research is very unlikely to change our confidence in the estimate of effect; Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; and Very low: Any estimate of effect is very uncertain.
ods, only a follow-up of less than 30 days exhibited a reduc-
tion in the PPCI group, with Peto OR 0.25 (95% CI 0.08-0.73),
but reduction in total mortality was observed with differ-
ent follow-up period (more than 1 year: Peto OF 0.53 (95% CI 0.30-0.93),
more than 30 days but less than 1 year: Peto OR 0.17 (95% CI 0.06-0.48)) in EPCI
group in which all trials followed more than 30 days regi-
men (Figures 8, 9).

When compared with the placebo or no treatment
group, nicorandil also demonstrated a beneficial effect on
total mortality in the PPCI and EPCI groups, CV death in
EPCI was significantly reduced with nicorandil, and total
mortality and CV death in both the PPCI and EPCI
groups were also reduced with long-term oral nicorandil.
Heart failure was only reduced in the PPCI group, irre-
spective of the control group or long-term administration
of oral nicorandil (Table IV). Using sensitivity analysis by
removing each included study at one time to obtain and
evaluate the remaining overall estimates of total mortality
did not demonstrate a remarkable change in the effect of
nicorandil.

Discussion

This systematic review and meta-analysis about the
effects of nicorandil on all-cause mortality and cardiac
events in CAD patients receiving PCI included 18 RCTs.
In both PPCI and EPCI, nicorandil treatment significantly
reduced total mortality and cardiovascular death. Heart
failure was only reduced in PPCI. A total mortality benefit
was only found in PPCI patients followed up for no more
than 30 days, but was demonstrated in EPCI patients for
both short-term and long-term follow-up. However, there
were no differences in myocardial infarction in both the
PPCI and EPCI groups. Subgroup analysis revealed that
nicorandil plus standard treatment compared with the pla-
 placebo plus standard treatment or standard treatment alone
group, significantly reduced total mortality in both PPCI
and EPCI and CV death in EPCI, and these findings are
consistent with the primary endpoint results. We also ob-
served that total mortality and CV death in both PPCI and
EPCI were reduced in the long-term oral nicorandil group.
Heart failure was reduced only in the PPCI group irre-
spective of the control group and long-term administration
of oral nicorandil.
Efficacy of Nicorandil in CAD Receiving PCI

Table 1: A forest plot showing the reduction in cardiovascular death in the nicorandil group in PPCI and EPCI.

Table 2: A forest plot showing the reduction in heart failure in the nicorandil group in PPCI.

Figure 3. A forest plot showing the reduction in cardiovascular death in the nicorandil group in PPCI.

Figure 4. A forest plot showing the reduction in heart failure in the nicorandil group in PPCI.

PCI has become an effective treatment choice for relieving myocardial ischemia in patients with stable CAD and acute coronary syndrome. However, periprocedural myocardial injury (PMI) occurs in 5-30% of patients after...
Figure 5. A forest plot showing no significant reduction in myocardial infarction.

Figure 6. Funnel plot comparison for primary endpoint.
PCI and poses a challenge in the long-term management of these patients.\textsuperscript{31,32} The ischemic preconditioning effect of nicorandil is a well-accepted mechanism for myocardial protection during PCI and leads to the prevention of heart failure in PPCI and long-term improvement of mortality and CV death.\textsuperscript{33,34} Our meta-analysis also demonstrated the benefits of nicorandil in reducing total mortality, CV death and heart failure in patients undergoing PPCI based on the low to moderate quality of evidence of outcomes.

Several studies have reported a myocardial protective effect of nicorandil in patients undergoing both PPCI or EPCI.\textsuperscript{35-38} A recent meta-analysis on pericardial myocard-
A forest plot showing reduction in total mortality of different follow-up period in the EPCI group.

Table IV. Effect of Nicorandil on Cardiac Events Based on Different Control Type and Long-Term Use of Oral Nicorandil in PPCI and EPCI Patients

| Control type                  | Total mortality | CV death | Heart failure | Myocardial infarction |
|-------------------------------|-----------------|----------|--------------|-----------------------|
|                               | Peto OR         | Peto OR  | Peto OR      | Peto OR              | RR        | RR        | RR        | RR        |
| No treatment control          | 0.47            | 0.53     | 0.46         | 0.38                  | 0.55      | 0.51      | 0.76      |           |
| 95% CI                        | [0.25, 0.90]    | [0.30, 0.94] | [0.21, 1.01] | [0.20, 0.80]          | [0.23, 1.62] | [0.21, 1.28] | [0.31, 1.87] |           |
| Active control                | 0.33            | 0.17     | 0.25         | NA                   | 0.13      | NA        | 0.42      | 0.64      |
| 95% CI                        | [0.09, 1.29]    | [0.06, 0.47] | [0.05, 1.30] | NA                   | [0.02, 0.98] | NA        | [0.07, 2.59] | [0.06, 6.85] |
| P value                       | 0.66            | 0.06     | 0.51         | NA                   | 0.31      | NA        | 0.85      | 0.89      |
| Long term oral Nicorandil    |                 |          |              |                      |           |           |           |           |
| Yes                           | 0.24            | 0.3      | 0.27         | 0.28                  | 0.37      | 0.56      | 0.52      | 0.79      |
| 95% CI                        | [0.08, 0.72]    | [0.16, 0.53] | [0.08, 0.90] | [0.12, 0.64]          | [0.19, 0.70] | [0.09, 3.47] | [0.13, 2.03] | [0.33, 1.88] |
| P value                       | 0.56            | 0.91     | 0.52         | 0.92                  | 0.34      | 0.6       | 0.48      | 0.37      |
| No                            | 0.28            | 0.10     | 0.23         | 0.26                  | 0.34      | 0.6       | 0.48      | 0.37      |
| 95% CI                        | [0.28, 1.10]    | [0.35, 2.36] | [0.22, 1.23] | [0.26, 3.24]          | [0.16, 0.73] | [0.10, 3.55] | [0.17, 1.33] | [0.02, 8.96] |
| P value                       | 0.2             | 0.05     | 0.39         | 0.12                  | 0.89      | 0.96      | 0.93      | 0.65      |

dial protection in patients undergoing EPCI revealed that the levels of myocardial enzymes (CK-MB, TnT, MPV) were significantly decreased in the nicorandil group after PCI. Thus, as a KATP agent, nicorandil could shorten the action potential duration and inhibit calcium overload.21 Kawai, et al. reported that nicorandil reduces no-reflow phenomenon as it could antagonize ADP induced platelet aggregation and improve microcirculation in ischemia areas. In addition, nicorandil could inhibit the formation of active oxygen, which is one of the mechanisms implicated in the protective effect on the myocardium.34 Another meta-analysis on the cardioprotective effects of nicorandil as an adjunctive therapy along with PCI in patients with acute myocardial infarction revealed that nicorandil was associated with improvement of coronary reflow and suppression of ventricular arrhythmia (RR, 0.53; 95% CI: 0.37 to 0.76) and left ventricular function ([MD, 3.08; 95% CI: 0.79 to 5.36) in PPCI. However, they concluded that due to the small sample size of the selected studies a clinical benefit of nicorandil was not evident.20 Similarly, cardioprotective effects of nicorandil were also observed in coronary heart disease patients undergoing EPCI as demonstrated by the decrease in PCI-related myocardial injury, rate of no-reflow, and improvement of LVEF.35
Our meta-analysis also demonstrated the benefits of nicorandil in reducing total mortality and CV death in patients undergoing PPCI or EPCI based on the low to moderate quality of evidence of outcomes.

A total mortality benefit was only found in PPCI patients followed up no more than 30 days, and this may be explained by the fact patients are at higher risk during that period of time and benefit more from nicorandil. In the long-term follow-up, total mortality was still lower in the nicorandil group, although the difference did not reach statistical significance.

Long-term oral nicorandil has been demonstrated to reduce CV events including CHD death, non-fatal MI, or unstable angina in stable angina patients in the INOA study in which 15% of the patients received PCI, indicating nicorandil acted as a pharmacological mimetic of the phenomenon of ischemic preconditioning to protect ischemic myocardium. The results of our meta-analysis also confirm the fact that long-term oral nicorandil treatment has an impact on reducing the total mortality and CV death in PCI patients based on low to moderate quality of evidence.

**Limitations and strengths:** The limitations of this meta-analysis should be acknowledged while interpreting the findings of the analysis. These findings were based on relatively few primary events, so positive treatment effects are susceptible to exaggeration. Thus, more evidence is needed to justify such a radical change when using nicorandil in PCI patients.

Due to the low quality of evidence and list of biases in the studies, we were limited at the individual study level. There was potential performance and attrition bias due to the lack of blinding of participants, personnel, and outcomes. Moreover, due to the small number of qualified studies, we did not limit the follow-up period in the inclusion criteria, which could lead to bias. The method of drug delivery was not uniform in all the studies included; in some it was oral, others intravenous, and in a few others it was coronary administration, which may lead to a bias. In addition, there is no uniformity in the dosage and timing of nicorandil, so the possibility of incorporating bias is further increased. Publication bias could be attributed to the low quality of small studies or true heterogeneity. There are several strengths in this meta-analysis: we conducted a complete search which minimized publication bias; we conducted subgroup analysis to minimize heterogeneity and limit confounding; and we used the Peto odds ratio method to analyze total mortality and CV death, which performs well when events are very rare. Overall, we demonstrated for the first time that there is a distinct benefit of nicorandil as an adjunctive therapy for PCI, no matter the dosage or drug delivery route, as shown in many randomized control trials. A large randomized controlled trial is needed to confirm this benefit.

**Conclusion**

Nicorandil as an adjunct therapy along with PCI is associated with reduced total mortality and cardiovascular death in PPCI and EPCI patients, and reduced heart failure in PPCI patients. Long-term administration of oral nicorandil after PCI seems to be associated with a lower risk of total mortality and CV death in CAD patients, and heart failure in PPCI patients.

**Acknowledgments**

The authors would like to acknowledge Dr. Anuradha Nalli (PhD) and Dr. Amit Bhat (PhD), Indegene, Bangalore, for providing the necessary writing assistance and editorial support during development of the manuscript funded by Merck Serono Co. Ltd, China (an affiliate of Merck KGaA Darmstadt, Germany).

**Disclosure**

**Conflicts of interest:** Dr. Qian Yu is an employee of Merck Serono Co. Ltd, China (an affiliate of Merck KGaA Darmstadt, Germany). All other authors have nothing to disclose.

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