Meta Analysis

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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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Keywords
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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.[6] 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 prespecified 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.[17] 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.[18] 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 I^2 statistics. If the P value of the Q test was < 0.05 or I^2 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 I^2 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.[19] 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.[9–11,13–15,20–37] 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,[33,34] or with and without subsequent oral nicorandil,[20] data between the (same) control group versus one of two

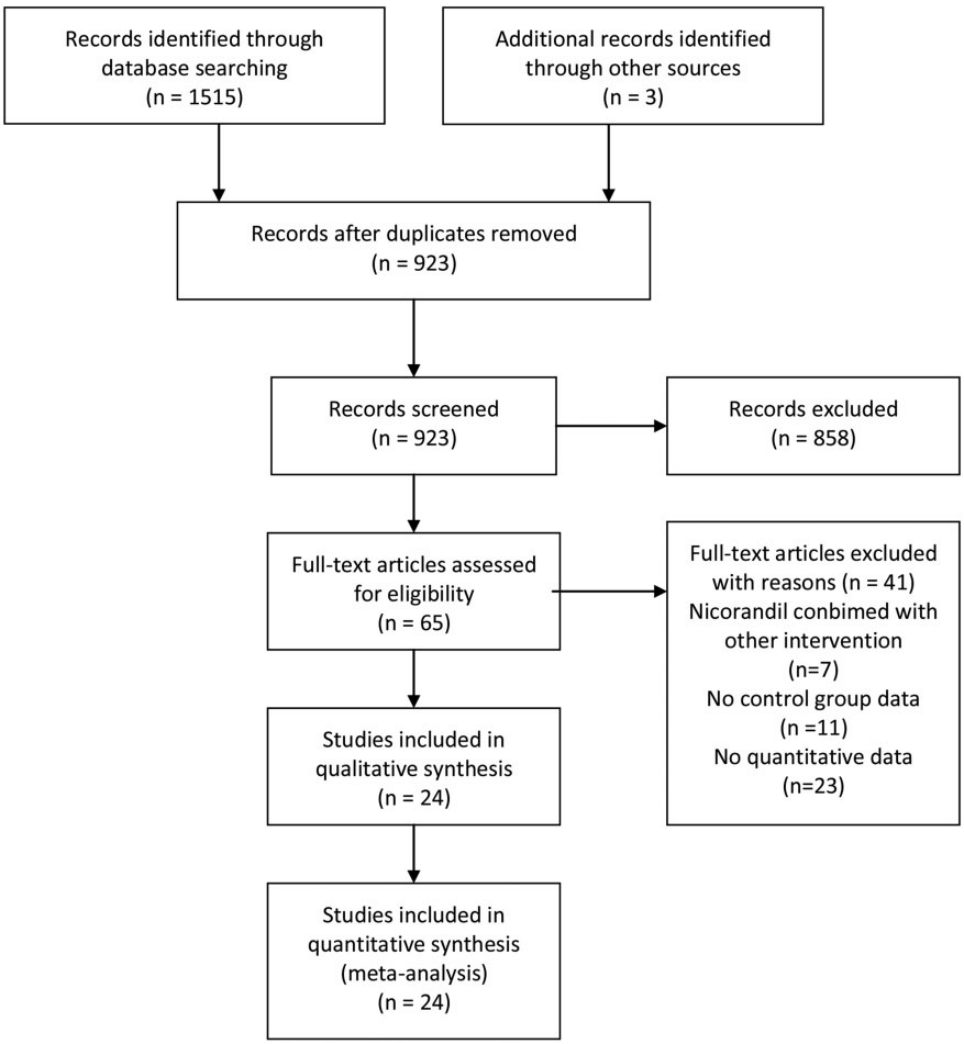

Figure 1. Flow diagram of the literature search and study selection.

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,[24,36] 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.[10,13,23,26,27,34,37] 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.

Table 1. Basic characteristics of the included studies.

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[20]	2006	Japan	NIC	20	68 ± 9	11	4	AMI	–	–	–	–	3 mo
			Control	10	61 ± 9	9	3.7		–	–	–	–	
An[21]	2008	Korea	NIC	37	56.4 ± 13	31	–	STEMI	10	10	–	32	1 mo
			Control	36	60.2 ± 12	30	–		12	13	–	25	
Chen[9]	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[22]	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[23]	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[14]	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[24]	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[25]	2013	Korea	NIC	41	66.2 ± 9	20	–	STEMI	27	15	–	14	6 mo
			Control	40	65.3 ± 10	25	–		27	14	–	14	
Ishii[26]	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[10]	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[27]	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[28]	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[29]	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[13]	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)

Table 1. 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[15]	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[30]	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[31]	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[32]	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[33]	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[34]	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[11]	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[35]	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[36]	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[37]	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.

Table 2. Characteristics of intervention in the included studies.

First author	Year	Route of administration	Dosage	Subsequent oral administration	Intervention of controls
Akagi[20]	2006	iv and ic	4 mg/hour iv for 48 hours + 2 mg ic	No	PCI only
		iv and ic	4 mg/hour iv for 48 hour + 2 mg ic	Yes	PCI only
An[21]	2008	ic	4-mg ic bolus	No	PCI only
Chen[9]	2015	ic	2-mg ic bolus	No	PCI only
Ezhilan[22]	2007	iv and ic	1-mg ic bolus + 2-mg ic bolus + 8 mg/hour iv for 24–48 hours	No	PCI only
Feng[23]	2018	ic	2 mg	No	Saline
Fujiwara[14]	2007	iv	4-mg bolus + 8 mg/hour iv for 24 hours	No	PCI only
Fukuzawa[24]	2000	iv and ic	4-mg ic bolus + 6 mg/hour iv for 24 hours	No	Placebo
Hwang[25]	2013	ic	2-mg ic bolus previously + 2-mg ic bolus before stent	No	PCI only
Ishii[26]	2005	iv	12 mg in 100 mL of 0.9% saline iv for 20–30 minutes	No	Saline
Ishii[10]	2006	iv	12 mg in 100 mL of 0.9% saline iv for 20–30 minutes	No	Saline
Ishii[27]	2007	iv	12 mg in 100 mL of 0.9% saline iv for 20–30 minutes	No	Saline
Ito[28]	1999	iv	4-mg iv bolus + 6 mg/hour iv for 24 hours	Yes (15 mg/day; mean, 28 days)	PCI only
Kasama[29]	2007	iv	4 mg/hour iv for 24 hours	Yes (15 mg/day)	Placebo
Kitakaze[13]	2007	iv	0.067 mg/kg bolus + 1.67 mg/kg per minute iv for 24 hours	No	Saline
Kobayashi[15]	1998	iv and ic	2-mg ic bolus + 6 mg/hour iv for 3 hours	No	PCI only
Lee[30]	2008	ic	2-mg ic bolus previously + 2-mg ic bolus before stent	No	PCI only
Nameki[31]	2004	iv and ic	4 mg iv, 4-mg ic bolus + 8 mg/hour iv for 24 hours	No	PCI only
Ono[32]	2004	iv	4-mg iv bolus + 8 mg/hour iv for 24 hours	No	PCI only
Ota[33]	2006	ic	1–2-mg ic bolus	No	PCI only
		iv and ic	1–2-mg iv bolus + 6 mg/hour iv for 24 hours	No	PCI only
Pi[34]	2019	iv and ic	4-mg ic bolus + 4 mg/hour iv for 24 hours	No	Saline
		ic	4-mg ic bolus		
Qi[11]	2018	ic	2-mg ic bolus	No	PCI only
Sugimoto[35]	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[36]	2006	iv and ic	4 mg/hour iv for 24 hours + 2-mg ic bolus	No	PCI only
Wang[37]	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.[9,11,13,15,21–23,26,28,30,32,33,35] 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; $I^2 = 0\%$; $P < 0.001$) (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.[9,11,23,30] 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; $I^2 = 6.4\%$; $P = 0.001$) (Table 3).

The number of patients who achieved complete STR was measured in five trials with seven comparisons.[9,11,25,34,37] In all of the included studies, complete STR was defined as a decrease in the sum ST-segment elevation by $\geq 70\%$. The nicorandil treatment group had a significantly

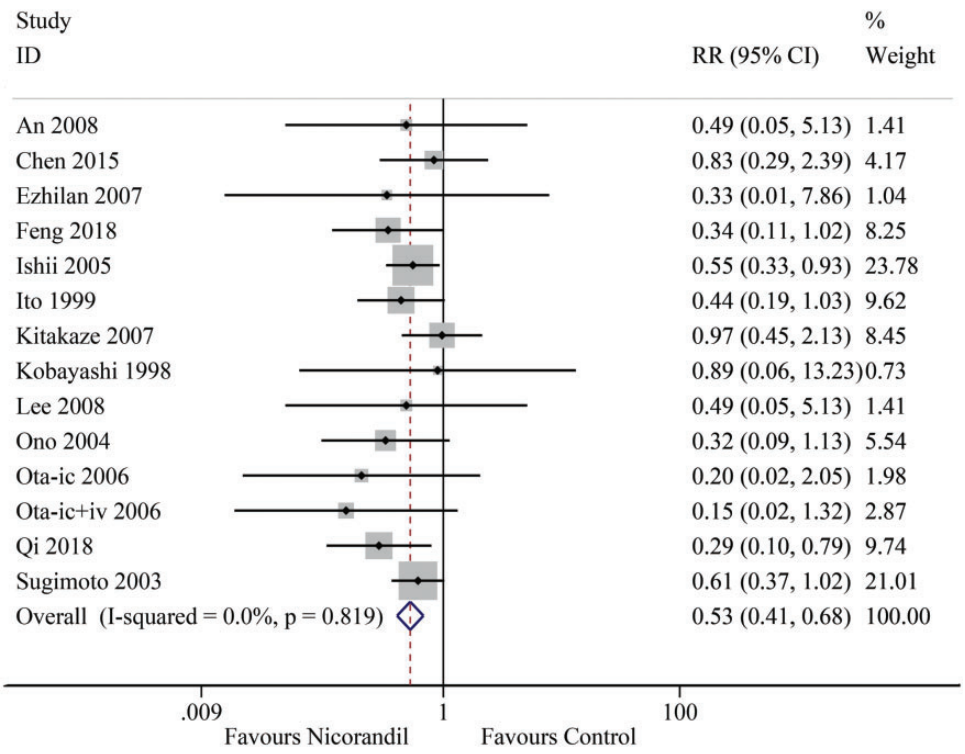

Figure 2. Forest plot of the incidence of the no-reflow phenomenon after percutaneous coronary intervention between the nicorandil treatment and control groups.
RR, risk ratio; CI, confidence interval.

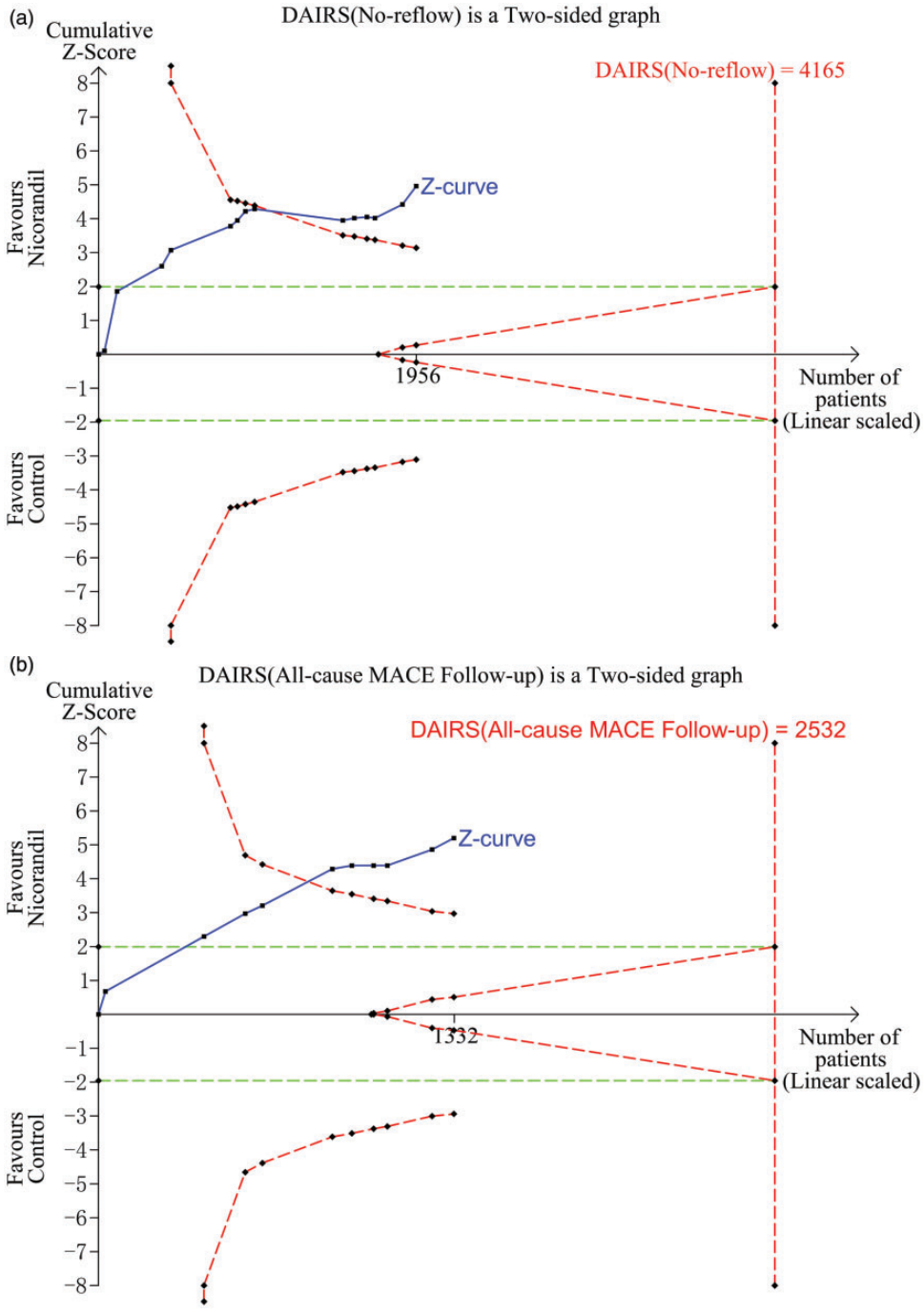

Figure 3. Trial sequential analysis of nicorandil versus controls for (a) the no-reflow phenomenon and (b) follow-up MACEs. Trial sequential analysis showed that the Z-curve (blue line) crossed the upper trial sequential monitoring boundary for benefit (upper red line). Therefore, there was sufficient 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.

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.

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.[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

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.[9,11,25,34,37] 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; $I^2 = 97.2\%7$) between the nicorandil treatment and control groups (Table 3).

Cardiac function

Effects of nicorandil on LVEF (11 trials),[11,13–15,20,23,28,29,31,32,36] LVEDVI (7 trials),[13,14,20,23,28,31,32] LVESVI (5 trials),[13,20,23,31,32] and WMS (6 trials)[11,24,28,31,35,36] 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.[9–11,22,23,25–28,30–34] 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 ventricular 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

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

Outcome	Number of studies	Number of comparisons	WMD	95% CI	P	I^2, %
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.

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 5. Overall results and subgroup analysis of clinical outcomes.

Outcome	Number of studies	Number of comparisons	RR	95% CI	P	I^2, %	RD	95% CI	P	I^2, %
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.

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

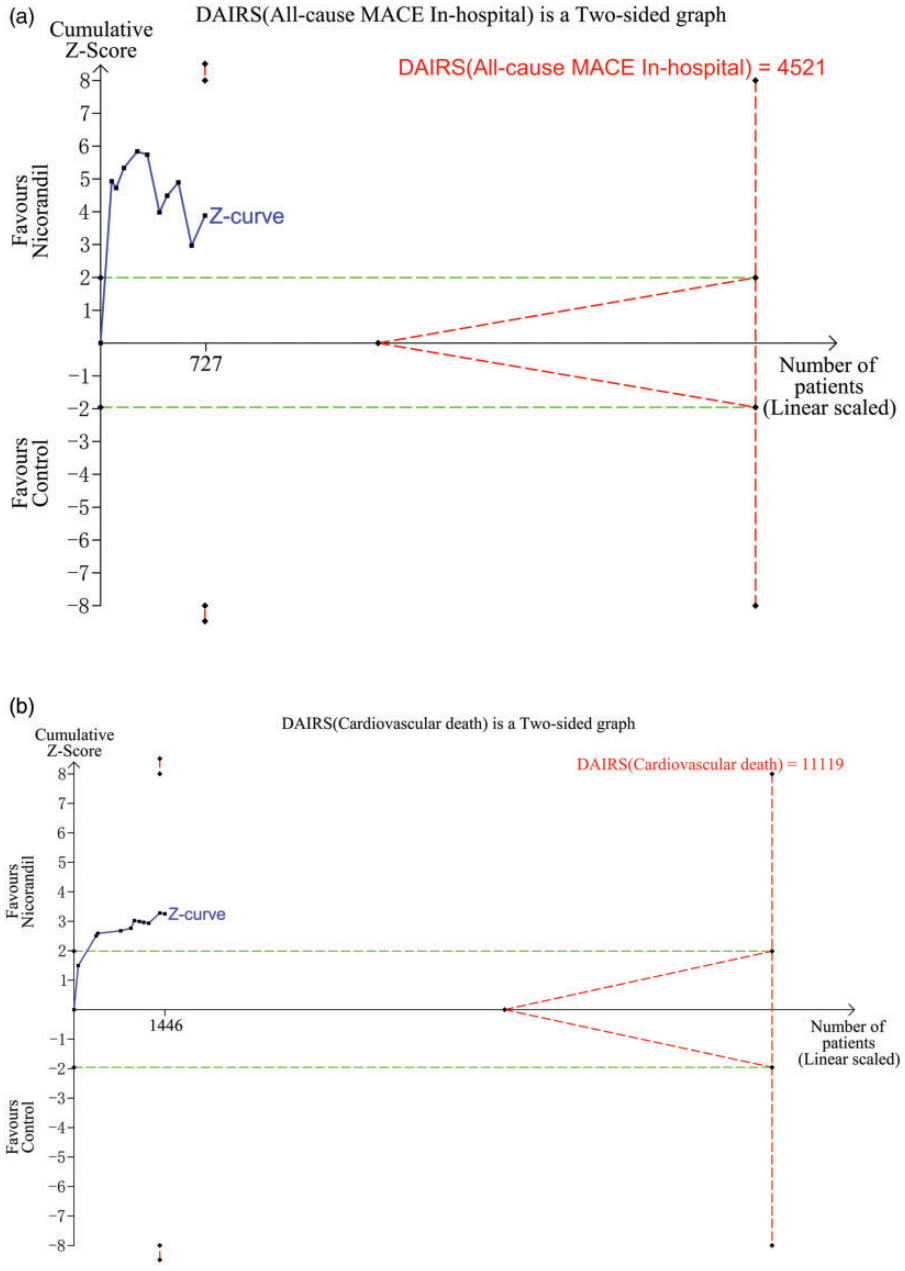

Figure 4. Trial sequential analysis of nicorandil versus controls for (a) in-hospital MACEs and (b) follow-up cardiovascular death. Trial sequential analysis showed that the Z-curve (blue line) crossed the conventional threshold for statistical significance (green line), but did not cross the upper trial 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.[38] 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.[39] 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.[13] Subsequent oral nicorandil treatment could also help to maintain lower QT dispersion during the chronic phase of AMI and reduced left ventricular size.[20,29] 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.[40] 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,[41,42] 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,[8,43] which might have underestimated the incidence of NRP.[44] 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.[45,46] 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.[8,39,42,47] 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.[48,49] 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: NCT 03445728, NCT02435797, NCT02449070, ChiCTR1800015932, and IRCT201405120 17666N1). 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.[29] 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.[27] 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.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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References

1. Kloner RA. Does reperfusion injury exist in humans? *J Am Coll Cardiol* 1993; 21: 537–545. DOI: 10.1016/0735-1097(93)90700-B.
2. Rezkalla SH and Kloner RA. No-Reflow Phenomenon. *Circulation* 2002; 105: 656–662. DOI: 10.1161/hc0502.102867.
3. Reffelmann T and Kloner RA. The "no-reflow" phenomenon: basic science and clinical correlates. *Heart* 2002; 87: 162–168. DOI: 10.1136/heart.87.2.162.
4. Liang T, Liu M, Wu C, et al. Risk Factors for No-Reflow Phenomenon after Percutaneous Coronary Intervention in Patients with Acute Coronary Syndrome. *Rev Invest Clin* 2017; 69: 139–145. DOI: 10.24875/ric.17002190.
5. Chan W, Stub D, Clark DJ, et al. Usefulness of Transient and Persistent No Reflow to Predict Adverse Clinical Outcomes Following Percutaneous Coronary Intervention. *J Am Coll Cardiol* 2012; 109: 478–485. DOI: 10.1016/j.amjcard.2011.09.037.
6. Taqueti VR and Di Carli MF. Coronary Microvascular Disease Pathogenic Mechanisms and Therapeutic Options: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2018; 72: 2625–2641. DOI: 10.1016/j.jacc.2018.09.042.
7. Tarkin JM and Kaski JC. Vasodilator Therapy: Nitrates and Nicorandil. *Cardiovasc Drugs Ther* 2016; 30: 367–378. DOI: 10.1007/s10557-016-6668-z.
8. Wu M, Huang Z, Xie H, et al. Nicorandil in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention: a systematic review and meta-analysis. *PLoS One* 2013; 8: e78231. DOI: 10.1371/journal.pone.0078231.
9. Chen C, Fu X, Li 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: 1059–1065. DOI: 10.3892/etm.2015.2623.
10. Ishii H, Ichimiya S, Kanashiro M, et al. Effects of Intravenous Nicorandil Before Reperfusion for Acute Myocardial Infarction in Patients With Stress Hyperglycemia. *Diabetes Care* 2006; 29: 202. DOI: 10.2337/diacare.29.02.06.dc05-1588.
11. Qi Q, Niu J, Chen T, et al. 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: 2767–2776. DOI: 10.12659/MSM.906815.
12. Kim SJ, Kim W, Woo JS, et al. Effect of myocardial protection of intracoronary adenosine and nicorandil injection in patients undergoing non-urgent percutaneous coronary intervention: A randomized controlled trial. *Int J Cardiol* 2012; 158: 88–92. DOI: 10.1016/j.ijcard.2011.01.011.
13. Kitakaze M, Asakura M, Kim J, 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: 1483–1493. DOI: 10.1016/S0140-6736(07)61634-1.
14. Fujiwara T, Matsunaga T, Kameda K, et al. Nicorandil suppresses the increases in plasma level of matrix metalloproteinase activity and attenuates left ventricular remodeling in patients with acute myocardial infarction. *Heart Vessels* 2007; 22: 303–309. DOI: 10.1007/s00380-007-0975-z.
15. Kobayashi Y, Goto Y, Daikoku S, et al. Cardioprotective Effect of Intravenous Nicorandil in Patients With Successful Reperfusion for Acute Myocardial Infarction. *Jpn Circ J* 1998; 62: 183–189. DOI: 10.1253/jcj.62.183.
16. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009; 151: 264–269, w264. DOI: 10.7326/0003-4819-151-4-200908180-00135.
17. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; 17: 1–12. DOI: 10.1016/0197-2456(95)00134-4.
18. Higgins JPT and Green S. *Cochrane handbook for systematic reviews of interventions version 5.1.0*. Updated March 2011. http://handbook.cochrane.org/.
19. Wetterslev J, Jakobsen JC and Gluud C. Trial Sequential Analysis in systematic reviews with meta-analysis. *BMC Med Res Methodol* 2017; 17: 39. DOI: 10.1186/s12874-017-0315-7.
20. Akagi T, Sarazawa K, Inai Y, et al. Continuous Administration of Nicorandil Decreases QT Dispersion During the Chronic Phase of Acute Myocardial Infarction. *Int Heart J* 2006; 47: 351–361. DOI: 10.1536/ihj.47.351.
21. An SG, Park TI, Hwang KW, et al. The Effect of Intra-coronary Nicorandil Prior to Reperfusion in Acute ST Segment Elevation Myocardial Infarction. *Korean Circ J* 2008; 38: 95–100. DOI: 10.4070/kcj.2008.38.2.95.
22. Ezhilan J, Juneja MS, George T, et al. Prevention of no flow/slow reflow phenomenon in primary PCI by Nicorandil. *Indian Heart J* 2007; 59: 246–249.
23. Feng C, Liu Y, Wang L, et al. Effects of Early Intracoronary Administration of Nicorandil During Percutaneous Coronary Intervention in Patients With Acute Myocardial Infarction. *Heart Lung Circ* 2019; 28: 858–865. DOI: 10.1016/j.hlc.2018.05.097.
24. Fukuzawa S, Ozawa S, Inagaki M, 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: 447–453. DOI: 10.1067/mnc.2000.107273.
25. Hwang J, Lee HC, Kim BW, et al. The effect on periprocedural myocardial infarction of intra-coronary nicorandil prior to percutaneous coronary intervention in stable and unstable angina. *J Cardiol* 2013; 62: 77–81. DOI: 10.1016/j.jjcc.2013.03.017.
26. Ishii H, Ichimiya S, Kanashiro M, et al. Impact of a single intravenous administration of nicorandil before reperfusion in patients with ST-segment-elevation myocardial infarction. *Circulation* 2005; 112: 1284–1288. DOI: 10.1161/CIRCULATIONAHA.104.530329.
27. Ishii H, Ichimiya S, Kanashiro M, et al. Effect of Intravenous Nicorandil and Preexisting Angina Pectoris on Short- and Long-Term Outcomes in Patients With a First ST-Segment Elevation Acute Myocardial Infarction. *Am J Cardiol* 2007; 99: 1203–1207. DOI: 10.1016/j.amjcard.2006.12.034.
28. Ito H, Taniyama Y, Iwakura K, 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: 654–660. DOI: 10.1016/S0735-1097(98)00604-4.
29. Kasama S, Toyama T, Sumino H, et al. Long-term nicorandil therapy improves cardiac sympathetic nerve activity after reperfusion therapy in patients with first acute

myocardial infarction. *J Nucl Med* 2007; 48: 1676–1682. DOI: 10.2967/jnumed.107.043075.
30. Lee HC, An SG, Choi JH, et al. Effect of Intra-Coronary Nicorandil Administration Prior to Reperfusion in Acute ST Segment Elevation Myocardial Infarction. *Circ J* 2008; 72: 1425–1429. DOI: 10.1253/circj.CJ-08-0212.
31. Nameki M, Ishibashi I, Miyazaki Y, 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: 192–197. DOI: 10.1253/circj.68.192.
32. Ono H, Osanai T, Ishizaka 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: 611. DOI: 10.1016/j.ahj.2004.05.014.
33. Ota S, Nishikawa H, Takeuchi M, 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: 1099–1104. DOI: 10.1253/circj.70.1099.
34. Pi SF, Liu YW, Li T, 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: 744–752. DOI: 10.21037/jtd.2019.02.23.
35. Sugimoto K, Ito H, Iwakura K, et al. Intravenous Nicorandil in Conjunction With Coronary Reperfusion Therapy is Associated With Better Clinical and Functional Outcomes in Patients With Acute Myocardial Infarction. *Circ J* 2003; 67: 295–300. DOI: 10.1253/circj.67.295.
36. Toyama T, Seki R, Hoshizaki H, et al. Nicorandil administration shows cardioprotective effects in patients with poor TIMI and collateral flow as well as good flow after AMI. *Ann Nucl Med* 2006; 20: 277–285. DOI: 10.1007/bf02984644.
37. Wang Z, Chen M, Liu D, 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. *Chinese Journal of Cardiology* 2017; 45: 26–33. DOI: 10.3760/cma.j.issn.0253-3758.2017.01.006.
38. Niu X, Zhang J, Bai M, et al. Effect of intracoronary agents on the no-reflow phenomenon during primary percutaneous coronary intervention in patients with ST-elevation myocardial infarction: a network meta-analysis. *BMC Cardiovasc Disord* 2018; 18: 3. DOI: 10.1186/s12872-017-0722-z.
39. Shi L, Chen L, Qi G, et al. Effects of Intracoronary Nicorandil on Myocardial Microcirculation and Clinical Outcomes in Patients with Acute Myocardial Infarction: A Meta-Analysis of Randomized Controlled Trials. *Am J Cardiovasc Drugs* 2020; 20: 191–198. DOI: 10.1007/s40256-019-00368-y.
40. Suematsu Y, Murasato Y, Miura SI, et al. Safety and feasibility of high-dose administration of nicorandil before reperfusion therapy in acute myocardial infarction. *Cardiovasc Interv Ther* 2013; 28: 352–361. DOI: 10.1007/s12928-013-0182-z.
41. Iwakura K, Ito H, Okamura A, et al. Nicorandil treatment in patients with acute myocardial infarction: a meta-analysis. *Circ J* 2009; 73: 925–931. DOI: 10.1253/circj.cj-08-1059.
42. Li J, Xu X, Zhou X, et al. Cardiovascular events associated with nicorandil administration prior to primary percutaneous coronary intervention in patients with acute ST-segment elevated myocardial infarction: a systematic review and meta-analysis. *Expert Opin Drug Saf* 2019; 18: 537–547. DOI: 10.1080/14740338.2019.1617848.
43. Ji Z, Zhang R, Lu W, et al. The effect of nicorandil in patients with acute myocardial infarction undergoing percutaneous coronary intervention: a systematic review and meta-analysis. *Ir J Med Sci* 2020; 189: 119–131. DOI: 10.1007/s11845-019-02034-3.
44. Gibson CM, Cannon CP, Murphy SA, et al. Relationship of TIMI myocardial perfusion grade to mortality after administration of

thrombolytic drugs. *Circulation* 2000; 101: 125–130. DOI: 10.1161/01.cir.101.2.125.
45. Porto I, Burzotta F, Brancati M, et al. Relation of Myocardial Blush Grade to Microvascular Perfusion and Myocardial Infarct Size After Primary or Rescue Percutaneous Coronary Intervention. *Am J Cardiol* 2007; 99: 1671–1673. DOI: 10.1016/j.amjcard.2007.01.045.
46. Sorajja P, Gersh BJ, Costantini C, et al. Combined prognostic utility of ST-segment recovery and myocardial blush after primary percutaneous coronary intervention in acute myocardial infarction. *Eur Heart J* 2005; 26: 667–674. DOI: 10.1093/eurheartj/ehi167.
47. Zhao XT, Zhang CF and Liu QJ. Meta-analysis of Nicorandil effectiveness on myocardial protection after percutaneous coronary intervention. *BMC Cardiovasc Disord* 2019; 19: 144. DOI: 10.1186/s12872-019-1071-x.
48. Thorlund K, Devereaux PJ, Wetterslev J, et al. Can trial sequential monitoring boundaries reduce spurious inferences from meta-analyses? *Int J Epidemiol* 2008; 38: 276–286. DOI: 10.1093/ije/dyn179.
49. Wetterslev J, Thorlund K, Brok J, et al. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. *J Clin Epidemiol* 2008; 61: 64–75. DOI: 10.1016/j.jclinepi.2007.03.013. zaq