

Nicorandil Treatment in Patients With Acute Myocardial Infarction

— A Meta-Analysis —

Katsuomi Iwakura, MD; Hiroshi Ito, MD; Atsushi Okamura, MD; Yasushi Koyama, MD;
Motoo Date, MD; Yoshiharu Higuchi, MD; Koichi Inoue, MD; Ryusuke Kimura, MD;
Hiroyuki Nagai, MD; Michio Imai, MD; Yuko Toyoshima, MD; Makito Ozawa, MD;
Norihsa Ito, MD; Yukinori Okazaki, MD; Masahiko Shibuya, MD;
Hideaki Suenaga, MD; Asuka Kubota, MD; Kenshi Fujii, MD

Background: It is controversial as to whether nicorandil would have cardioprotective effects in patients with acute myocardial infarction (AMI) who are undergoing reperfusion therapy. A meta-analysis was performed to study the impacts of nicorandil on functional outcomes after AMI.

Methods and Results: Randomized prospective cohort or retrospective cohort publications were identified up to October 2007 by means of a computer search of MEDLINE and Google Scholar databases. Two reviewers checked the quality of the studies and extracted data regarding patient and disease characteristics, study design, functional parameters such as Thrombolysis In Myocardial Infarction (TIMI) flow grade after reperfusion, left ventricular ejection fraction (LVEF) and left ventricular end-diastolic volume index (LVEDVI). Seventeen studies were included for the meta-analysis in this study. Nicorandil treatment reduced the incidence of TIMI flow grade ≤ 2 in 1,337 patients of 10 studies (risk ratio 0.63; 95% confidence interval (CI) 0.44 to 0.91). While no beneficial effect was observed on the peak creatine kinase value, nicorandil treatment was associated with greater LVEF (by 3.7%, 95%CI 1.8 to 5.7%), and lower LVEDVI (by 8.8 ml/kg, -14.4 to -3.3 ml/kg) in 905 patients of 11 studies.

Conclusions: The meta-analysis demonstrated that nicorandil treatment adjunctive to reperfusion therapy has beneficial effects on microvascular function and on functional recovery after AMI. (Circ J 2009; 73: 925–931)

Key Words: Acute myocardial infarction; Meta-analysis; Nicorandil; No-reflow

Adenosine triphosphate sensitive potassium channel openers (K_{ATP} channel opener) exert cardioprotective effects in ischemic myocardium, and these effects are, at least in part, mediated through mimicking of ischemic preconditioning^{1–3}. Nicorandil is a hybrid of the K_{ATP} channel opener and nitrate, and several studies have demonstrated that nicorandil could reduce infarct size and improve functional and clinical outcomes after acute myocardial infarction (AMI) when administered adjunctively to coronary intervention. The K_{ATP} channel opener also attenuates microvascular dysfunction after reperfusion in experimental models^{4,5} and an improvement of microvascular function could be one of the mechanisms of the cardioprotectiveness effects of nicorandil⁶. However, most of the prior clinical studies are based on single-center and/or small-scale trials. A recent large-scale, multi-center trial failed to demonstrate the beneficial effects of nicorandil on infarct size,

functional recovery and clinical outcomes after AMI⁷. Thus, the capability of nicorandil as an adjunctive treatment is still controversial. We performed a meta-analysis on the impacts of adjunctive nicorandil treatment on coronary microcirculation, functional recovery and left ventricular remodeling in patients with reperfused AMI.

Methods

Eligible Articles

The peer-reviewed articles were identified by using MEDLINE and Google Scholar search up to October 2007, using key words such as nicorandil, potassium channel opener, and acute myocardial infarction. Eligible for inclusion were prospective cohort studies and retrospective cohort studies on nicorandil treatment adjunctive to coronary reperfusion therapy in patients with AMI. Nicorandil should be administered before or at the time of coronary reperfusion therapy, and both intracoronary and intravenous administrations were eligible for inclusion. They could be eligible irrespective of subsequent oral nicorandil. For a 3-arm trial consisting of the control and 2 nicorandil arms with and without subsequent oral nicorandil, we compared the data between the (same) control group vs 1 of 2 nicorandil groups⁸. For 4-arm studies in which the study patients were divided into 2 groups before randomization, based on pre-existing angina⁹ or on coronary flow grade before coro-

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Cardiovascular Center, Sakurabashi Watanabe Hospital, Osaka, Japan

Mailing address: Katsuomi Iwakura, MD, Division of Cardiology, Sakurabashi Watanabe Hospital, 2-4-32 Umeda, Kita-ku, Osaka 530-0001, Japan. E-mail: iwakura@mac.com

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Table. Overview of Trials Included in a Meta-Analysis

Study	Year	Design	Number of patients (Control/Nicorandil)	Administration	Dose (duration)	Age; control/ Nicorandil	%Male; control/ Nicorandil	Subsequent oral administration
Kobayashi et al ²⁰	1998	Randomized/ Single center	36 (17/19)	Intravenous/ Continuous	2–6 mg/h (3 h)	66±11/65±8	88/89	NA
Ito et al ⁶	1999	Randomized/ Single center	81 (41/40)	Intravenous/ Continuous	6 mg/h (24 h)	60±10/60±10	78/80	Yes
Fukuzawa et al ⁹	2000	Randomized/ Single center	62 (14/17)	Intravenous/ Continuous	6 mg/h (24 h)	58±12/64±11	74/71	NA
Sugimoto et al ³⁸	2003	Retrospective cohort	272 (114/158)	Intravenous/ Continuous	6 mg/h (24 h)	61±11/61±11	80/79	Yes
Ikeda et al ³⁰	2004	Randomized/ Single center	60 (30/30)	Intravenous/ Continuous	6 mg/h (72 h)	63±10/60±9	83/77	NA
Lim et al ²⁹	2004	Randomized/ Single center	50 (25/25)	Intracoronary/ Bolus	2–4 mg	67±10/66±10	52/68	NA
Nameki et al ⁴³	2004	Randomized/ Single center	27 (14/13)	Intravenous/ Continuous	4 mg/h (24 h)	62±11/64±10	79/85	NA
Ono et al ⁴⁴	2004	Randomized/ Single center	58 (25/33)	Intravenous/ Continuous	8 mg/h (24 h)	66±12/64±13	64/66	NA
Ueda et al ¹⁸	2004	Retrospective cohort	83 (37/46)	Intravenous/ Continuous	4 mg/h (48 h)	60±6/62±11	81/74	NA
Ishii et al ³⁹	2005	Randomized/ Single center	368 (183/185)	Intravenous/ Bolus	12 mg	64±10/63±9	84/78	NA
Kasama et al ⁴⁵	2005	Randomized/ Single center	50 (25/25)	Intravenous/ Continuous	4 mg/h (>48 h)	63±11/62±11	76/72	Yes
Akagi et al ¹⁷	2006	Randomized/ Single center	30 (10/20)	Intravenous/ Continuous	4 mg/h (48 h)	61±9/68±9	60/70	Yes/No
Ota et al (SMART) ¹⁰	2006	Randomized/ Multi-center	90 (32/58)	Intracoronary/ Bolus, Intravenous/ Continuous	1–2 mg, 6 mg/h (...)	64±11/61±11	84/78	NA
Toyama et al ⁴²	2006	Randomized/ Single center	68 (35/33)	Intravenous/ Continuous	4 mg/h (24 h)	63±12/63±10	60/70	NA
Fujiwara et al ⁴⁶	2007	Randomized/ Single center	62 (31/31)	Intravenous/ Continuous	8 mg/h (24 h)	62±2/62±2	81/81	No
Hara et al ¹⁹	2007	Randomized/ Single center	40 (21/19)	Intravenous/ Continuous	6 mg/h (24 h)	63±13/63±9	86/68	NA
Kitakaze et al (J-WIND) ⁷	2007	Randomized/ Multi-center	545 (269/276)	Intravenous/ Continuous	0.1 mg·kg ⁻¹ ·h ⁻¹ (24 h)	64±10/61±11	82/89	Yes/No

nary intervention,¹⁰ the comparisons were considered as 2 separate ones between the control- and the corresponding nicorandil arm within a group. For duplicate publications, the studies with the smaller study population were excluded.

Data Extraction

We systematically extracted information on patient and disease characteristics, study design, quality characteristics (blinding, mode of generation of the randomization sequence, and description of withdrawals), and functional and clinical outcomes. The peak creatine kinase (CK) value was used as a rough estimate of infarct size, and it was estimated from a graph in 1 article⁹. As for functional outcomes, we used left ventricular end-diastolic volume index (LVEDVI; ml/m²) and left ventricular ejection fraction (LVEF; %) in the follow-up study. We also determined the incidences of Thrombolysis In Myocardial Infarction (TIMI) flow grade of ≤2 on coronary angiography after reperfusion. Two investigators (KI and HI) extracted data independently, discussed discrepancies, and eventually reached consensus on all items.

Statistical Analysis

For analyses of continuous measures, we first determined standardized effect sizes for each trial, and then calculated the overall effect size for each outcome by weighting each effect size by the reciprocal of the variance.¹¹ We used the risk ratio as the metric of choice for the incidence of TIMI

flow grade-2 after coronary reperfusion. We presented these scores with 95%CI. We used a Q test to explore the heterogeneity between studies. Data were combined across the studies and presented with a random-effects (DerSimonian and Laird) model,¹² which incorporates statistical heterogeneity. Funnel plots were drawn and their asymmetry was assessed to determine the possible influence of publication biases. When a significant heterogeneity was observed between studies, we performed a rank-based data augmentation technique (a “trim-and-fill” method) to produce an adjusted estimate of test accuracy by imputing suspected missing studies.¹³ Analyses were performed using R version 2.6.1 (R Foundation for Statistical Computing, Vienna, Austria) with an add-on “meta” (by Guido Schwarzer, 2005).

Results

We identified 21 publications describing the impacts of nicorandil in patients with reperfused AMI by using MEDLINE and Google Scholar. We excluded 4 studies; 2 substudies of the larger data sets,^{14,15} another study that observed only the effects of long-term oral nicorandil following initial treatment,¹⁶ and another that described only the effect on QT dispersion.¹⁷ Finally, 17 studies were eligible for the present meta-analysis (**Table**). Fifteen studies were randomized, prospective trials, 2 of which were multi-center trials.^{7,10} Nicorandil was administered by continuous

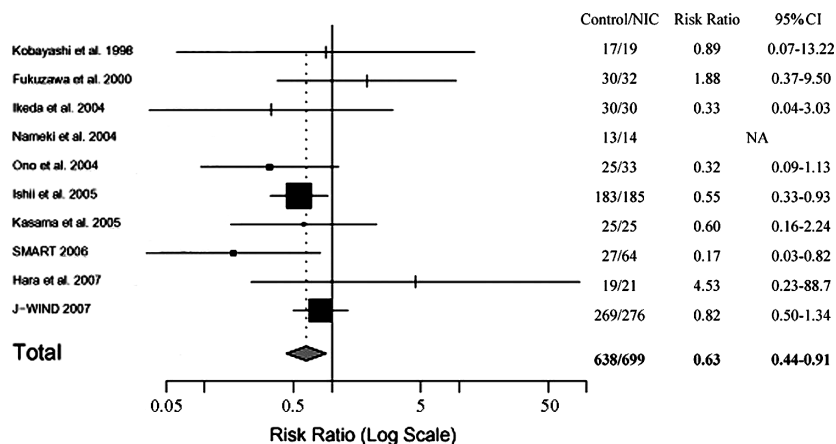


Figure 1. Meta-analysis of the treatment effect of nicorandil (NIC) on the incidence of Thrombolysis In Myocardial Infarction flow grade of ≤ 2 after percutaneous coronary intervention. Point estimates or risk ratio for treatment effect are shown as squares, and 95% confidence intervals (CI) are depicted by the width of horizontal lines.

intravenous infusion in 15 studies. A loading dose of nicorandil (2–4 mg) was administered in all continuous-infusion studies with the exception of 2 trials.^{18,19}

Post-Ischemic Microvascular Function

Coronary reperfusion was achieved with thrombolysis and/or percutaneous coronary intervention (PCI) in 1 study,²⁰ and with primary PCI in another 16 studies. The TIMI flow grade after reperfusion was evaluated on coronary angiogram in 1,337 patients from 10 studies, all of which were prospective studies (Figure 1). After coronary reperfusion, the TIMI flow grade of ≤ 2 was observed in 88 (13.8%) out of 638 patients in the control group and in 61 (8.7%) out of 699 patients in the nicorandil-treated group. Nicorandil treatment significantly ($P=0.01$) reduced the incidence of the TIMI flow grade of ≤ 2 (combined risk ratio 0.63, 95% CI; 0.44 to 0.91). There was no heterogeneity in the risk ratio in these 10 studies (Q test; $P=0.35$), as shown in a funnel plot (Figure 2).

We also investigated the influence of a different dose of nicorandil among studies by meta-regression analysis. Nicorandil was administered continuously at the fixed dose in 7 out of 10 studies, and no significant relationship was observed between the effect sizes and doses of nicorandil for these studies ($P=0.43$).

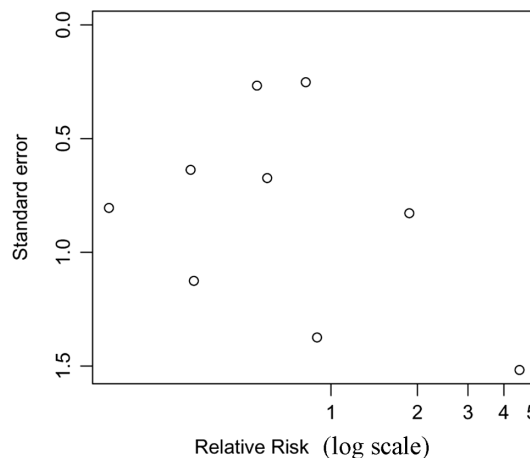


Figure 2. Funnel plot of effect size for the incidence of coronary flow grade ≤ 2 after coronary reperfusion.

Infarct Size and Functional Outcomes

The peak CK value was evaluated in 1,620 patients from 15 studies (Figure 3). Its value was lower in the nicorandil group by 249 IU/L (95% CI; -500 to +3 IU/L) than in the control group, but the difference did not reach statistical significance ($P=0.052$). A significant heterogeneity in peak

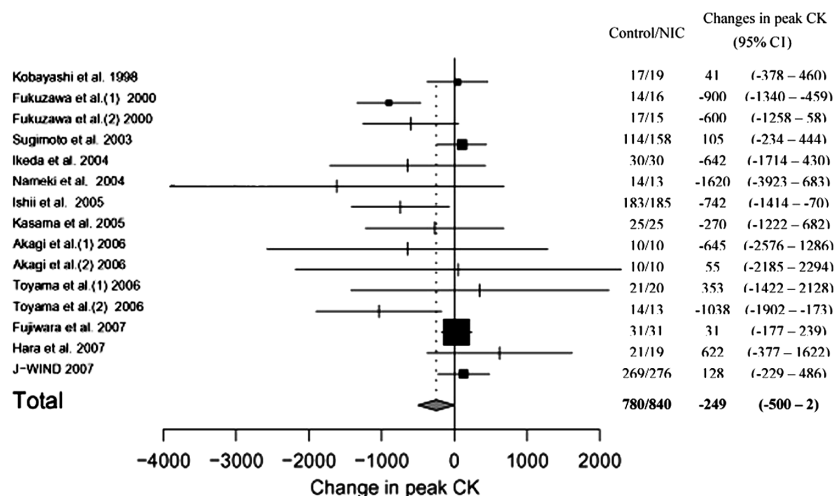


Figure 3. Meta-analysis of the treatment effect of nicorandil (NIC) on peak creatine kinase (CK) values. Arrangement of data as in Figure 1. The study by Fukuzawa et al⁹ corresponds to: (1) the comparison among patients with preinfarction angina; and (2) to that among those without angina. The study by Akagi et al⁸ corresponds to: (1) the comparison between the control vs NIC with subsequent oral treatment; and (3) to that between the same control group vs NIC without oral treatment. The study by Toyama et al⁴² corresponds to: (1) the comparison among patients with poor flow before reperfusion; and (2) to that among those with good flow. CI, confidence interval.

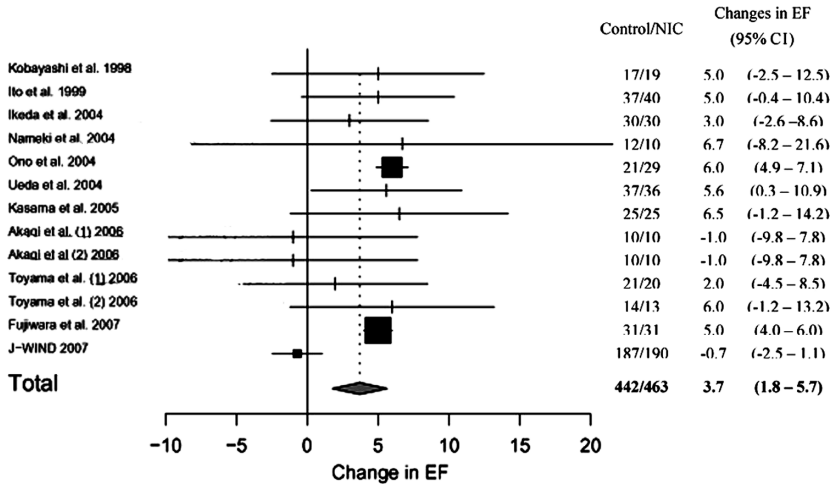


Figure 4. Meta-analysis of the treatment effect of nicorandil (NIC) on ejection fraction (EF). Arrangement of data is as per Figure 3. CI, confidence interval.

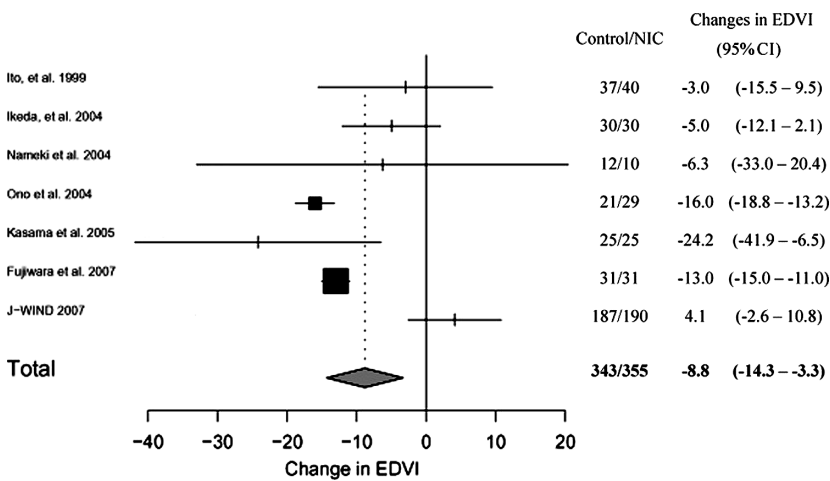


Figure 5. Meta-analysis of the treatment effect of nicorandil (NIC) on end-diastolic volume index (EDVI). Arrangement of data is as per Figure 1. CI, confidence interval.

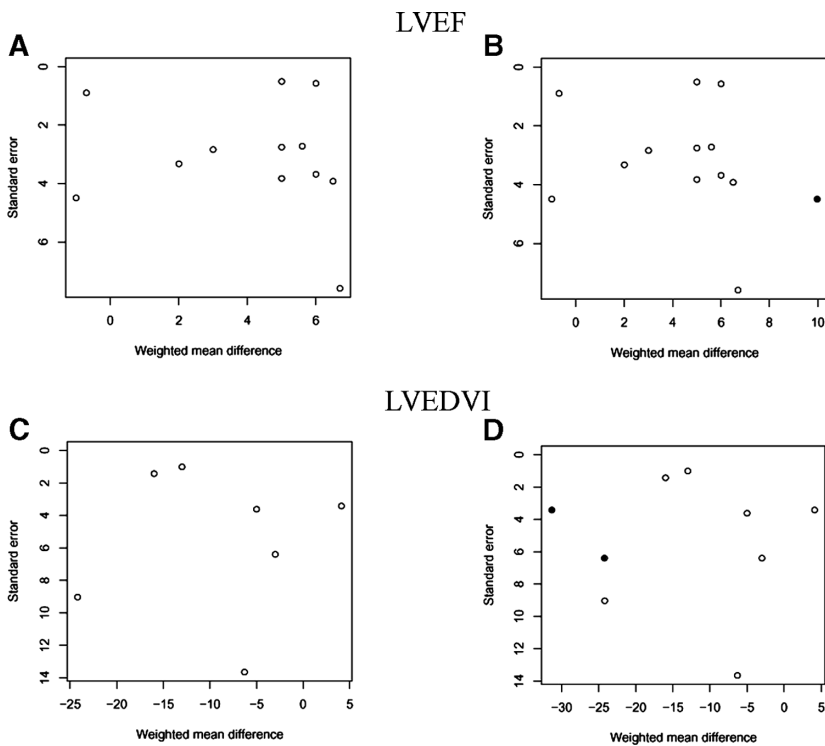


Figure 6. Funnel plots for left ventricular ejection fraction (LVEF) and left ventricular end-diastolic volume index (LVEDVI), and their adjustment with a “trim-and-fill” technique. Funnel plots for LVEF (A) and for LVEDVI (C) showed asymmetry because of heterogeneity between studies. The trim-and-fill method provided adjusted estimates of test accuracy by imputing suspected missing study data, as shown by closed circles in (B) and (D).

CK value was observed between the studies ($P=0.001$). The corrected estimation by the trim-and-fill method showed almost no difference in peak CK value (-18 IU/L, 95%CI; -303 to 268 IU/L) between the 2 groups. We also investigated the influence of a different dose of nicorandil among studies by using meta-regression analysis. Nicorandil was administered continuously at the fixed dose in 7 out of 10 studies, but no significant relationship was observed between effect sizes and doses of nicorandil for these studies ($P=0.43$).

LVEF was measured at 4 ± 2 months after AMI in 905 patients from 11 studies by using left ventriculography, except in 1 study, which used echocardiography.⁸ LVEDVI was measured in 698 patients from 7 studies, all of which were prospective studies. LVEF was greater by 3.7% (95%CI; 1.8 to 5.7%) and LVEDVI was lower by 8.8 ml/m² (95%CI; -14.4 to -3.3 ml/m²) in the nicorandil arm than in the control arm (Figures 4,5). Although there were significant ($P<0.001$) heterogeneities in both values between the studies, LVEF was still higher (+3.9%, 95%CI; +2.0 to +5.8%) and LVEDVI was lower (-13.2 ml/m², -19.1 to -7.3 ml/m²) in the nicorandil group after correction with the trim-and-fill technique (Figure 6). Even when 1 retrospective study¹⁸ was excluded from the analysis, the nicorandil group showed a better LVEF by 3.6% (95%CI; 1.5 to 5.6%, $P=0.0007$), or by 3.8% (95%CI; 1.8 to 5.8%, $P=0.0002$) after the trim-and-fill correction.

The dose dependency of the effects of nicorandil was assessed by using meta-regression analysis. Nicorandil was continuously administered at the fixed dose in 11 studies for LVEF analysis and in 6 studies for LVEDVI analysis. No significant relationships were observed between effect sizes and doses of nicorandil for these studies (LVEF, $P=0.75$; LVEDVI, $P=0.94$).

Discussion

The present meta-analysis revealed that nicorandil treatment, adjunctive to coronary reperfusion therapy, significantly decreases the incidence of angiographical no-reflow after reperfusion in patients with AMI. Patients receiving nicorandil also had higher LVEF and lower LVEDVI on the convalescent stage. Although there were significant heterogeneities in both parameters, the nicorandil group showed better values even after adjustment by the trim-and-fill technique.

Cardioprotective Effects of Nicorandil Treatment in Patients With AMI

Most of the clinical studies reporting beneficial effects of adjunctive nicorandil treatment were the small-sized and/or single-center ones. Only 2 studies were randomized, multicenter trials, and 1 of them enrolled only 90 patients.¹⁰ In the other multicenter study, which is the largest one among the included studies, nicorandil treatment showed no significant improvement in infarct size, or in terms of LVEF and LVEDVI.⁷ Their study might be underpowered for detecting the beneficial effects of nicorandil, which could be mediated through reducing the incidence of the no-reflow. In that trial, interestingly, only patients receiving subsequent oral administration in the nicorandil group showed a significant increase in LVEF between acute and chronic phases.⁷ Subsequent oral nicorandil treatment also decreases QT dispersion on electrocardiogram⁸ and reduces left ventricular size among patients receiving initial nicorandil treatment.¹⁶

A scintigraphy study using ¹²³I-metaiodobenzylguanidine demonstrated that subsequent long-term treatment improves cardiac sympathetic nerve activity even among those who received initial nicorandil treatment,¹⁶ and this mechanism could contribute to preventing left ventricular remodeling. Because long-term nitrate therapy does not improve outcomes after AMI,²¹ the beneficial effects of oral nicorandil would be mediated not through its nitrate action but through potassium channel opening action. Thus, long-term oral administration of nicorandil might be related to beneficial effects on LVEF and LVEDVI in the present analysis. Most of the included studies did not describe the subsequent oral nicorandil treatment, and we were not able to analyze its effects (Table). Sub-analysis of the Japanese Coronary Artery Disease (JCAD) study,²² a large-scale multicenter prospective trial, might provide some information on the effects of chronic nicorandil treatment, however, its results have not been fully published yet.

Slow coronary flow on an angiogram is a definitive sign of severe microvascular dysfunction,²³⁻²⁵ and is associated with very poor outcomes after AMI.^{24,25} However, its 40% reduction could not be the sole mechanism to improve functional and morphological outcomes in the study patients. Microvascular dysfunction is observed on myocardial contrast echocardiogram (MCE) in approximately 20% of patients showing TIMI flow grade-3^{23,26} and it is associated with systolic dysfunction, left ventricular remodeling^{27,28} and poor prognosis,²⁵ even in these cases. Thus, microvascular protection by nicorandil, which is observed in our previous MCE study⁹ might not be fully assessed with evaluation of TIMI flow grade. Myocardial blush grade,^{9,29} coronary flow velocity pattern,³⁰ ST resolution on electrocardiogram¹⁰ and contrast-enhanced magnetic resonance imaging^{31,32} can also evaluate microvascular function, and the incidences of the microvascular dysfunction vary among these modalities. Further studies using these modalities are required to clarify the effects of nicorandil on microcirculation. Besides improving microvascular function, nicorandil can directly protect myocardial cells exposed to ischemia/reperfusion through mechanisms including generation of a pro-oxidant environment,³³ attenuation of intracellular calcium overload³⁴ or an antiapoptotic effect.³⁵

Both LVEF and ventricular size are the most important determinants of prognosis after AMI,³⁶ and their improvement could lead to the lower event rate after nicorandil treatments. An IONA study documented that nicorandil improves clinical outcome through a reducing major coronary event rate in patients with stable angina.³⁷ Prevention of ischemic events also might be related to better clinical outcomes after AMI.

Study Limitations

The publication bias is one of the most important sources of heterogeneity. The trim-and-fill technique is developed for estimating and adjusting for numbers and outcomes of the possible missing publications due to this bias.¹³ However, the potential of this correction should not be overestimated. The studies involved in the analysis also have several heterogeneities in their study conditions in addition to publication bias, including the differences in administration mode (intracoronary vs intravenous, bolus vs continuous), dose of nicorandil, and subsequent long-term oral administration. The present meta-analysis failed to indicate the dose-dependency of nicorandil treatment. Only a part of the collected studies used fixed doses of nicorandil, and therefore the

present analysis on dose-dependency could be incomplete and not conclusive. Nicorandil mimics ischemic preconditioning, and its effects might be abolished in patients showing preinfarction angina.¹⁵ The numbers of the studies involved were too small for us to analyze the impacts of these differences.

Among the collected studies, only 4 studies reported the incidence of major adverse cardiac events beyond the initial hospital-stay^{7,29,38,39} and a P value of log-rank test was described only as 'P<0.02' in one of them.³⁸ The other study had only 50 study patients, a follow-up period of only up to 6 months and an insufficient data presentation for a meta-analysis.²⁹ Thus, we could not have a sufficient amount of publication data for a meta-analysis on the effects of nicorandil on major adverse cardiac events after AMI.

Clinical Implications

Several adjunctive medical treatments are proposed to improve functional and clinical outcomes after AMI. The no-reflow phenomenon is observed only in a part of patients with AMI, but these cases are at a high risk of life-threatening complications and poor clinical prognosis. Therefore, prevention of microvascular dysfunction could reduce the number of patients at high risk, though such effects might not always lead to remarkable improvements in the overall population. Human atrial natriuretic peptide is a very promising drug to limit infarct size, improve LVEF and to reduce cardiovascular death and heart failure after AMI, but it would not reduce the angiographical no-reflow.⁷ In contrast, adenosine treatment reduces the incidence of the no-reflow after primary PCI,⁴⁰ but did not improve the clinical outcomes after AMI in a large-scale trial.⁴¹ Compared to these drugs, nicorandil prevents no-reflow and improves functional outcomes, and therefore, could be a more promising adjunctive therapy.

Disclosure

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