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Original article

Oral treatment with nicorandil at discharge is associated with reduced mortality after acute myocardial infarction

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KEYWORDS
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Summary
Background: Previous studies showed that nicorandil can reduce coronary events in patients with coronary artery disease. However, it is unclear whether oral nicorandil treatment may reduce mortality following acute myocardial infarction (AMI).
Methods and Results: We examined the impact of oral nicorandil treatment on cardiovascular events in 1846 AMI patients who were hospitalized within 24 h after AMI onset, treated with emergency percutaneous coronary intervention (PCI), and discharged alive. Patients

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were divided into those with (Group N, $n = 535$) and without (Group C, $n = 1311$) oral nicorandil treatment at discharge. No significant differences in age, gender, body mass index, prevalence of coronary risk factors, or history of myocardial infarction existed between the two groups; however, higher incidences of multi-vessel disease, and a lower rate of successful PCI were observed in Group N. During the median follow-up of 709 (340—1088) days, all-cause mortality rate was 43% lower in Group N compared with Group C (2.4% vs. 4.2%, stratified log-rank test: $p = 0.0358$). Multivariate Cox regression analysis revealed that nicorandil treatment was associated with all-cause death after discharge (Hazard ratio 0.495, 95% CI: 0.254—0.966, $p = 0.0393$), but not for other cardiovascular events such as re-infarction, admission for heart failure, stroke and arrhythmia.
Conclusions: The results suggest that oral administration of nicorandil is associated with reduced incidence of death in the setting of secondary prevention after AMI.

Introduction

Although recent progress in the management of acute myocardial infarction (AMI) has decreased mortality [1—3], long-term mortality remains high in post-AMI patients [4]. To further decrease mortality rates in the clinical setting after AMI, numerous efforts have been directed towards the pharmacological modification of left ventricular (LV) performance and remodeling, as well as stabilization of atherosclerotic coronary plaques, as it has been shown to be associated with prognosis [5]. In this context, the anti-anginal drug nicorandil is one of the promising candidates for improving outcomes of post-AMI patients due to its cardioprotective properties [6—19].

Nicorandil is a nicotinamide ester that possesses K-ATP channel-activating and nitrate-like properties and is being increasingly used to treat coronary artery disease (CAD). Nicorandil relieves symptoms of ischemia and also has numerous cardioprotective properties, such as pharmacological preconditioning [6—8], restoration of cardiac blood flow to ischemic and no-reflow myocardium [9—13], prevention of Ca^{2+} overload [14,15], and attenuation of cardiac sympathetic nerve injury [16—18], and so on. However, although the effects of nicorandil in protection of the myocardium during acute ischemic injury have been extensively reported in the clinical setting [9—13,17,20—25], little is known about the long-term impacts of nicorandil on mortality and secondary complications after AMI [18,26].

In the present study, we examined the mortality impact of oral nicorandil at discharge using a relatively large patient cohort in the setting of secondary prevention after AMI.

Methods

The Osaka acute coronary insufficiency study (OACIS)

The Osaka acute coronary insufficiency study (OACIS) is a prospective, multi-center observational study designed to collect and analyze demographic, procedural, outcome data, and blood samples in patients with AMI at 25 collaborating hospitals in the Osaka region of Japan [3,27—30]. As part of the OACIS, research cardiologists and specialized research nurses recorded data on socio-demographic variables, medical histories, therapeutic procedures, and clinical events during patient hospitalization, and also obtained follow-up clinical data at 3, 6, and 12 months after the occurrence of AMI, and annually thereafter. Information was obtained from hospital medical records and by direct interviews with patients, their family members, and their treating physicians. All data were transmitted to the data collection center at the Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Suita, Japan for processing and analysis. The diagnosis of AMI required the presence of two of the following three criteria: (1) history of central chest pressure, pain, or tightness lasting more than 30 min, (2) ST-segment elevation 0.1 mV in 1 limb lead or 2 precordial leads, and (3) an increase in serum creatine kinase (CK) concentration of two times the upper limit of normal.

Patients

Among the patients registered with the OACIS registry, 1846 consecutive patients fulfilling the following criteria: (1) admission within 24 h after the onset of AMI between January 2005 and March 2009, (2) treatment with emergency percutaneous coronary intervention (PCI) on admission, and (3) survival discharge, were enrolled in the study. Of these patients, 535 were treated with oral nicorandil at discharge (Group N), while the remaining 1311 patients did not receive nicorandil at discharge (Group C).

Clinical endpoints

The demographic and clinical data and the primary endpoints during the five-year period following discharge, all-cause mortality, non-fatal re-infarction, re-admission for heart failure, and coronary revascularization, including PCI and coronary artery bypass grafting, were compared between patients in Groups N and C.

Statistical analysis

Results are expressed as medians (25th and 75th percentiles) or mean ± SD for continuous variables, and qualitative data are presented as numbers or percentages. Differences of continuous variables between groups were assessed using the Student's *t*-test, whereas categorical variables were compared using the chi-square test. Factors influencing mortality were analyzed using a multivariate Cox proportional hazard regression model with 14 variables from major patient backgrounds and treatments to minimize

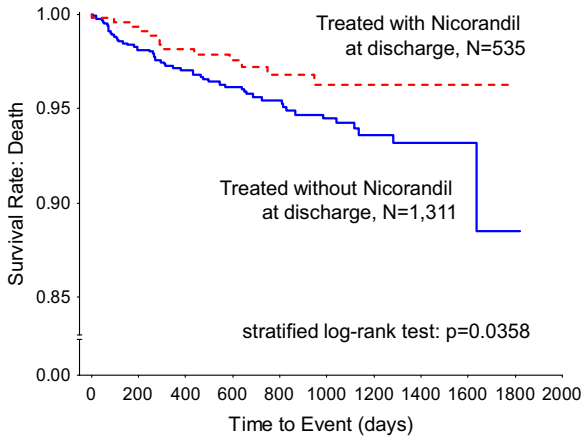

Figure 1 Kaplan—Meier plots for mortality during the five-year follow-up period following discharge for AMI. *p* value after adjustment with variables that had *p* values of <0.1 in the multivariate cox proportional hazard model is <0.05.

the effect of co-founders. Variables included in the model were age, gender, obesity, diabetes, hypertension, dyslipidemia, smoking, multi-vessel disease, PCI success, and prescription of statins, renin angiotensin system inhibitors, or beta-blockers. Survival curves were constructed using the Kaplan—Meier method, and the significance of differences in survival was assessed using the stratified log-rank test with variables as strata suggested by Cox regression. Analysis was performed using SAS version 9.1.3 for Windows (SAS Inc., Cary, NC) and PASW Statistics, version 18.0 (SPSS Inc., Chicago, IL). For all analyses, statistical significance was set at $p < 0.05$.

Results

The study population consisted of 535 patients who received nicorandil at discharge (Group N) and 1311 patients who did not (Group C). The patient baseline characteristics, including the cardiovascular medications being taken before and during the study, are summarized in Table 1. No significant differences in age, gender, body mass index, prevalence of coronary risk factors of diabetes, hypertension, dyslipidemia, obesity and smoking, or history of myocardial infarction were found between the two groups. However, a higher incidence of multi-vessel disease and treatment with intra-aortic balloon pumping, and a lower rate of successful PCI, defined as presence of TIMI3 flow grade after the procedures, were noted in Group N, suggesting that Group N included patients with more severe clinical conditions.

The median follow-up period was 709 (340—1088) days. During the follow-up period, the all-cause mortality rate was 43% lower in Group N compared with Group C, although this difference was not significant (2.4% vs. 4.2%, log-rank test: $p = 0.0849$). However, multivariate Cox proportional hazard analysis revealed that several variables were correlated with mortality following discharge of the AMI patients. After adjustment with the variables, Kaplan—Meier curves for mortality showed a significant difference between Groups N and C (stratified log-rank test: $p = 0.0358$, Fig. 1).

Despite the fact that patients of both groups were also administered other secondary prevention drugs, nicorandil was the only drug to have an association with decreased mortality (Table 2). Multivariate Cox proportional hazard analysis revealed that nicorandil treatment was a predictor for all-cause death after discharge (Hazard ratio (HR) 0.495, 95% CI: 0.254—0.966, $p = 0.039$), but not for re-infarction, admission for heart failure, arrhythmia and stroke (Table 3). Subgroup analysis revealed that no significant interaction were detected between the impact of nicorandil and variables of age, gender, diabetes, hypertension, dyslipidemia, multi-vessel disease, PCI success, and peak CK levels (Table 4), suggesting that nicorandil treatment displayed a significant reduction in mortality regardless of the subgrouping. In addition, subgroup analysis also suggested that nicorandil treatment was particularly associated with reduced mortality for patients with ages of <75 y.o., with hypertension, or of male gender (Table 4).

Discussion

This is the first study suggesting a mortality benefit of nicorandil for post-AMI patients in the clinical setting. In this retrospective analysis with a relatively large-scale AMI cohort, we have demonstrated that AMI patients who received oral nicorandil treatment displayed a reduction in all-cause mortality during a five-year follow-up period. Our results suggest that nicorandil may have the potential to improve survival outcomes in the setting of secondary prevention after AMI.

The most important finding of the present study is that nicorandil treatment was associated with a nearly 50% reduction in all-cause mortality following discharge for AMI (HR 0.495, 95% CI: 0.254—0.966, $p = 0.0393$). This finding also supports the results of a recent large-scale randomized control study, the Impact of Nicorandil in Angina [IONA] study [31], and a retrospective sub-analysis of the Japanese Coronary Artery Disease (JCAD) study [32], which suggested that nicorandil had a beneficial impact on mortality and morbidity in CAD patients. In the IONA study, a 20 mg twice-daily oral nicorandil treatment group ($N = 2565$) displayed a significant reduction in all cardiovascular events over a placebo group ($N = 2561$) [31]. In addition, the nicorandil group had a trend of reduced mortality compared to the placebo group (4.3% vs. 5.0%, respectively; HR 0.85, $p = 0.222$), although the difference was not statistically significant, likely due to the relatively short follow-up period (mean: 1.6 years). The JCAD study is a large multicenter collaborative prospective observational study designed to investigate risk factors, medication use, and outcomes of CAD patients in Japan ($N = 13,812$) [33]. In a retrospective analysis of the JCAD study, Horinaka et al. [32] compared the incidence of cardiovascular events between 2558 nicorandil-treated and 2558 control patients (mean follow-up: 2.7 years) in the JCAD cohort and revealed that death from all causes (primary endpoint) was 35% lower (HR 0.65, $p = 0.0008$) in the nicorandil group. Further, marked reductions in several secondary endpoints, including cardiac death (56%), fatal myocardial infarction (56%), cerebral or vascular death (71%), and congestive heart failure (33%), were noted in the nicorandil group [32]. Taken together, these lines of evidence suggest

Table 1 Patient characteristics of the nicorandil (Group N) and non-nicorandil (Group C) groups.

Variable	Group C ($n = 1311$)	Group N ($n = 535$)	p Value
Age (years)	65.7 ± 12.1	66.2 ± 11.8	0.388
Male	990 (75.5%)	411 (76.8%)	0.589
Symptom to admission time (h)	5.2 ± 5.5	4.9 ± 5.5	0.255
STEMI	1129 (86.8%)	467 (87.5%)	0.76
Killip class >1	1067 (85.3%)	429 (82.7%)	0.192
Cardiac pulmonary arrest	38 (2.9%)	12 (2.2%)	0.528
Peak creatine kinase (U/L)	2971 ± 2645	3144 ± 2634	0.223
Serum creatinine (mg/dL)	1.04 ± 1.16	1.06 ± 1.19	0.752
Common comorbidities			
Obesity	405 (32.6%)	174 (33.5%)	0.739
Diabetes mellitus	416 (31.7%)	192 (35.9%)	0.091
Hypertension	838 (65.5%)	342 (65.9%)	0.913
Dyslipidemia	557 (44.3%)	250 (48.3%)	0.142
Smoking history	786 (60.9%)	328 (62.4%)	0.595
Previous MI	149 (11.5%)	58 (11.0%)	0.807
Angiographic information			
Initial TIMI grade			0.484
0	754 (57.8%)	304 (57.3%)	
1	142 (10.9%)	54 (10.2%)	
2	246 (18.9%)	93 (17.5%)	
3	163 (12.5%)	80 (15.1%)	
Multiple vessel disease	534 (41.0%)	269 (50.5%)	
Collateral vessels	402 (31.2%)	164 (31.5%)	
Infarct related artery: LAD	552 (41.8%)	242 (46.0%)	
Reperfusion therapy			
PCI	1331 (100%)	535 (100%)	1
Stent	1225 (93.5%)	507 (94.9%)	0.282
Thrombectomy	921 (70.3%)	354 (66.2%)	0.086
Drug-eluting stent	89 (6.8%)	35 (6.8%)	0.918
PCPS	29 (2.2%)	6 (1.1%)	0.135
IABP	184 (14.0%)	97 (18.1%)	0.032
Emergent CABG	9 (0.7%)	5 (0.9%)	0.563
Temporary pacing	275 (21.3%)	101 (19.3%)	0.371
Successful reperfusion	1217 (93.6%)	481 (91.1%)	0.07
No-reflow phenomenon	36 (5.5%)	16 (6.8%)	0.517
Medications at discharge			
Anti-platelets	1289 (98.3%)	529 (98.9%)	0.529
ACEIs	419 (32.0%)	279 (52.1%)	<0.001
ARBs	647 (49.4%)	175 (32.7%)	<0.001
ACEI and/or ARB	1038 (79.2%)	435 (81.3%)	0.038
β-Blockers	813 (62.0%)	303 (56.6%)	0.036
Statin	689 (52.6%)	298 (55.7%)	0.237
Ca channel blockers	205 (15.6%)	70 (13.1%)	0.171
Nitrates	255 (19.5%)	91 (17.0%)	0.237
Diuretics	336 (25.6%)	143 (26.7%)	0.64

Results are expressed as mean ± SD for continuous variables. ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass graft; IABP, intraaortic balloon pumping; MI, myocardial infarction; PCI, percutaneous coronary intervention; PCPS, percutaneous cardio-pulmonary support; STEMI, ST elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction.

that nicorandil has a beneficial effect for reducing mortality in patients with CAD, including post-AMI patients.

It is noteworthy that nicorandil treatment at discharge was associated with mortality reduction (Table 1), although nicorandil had been likely used as an adjunct to other cardioprotective drugs, rather than as an alternative, which is supported by the comparable prevalence of secondary prevention drugs between Groups N and C. Accordingly, nicorandil is potentially a good candidate to be given in an additive manner with popular cardiovascular secondary

Table 2 Predictors for death after discharge.

Variable	Multivariate cox proportional hazard model			
	HR	Lower limit	Upper limit	*p* Value
Statins	0.904	0.516	1.583	0.7247
RAS inhibitors	0.894	0.488	1.638	0.7166
Beta blockers	1.408	0.802	2.470	0.2332
Ca channel blockers	0.493	0.221	1.102	0.0849
Nicorandil	0.495	0.254	0.966	0.0393

Variables: age, gender, diabetes mellitus, hypertension, dyslipidemia, smoking, multi-vessel disease, successful percutaneous coronary, intervention, peak creatine kinase level, beta-blockers, renin-, angiotensin inhibitors, statins, calcium channel blockers, and nicorandil.

Table 3 Impact of oral nicorandil on cardiac events.

Cardiovascular event	HR	95% CI	*p* Value
Death	0.495	(0.254—0.966)	0.039
Myocardial infarction	0.873	(0.469—1.624)	0.667
Admission for heart failure	0.741	(0.410—1.338)	0.319
Arrhythmia	0.737	(0.360—1.509)	0.366
Stroke	0.363	(0.107—1.229)	0.103

Variables: age, gender, diabetes mellitus, hypertension, dyslipidemia, smoking, multi-vessel disease, successful percutaneous coronary, intervention, peak creatine kinase level, beta-blockers, renin-, angiotensin inhibitors, statins, calcium channel blockers, and nicorandil.

Table 4 Predictors for death after discharge.

Subgroup		*N*	HR	95% CI	*p* Value	*p* for Interaction
Age (years)	<75	1242	0.294	(0.088—0.984)	0.0471	0.2012
	≥75	435	0.817	(0.371—1.797)	0.6145	
Gender	Female	431	0.792	(0.219—2.866)	0.7224	0.4888
	Male	1394	0.474	(0.227—0.991)	0.0472	
Diabetes mellitus	No	1210	0.481	(0.182—1.269)	0.1391	0.6086
	Yes	608	0.610	(0.259—1.438)	0.2587	
Hypertension	No	618	0.802	(0.215—2.990)	0.7425	0.1672
	Yes	1180	0.429	(0.200—0.921)	0.0298	
Dyslipidemia	No	954	0.542	(0.250—1.173)	0.1199	0.6556
	Yes	805	0.308	(0.082—1.152)	0.0802	
Multi-vessel disease	No	1006	0.596	(0.205—1.733)	0.3423	0.8772
	Yes	803	0.483	(0.213—1.096)	0.0815	
PCI success	No	130	0.365	(0.041—3.291)	0.3692	0.9888
	Yes	1647	0.544	(0.277—1.069)	0.0775	
Peak CK level (U/L)	<3000	1203	0.532	(0.227—1.247)	0.1464	0.7414
	≥3000	621	0.530	(0.198—1.418)	0.2061	

CK, creatine kinase; PCI, percutaneous coronary intervention.

prevention drugs, such as beta-blockers and/or rennin-angiotensin system inhibitors. It is also noteworthy that the present study suggested that nicorandil was beneficial for all patients in the secondary prevention settings after AMI, because no significant interaction were detected after subgroup analysis (Table 4). In addition, the mortality benefit of nicorandil seemed particularly apparent for patients with ages <75 y.o., with hypertension, and of male gender (Table 4). Notably, a 71% reduction in mortality rate was found in nicorandil-treated patients with ages <75 y.o. (HR 0.294, 95% CI: 0.088—0.984, $p = 0.047$). Therefore, we suggest that nicorandil may represent a potent first-line drug for all patients after AMI, particularly for those with ages <75 y.o., male gender, or hypertension.

Although details of the mechanisms are unclear, the following pharmacologic and other properties of nicorandil may explain why this drug improves survival in patients with CAD or AMI. First, cardioprotective effects exerted by nicorandil during the acute stage of AMI and/or acute myocardial ischemia [9—13,17,20—25] may have also provided benefits in the convalescent or chronic stages of AMI. Second, as suggested in the J-WIND study [26], nicorandil treatment during the chronic phase of AMI may have improved left ventricular function, resulting in a reduction of mortality. Third, the positive effects of nicorandil on sympathetic nerve activity might have played a role in improving survival. Indeed, although it was a small sample-size study from a single center, Kasama et al. [18] reported that the long-term (six months) administration of 15 mg/dL nicorandil resulted in improved cardiac sympathetic nerve activity in AMI patients. Fourth, the anti-hypertensive properties of nicorandil might have reduced long-term mortality [34]. As discussed previously, nicorandil appeared to have been prescribed in an additive manner in the present cohort, rather than as an alternative to the other administered cardioprotective or antihypertensive drugs. Accordingly, the adjunctive use of nicorandil may have lowered blood pressure more effectively than in the control group, resulting in a reduction in long-term mortality. Finally, better long-term compliance and lack of tolerance to nicorandil [35] might be associated with improved mortality.

In the present study, we did not observe significant reductions in other cardiac events in Group N patients, unlike the results from the IONA study [31] and JCAD sub-study [32]. This discrepancy may have been due to differences in the backgrounds of the study populations; we only included patients who survived AMI in the present study, whereas the other two studies included individuals with stable angina or CAD [31,32]. Accordingly, it appears that the study cohort might have been more strictly treated with secondary prevention medications in the present study, as the prevalence of co-administered cardioprotective drugs such as antiplatelets, ACE inhibitors, angiotensin II receptor blockers (ARBs), β-blockers, and statin was higher than or at least equal to those in the IONA and JCAD studies [31,32]. In addition, the cohort subjects in the present study had all received emergent PCI for infarct related arteries and were likely to have undergone subsequent PCI for other diseased coronary arteries in the acute or convalescent stage of AMI, possibly resulting in a reduction of residual myocardial ischemia and prevention of ischemia-related cardiovascular complications. Therefore, the beneficial effects of nicorandil on cardiovascular events other than mortality may have been masked by the increased usage of co-administered cardioprotective drugs, as well as differences in the management of diseased coronary arteries.

A few limitations of the study warrant mention. First, as this was a retrospective observational study, precise information concerning the dose, duration and patient compliance for nicorandil treatment, was not available. In addition, information about cardiac function at discharge was not obtained in the present study. Second, as it was also observed that patients in Group N appeared to have more severe clinical CAD conditions, including a higher incidence of multi-vessel disease and a lower rate of successful PCI, the overall efficacy of nicorandil may have been underestimated. Third, the present study enrolled only the subjects who underwent emergent PCI in the acute stage of AMI. Accordingly, caution may be needed when interpreting the results for AMI patients who did not receive emergent PCI. Fourth, although the results suggested that nicorandil was effective to reduce mortality in those with age of <75 y.o. or those with male gender, the mechanisms were unclear and thus remain to be disclosed.

In conclusion, we have demonstrated that the oral administration of nicorandil following AMI was associated with reduced incidence of death for all patients, particularly in individuals with ages <75 y.o., male gender and hypertension. Although further randomized clinical investigations are needed, the promising clinical outcomes presented here suggest that nicorandil on oral administration may be effective for treating CAD and is expected to improve patient survival in the secondary prevention setting following AMI.

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