Effects of Nicorandil on Cardiovascular Events in Patients With Coronary Artery Disease in The Japanese Coronary Artery Disease (JCAD) Study

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Background: Nicorandil has cardioprotective effects in the ischemic myocardium, mimicking ischemic preconditioning, and is thus expected to improve the prognosis of ischemic heart disease (IHD). As part of the Japanese Coronary Artery Disease (JCAD) Study, a multicenter collaborative prospective observational study of a large cohort of coronary artery disease patients, the effect of nicorandil on outcome was examined.

Methods and Results: In total, 2,558 patients with nicorandil treatment and controls subjected to propensity score matching were eligible among 13,812 patients registered in the JCAD study. The mean follow-up interval was 2.7 years. The primary endpoint, death from all causes, was significantly lower, by 35% (hazard ratio 0.65, $P=0.0008$), in the nicorandil group than in the control group. There were also significant reductions in secondary endpoints, including cardiac death (56%), fatal myocardial infarction (56%), cerebral or vascular death (71%), and congestive heart failure (33%) in the nicorandil group, with no excess of deaths from other non-cardiovascular causes. Treatment with nicorandil reduced the number of deaths from all causes to a similar extent with or without treatment with sulfonylureas.

Conclusions: The reduction in cardiovascular death with nicorandil was large in patients with IHD, which has important implications for treatment. (*Circ J* 2010; **74**: 503–509)

Key Words: Cardiovascular events; Coronary artery disease; Japanese Coronary Artery Disease (JCAD) Study; Nicorandil

Nicorandil has a potassium channel-opening effect that activates adenosine triphosphate-sensitive potassium (K-ATP) channels and induces nitric oxide in the same fashion as nitrates, resulting in increased intracellular cyclic GMP.^{1,2} Nicorandil also has cardioprotective effects in the ischemic myocardium, as demonstrated by reduced myocardial necrosis and improvement of myocardial stunning following coronary artery reperfusion, and thus mimics ischemic preconditioning.^{3–7} These characteristics are expected to improve the prognosis of ischemic heart disease (IHD).

The Impact of Nicorandil in Angina (IONA) study, a randomized placebo-controlled trial, demonstrated significant reductions in the primary composite endpoint of coronary heart disease death, nonfatal myocardial infarction (MI) or unplanned hospital admission for cardiac chest pain after

nicorandil administration in patients with stable angina.⁸ However, it has never been clearly determined in a large-scale study whether nicorandil is useful in high-risk patients with IHD such as acute MI and unstable angina. Another important issue remaining from the IONA study is whether K-ATP channel blockers used to treat diabetes eliminate the effects of nicorandil in patients with IHD. Furthermore, it is uncertain which dosage of nicorandil is most appropriate in the treatment of IHD.

The Japanese Coronary Artery Disease (JCAD) Study, which featured a period of observation longer than in IONA, was a multicenter collaborative prospective observational study of a large cohort of coronary artery disease patients performed to investigate risk factors and current status of medication use and examine differences in outcomes of coronary artery disease.^{9–11} As a part of this study, we exam-

Received August 27, 2009; revised manuscript received November 16, 2009; accepted November 17, 2009; released online January 18, 2010 Time for primary review: 3 days

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Grant from the Japanese Circulation Foundation.

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ISSN-1346-9843 doi:10.1253/circj.CJ-09-0649

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Table 1. Patient Characteristics, Angiographic Findings, and Treatments in the Nicorandil and Control Groups After Propensity Score Matching

	Control	Nicorandil	P value
N	2,558	2,558	
Age (years)	67.0 (27–93)	67.0 (30–94)	0.8362
Male	74.9%	75.2%	0.8211
SBP	132.9±19.7	132.8±20.3	0.6938
DBP	74.7±11.7	73.9±11.6	0.0060
Hypertension	53.4%	55.1%	0.2066
Hyperlipidemia	50.4%	53.0%	0.0609
Impaired glucose tolerance	41.4%	41.5%	0.9096
BMI >25 kg/m ²	34.2%	31.0%	0.0133
Smoker	37.1%	37.6%	0.7072
Family history	13.6%	15.9%	0.0199
Heart failure	10.3%	11.1%	0.3659
Left main coronary artery stenosis	3.5%	4.3%	0.1472
No. of coronary artery stenoses	1.87±0.81	1.86±0.82	0.7606
Medications			
Statins	35.8%	35.7%	0.9303
β-blockers	19.9%	22.0%	0.0740
Diuretics	18.3%	18.3%	0.9423
ACEIs	33.3%	29.2%	0.0012
ARBs	14.3%	14.9%	0.5530
Sulfonylureas	10.2%	10.3%	0.8901

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

ined whether nicorandil improved the outcome of coronary artery disease in actual clinical practice.

Methods

The JCAD study included consecutive patients with IHD who exhibited at least 75% organic stenosis of a major coronary on coronary angiography. All patients gave written informed consent to participate in this study. A total of 15,628 patients were registered and of them 13,812 could be followed and analyzed (follow-up rate 88.4%; mean follow-up interval 2.7 years). All medications and risk factors for coronary artery disease were recorded. In total, 2,558 patients were treated with nicorandil. In this subgroup analysis, primary and secondary endpoints were compared between patients with and without nicorandil treatment. The primary endpoint was all-cause death. Secondary endpoints were cardiac death, fatal MI, nonfatal MI, cerebral and vascular death, other causes of death, all events, cardiac events, congestive heart failure, and cardiopulmonary arrest on arrival (CPAOA). In this study, in-hospital deaths because of acute MI or CPAOA were defined as fatal MI.

Another subgroup analysis examined whether all-cause death or cardiac death differed depending on sulfonylurea treatment (glibenclamide, gliclazide or glimepiride) in patients being treated with nicorandil.

Clinical events were defined as in a previous report.⁹ In brief, all-cause death included cardiac, cerebral, vascular, and other deaths. Cerebral events included cerebral hemorrhage, cerebral infarction, and transient ischemic attack. Cardiac events consisted of fatal and nonfatal MI, unstable angina, congestive heart failure, coronary bypass graft surgery, resuscitated cardiac arrest, and CPAOA. Angiographic restenosis when incidentally detected during routine follow-up coro-

nary angiography without clinical symptoms was excluded from events. Aortic dissection and rupture of aortic aneurysm were classified as vascular events.

Statistical Analysis

Intention-to treat analysis was performed, with the assumption that the medications used at discharge remained unchanged during the follow-up period.

In the observational study, covariates between the control group and treatment group could not be adjusted for, so bias regarding determination of the effects of medication was thus possible. However, propensity score analysis including the conditional probability of taking a medication using covariates may produce a good balance of covariates between 2 groups and is able to reduce this type of bias. A propensity score for each patient indicating the probability of taking medication was therefore calculated by multiple logistic regression analysis.¹² All clinical characteristics and medications except nicorandil were used in this calculation. The log-rank procedure and Cox's proportional hazards model were used to calculate confidence intervals. Cumulative incidence curves were generated by the Kaplan-Meier method for endpoints in the nicorandil and control groups. All calculated values are expressed as the mean±standard deviation. P values for background characteristics, all medications, and risk factors were calculated by the chi-square test. Statistical analysis was performed with SAS version 9.1 (SAS Institute Inc, Cary, NC, USA). Statistical significance was accepted at P<0.05.

Results

After propensity score matching, there were 2,558 patients in each group. Baseline covariates likely to influence differ-

Figure 1. Cumulative incidence of the primary endpoint, deaths from all causes. HR, hazard ratio.

	Control (n=2,558)	Nicorandil (n=2,558)	HR (95%CI)	P value
	Rate per 1,000 patient-years	Rate per 1,000 patient-years		
Primary endpoint				
All-cause deaths	22.61	15.23	0.65 (0.51–0.84)	0.0008
Secondary endpoints				
Cardiac deaths	11.23	4.93	0.44 (0.29–0.66)	0.0001
Fatal MI	6.29	2.77	0.44 (0.26–0.76)	0.0022
Nonfatal MI	5.74	7.19	1.22 (0.80–1.86)	0.3525
Cerebral or vascular death	1.90	0.58	0.29 (0.09–0.89)	0.0299
Non-CVD deaths	9.48	9.72	0.98 (0.69–1.38)	0.9000
All events	70.69	63.47	0.88 (0.77–1.01)	0.0730
Cardiac events	53.65	48.26	0.89 (0.76–1.04)	0.1375
CHF	14.23	9.71	0.67 (0.49–0.92)	0.0140
CPAOA	4.38	1.60	0.36 (0.18–0.73)	0.0042

HR, hazard ratio; CI, confidence interval; MI, myocardial infarction; CVD, cardiovascular disease; CHF, congestive heart failure; CPAOA, cardiopulmonary arrest on arrival.

ences in the rate of occurrence of cardiovascular events between the nicorandil-treated and control groups were adjusted for using propensity score matching (Table 1). Although there was a minimal difference between the control and nicorandil groups in median diastolic blood pressure, the median systolic blood pressure did not differ between the 2 groups. However, the frequencies of body mass index $>25\text{ kg/m}^2$ and angiotensin-converting enzyme inhibitor use were higher in the control than in the nicorandil group. Family history of cardiovascular disease was more common in the nicorandil than in the control group. The mean dosage of nicorandil was $15.04\pm 4.74\text{ mg}$.

The primary endpoint of all-cause death was significantly

lower, by 35% (hazard ratio (HR)=0.65 [0.51–0.84], $P=0.0008$), in the nicorandil group than in the control group (Figure 1, Table 2).

In the nicorandil group, there were also significant reductions in 5 of the 9 secondary endpoints, some of which were incorporated in the primary endpoint: cardiac death (56%) (Figure 2), fatal MI (56%) (Figure 3), cerebral or vascular death (71%), congestive heart failure (33%), and CPAOA (64%). In contrast, nonfatal MI slightly increased (22%), though not to a significant extent (Figure 3). The number of all events tended to be reduced, by 12%, with non-significantly fewer cardiac events and no excess of deaths from other non-cardiovascular causes (9.48 vs 9.72/1,000 patient-

year) (Table 2). Interestingly, cardiac death was almost completely eliminated by nicorandil during the first year of treatment (Figure 2).

In the group without sulfonylurea treatment, treatment with nicorandil significantly reduced all-cause deaths and cardiac deaths compared with the controls. Similarly, nicorandil treatment with sulfonylureas tended to reduce all-cause deaths compared with the control group, although this difference was not significant ($P=0.0719$). However, there was no significant difference in the proportional incidence of cardiac deaths between the control group and the group with nicorandil treatment and sulfonylureas, though cardiac deaths, which occurred in relatively few patients, did not increase in the group with nicorandil treatment with sulfonylureas compared with the controls (6.10 vs 4.49/1,000 patient-year) (Table 3).

The cardiac mortality rate was significantly higher in diabetic patients than in non-diabetic patients with or without nicorandil (control group: $HR=1.65$, $P=0.035$; nicorandil group: $HR=2.72$, $P=0.007$), and cardiac mortality rate was thus higher in patients with diabetes than in those without in this study. Sulfonylureas were used by 29.0% of all diabetic patients, and 28.8% of the patients not taking sulfonylureas had diabetes. Both total and cardiac mortalities were fewer in the sulfonylurea group than in the non-sulfonylurea group, though not to a significant extent ($HR=0.72$, $P=0.132$; $HR=0.62$, $P=0.171$, respectively). Moreover, the cardiac mortality rates in the analysis of only the diabetic patients in the non-sulfonylurea groups were higher (control group: 15.94/1,000 patient-year (33/766), nicorandil group: 8.50/1,000 patient-year (17/740)) than in all patients in the non-sulfonylurea group (Table 3).

Table 3. Incidence of All-Cause Death and Cardiac Death With or Without Sulfonylurea Treatment

	Control (n=2,558)	Nicorandil (n=2,558)	HR (95%CI)	P value
	Rate per 1,000 patient-years	Rate per 1,000 patient-years		
All-cause deaths	22.61	15.23	0.65 (0.51–0.84)	0.0008
Sulfonylurea (–)	23.03 (139/2,258)	16.16 (97/2,228)	0.68 (0.52–0.88)	0.0034
Sulfonylurea (+)	19.53 (16/300)	8.98 (8/330)	0.46 (0.20–1.07)	0.0719
Cardiac deaths	11.23	4.93	0.44 (0.29–0.66)	0.0001
Sulfonylurea (–)	11.93 (72/2,258)	5.00 (30/2,228)	0.42 (0.27–0.64)	0.0001
Sulfonylurea (+)	6.10 (5/300)	4.49 (4/330)	0.73 (0.20–2.73)	0.6441

HR, hazard ratio; CI, confidence interval.

Discussion

Our findings from the JCAD study show that in patients with coronary artery disease confirmed by coronary angiography, which is generally associated with a high risk of cardiovascular events, treatment with 15 mg nicorandil conferred a 35% reduction in all-cause deaths compared with the control group. This difference was mainly because of a significant reduction in cardiac deaths, especially fatal MI. In this study, in-hospital deaths because of MI or CPAOA were defined as fatal MI. It has been reported in population-based studies that half of acute MIs are fatal before hospitalization, and that most such deaths occurred within the first hour after onset of acute symptoms.^{13,14} In the present study, the majority of cases of CPAOA might have been related to MI, because all of the patients had significant stenosis of a major coronary artery on coronary angiography.

Our results confirm and extend observations of the effects of nicorandil on coronary events in patients with stable angina (IONA study).⁸ In an on-treatment analysis of IONA, 40 mg nicorandil yielded a 17% significant reduction in the primary composite endpoint of coronary heart disease deaths, nonfatal MI, and unplanned hospital admission for chest pain, as well as a 14% significant reduction in all cardiovascular events. Clinical characteristics such as age and sex were almost the same in our study and in IONA.⁸ Medications such as β -blockers and statins were less frequently used and angiotensin II receptor blockers more frequently used in our study than in IONA. Although 60% of patients had previously undergone coronary angiography and some had a positive exercise test with additional risk factors in IONA, in our study all patients underwent coronary angiography, and the mean number of significant coronary artery stenosis was almost 1.9. Moreover, the inclusion criterion in IONA was recently diagnosed stable angina that was neither unstable nor chronic. Some patients with acute MI (21.4%) or unstable angina (14.8%) were included in our study, so coronary artery lesions might have been more severe and vulnerable in the present patients than in those in IONA. Furthermore, the mean follow-up period was longer in JCAD than in IONA, at 2.7 and 1.6 years, respectively. Rates of all-cause mortality were 129/2561 patients (5.0%) and 156/2,558 patients (6.1%) in the IONA placebo and JCAD control groups, respectively. The reason for the higher rate of mortality in JCAD than in IONA might thus have been that IHD was more severe and the observational period longer. The subgroup analysis of IONA also suggested that nicorandil treatment of high-risk patients who were taking more anti-anginal medications or who had higher Canadian Cardiovascular Society (CCS) functional status scores would achieve the greatest absolute

risk reduction.¹⁵

Nicorandil is a hybrid drug that functions as a K-ATP channel opener and nitric oxide releaser.¹ It suppresses not only myocardial stunning but also myocardial necrosis in ischemic reperfusion.^{3–5} Pretreatment with K-ATP channel openers maintains mitochondrial respiration without inhibiting the increase in intracellular sodium and decrease in intracellular ATP and phosphocreatine during ischemia, and accelerates recovery of ATP concentration in tissues after ischemia.^{16,17} Moreover, K-ATP channel openers protect endothelial function in the coronary arteries from ischemic reperfusion injury via activation of mitochondrial K-ATP channels.^{18,19} The mitochondrial K-ATP channel may thus be an important mediator of protection of myocardial cells and coronary endothelium, and these mechanisms may thus have significantly reduced cardiovascular deaths associated with fatal MI and other ischemic events in the present nicorandil group compared with the control group. The early dissociation of the Kaplan-Meier curve in the case of cardiac deaths as well as all-cause deaths also suggests pharmacological preconditioning rather than stabilization of plaque and/or improvement of endothelial function with nicorandil, because the latter mechanisms are unlikely to function in the early phase.

Interestingly, there was no significant difference between the nicorandil and control groups in the incidence of acute MI in this study. Fatal MI significantly decreased and nonfatal MI slightly increased in the nicorandil group compared with the control. These findings also suggest that nicorandil had a pharmacological preconditioning effect, which salvages the ischemic myocardium and reduces necrosis of infarct-related myocardium in patients with acute MI. Moreover, on detailed analysis of the type of fatal MI, we found that CPAOA itself was significantly reduced in the nicorandil group compared with the control. The cause of these deaths before hospitalization is often ventricular fibrillation or cardiogenic shock. It has been reported that nicorandil reduces lethal ventricular arrhythmia in the initial phase after acute coronary syndrome.²⁰ This mechanism might also play a role in reducing fatal MI.

In this study, the dose of nicorandil (15 mg/day) was smaller than that used in IONA (40 mg/day). The recommended dosage in Europe and Oceania is 10–40 mg twice daily, and 7.5–30 mg three times daily in Asia.²¹ It has been found that oral nicorandil (15 mg/day) may have preconditioning effects in patients with stable angina undergoing coronary angioplasty.²² Ishii et al also reported that nicorandil (15 mg/day) improved clinical outcomes in patients with IHD receiving hemodialysis following coronary angioplasty.²³ These findings thus suggest that 15 mg/day of nicorandil

andil is adequate to activate K-ATP channels. However, the optimal dosage of nicorandil remains to be determined.

In this study, the incidence of congestive heart failure as a secondary endpoint was significantly reduced in the nicorandil group compared with the control group. The pharmacological preconditioning induced by nicorandil does not explain this suppressive effect, suggesting that another mechanism is responsible for it. Possible mechanisms include improvements of endothelial function and left ventricular function through improved microvascular circulation and/or cardiac sympathetic nerve activity.^{24,25} Sanada et al reported that nicorandil attenuated cardiac remodeling by inhibiting 70-kd S6 kinesis in long-term inhibition of nitric oxide synthase with N^ω-nitro-L-arginine methyl ester rats.²⁶ We also reported that nicorandil prevented left ventricular remodeling and loss of cardiac function in Dahl salt-sensitive hypertensive rats with congestive heart failure; these effects were mediated in part by enhanced endothelial nitric oxide synthase expression via activated K-ATP channels in the heart.²⁷ These mechanisms are also suggested by the finding that the Kaplan-Meier curves for the incidence of congestive heart failure in the 2 groups in this study gradually dissociated (data not shown). Recently, Kitakaze et al demonstrated that oral administration of nicorandil in the chronic phase after acute MI with successful catheter intervention increased left ventricular ejection fraction.²⁸ These findings may explain the significant reduction in the incidence of congestive heart failure in the nicorandil group in this study.

One important issue, whether the sulfonylureas eliminate the effects of nicorandil, remained following IONA. Concomitant treatment with a sulfonylurea was excluded in IONA, because these drugs inhibit the opening of K-ATP channels. One-third of patients with IHD have diabetes, and this complication augments cardiovascular events. Sulfonylureas may eliminate the myocardial and vascular protective effects of nicorandil when adequate dosages of them, which inhibit SUR2 or mitochondrial K-ATP channels, are administered. Recently, it was demonstrated that differences in selectivity for SUR type exist among the various types of sulfonylureas. Gliclazide did not inhibit the reconstructed cardiac and vascular type of K-ATP channel via activation of nicorandil,²⁹ whereas glimepiride did not inhibit the mitochondrial K-ATP channel in isolated myocardial cells.³⁰ Our findings also demonstrated that sulfonylureas did not absolutely eliminate the favorable effects of nicorandil, because nicorandil treatment with sulfonylureas tended to reduced all-cause deaths but not cardiac deaths. Lee et al also reported that ischemic preconditioning could be induced by nicorandil in diabetic glibenclamide-treated patients, although it was attenuated by impairment of intrinsic activation of cardiac K-ATP channels.³¹ These findings suggest that the cardioprotective effect of nicorandil mediated via activated K-ATP channels is partially impaired in diabetic patients being treated with sulfonylureas. However, because the mortality rates in the present study for the relatively few patients treated with nicorandil and sulfonylureas (630 patients) might have failed to exhibit significant differences from those in other groups, our findings need to be confirmed in additional studies.

In this study, slightly higher mortality rates were observed in the non-sulfonylureas than in the sulfonylureas group, which finding might be related to the poor prognosis of patients with diabetes not on sulfonylureas observed in this study or/and improvement of prognosis with sulfonylureas.

Study Limitations

This was a multicenter collaborative prospective observational study in a large cohort of coronary artery patients with similar clinical treatments based on coronary angiographic data, with data on clinical outcome collected in blind fashion. However, it was an observational and not a randomized, double-blind, controlled study. Thus, control was limited to variables for which data were available, although propensity score analysis was performed to reduce the conditional probability of taking a medication using covariates between the nicorandil and control groups. Moreover, precise information on the timing of nicorandil initiation, duration of treatment, and extent of compliance during the follow-up period could not be obtained. Categorization under a specific diagnostic label might also not be possible in the early stage of cardiac illness during the prehospital phase in patients with CPAOA. Nevertheless, the results obtained for various endpoints were internally consistent in this study, and mortality was a completely unbiased endpoint.

In conclusion, the reductions observed in cardiovascular deaths with nicorandil in this study were large, given the short period of follow-up, in patients with IHD, which has important implications for their treatment.

Acknowledgment

This work was supported by a grant from the Japanese Circulation Foundation.

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