Oral Nicorandil for Prevention of Cardiac Death in Hemodialysis Patients without Obstructive Coronary Artery Disease: A Propensity-Matched Patient Analysis

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Key Words

Acute myocardial infarction • Heart failure • Ischemia • Microangiopathy • Preconditioning • Sudden death

Abstract

Background/Aims: We examined the potential of oral administration of nicorandil for protecting against cardiac death in hemodialysis patients without obstructive coronary artery disease. **Methods:** This study was based on a cohort study of 155 hemodialysis patients with angiographic absence of obstructive coronary lesions, with analysis performed in 100 propensity-matched patients (54 men and 46 women, 64 ± 10 years), including 50 who received oral administration of nicorandil (15 mg/day, nicorandil group) and 50 who did not (control). The efficacy of nicorandil in preventing cardiac death was investigated. **Results:** Over a mean follow-up period of 5.3 ± 1.9 years, we observed 25 cardiac deaths among 100 propensity-matched patients, including 6 due to acute myocardial infarction, 11 due to heart failure, and 8 due to sudden cardiac death. The incidence of cardiac death was lower ($p < 0.001$) in the nicorandil group

(4/50, 8%) than in the control (21/50, 42%). On multivariate Cox hazard analysis, cardiac death was inversely associated with oral nicorandil (hazard ratio, 0.123; $p = 0.0002$). On Kaplan-Meier analysis, cardiac death-free survival rates at 5 years were higher in the nicorandil group than in the control group (91.4 vs. 66.4%). **Conclusion:** Oral nicorandil may inhibit cardiac death of hemodialysis patients without obstructive coronary artery disease.

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Introduction

Cardiac diseases are important causes of death in patients with end-stage renal disease on maintenance hemodialysis [1–3]. While coronary artery disease (CAD) is undoubtedly involved in cardiac death induced by acute myocardial infarction (MI) or congestive heart failure (CHF) and in sudden cardiac death (SCD) [4, 5], cardiac death occurs in patients on hemodialysis without extant CAD. The 5-year cumulative incidences of cardiac death among patients on hemodialysis were 48.3 and 40.2%, re-

spectively, in patients with and without prior CAD, although not all patients had undergone coronary angiography (CAG) [6]. We recently reported in a prospective cohort study that cardiac deaths occurred in approximately one fourth of hemodialysis patients without angiographic evidence of obstructive CAD [7]. However, few studies have investigated how cardiac death in hemodialysis patients without obstructive CAD can be inhibited.

Nicorandil, *N*-(2-hydroxyethyl)-nicotinamide, is an antianginal drug that causes vasodilation of both epicardial arteries and microvessels, with little reduction in blood pressure [8]. These effects of nicorandil involve activation of adenosine triphosphate (ATP)-sensitive potassium (K_{ATP}) channels and increase in the production of cyclic guanylate monophosphate [9]. In addition, nicorandil acts as a pharmacologic preconditioning agent for ischemia by opening mitochondrial K_{ATP} channels [10]. The Impact of Nicorandil in Angina trial showed that oral administration of nicorandil was associated with significantly lower rates of cardiovascular accidents including cardiac death in patients with stable angina [11]. We reported the potential of oral nicorandil to inhibit the occurrence of major adverse cardiac events in asymptomatic hemodialysis patients [12]. Oral administration of nicorandil has been reported to inhibit cardiac events or cardiac death after coronary revascularization by percutaneous coronary artery intervention in patients on

maintenance hemodialysis [13, 14]. In the present study, we examined whether oral administration of nicorandil could inhibit cardiac death in hemodialysis patients without obstructive CAD.

Methods

Patients

This study was based on a cohort study designed to investigate the involvement of impaired myocardial fatty acid metabolism and insulin resistance in cardiac death of hemodialysis patients (ClinicalTrials.gov, NCT01068080). Details of this study are provided elsewhere [7]. Figure 1 summarizes entry and exclusion criteria for the study, which proceeded at three dialysis centers associated with the Toujinkai Group. Four hundred and twenty-two patients with end-stage renal disease on maintenance hemodialysis at the Toujinkai Group underwent CAG for the first time to determine the presence or absence of CAD between January 1, 2001, and December 31, 2004. No significant stenotic coronary lesions (diameter stenosis greater than 50%) were identified in 205 of the 422 patients. Among them, 50 patients were excluded from the study for the reasons indicated in figure 1. Consequently, 155 hemodialysis patients without significant obstructive coronary lesions were enrolled in this cohort study (89 men and 66 women; mean age: 64 ± 11 years; mean duration of dialysis: 91 ± 97 months). The participants were enrolled at the time of homeostasis model assessment-insulin resistance (HOMA-IR) measurements (between January 1, 2001, and December 31, 2004), and followed through December 31, 2008 until the end point described below.

Nicorandil was orally administered within one week of CAG through the end of the study to patients who had exhibited any of the following clinical signs or findings: (1) recurrent abrupt hypotension during dialysis, (2) transient ST segment depression on the electrocardiogram during dialysis, (3) new ST-T changes (including nonspecific changes) on routine electrocardiography, or (4) severely impaired myocardial fatty acid metabolism on imaging (iodine-123- β -methyl iodophenyl-pentadecanoic acid, BMIPP, summed scores of 12 or more). The first three of these findings are suggestive of the presence of myocardial ischemia in dialysis patients according to the K/DOQI guidelines [15], while the fourth finding may indicate risk of cardiac death in hemodialysis patients [16]. Of the 155 study patients, 77 exhibited one or more of these four findings: 67 patients agreed to undergo administration of nicorandil (nicorandil group), while the other 10 patients did not. These 10 patients and 78 patients who had not exhibited the above signs or findings and had not received administration of nicorandil were designated the non-nicorandil group. Nicorandil was never administered to patients of the non-nicorandil group during the study. No patients discontinued administration of nicorandil before the end point or end of the study. The dose for oral administration of nicorandil was uniformly 15 mg/day, the approved dosage in Japan. Other cardiovascular drugs prescribed before the study were continued during it. Smoking was defined as 10 or more cigarettes per week and alcohol consumption as alcohol intake of 20 g or more per week. The Ethics Committee for Human Research of Toujinkai Hospital approved this study, and all patients provided written informed consent to all procedures associated with the study prior to participation. The study was performed in accordance with the principles of the Declaration of Helsinki.

Coronary Angiography

Experienced cardiologists performed quantitative CAG at the Department of Interventional Cardiology of Kyoto Second Red Cross Hospital using a validated automated edge-detection program (CCIP-310/W, CATHEX, Tokyo, Japan). Significant coronary artery stenosis was defined as stenosis >50% diameter on CAG images.

Radionuclide Imaging

All patients underwent resting BMIPP and ^{201}Tl Thallium (Tl) dual single-photon emission computed tomography (SPECT) within one month before first CAG. Details of the dual BMIPP-Tl SPECT procedure are provided elsewhere [16–18]. Images were divided into 17 segments for semiquantitative analysis according to the standard myocardial segmentation for tomographic heart imaging established by the American Heart Association. The amount of radioactivity taken up by each segment was visually graded and assigned an uptake score of 0 (normal), 1 (mildly reduced), 2 (moderately reduced), 3 (severely reduced), or 4 (none). BMIPP and Tl SPECT scores for the 17 myocardial segments were designated the summed BMIPP and Tl scores, respectively. The interobserver and intraobserver variability in the summed scores at our institution was 6.8 ± 1.4 and $5.4 \pm 1.4\%$, respectively [7].

Echocardiography

The patients underwent two-dimensionally guided echocardiography using a single ultrasonographic recorder (UF-8800,

Fukuda Denshi, Tokyo, Japan) within one month before CAG. Left ventricular dimensions and left ventricular ejection fraction were quantified using the biplanar Simpson's rule. Left ventricular mass was measured as recommended by the American Society of Echocardiography, normalized to body surface area, and described herein as left ventricular mass index.

Biochemical and Hematological Determinations

On a midweek dialysis day within 30 days after CAG, blood samples (10 ml) were obtained in the morning from patients who had fasted overnight and rested for 10 min. Hemoglobin (and hemoglobin A1c for diabetic patients), plasma concentrations of intact parathyroid hormone and B-type natriuretic hormone, and serum concentrations of calcium, inorganic phosphorus, albumin, total cholesterol, and high-sensitivity C-reactive protein were determined.

Assessment of Insulin Resistance

We used fasting plasma glucose and fasting plasma insulin concentrations to calculate the HOMA-IR value as described by Mathews et al. [19] as fasting glucose concentration (mmol/l) $\times$ fasting insulin concentration ($\mu\text{U/ml}$)/22.5. Blood samples were collected on the same day to measure other biochemical and hematological parameters.

End Point

All participants of this study had been followed in the hospital or clinics of the Toujinkai Group until the end point or the end of study (December 31, 2008). The end point was cardiac-derived death (SCD or death due to acute MI or CHF). We defined SCD as death within 24 h of the time the patient was last seen alive in a normal state of health and for which cardiac diseases such as malignant arrhythmias or acute coronary syndrome were considered the cause. Cerebrovascular accidents were ruled out by postmortem examination. Acute MI was diagnosed when new abnormal Q waves appeared on electrocardiograms together with anterior chest pain or discomfort, when abnormal left ventricular wall motion was recognized on echocardiograms, and when serum concentrations of troponin-T and creatine phosphokinase-MB fraction were significantly elevated. Death due to CHF did not include death due to heart failure caused by acute MI. When the death of a patient occurred at home or away from home, or in the hospital or clinics of the Toujinkai Group, cardiologists and internists of Toujinkai Hospital confirmed the death and diagnosed cardiac death. In cases in which death of a patient occurred at Kyoto Second Red Cross Hospital due to acute MI, cardiologists of that hospital diagnosed acute MI as the cause of death.

Statistical Analysis

Values are the means $\pm$ SD. To guarantee maximum validity of this retrospective analysis, propensity scoring was used to match patients between the nicorandil ($n = 67$) and non-nicorandil ($n = 88$) groups. Propensity scoring can reduce bias resulting from the nonrandom nature of treatment assignment seen in observational studies [20]. The propensity score is the expected probability of receiving one treatment over another for a given patient, based on that patient's baseline characteristics. A logistic regression model of the actual treatment received is fit to the data, and the propensity score for each patient is then esti-

Table 1. Clinical characteristics of the nicorandil and non-nicorandil groups

	Total (n = 155)	Control (n = 88)	Nicorandil (n = 67)	p value
Age, years	63.7 ± 10.8	64.4 ± 11.1	62.9 ± 10.4	0.396
Male	89 (57.4)	51 (58.0)	38 (56.7)	0.877
Hemodialysis duration, months	90.5 ± 97.3	88.9 ± 95.9	92.7 ± 99.7	0.811
Body mass index	21.2 ± 4.3	20.2 ± 4.2	22.6 ± 4.1	0.0005
Smoking	60 (38.7)	34 (38.6)	26 (38.8)	0.983
Alcohol	60 (38.7)	31 (35.2)	29 (43.3)	0.308
Cardiothoracic ratio, %	52.1 ± 5.2	52.6 ± 5.2	51.5 ± 5.2	0.207
Systolic blood pressure before dialysis, mm Hg	143.7 ± 15.8	144.5 ± 15.9	142.7 ± 15.8	0.502
Diastolic blood pressure before dialysis, mm Hg	79.0 ± 17.5	76.9 ± 14.7	81.7 ± 20.4	0.103
Diabetes mellitus	59 (38.1)	35 (39.8)	24 (35.8)	0.616
Kt/V _{urea}	1.79 ± 0.23	1.81 ± 0.24	1.77 ± 0.21	0.299
Left ventricular ejection fraction, %	63.3 ± 14.6	62.3 ± 15.5	64.6 ± 13.3	0.327
Left ventricular mass index, g/m ²	140.3 ± 49.3	138.8 ± 46.1	142.3 ± 53.5	0.661
Blood hemoglobin, g/l	104.5 ± 11.5	104.4 ± 12.2	104.6 ± 10.6	0.890
Serum calcium, mmol/l	2.3 ± 0.2	2.3 ± 0.2	2.2 ± 0.2	0.239
Serum inorganic phosphorus, mmol/l	1.7 ± 0.3	1.3 ± 0.4	1.7 ± 0.3	0.355
Serum albumin, g/l	37.8 ± 3.4	37.6 ± 3.4	38.1 ± 3.4	0.821
Serum total cholesterol, mmol/l	4.4 ± 0.9	4.4 ± 0.9	4.4 ± 1.0	0.976
Serum high-sensitivity C-reactive protein, mg/l	3.8 ± 2.9	3.7 ± 3.0	4.0 ± 2.8	0.595
Plasma intact parathyroid hormone, ng/l, log	2.2 ± 0.3	2.2 ± 0.4	2.3 ± 0.3	0.274
Plasma B-type natriuretic peptide, ng/l, log	2.4 ± 0.4	2.4 ± 0.4	2.4 ± 0.4	0.971
BMIPP summed score	9.6 ± 8.6	9.8 ± 9.1	9.3 ± 7.9	0.707
Tl summed score	4.5 ± 4.4	4.4 ± 4.3	4.6 ± 4.6	0.715
HOMA-IR, mmol/l·μU/ml	4.8 ± 1.9	4.8 ± 2.0	4.9 ± 1.8	0.803
Medications				
α ₁ -Blockers	14 (9.0)	8 (9.1)	6 (9.0)	0.977
β-Blockers	39 (25.2)	23 (26.1)	16 (23.9)	0.749
Calcium channel blockers	44 (28.4)	24 (27.3)	20 (29.9)	0.724
Nitrates	22 (14.2)	11 (12.5)	11 (16.4)	0.489
Angiotensin I-converting enzyme inhibitors	4 (2.6)	2 (2.3)	2 (3.0)	0.782
Angiotensin II receptor blockers	39 (25.2)	21 (23.9)	18 (26.9)	0.670
Antiplatelet drugs	84 (54.2)	47 (53.4)	37 (55.2)	0.822
Anticoagulation drugs	1 (0.6)	1 (1.1)	0	0.381
Statins	34 (21.9)	15 (17.0)	19 (28.4)	0.092
Vitamin D	91 (58.7)	53 (60.2)	38 (56.7)	0.663
Digoxin	12 (7.7)	6 (6.8)	6 (9.0)	0.625
Class 1 antiarrhythmic drugs	10 (6.5)	6 (6.8)	4 (6.0)	0.833

Figures are means ± SD or numbers with percentages in parentheses.

mated. Many covariates, in addition to higher-order terms and covariate interactions, can be condensed into a single scalar variable, the propensity score [21]. Thus, logistic regression analysis was used to develop the propensity score, and baseline data, including cardiothoracic ratio, diastolic blood pressure before dialysis, body mass index, and administration of statins were used as covariates. Patients in the nicorandil group and those in the non-nicorandil group were matched in a 1:1 ratio with 1 digit, based on the estimated propensity score for treatment with oral nicorandil. As a result, estimated propensity scores could be used to match 50 patients each from the nicorandil and non-nicorandil groups. The statistical analyses de-

scribed below were performed for these 100 propensity-matched patients. The t test was used to compare means of continuous variables, and categorical data were analyzed using the χ^2 test. Kaplan-Meier analysis and the log-rank test were used to examine survival. Multivariate analysis of prognosis was performed using the stepwise Cox proportional hazard model. Variables with p values of <0.2 on univariate analysis were entered into multivariate analysis. p values of <0.05 were considered significant. Individuals without knowledge of patient profiles and clinical data performed all statistical analyses.

Table 2. Clinical characteristics of the subjects included in propensity analysis

	Total (n = 100)	Control (n = 50)	Nicorandil (n = 50)	p value
Age, years	64.2 ± 10.3	64.7 ± 10.2	63.6 ± 10.5	0.590
Male	54 (54.0)	27 (54.0)	27 (54.0)	1.000
Hemodialysis duration, months	94.0 ± 101.6	86.3 ± 100.1	101.8 ± 103.5	0.448
Body mass index	21.5 ± 4.0	21.4 ± 4.2	21.6 ± 3.9	0.853
Smoking	40 (40.0)	18 (36.0)	22 (44.0)	0.414
Alcohol	35 (35.0)	15 (30.0)	20 (40.0)	0.295
Cardiothoracic ratio, %	52.0 ± 5.4	52.1 ± 5.5	51.9 ± 5.4	0.883
Systolic blood pressure before dialysis, mm Hg	143.8 ± 16.4	145.4 ± 15.9	142.1 ± 16.8	0.310
Diastolic blood pressure before dialysis, mm Hg	78.7 ± 14.9	79.3 ± 15.8	78.1 ± 14.0	0.698
Diabetes mellitus	38 (38.0)	22 (44.0)	16 (32.0)	0.216
Kt/V _{urea}	1.79 ± 0.21	1.76 ± 0.23	1.74 ± 0.19	0.624
Left ventricular ejection fraction, %	63.3 ± 14.4	61.5 ± 16.4	65.0 ± 12.0	0.225
Left ventricular mass index, g/m ²	134.7 ± 47.4	130.8 ± 44.4	138.5 ± 50.4	0.422
Blood hemoglobin, g/l	104.1 ± 11.7	105.0 ± 13.4	103.2 ± 9.9	0.451
Serum calcium, mmol/l	2.3 ± 0.2	2.3 ± 0.2	2.3 ± 0.2	0.562
Serum inorganic phosphorus, mmol/l	1.7 ± 0.4	1.7 ± 0.4	1.7 ± 0.3	0.404
Serum albumin, g/l	37.8 ± 3.5	37.6 ± 3.4	38.0 ± 3.5	0.567
Serum total cholesterol, mmol/l	4.3 ± 0.9	4.4 ± 0.8	4.2 ± 0.9	0.546
Serum high-sensitivity C-reactive protein, mg/l	4.0 ± 3.0	4.2 ± 3.1	3.7 ± 2.9	0.450
Plasma intact parathyroid hormone, ng/l, log	227.9 ± 165.2	2.3 ± 0.3	2.2 ± 0.3	0.974
Plasma B-type natriuretic peptide, ng/l, log	2.4 ± 0.4	2.4 ± 0.4	2.5 ± 0.3	0.211
BMIPP summed score	9.2 ± 8.4	9.4 ± 9.1	9.0 ± 7.7	0.823
TI summed score	4.4 ± 4.1	4.1 ± 3.8	4.8 ± 4.4	0.357
HOMA-IR, mmol/l·μU/ml	4.8 ± 1.8	4.9 ± 2.0	4.8 ± 1.5	0.677
Medications				
α ₁ -Blockers	9 (9.0)	6 (12.0)	3 (6.0)	0.487
β-Blockers	28 (28.0)	15 (30.0)	13 (26.0)	0.656
Calcium channel blockers	22 (22.0)	13 (26.0)	9 (18.0)	0.334
Nitrates	26 (26.0)	17 (34.0)	9 (18.0)	0.585
Angiotensin I-converting enzyme inhibitors	2 (2.0)	1 (2.0)	1 (2.0)	1.000
Angiotensin II receptor blockers	25 (25.0)	13 (26.0)	12 (24.0)	0.817
Antiplatelet drugs	57 (57.0)	26 (52.0)	31 (62.0)	0.313
Anticoagulation drugs	0	0	0	
Statins	19 (19.0)	10 (20.0)	9 (18.0)	0.799
Vitamin D	56 (56.0)	27 (54.0)	29 (58.0)	0.691
Digoxin	9 (9.0)	4 (8.0)	5 (10.0)	0.730
Class 1 antiarrhythmic drugs	8 (8.0)	4 (8.0)	4 (8.0)	1.000

Figures are means ± SD or numbers with percentages in parentheses.

Results

During follow-up of 155 patients on hemodialysis, we observed 42 cardiac deaths (7 acute MI, 18 CHF, 17 SCD) over a mean of 5.1 ± 2.0 years. Table 1 shows the baseline clinical characteristics of all participants, those administered nicorandil (nicorandil group: n = 67), and those not administered nicorandil (non-nicorandil group: n = 88). Mean body mass index was higher in the nicorandil group than in the non-nicorandil group, and rate of pre-

scription of statins tended to be higher in the nicorandil than the non-nicorandil group. To decrease bias, we performed a propensity-matched analysis as described above.

Cardiac Death in Propensity-Matched Patients

Estimated propensity scores matched 50 patients each from the nicorandil and non-nicorandil groups (54 men and 46 women; age, 64 ± 10 years; duration of dialysis, 94 ± 104 months). The baseline clinical characteristics of the patients listed in table 2 did not differ between the

Table 3. Univariate Cox hazard analysis of cardiac death

	Hazard ratio	95% confidence interval	p
Age (1 year)	1.048	1.012–1.087	0.001
Male (1 = yes, 0 = no)	1.119	0.508–2.467	0.780
Duration of hemodialysis (1 month)	1.001	0.997–1.005	0.762
Body mass index (1)	0.955	0.869–1.049	0.337
Smoking (1 = yes, 0 = no)	0.978	0.439–2.177	0.956
Alcohol (1 = yes, 0 = no)	0.529	0.211–1.327	0.175
Cardiothoracic ratio (1%)	1.057	0.987–1.133	0.115
Systolic blood pressure before dialysis (1 mm Hg)	0.983	0.959–1.007	0.260
Diastolic blood pressure before dialysis (1 mm Hg)	0.995	0.966–1.024	0.731
Diabetes mellitus (1 = yes, 0 = no)	1.138	0.511–2.535	0.751
Kt/V _{urea} (1)	0.692	0.092–5.199	0.720
Left ventricular ejection fraction (1%)	0.964	0.942–0.987	0.002
Left ventricular mass index (1 g/m ²)	0.997	0.988–1.006	0.459
Blood hemoglobin (1 g/l)	1.002	0.969–1.035	0.922
Serum calcium (1 mmol/l)	0.874	0.093–8.174	0.906
Serum inorganic phosphorus (1 mmol/l)	0.541	0.171–1.711	0.296
Serum albumin (1 g/l)	0.964	0.865–1.074	0.509
Serum total cholesterol (1 mmol/l)	0.903	0.577–1.412	0.654
Serum high-sensitivity C-reactive protein (1 mg/l)	0.946	0.823–1.088	0.438
Plasma intact parathyroid hormone (1 ng/l, log)	1.523	0.452–5.137	0.497
Plasma B-type natriuretic peptide (1 ng/l, log)	0.497	0.170–1.450	0.201
BMIPP summed score (1)	1.090	1.058–1.123	0.0001
Tl summed score (1)	1.162	1.082–1.249	0.0001
HOMA-IR (1 mmol/l·μU/ml)	1.476	1.244–1.752	0.0001
α ₁ -Blockers (1 = yes, 0 = no)	0.767	0.181–3.254	0.719
β-Blockers (1 = yes, 0 = no)	1.151	0.496–2.672	0.743
Calcium channel blockers (1 = yes, 0 = no)	1.333	0.556–3.193	0.519
Nitrates (1 = yes, 0 = no)	0.914	0.314–2.665	0.869
Angiotensin I-converting enzyme inhibitors (1 = yes, 0 = no)	2.451	0.331–18.165	0.380
Angiotensin II receptor blockers (1 = yes, 0 = no)	1.529	0.660–3.546	0.322
Nicorandil (1 = yes, 0 = no)	0.157	0.054–0.459	0.0007
Antiplatelet drugs (1 = yes, 0 = no)	0.976	0.443–2.151	0.952
Statins (1 = yes, 0 = no)	0.817	0.280–2.182	0.712
Vitamin D (1 = yes, 0 = no)	0.760	0.346–1.669	0.495
Digoxin (1 = yes, 0 = no)	1.434	0.427–4.817	0.560
Class I antiarrhythmic drugs (1 = yes, 0 = no)	0.396	0.053–2.929	0.364

nicorandil and control groups. During follow-up of these 100 patients for 5.3 ± 1.9 years, cardiac deaths occurred in 25 patients (6 acute MI, 11 CHF, 8 SCD). Cardiac death occurred in 4 patients of the nicorandil group (8%) and 21 of the control (42%), whereas non-cardiac death occurred in 8 patients of the nicorandil group (16%) and 7 patients of the control (14%). All 6 patients who died of acute MI were in the control group. The 4 cardiac deaths observed in the nicorandil group included 3 due to CHF and 1 due to SCD.

Risk Analysis of Cardiac Death

On univariate Cox hazard analysis, age, left ventricular ejection fraction, HOMA-IR, BMIPP or Tl summed scores, and administration of nicorandil were significantly associated with the occurrence of cardiac death (table 3). On stepwise Cox hazard analysis among these factors and other factors with $p < 0.2$ on univariate Cox hazard analysis (history of alcohol consumption and cardiothoracic ratio), BMIPP summed score, Tl summed score, and administration of nicorandil were significantly associated with cardiac death (table 4). Kaplan-Meier

Fig. 2. Cardiac death-free survival rates in the propensity-matched nicorandil (n = 50) and control groups (n = 50), p = 0.0001, log-rank test.

Table 4. Stepwise Cox hazard analysis of cardiac death

	Hazard ratio	95% confidence interval	p
BMIPP summed score (1)	1.086	1.039–1.136	0.0003
Tl summed score (1)	1.096	0.987–1.216	0.0870
Nicorandil (1 = yes, 0 = no)	0.123	0.041–0.368	0.0002

survival estimates revealed that cardiac death-free survival rates at 5 years were 91.4 and 66.4% for patients with and without nicorandil, respectively (fig. 2).

Discussion

Oral administration of nicorandil particularly inhibited death due to acute MI. In our previous study, oral nicorandil did not reduce the incidence of acute MI, but significantly inhibited death due to acute MI in asymptomatic hemodialysis patients [12]. Nicorandil acts as a pharmacologic preconditioning agent by opening mitochondrial K_{ATP} channels and thus enhancing the tolerance of the heart to subsequent ischemia [10]. In addition, nicorandil improves endogenous fibrinolytic activity by increasing circulating plasminogen activator inhibitor [22] and inhibits cardiac sympathetic activity [23] and ox-

idative stress-induced apoptosis in myocardial cells [24]. Recently, Izumiya et al. [25] reported that long-term oral administration of nicorandil stabilizes coronary plaque in patients with stable angina pectoris and in Apo-E-deficient mice by mechanisms different from those of statins. Oral administration of nicorandil may have reduced the extent of myocardial injury in acute coronary syndrome as a result of the pharmacologic effects described above, resulting in reduction of death due to acute MI.

Oral administration of nicorandil also inhibited the occurrence of SCD. SCD accounts for approximately one fourth of all-cause mortality in dialysis patients [26]. The main causes of SCD are believed to be hemodynamic collapse due to malignant arrhythmias such as ventricular fibrillation [27] as well as cardiogenic shock due to acute coronary syndrome. In our previous study [13], oral administration of nicorandil strongly inhibited the occurrence of SCD in hemodialysis patients who had undergone coronary revascularization by percutaneous coronary artery intervention. Nicorandil might have decreased SCD by interfering with the pathogenic mechanisms responsible for SCD of dialysis patients.

Intramyocardial arteriolar thickening, reduced capillary density, and myocardial fibrosis are pathological characteristics of the hearts of dialysis patients [28, 29]. Such myocardial abnormalities readily produce myocardial microcirculatory disorders. The existence of histologically proven microvasculopathy has been reported to increase mortality after heart transplantation by induc-

ing fatal cardiac events [30]. Dikow et al. [31] reported that tolerance of the heart to subsequent ischemia decreased in rats with impaired renal function, and that the size of myocardial infarcts induced by reperfusion ischemia was larger in rats with renal failure than in those without it. They speculated that myocardial microcirculatory disturbance was involved in the decreased tolerance to ischemia in rats with impaired renal function. Experimental models of microangiopathy induced by coronary microembolization exhibited arrhythmias leading to sudden death [32, 33]. Nicorandil exhibits a vasodilatory effect on coronary arterial microvessels <100 μm in diameter by opening K_{ATP} channels [34]. Nicorandil improved microvascular abnormalities, as assessed by ^{201}Tl myocardial perfusion imaging and echocardiographic determination of left ventricular function, in patients with ischemic cardiomyopathy [23]. The effects of nicorandil on the myocardial microcirculation are expected to reduce SCD by inhibiting the occurrence of malignant arrhythmias or cardiogenic shock in hemodialysis patients with acute coronary syndrome.

This study had several limitations. First, this was a retrospective study, using propensity-matched patient analysis. Although many large observational cohort studies have used propensity-matched patient analysis to minimize selection bias [20, 21], we could not fully eliminate selection bias since the sample size was small. Relationships observed between oral nicorandil and cardiac death cannot be concluded to be causal. Second, we used CAG to confirm the presence of suspected myocardial ischemia. 'Without significant obstructive CAD' does not necessarily mean that the epicardial coronary arteries are normal. Since histopathological and intravascular ultrasound studies have demonstrated the propensity of angiography to underestimate lesion severity [35, 36], we cannot exclude the possibility that some angiographically nonsignificant lesions were flow-limiting. Third, the cumulative cardiogenic and all-cause mortalities of our population for about 5 years were 25 and 40%, respectively, and apparently lower than those previously reported in other countries. Absence of obstructive CAD in the participants may be one of the reasons for the low mortality. Elimination of patients with CHF of NYHA grades III–IV, significant valvular heart disease, permanent pacemaker implantation, pulmonary diseases, idiopathic cardiomyopathy, or malignancy from study participants (fig. 1) could be another reason. Racial differences, a non-increased incidence of diabetes (38%), the complete lack of withdrawal of patients from dialysis, and adequate dialysis as indicated by high mean $\text{Kt/V}_{\text{urea}}$ (1.79 ± 0.21) might have contributed to re-

ducing the mortality of our dialysis population. Lastly, the mean age of this study's participants was high, at 64 years among 100 propensity-matched patients, and advanced age is generally an independent risk factor for cardiac death. The results obtained in this study may thus not be applicable to all hemodialysis patients.

Cardiac death occurs at high incidence among hemodialysis patients without CAD. The results of this study indicate the efficacy of oral administration of nicorandil in inhibiting cardiac death, particularly acute MI death and SCD, in hemodialysis patients without significant stenotic CAD. Pharmacological effects such as preconditioning to ischemia, stabilization of coronary plaque, and improvement of impaired myocardial microcirculation may play roles in reducing cardiac death among hemodialysis patients administered oral nicorandil. Oral nicorandil may contribute to improving the survival of hemodialysis patients without obstructive CAD by inhibiting the occurrence of cardiac death. Since this is a retrospective study, we could not clearly determine the clinical value of oral nicorandil in prevention of cardiac death. Large, prospective, randomized clinical trials are needed to establish the clinical usefulness of oral nicorandil among this population.

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Disclosure Statement

None.

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