

# Preventive Effect of Pretreatment with Intravenous Nicorandil on Contrast-Induced Nephropathy in Patients with Renal Dysfunction Undergoing Coronary Angiography (PRINCIPLE Study)

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**Purpose:** To investigate the effect of pretreatment with intravenous nicorandil on the incidence of contrast-induced nephropathy (CIN) in patients with renal dysfunction undergoing coronary angiography. **Materials and Methods:** This randomized controlled multicenter study enrolled a total of 166 patients (nicorandil n=81; control n=85) with an estimated glomerular filtration rate <60 mL/min. Nicorandil 12 mg dissolved in 100 mL of 0.9% saline was administered intravenously for 30 minutes just prior to coronary angiography in the nicorandil group. The same volume of only saline was given to the control group. The primary endpoint was the incidence of CIN, defined as >0.5 mg/dL increase or >25% rise in serum creatinine (SCr) concentration within 48 hours of contrast exposure compared to baseline. **Results:** The final analysis included 149 patients (nicorandil n=73; control n=76). The baseline characteristics and the total volume of the used contrast (Iodixanol, 125.6±69.1 mL vs. 126.9±74.6 mL,  $p=0.916$ ) were similar between the two groups. The incidence of CIN also did not differ between the nicorandil and control groups (6.8% vs. 6.6%,  $p=0.794$ ). There was no difference between the two groups in the relative change in SCr from baseline to peak level within 48 hours after coronary angiography (-1.58±24.07% vs. 0.96±17.49%,  $p=0.464$ ), although the nicorandil group showed less absolute change in SCr than the control group (-0.01±0.43 mg/mL vs. 0.02±0.31 mg/mL,  $p=0.005$ ). **Conclusion:** Prophylactic intravenous infusion of nicorandil did not decrease the incidence of CIN in patients with renal dysfunction undergoing coronary angiography.

**Key Words:** Contrast media, acute kidney injury, coronary artery disease

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## INTRODUCTION

With the widespread use of computed tomography and angiography as diagnostic

tools for various diseases, the prevalence of contrast-induced nephropathy (CIN) is increasing, and CIN is a common cause of hospital-acquired acute renal failure.<sup>1-3</sup> Risk factors for CIN include chronic kidney disease, diabetes mellitus, advanced age, congestive heart failure, nephrotoxic drug use, hypovolemia, and excessive contrast media volume.<sup>4,5</sup> The incidence of CIN is less than 5% in patients without risk factors but can increase to 50% among patients with multiple risk factors.<sup>4,5</sup> Although the underlying pathomechanism for CIN is not fully understood, the reduction in renal perfusion caused directly from the effect of contrast media on the kidney plays an important role in the development of CIN.<sup>6,7</sup> Nicorandil is an anti-anginal medication that has the dual properties of a  $K_{ATP}$  channel agonist and a nitric oxide (NO) donor.<sup>8</sup> A recent study showed that activation of the  $K_{ATP}$  channel reduced renal injury due to ischemia and reperfusion by preventing accumulation of reactive oxygen radicals.<sup>9</sup> These data suggest that nicorandil may protect the kidney from ischemic injury associated with the use of contrast media by decreasing calcium inflow to the tubular cells, inhibiting the accumulation of reactive oxygen species (ROS), suppressing synthesis of endothelin-1, and inducing NO production. The purpose of the present study is to evaluate the effect of pretreatment with intravenous nicorandil on the incidence of CIN in patients with renal dysfunction undergoing coronary angiography.

## MATERIALS AND METHODS

### Study population

Patients admitted with renal dysfunction [i.e., estimated glomerular filtration rate (eGFR)  $\leq 60$  mL/min by Cockcroft-Gault formula and serum creatinine (SCr)  $\geq 1.1$  mg/dL] scheduled to undergo coronary angiography on the next day were screened. The exclusion criteria were age  $< 18$  years, acute myocardial infarction requiring primary or rescue coronary intervention, allergy to contrast dye or nicorandil, previous exposure to nicorandil or contrast medium within the preceding 7 days, pregnancy, left ventricular ejection fraction (LVEF)  $< 30\%$  by echocardiogram or evident by pulmonary edema, acute renal failure, renal failure requiring dialysis, a single functioning kidney, history of kidney transplantation, life expectancy  $< 6$  months, or the use of nonsteroidal anti-inflammatory drugs except for low dose aspirin, dopamine, mannitol, N-acetylcysteine, ascorbic acid, or sodium bicarbonate within 48 hours of the pro-

cedure.

This study was conducted according to the principles of the revised Declaration of Helsinki and good clinical practice guidelines and was approved by the local Institutional Review Board of the participating hospitals. All patients gave written informed consent prior to study entry. The trial was registered with <http://www.clinicaltrials.gov> (trial identifier: NCT01103336).

### Study protocol

The present study was designed as an investigator-initiated, prospective, randomized, open-label, multicenter trial. Patients were randomized in a 1 : 1 ratio either to the nicorandil or to the control group. Randomization was stratified for the participating centers and the severity of the renal dysfunction (eGFR  $\leq 40$  or  $> 40$  mL/min). In the nicorandil group, nicorandil (Sigmart for injection, Choongwae Pharma, Seoul, Korea) 12 mg nicorandil was diluted in 100 mL of 0.9% saline and administered intravenously over a 30-minute period just prior to coronary angiography. In the control group, 100 mL of 0.9% saline was given by the same method. In all enrolled patients, an intravenous infusion of 0.45% saline at a rate of 1 mL/kg/hr (0.5 mL/kg/hr for patients with LVEF  $< 40\%$ ) was administered at least 8 hours before and after an elective coronary procedure. Elective coronary procedures were performed according to standard technique by a radial or femoral approach. Iodixanol (Visipaque, GE Healthcare Korea, Seoul, Korea), an iso-osmolar, non-ionic, dimeric contrast medium, was used for all patients.

Blood samples were collected at baseline and on days 1 and 2 after the procedure for the measurement of serum Cr and cystatin C levels. Laboratory personnel in a central core laboratory (Seoul Clinical Laboratory, Seoul, Korea) that were fully blinded to the clinical data performed the measurements. The primary endpoint was the incidence of CIN, defined as  $> 0.5$  mg/dL increase or  $> 25\%$  rise in SCr concentration within 48 hours of contrast exposure compared to baseline. Additional endpoints were maximal increase in serum Cr and cystatin C levels within 48 hours after the procedure. Major adverse events including death, myocardial infarction, stroke, renal failure requiring dialysis, and acute pulmonary edema confirmed by chest X-ray films were also recorded.

### Statistical analysis

The calculation of the sample size was based on a two sam-

ple and two-sided inequality test. The incidence of CIN was approximated at 15% in the control group based on previous studies.<sup>4,5,10</sup> Pretreatment with nicorandil was hypothesized to reduce this incidence to 2%. Based on an alpha level of 0.05 and statistical power of 80%, 73 patients were required for each group. Continuous variables were expressed as mean±standard deviation, and categorical variables were described as a number (percentage). Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Student's t-tests were used to compare normally and non-normally distributed continuous variables. Statistical significance was considered if the *p*-value was <0.05. The impact of the pretreatment of nicorandil on the incidence of CIN was evaluated in a logistic regression analysis after adjustment of all variables associated with CIN in univariate analysis with a *p*-value <0.2. All statistical analyses were conducted using IBM PASW Statistics 18.0 (IBM Corporation, New York, NY, USA).

## RESULTS

### Baseline characteristics

A total of 173 patients were enrolled in this study and were randomized to either the nicorandil group (n=85) or the control group (n=88). Two patients from each group withdrew consent for study participation after enrollment. An additional 20 patients, 10 from each group, were excluded from the analysis because of incomplete laboratory evaluations. Consequently, 73 patients in the nicorandil group and 76 patients in the control group remained for statistical analysis. Clinical characteristics of the patients are summarized in Table 1. No significant differences were identified between the two patient groups regarding age, gender, weight, body mass index, diabetes mellitus, hypertension, hypercholesterolemia, current smoking, acute coronary syndrome, acute myocardial infarction, multi-vessel disease, eGFR, Mehran

**Table 1. Clinical Characteristics of the Study Population**

	Nicorandil (n=73)	Control (n=76)	<i>p</i> value
Age, yrs	70.8±9.6	69.1±10.3	0.291
Male (%)	53 (72.6)	51 (67.1)	0.581
Weight, kg	63.8±11.6	65.4±11.1	0.383
BMI, kg/m <sup>2</sup>	24.1±3.2	24.8±3.7	0.229
Diabetes mellitus (%)	30 (41.1)	42 (55.3)	0.117
Hypertension (%)	57 (78.1)	61 (80.3)	0.900
Hypercholesterolemia (%)	21 (28.8)	28 (36.8)	0.382
Current smoker (%)	17 (23.3)	18 (23.7)	0.892
Acute coronary syndrome (%)	24 (32.9)	21 (27.6)	0.604
AMI (%)	5 (6.8)	5 (6.6)	0.794
Multi-vessel disease (%)	35 (47.9)	28 (36.8)	0.228
LVEF ≤45% (%)	11 (15.1)	5 (6.6)	0.159
Baseline eGFR, mL/min	37.5±13.4	40.1±13.9	0.248
eGFR <40 mL/min (%)	37 (50.7)	40 (52.6)	0.941
Mehran score (%)			0.571
0-5	20 (27.4)	21 (27.6)	
5-10	35 (47.9)	36 (47.4)	
11-16	18 (24.7)	17 (22.4)	
>16	0 (0)	2 (2.6)	
Mean	7.8±3.5	7.9±3.8	0.974
Previous medications (%)*			
ACEI or ARB	47 (64.4)	43 (56.6)	0.420
β-blocker	42 (57.5)	35 (46.1)	0.216
Calcium-channel blocker	34 (46.6)	36 (47.4)	0.919
Nitrate	37 (50.7)	43 (56.6)	0.485
Statin	37 (50.7)	43 (56.6)	0.640

BMI, body mass index; AMI, acute myocardial infarction; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker.

\*Medications prior to coronary angiography.

score, and previous medications. However, the nicorandil group had a trend toward a higher frequency of LVEF  $\leq 45\%$  compared to the control group (15.1% vs. 6.6%,  $p=0.159$ ).

### Contrast-induced nephropathy (CIN)

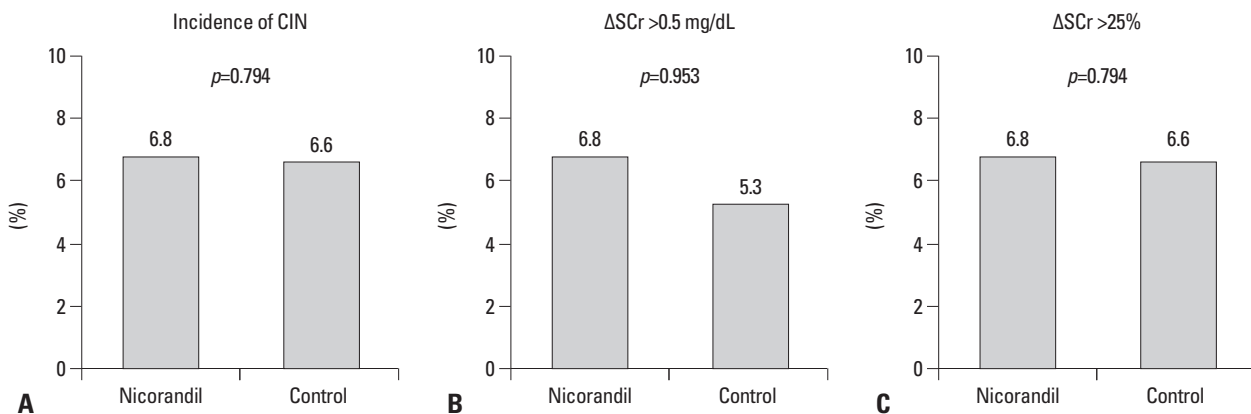
The procedural and biochemical characteristics are presented in Table 2. The frequency of percutaneous coronary intervention (PCI) (41.1% vs. 36.8%,  $p=0.716$ ) and the volume of contrast media (125.6 $\pm$ 69.1 mL vs. 126.9 $\pm$ 74.6 mL,  $p=0.916$ ) did not differ between the nicorandil and control groups, respectively. Baseline serum Cr (1.67 $\pm$ 0.67 mg/dL vs. 1.56 $\pm$ 0.45 mg/dL,  $p=0.173$ ) and cystatin C levels (1.42 $\pm$ 0.51 mg/L vs. 1.35 $\pm$ 0.47 mg/L,  $p=0.406$ ) were similar between the nicorandil and control groups. Serum Cr levels at

24 and 48 hours after the procedure did not show any significant difference between the two groups. The primary endpoint (incidence of CIN) was also similar between the nicorandil and control groups (6.8% vs. 6.6%,  $p=0.794$ ) (Fig. 1). The change in absolute serum Cr level within 48 hours after the exposure to contrast media showed significantly less change in the nicorandil group compared to the control group, respectively (-0.01 $\pm$ 0.43 mg/dL vs. 0.02 $\pm$ 0.31 mg/dL,  $p=0.005$ ). However, the relative changes in serum Cr from baseline to maximal Cr level within 48 hours were not significantly different between the nicorandil and control groups (-1.58 $\pm$ 24.07% vs. 0.96 $\pm$ 17.49%,  $p=0.464$ ). The absolute (0.08 $\pm$ 0.25 mg/L vs. 0.09 $\pm$ 0.15 mg/L,  $p=0.867$ ) and relative changes in the serum cystatin C levels (5.57 $\pm$

**Table 2.** Procedural and Biochemical Data before and after Coronary Angiography

	Nicorandil (n=73)	Control (n=76)	<i>p</i> value
PCI performed (%)	30 (41.1)	28 (36.8)	0.716
Contrast media			
Volume (mL)	125.6 $\pm$ 69.1	126.9 $\pm$ 74.6	0.916
Volume $\geq 150$ mL (%)	20 (27.4)	17 (22.4)	0.603
SCr			
Baseline, mg/dL	1.73 $\pm$ 0.60	1.61 $\pm$ 0.44	0.166
At 24 hrs	1.63 $\pm$ 0.72	1.55 $\pm$ 0.54	0.441
At 48 hrs	1.68 $\pm$ 0.78	1.58 $\pm$ 0.56	0.410
Peak within 48 hrs, mg/dL	1.72 $\pm$ 0.78	1.63 $\pm$ 0.57	0.469
Max absolute change, mg/dL	-0.01 $\pm$ 0.43	0.02 $\pm$ 0.31	0.005
Max relative change, %	-1.58 $\pm$ 24.07	0.96 $\pm$ 17.49	0.464
Cystatin C			
Baseline, mg/L	1.42 $\pm$ 0.51	1.35 $\pm$ 0.47	0.406
At 24 hrs	1.44 $\pm$ 0.55	1.40 $\pm$ 0.51	0.612
At 48 hrs	1.45 $\pm$ 0.64	1.38 $\pm$ 0.48	0.464
Peak within 48 hrs, mg/L	1.50 $\pm$ 0.60	1.45 $\pm$ 0.52	0.609
Max absolute change, mg/L	0.08 $\pm$ 0.25	0.09 $\pm$ 0.15	0.867
Max relative change, %	5.57 $\pm$ 15.89	6.66 $\pm$ 11.21	0.648

PCI, percutaneous coronary intervention; SCr, serum creatinine; Max, maximum.



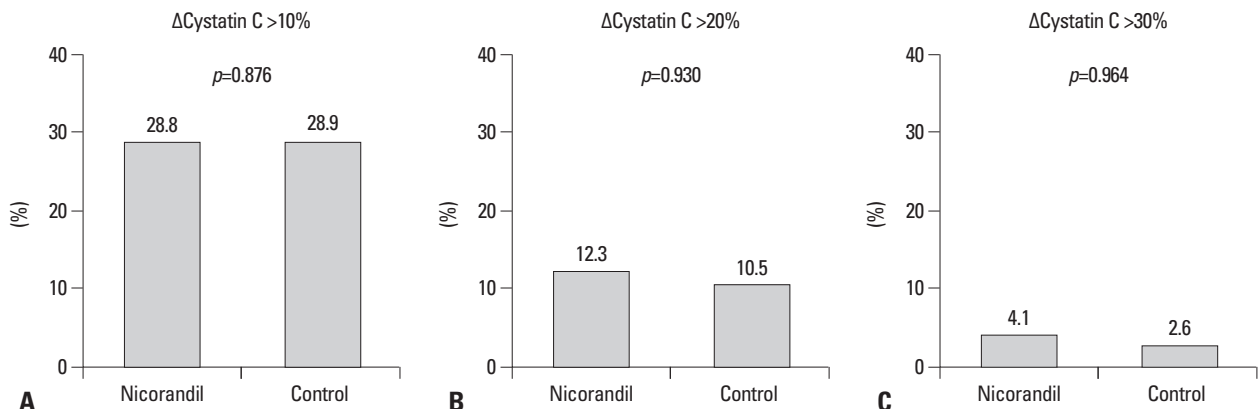
**Fig. 1.** Changes in serum creatinine levels. (A) Incidence of contrast-induced nephropathy. (B) Frequency of an increase in serum creatinine level >0.5 mg/dL from baseline. (C) Frequency of an increase in serum creatinine level >25% from baseline. CIN, contrast-induced nephropathy; SCr, serum creatinine.

15.89% vs. 6.66±11.21%,  $p=0.648$ ) were also similar between the two groups. The incidences of an increase in serum cystatin C levels >10%, >20%, and 30% from baseline were similar between the nicorandil and control groups (Fig. 2). In subgroups either with baseline eGFR >30 mL/min or with eGFR ≤30 mL/min, the incidences of CIN and the increase in serum cystatin C >10% did not differ between the nicorandil and control groups (Fig. 3). In the multivariate logistic regression analysis, the effect of the pretreatment with nicorandil on the development of CIN was evaluated

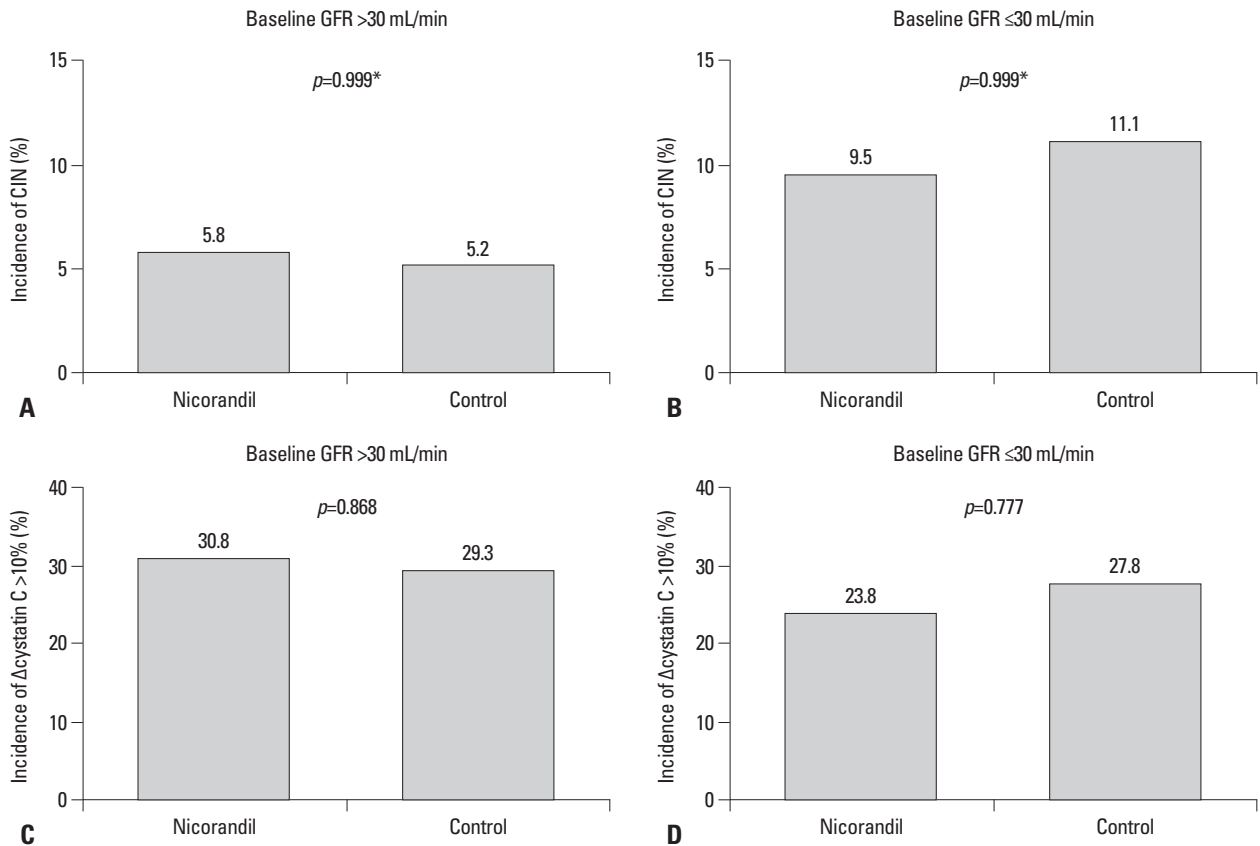
after adjusting for the influence of variables found to be associated with CIN in univariate analysis. These included age, sex, diabetes mellitus, acute coronary syndrome, baseline serum Cr, left ventricular ejection fraction <45%, and multivessel disease. The analysis showed that prophylactic pretreatment with nicorandil did not reduce the risk for CIN (Table 3).

**Clinical outcomes**

No symptoms or hemodynamic changes related to the in-



**Fig. 2.** Changes in serum cystatin C levels. Frequency of increases in serum cystatin C >10% (A), >20% (B), and >30% (C) from baseline.



**Fig. 3.** Incidences of CIN (A and C) and increase in serum cystatin C >10% from baseline (B and D) in patient subgroups with baseline glomerular filtration rate (GFR) >30 mL/min (A and B) and ≤30 mL/min (C and D). \*p value by Fisher exact test. CIN, contrast-induced nephropathy.

**Table 3.** Impact of the Pretreatment with Nicorandil on the Incidence of Contrast-Induced Nephropathy in a Logistic Regression Analysis after Adjustment of Covariates

	Crude OR			Adjusted OR		
	OR	95% CI	<i>p</i> value	OR	95% CI	<i>p</i> value
Pre-treatment						
Nicorandil	1.04	0.29-3.77	0.947	0.77	0.16-3.81	0.748
Covariates for adjustment						
Age	0.96	0.90-1.01	0.150	0.95	0.89-1.02	0.151
Sex	4.17	0.51-33.93	0.182	2.93	0.30-28.87	0.357
Diabetes mellitus	4.69	0.96-22.87	0.056	4.41	0.68-28.45	0.119
Baseline SCr	3.34	1.33-8.35	0.010	1.38	0.42-4.56	0.593
LVEF <45%	4.54	1.04-19.85	0.045	4.06	0.51-32.25	0.185
ACS	3.85	1.03-14.37	0.045	3.62	0.81-16.10	0.091
Multivessel disease	3.46	0.86-13.95	0.081	1.69	0.33-8.72	0.529

OR, odds ratio; CI, confidence interval; SCr, serum creatinine; LVEF, left ventricular ejection fraction; ACS, acute coronary syndrome. All variables found to be associated with contrast-induced nephropathy in univariate analysis with  $p < 0.2$  were included as covariates.

travenous administration of nicorandil were observed during and immediately after the intravenous nicorandil infusion. The length of hospital stay after the procedure did not differ between the nicorandil and control group, respectively ( $5.4 \pm 5.4$  days vs.  $4.7 \pm 4.4$  days,  $p = 0.399$ ). Major adverse events occurred in 3 patients (2 cardiac deaths and 1 dialysis) in the nicorandil group and in 2 patients (2 myocardial infarctions) in the control group ( $p = 0.974$ ). Acute pulmonary edema was observed in 2 of the 3 patients with major adverse events in the nicorandil group and in 1 of the 2 patients with major adverse events in the control group.

## DISCUSSION

This study evaluated whether pretreatment with single intravenous dose of nicorandil prevented CIN in patients with renal insufficiency undergoing coronary angiography. However, the results failed to identify any preventive pretreatment effect of nicorandil on the development of CIN.

Although the exact pathomechanisms of CIN is unknown, renal ischemia from an imbalance in vasodilatory and vasoconstrictive factors, as well as the direct toxic effects of contrast media on tubular epithelial cells, are thought to be involved in the development of CIN.<sup>6,7</sup> Normally, the majority of renal blood flow goes to the cortex, and only 10% is delivered to the medulla.<sup>7</sup> The deeper portion of the outer medulla is particularly vulnerable to ischemia because the epithelial cells of the thick ascending limb have a relatively high oxygen requirement in order to reabsorb salt. The complex interaction of vasodilators and vasoconstrictors modulates renal microcirculation in response to the metabolic re-

quirements of the kidney as a whole, and particularly the outer medulla.<sup>11</sup> Released by endothelial cells, endothelin and adenosine are strong vasoconstrictors in the kidney. NO and prostaglandin E2 act as potent vasodilators.<sup>12,13</sup> One study demonstrated that infusion of contrast media markedly decreased blood flow to both the cortex and medulla by decreasing activity of NO synthase and by increasing adenosine through hydrolysis of adenosine triphosphate (ATP).<sup>13</sup> Catabolism of adenosine generates ROS that scavenge NO. Induced by exposure to contrast media, release of endothelin and prostaglandin from endothelial cells and the increase in adenosine result in decreased blood flow and hypoxia in the medulla.<sup>7,14</sup>

Various preventive measures have been investigated to help prevent CIN. Diuretics, mannitol, dopamine, atrial natriuretic peptide, endothelin receptor antagonists, fenoldopam, theophylline, ascorbic acid, N-acetylcysteine, and statins have all been evaluated in well-designed, prospective, randomized, double-blinded trials, but either failed to show a positive impact on CIN prevention or remained controversial.<sup>6,15</sup> A recent study demonstrated that iloprost, an analog of prostacyclin, significantly reduced the risk of CIN in patients with renal insufficiency undergoing coronary angiography or intervention.<sup>16</sup> Trimetazidine, an anti-ischemic agent, has also shown to be effective in reducing the incidence of CIN in patients with pre-existing renal dysfunction.<sup>17</sup> The efficacy of these agents for the prevention of CIN requires further clinical validation. However, these studies indicate that anti-ischemic drugs may play a beneficial role in the prevention of CIN.

Nicorandil, a  $K_{ATP}$  channel opener and a NO donor, is currently used in the treatment of angina and acute heart

failure.<sup>8</sup>  $K_{ATP}$  channels, which are widely distributed in various tissues, respond to alterations in the metabolic activity of the cell and thereby act as sensors of glucose and oxygen availability.<sup>18,19</sup> Nicorandil has been found to prevent reperfusion injury and protect the heart against ischemic injury by promoting ischemic preconditioning.<sup>20</sup> A recent study showed that activation of  $K_{ATP}$  channels reduced renal injury due to ischemia and reperfusion by preventing the accumulation of reactive oxygen radicals in mitochondria.<sup>9</sup> Shimizu, et al.<sup>21</sup> found that the renal expression of  $K_{IR}6.2$  channels, a major subunit of the  $K_{ATP}$  channel, in the ischemia-reperfusion injury rats was significantly lower than in the control rats. However, the down-regulation of the  $K_{IR}6.2$  expression was reversed by administration of nicorandil. Nicorandil has also been reported to suppress renal synthesis of endothelin-1 and reduce proteinuria in patients with hypertension.<sup>22</sup>

Based on these observations, we hypothesized that nicorandil may protect the kidney from ischemic injury associated with the use of contrast media by inhibiting the accumulation of ROS, suppressing synthesis of endothelin-1, and inducing NO production. Despite these theoretical advantages, nicorandil did not demonstrate a preventive effect on CIN in this study. Several explanations can be speculated for the negative results of our study. First, nicorandil may not have a preventive effect on the development of CIN. However, intravenous nicorandil might be effective when administered at a different dose or frequency. The dose was derived from the regimen for the pretreatment of patients with ST-segment elevation myocardial infarction prior to reperfusion in a clinical study conducted by Ishii, et al.<sup>23</sup> Significantly improved clinical outcomes were reported after pretreatment with a single dose of intravenous nicorandil in patients undergoing primary PCI. Indeed the dose required for the prevention of CIN may be different from the dose used for protection from ischemia-reperfusion injury in the myocardium. Additionally, the majority (>75%) of the patients included in our study had Mehran scores  $\leq 10$  and belonged to relatively lower CIN risk groups. PCI was performed in 38.9% of the study patients, and only 24.8% of the enrolled patients required contrast media volume  $\geq 150$  mL. These circumstances possibly led to an incidence of CIN in the present study that was much lower than we had assumed for the calculation of the study sample size. Therefore, the present study was underpowered to evaluate the primary study objective. We cannot rule out the possibility that later measurements of serum creatinine and cystatin C may have

shown differences between the nicorandil and control groups since serum creatinine can peak later than 48 hours after the procedure. However, The Acute Kidney Injury Network criteria also suggested a period of 48 h for diagnosis to ensure that the process being diagnosed is acute and representative.<sup>24</sup> The most common definitions of CIN used in previous studies were based on the serial measurements of serum Cr with 48 hours after contrast exposure.<sup>25</sup> A recent study reported that measurement of cystatin C at 24 hours after administration of contrast agents was efficient for early detection of CIN.<sup>26</sup> In our study, there were no significant changes in serum cystatin C between the two groups.

In conclusion, this study did not demonstrate a preventive effect of single dose intravenous nicorandil on the development of CIN in patients undergoing coronary angiography or PCI. The role of anti-ischemic agents in the prevention of CIN needs to be investigated in further clinical trials.

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