Journal of the American College of Cardiology Vol. 49, No. 12, 2007

ISSN 0735-1097/07/$32.00
doi:10.1016/j.jacc.2006.11.034

The Reno-Protective Effect of Hydration With Sodium Bicarbonate Plus N-Acetylcysteine in Patients Undergoing Emergency Percutaneous Coronary Intervention

The RENO Study

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Objectives This study was designed to determine the effectiveness of a protocol for rapid intravenous hydration to prevent contrast-induced nephropathy (CIN) in patients undergoing emergency percutaneous coronary intervention (PCI).

Background Contrast-induced nephropathy frequently complicates PCI, resulting in prolonged hospitalization and increased in-hospital and long-term morbidity and mortality. Little is known regarding prevention of CIN in patients undergoing urgent PCI.

Methods We conducted a prospective, controlled, randomized, single-center trial in 111 consecutive patients with acute coronary syndrome undergoing emergency PCI. As part of the hydration therapy, 56 patients (group A) received an infusion of sodium bicarbonate plus N-acetylcysteine (N-AC) started just before contrast injection and continued for 12 h after PCI. The remaining 55 patients (group B) received the standard hydration protocol consisting of intravenous isotonic saline for 12 h after PCI. In both groups, 2 doses of oral N-AC were administered the next day.

Results The 2 groups were similar with respect to age, gender, diabetes mellitus, and baseline serum creatinine. A serum creatinine concentration >0.5 mg/dl from baseline after emergency PCI was observed in 1 patient in group A (1.8%) and in 12 patients in group B (21.8%; $p < 0.001$). Acute anuric renal failure was observed in 1 patient (1.8%) in group A and in 7 patients (12.7%) in group B ($p = 0.032$).

Conclusions Rapid intravenous hydration with sodium bicarbonate plus N-AC before contrast injection is effective and safe in the prevention of CIN in patients undergoing emergency PCI. (J Am Coll Cardiol 2007;49:1283–8) © 2007 by the American College of Cardiology Foundation

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Iodinated contrast media are being used increasingly in the catheterization laboratory during diagnostic catheterization and percutaneous coronary intervention (PCI). Contrast-induced nephropathy (CIN) is a major cause of morbidity and mortality associated with PCI (1). The overall incidence of CIN after PCI has been reported between 3.3% and 16.5% (1,2), although this figure increases up to 50% in high-risk patients (3). In Europe, CIN is the third highest cause of acute renal failure, accounting for 10% of all causes of hospital-acquired renal failure (4). Several therapies for preventing CIN have been tested in patients undergoing elective PCI, with differing results. Only intravenous hydration with saline has been shown repeatedly to provide effective and safe prophylaxis for CIN in these patients (5). In the pathogenesis of CIN, renal ischemia and free radical formation induced by the contrast medium play an important role (6). Based on the hypothesis that alkalizing the renal tubule should confer protection against CIN in a prospective trial, Merten et al. (7) compared hydration with intravenous sodium bicarbonate and sodium chloride starting 1 h before contrast exposition. They showed that intravenous hydration with sodium bicarbonate provides greater benefits in the prevention of CIN (1.7% vs. 13.6%, $p = 0.02$). The results from the study by Merten et al. (7) with bicarbonate have not been replicated by others. N-acetylcysteine (N-AC), a potent antioxidant either directly as a free radical scavenger or indirectly through glutation production (8,9), may play an additional role in the prevention of CIN. Although several studies on the prophylactic effect of N-AC have given conflicting results, recent studies support a dose-dependent effect (10–12), suggesting that a higher dose could be needed in high-risk patients, in whom greater amounts of contrast could be administered.

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Manuscript received August 16, 2006; revised manuscript received November 1, 2006, accepted November 16, 2006.

JACC Vol. 49, No. 12, 2007
March 27, 2007:1283–8

Abbreviations and Acronyms

ACS = acute coronary syndrome
BUN = blood urea nitrogen
CI = confidence interval
CIN = contrast-induced nephropathy
GFR = glomerular filtration rate
N-AC = N-acetylcysteine
OR = odds ratio
PCI = percutaneous coronary intervention
SCr = serum creatinine

Patients undergoing emergency PCI represent a high-risk population for CIN, as opposed to those undergoing elective PCI (13). Various conditions may contribute to renal injury in this setting (i.e., hypotension and exposure to large volumes of contrast media), along with difficulties in establishing a prophylactic therapy in the acute setting.

A rapid hydration with saline sodium bicarbonate, in addition to causing intravascular volume expansion, could provide additional effects over the free radical scavenger properties of N-AC. To assess the effectiveness and safety of a CIN prevention protocol with sodium bicarbonate hydration plus N-AC, we carried out the RENO (Reno-Protective Effect of Hydration With Sodium Bicarbonate Plus N-Acetylcysteine in Patients Undergoing Emergency Percutaneous Coronary Intervention) study, a randomized, single-blind, single-center trial in patients undergoing emergency PCI.

Methods

Patients. We prospectively studied 111 consecutive acute coronary syndrome (ACS) patients who were admitted to our coronary care unit between December 2004 and May 2005. All patients with myocardial infarction treated with primary PCI or rescue PCI, as well as patients with high-risk non–ST-segment elevation ACS needing urgent revascularization, were included. Urgent PCI was considered in high-risk non–ST-segment elevation ACS, defined by the following criteria: recurrent resting chest pain not responding to treatment, hemodynamic instability and cardiogenic shock, major arrhythmias, and early postinfarction unstable angina (14). In all cases, the coronary angiography was performed within the first 12 h from the onset of symptoms.

Cardiogenic shock was defined as prolonged hypotension (systolic blood pressure <90 mm Hg for at least 30 min) caused by severe left ventricular dysfunction or right ventricular infarction, requiring inotropic support medication and/or intra-aortic balloon pump to maintain a systolic blood pressure of ≥90 mm Hg (15).

There were no inclusion criteria based on glomerular filtration rate (GFR). Patients with end-stage renal failure on dialysis, uncontrolled hypertension (systolic blood pressure >160 mm Hg and/or diastolic blood pressure >100 mm Hg) and signs of cardiac failure not responding to medical treatment, known severe aortic valve stenosis (area <1.0 cm^2), allergy to iodated contrast or N-AC, and pregnancy were excluded from the study. The study protocol was reviewed and approved by the local ethics committee, and all patients gave written informed consent before the study entry.

Study protocol. Patients were randomly assigned to an active prophylactic treatment before PCI (group A) or to standard hydration after the procedure (group B). The patients allocated to group A received an initial intravenous bolus of 5 ml/kg/h of alkaline saline solution with 154 mEq/l of sodium bicarbonate in 5% glucose and H_2O (adding 77 ml of 1,000 mEq/l sodium bicarbonate to 433 ml of 5% glucose in H_2O) plus 2,400 mg of N-AC in the same solution over 1 h. In all patients, the bolus was administered in the 60 min preceding contrast injection. Afterward, patients received fluid therapy, without N-AC, at 1.5 ml/kg/h perfusion rate in the 12 h after the procedure plus 2 doses of 600 mg N-AC orally the next day. Patients in group B were treated according to our institution protocol with perfusion of isotonic saline (0.9%) at rate of 1 ml/kg/h for 12 h after PCI plus 2 doses of 600 mg N-AC orally the next day. In both groups, the maximum dose administered was that administered for patients weighing 100 kg.

There was no limitation in concomitant treatment, including diuretics and angiotensin-converting enzyme inhibitors, which were left to the discretion of the interventional and coronary care unit cardiologists. Only the patients were blinded and not told to which group they were randomized.

Coronary angiography was performed according to standard clinical practice using the femoral approach. The low-osmolality nonionic contrast medium Iomeprol (Iomeron, Bracco s.p.a, Milan, Italy) with 350 mg/ml of iodine content was used in all cases. All decisions regarding procedural hemodynamics, including contrast doses, were left to the discretion of the interventional cardiologist.

Serum creatinine (SCr) and blood urea nitrogen (BUN) concentrations were measured at admission, daily for the next 3 days, and on day 7 after the procedure. The GFR was calculated using the Modification of Diet in Renal Disease Study group equation (16). Likewise, arterial blood pH was assessed immediately before the procedure and 2 h thereafter. Diuresis was collected for 24 h after the procedure.

The primary end point was the development of acute CIN, defined as an absolute increase in SCr concentration of 0.5 mg/dl or more from baseline value in the 3 days after PCI (17–19). The following secondary end points were assessed: 1) other conventional definitions of CIN: an increase in SCr >25% over the baseline value and >50% over the baseline value, both within the first 3 days (6,19); and 2) adverse clinical events, including acute pulmonary edema during and after the procedure, acute anuric renal failure that did or did not result in temporary renal replacement therapy, and death in the 7 days after the procedure. Renal replacement therapy (hemodialysis or hemofiltration) was undertaken in patients with anuria (urine output <20 ml/h) despite the administration of more than 1 g intravenous furosemide and presence of volume overload and/or BUN >200 mg/dl.

Statistical analysis. We calculated the sample size of our study assuming a CIN rate of 20% in group B based on the rate previously reported by Marenzy et al. (13) in patients

undergoing primary PCI. For group A, patients treated with sodium bicarbonate and a high dose of N-AC, we assumed a CIN rate of 3%, similar to that reported by Briguori et al. (11) using high doses of N-AC (3.5%) and by Merten et al. (7) using sodium bicarbonate (1.7%). Analysis indicated that a sample size of 55 patients would be necessary in each arm to detect a statistically significant different with a power of 80%, with a type I error of 0.05.

Analysis was conducted on an intention-to-treat basis. Categorical variables were expressed as percentages and analyzed by chi-square or Fisher exact test as appropriate. Continuous variables were expressed as mean ± SD and compared with the *t* test, except levels of SCr and BUN, which were compared with the nonparametric Wilcoxon-Mann-Whitney *U* test. We used Spearman correlation coefficients to evaluate the relationship between volumes of contrast medium administered during procedure and maximum change in SCr from the baseline value in the first 3 days after PCI. A repeated-measures analysis of variance was used to test the interaction of treatment in the evolution of GFR during follow-up. Multivariate logistic regression analysis was performed to examine the effects of different possible confounding variables on the incidence of CIN. All statistical analyses were performed with the Statistical Package for the Social Sciences version 13.0 (SPSS Inc., Chicago, Illinois). A 2-sided p value of <0.05 was considered to be significant.

Results

Baseline characteristics. Of the 120 patients randomized, 111 (34 women, ages 65 ± 10 years) had SCr measurements completed and were included in the study. The baseline characteristics of the patients are shown in Table 1.

Treatment compliance. In group A, the therapy was discontinued prematurely in 2 patients; in 1 diabetic patient with severe left ventricular dysfunction, the protocol was stopped after bolus perfusion as a result of a pulmonary edema clinic just after a left ventriculography was performed. This patient required intravenous nitrates and furosemide and CIN developed afterward, with a maximum SCr of 1.7 mg/dl. The other case was a high-risk non–ST-segment elevation ACS patient with PCI on the right coronary artery, in whom perfusion was stopped 4 h after PCI subsequent to the development of a right ventricular infarction. Bolus administration of sodium saline was given before a new procedure was carried out because of an acute in-stent thrombosis that was treated with a new bare-metal stent; CIN did not develop in this patient.

Intervention data and analyses. There were no significant differences in SCr and BUN values measured immediately before the procedure (baseline) (Table 2). Arterial blood pH before the catheterization was similar in both groups (7.37 ± 0.04 in group A vs. 7.37 ± 0.04 in group B, p = 0.84). Two hours after contrast administration, patients in group A showed a serum alkalinization, whereas patients in group B experienced a decrease in serum pH (7.41 ± 0.03 vs. 7.36 ± 0.03 respectively, $p < 0.0001$) (Table 2).

Table 1 Baseline Characteristic of the Study Patients

	Group A n = 56	Group B n = 55	p Value
Age	65 ± 10	64 ± 9	0.92
Age ≥70 yrs	17 (30%)	18 (33%)	0.84
Gender, male	38 (68%)	39 (71%)	0.84
Hypertension	33 (60%)	32 (58%)	0.94
Diabetes mellitus	18 (32%)	15 (27%)	0.58
Dyslipidemia	32 (57%)	29 (52%)	0.64
Baseline serum creatinine (mg/dl)*	1.0 (0.8–1.1)	1.0 (0.9–1.2)	0.31†
Baseline glomerular filtration rate (ml/min)	75 ± 21	74 ± 20	0.82
History of congestive heart failure	6 (11%)	10 (18%)	0.26
History of myocardial infarction	14 (25%)	9 (16%)	0.26
Peripheral vascular disease	4 (7%)	5 (9%)	0.74
Previous treatment with ACE inhibitors	27 (48%)	23 (47%)	0.89
LVEF (%)	50 ± 11	51 ± 11	0.71
LVEF <40%	11 (20%)	8 (15%)	0.62
Previous chronic renal insufficiency	4 (7%)	5 (9%)	0.74
Glomerular filtration rate <60 (ml/min)	16 (29%)	14 (25%)	0.83
Anterior ischemia	27 (48%)	20 (36%)	0.21
STEMI	32 (57%)	34 (62%)	0.61
NSTEMI	24 (43%)	21 (38%)	0.61
Primary PCI	23 (41%)	25 (46%)	0.64
Rescue PCI	9 (16%)	9 (16%)	0.97
Cardiogenic shock	5 (9%)	4 (7%)	0.75

Plus-minus values are mean ± SD by Fisher exact test. Group A: sodium bicarbonate infusion plus high-dose N-acetylcysteine started just before procedure. Group B: standard hydration protocol. *Median and interquartile ranges. †By nonparametric Wilcoxon rank test.

ACE = angiotensin-converting enzyme; LVEF = left ventricular ejection fraction; NSTEMI = non–ST-segment elevation acute myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation acute myocardial infarction.

The diuresis measured in the 24 h after contrast infusion was significantly lower in group B than group A (1,955 ± 529 ml/24 h vs. 3,098 ± 693 ml/24 h, $p < 0.0001$). The mean contrast volume administered was not significantly different in group A versus group B (Table 2). However, when the response of individuals patients was assessed in each group, we found that in group B patients there was a higher change in SCr in patients who received a large volume of contrast medium ($r = 0.45$; $p < 0.0006$) (Fig. 1). In group A patients, however, no relationship was found between contrast volume administered and change in SCr levels ($r = 0.034$; $p = 0.80$).

CIN incidence and clinical outcomes. In a total of 13 patients CIN developed: 12 in group B (21.8%) and 1 (1.8%) in group A (difference 20%, 95% confidence interval [CI] 8% to 31%, $p = 0.0009$) with an odds ratio (OR) of 0.065 (95% CI 0.008 to 0.521, $p = 0.01$) for patients in group A. The absolute risk reduction of CIN in group A compared with group B was 20%, resulting in a number required to treat of 5 patients to prevent 1 case of CIN. In the multivariate analysis adjusted for age, baseline SCr, left

Table 2 Basal Renal Function, Contrast Volume, and Serum pH in Control Group and Treatment Group

	Group A	Group B	p Value
Baseline serum creatinine (mg/dl)*	1.0 (0.8–1.1)	1.0 (0.9–1.2)	0.31†
Baseline blood urea nitrogen (mg/dl)*	17.76 (14.02–22.20)	17.76 (16.01–21.03)	0.31†
Baseline glomerular filtration rate (ml/min)	75 ± 21	74 ± 20	0.82
Contrast volume (ml)	290 ± 114	279 ± 94	0.59
Precontrast serum pH	7.37 ± 0.04	7.37 ± 0.04	0.84
Postcontrast serum pH	7.41 ± 0.03	7.36 ± 0.03	<0.0001

To convert serum creatinine to μmol/l, multiply by 88.4. Plus-minus values are mean ± SD by Fisher exact test. *Median and interquartile ranges. †By nonparametric Wilcoxon rank test.

ventricular function, and volume of contrast medium, the OR in patients allocated to group A was 0.002 (95% CI 0.0004 to 0.102, p = 0.002). The incidences of CIN using different criteria are shown in Figure 2.

The difference found in CIN rates between groups was not related to depressed left ventricular function nor on baseline reduced renal function. No significant interactions were found between protocol and left ventricular function (p = 0.17) or GFR (p = 0.29).

The GFR measured at baseline was comparable in the 2 groups (74 ± 20 ml/min in the control group vs. 75 ± 21 ml/min in the treatment group, p = 0.82). As shown in Figure 3, in group B there was a significant deterioration of GFR that reached a trough at day 3 after the procedure, and there was a significant improvement in GFR in group A, evident from the first day (p < 0.009 for the trend).

There was a significant difference between groups in the rate of acute anuric renal failure, 7 patients (12.7%) and 1 patient (1.8 %) in groups B and A, respectively (p = 0.032, 95% CI 0.2 to 0.13). Four patients required renal replacement therapy, 3 in group B and 1 in group A. Acute renal failure developed in this latter patient more than 72 h after admission, and therefore did not meet criteria for CIN (Table 3).

Acute heart failure during the catheterization developed in 2 patients in group B and 1 in group A (3.6% vs. 1.8%, p = 0.62). The CIN developed during the monitoring in these 3 patients.

In our study, the global mortality was 4.5%, but we did not find a significant difference in global mortality during the 7 days of monitoring between groups, 1 patient in group A (died of cardiogenic shock) and 4 patients in group B (2 patients died of cardiogenic shock and 2 patients died of multiorgan failure) (Table 3).

Discussion

The results of our study suggest that in patients undergoing emergency PCI, rapid hydration with saline sodium bicarbonate and high doses of N-AC just before contrast injection reduce renal dysfunction and the rate of CIN as a result of reduced oxidative stress.

The overall incidence of acute pulmonary edema (2.7%) was similar to that reported in previous studies (7,10,13). It

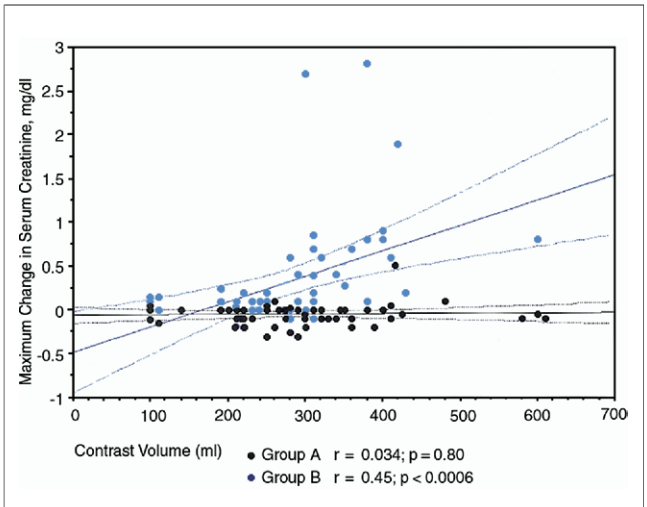

Figure 1 Volumes of Contrast Medium (ml) Correlated With Maximum Change in SCr 72 h After PCI

The **solid lines** represent the point estimated, and the **upper and lower lines** represent 2 SD. PCI = percutaneous coronary intervention; SCr = serum creatinine.

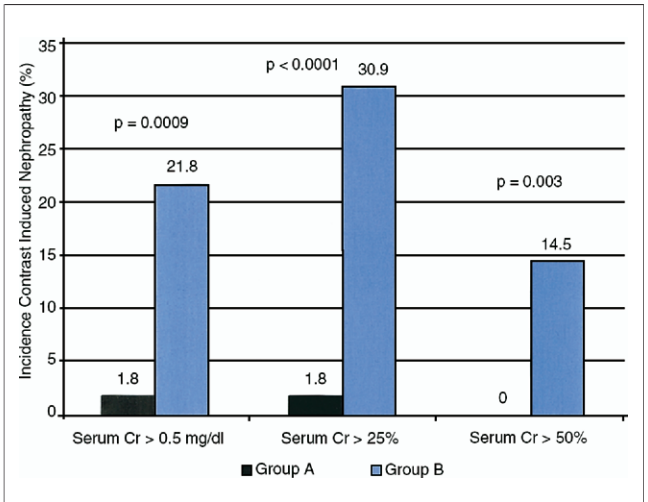

Figure 2 Incidence of Contrast-Induced Nephropathy Based on the Criteria Used

Cr = creatinine.

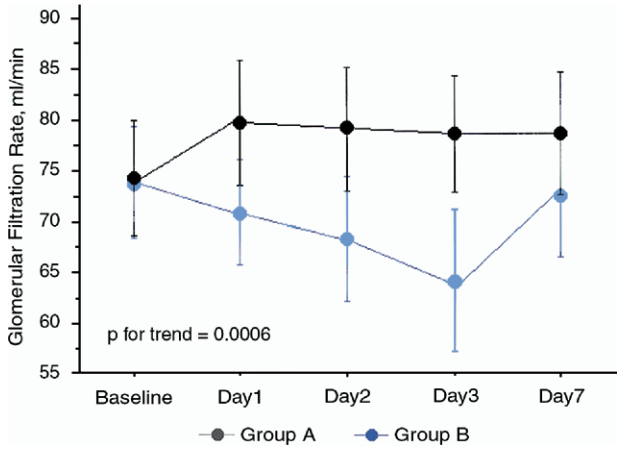

Figure 3 **Evolution of GFR at Baseline (Before PCI) and Days 1, 2, 3, and 7**

Data are mean ± 2 SD. GFR = glomerular filtration rate, estimated using the Levey formula (16); PCI = percutaneous coronary intervention.

is worth noting that the incidence of acute pulmonary edema did not differ between groups.

We used SCr for assessment of renal function. However, it is conceivable that cystatin C levels, a marker of GFR that is not affected by tubular transport, could have been a better indicator of kidney function (20).

Several studies have shown that CIN after an interventional procedure is a frequent complication associated with poor outcome (1,2,21). A standardized saline hydration strategy has been shown to be effective in decreasing the risk of CIN (17,22). Most studies have evaluated intravenous hydration regimens with saline at a rate of 1 ml/kg/h, 6 to 12 h before and after contrast exposure in patients undergoing elective procedures (11,23,24). Actually, international guidelines such as those of the European Society of Urogenital Radiology recommend the routine use of a hydration protocol before contrast exposition (18). Given the fact that an acidic environment promotes free radical formation, hydration with bicarbonate theoretically should be more effective, as proven by Merten et al. (7).

In patients at high risk of developing CIN, the addition of high-dose N-AC (1,200 mg twice both on the day before and the day after the procedure) could play an important role in CIN prevention (11,25,26). In this setting, Ochoa et al. (27) assessed that administration of high doses of N-AC with a shortened hydration protocol results in a notably lower incidence of CIN.

Critical patients, especially those with an ACS undergoing primary PCI or urgent procedures, constitute a group at high risk of developing CIN (28,29). This also holds true for patients with normal renal function, in whom higher morbidity and mortality rates are found (13). In our study, the incidence of CIN was significantly higher in patients in group B, allocated to standard hydration after PCI, as compared with group A, in which patients received high doses of N-AC plus an infusion of sodium bicarbonate just before contrast injection. This fact was related to a higher, although not significant, incidence of acute renal failure requiring renal replacement therapy and mortality, and both were similar to previously reported data (12,30–32).

Several conditions contribute to renal damage: hemodynamic instability and hypotension with reduced cardiac output, metabolic acidosis secondary to myocardial infarction (33), the use of large volumes of contrast media, and difficulties in establishing a prophylactic therapy in the acute setting. In patients undergoing emergency PCI, hypotension and reduced cardiac output, as well certain degree of dehydration secondary to vomiting and diaphoresis, could contribute to prerenal azotemia. We found a relatively high BUN level at baseline in both groups, with levels toward the upper limit of normal, but with normal SCr levels. This prerenal azotemia seems to play an important role in the activation of tubuloglomerular feedback and the renin-angiotensin system. The rapid bicarbonate infusion, with the subsequent volume expansion, could stimulate diuresis, diluting circulating contrast medium and vasoconstriction mediator concentrations and preventing activation of tubuloglomerular feedback (34).

The generation of reactive oxygen species formed as a result of postischemic oxidative stress, a pH-dependent reaction, is known to play a pathogenic role in CIN. In patients undergoing emergency PCI, this oxidative stress could be increased because of metabolic acidosis secondary to myocardial ischemia (6).

Recently Marenzi et al. (12) have shown a dose-dependent effect of N-AC for the prevention of CIN in patients undergoing primary angioplasty. In this study, patients allocated to receive high doses of N-AC (1,200-mg intravenous bolus of N-AC just before contrast medium injection plus 1,200 mg orally twice daily for the 48 h after PCI) showed a CIN rate of 8% in contrast to 33% of the patients in the control group ($p < 0.001$). As CIN criteria, they used a SCr increase of 25% or more from baseline.

For the same CIN criteria, our study shows a similar incidence of CIN in group B, but with an interesting

Table 3 **Incidence of CIN and Clinical Outcomes**

	Group A	Group B	p Value
Incidence of CIN (serum creatinine ≥0.5 mg/dl)	1 (1.8%)	12 (21.8%)	0.0009*
Acute pulmonary edema	1 (1.8%)	2 (3.6%)	0.62
Anuric acute renal failure	1 (1.8%)	7 (12.7%)	0.032†
Acute renal failure requiring renal replacement therapy	1 (1.8%)	3 (5.5%)	0.36
Mortality at 7 days	1 (1.8%)	4 (7.3%)	0.21

By Fisher exact test. *95% confidence interval 0.08 to 0.31. †95% confidence interval 0.2 to 0.13. CIN = contrast-induced nephropathy, absolute increase in serum creatinine ≥0.5 mg/dl from baseline.

reduction of CIN in group A. We are aware that our relatively small sample size calls for caution in the interpretation of the results, and that our findings need to be confirmed in large multicenter studies.

Our study suggests that a rapid hydration with saline sodium bicarbonate provides a cumulative effect over reactive oxygen species scavenging properties of N-AC, reducing the formation of these reactive oxygen species.

Study limitations. The relative limitations of our study are those inherent in a single-blind, single-center study with a small sample size. Thus, these findings should be confirmed in a larger multicenter trial.

Conclusions. In conclusion, this study shows that a systematic protocol of a rapid intravenous hydration with sodium bicarbonate plus high doses of N-AC is an effective and safe approach in preventing CIN in patients undergoing urgent PCI.

Acknowledgments

The authors acknowledge assistance of the staff of the catheterization and coronary care unit, and Maria Dolores Mellado and Mireia Bastante for their contributions.

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