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Renal Insufficiency After Contrast Media Administration Trial II (REMEDIAL II)

RenalGuard System in High-Risk Patients for Contrast-Induced Acute Kidney Injury

Carlo Briguori, MD, PhD; Gabriella Visconti, MD; Amelia Focaccio, MD; Flavio Airoldi, MD; Marco Valgimigli, MD, PhD; Giuseppe Massimo Sangiorgi, MD; Bruno Golia, MD; Bruno Ricciardelli, MD; Gerolama Condorelli, MD, PhD; for the REMEDIAL II Investigators

Background—The RenalGuard System, which creates high urine output and fluid balancing, may be beneficial in preventing contrast-induced acute kidney injury.

Methods and Results—The Renal Insufficiency After Contrast Media Administration Trial II (REMEDIAL II) trial is a randomized, multicenter, investigator-driven trial addressing the prevention of contrast-induced acute kidney injury in high-risk patients. Patients with an estimated glomerular filtration rate ≤ 30 mL · min^{-1} · 1.73 m^{-2} and/or a risk score ≥ 11 were randomly assigned to sodium bicarbonate solution and N-acetylcysteine (control group) or hydration with saline and N-acetylcysteine controlled by the RenalGuard System and furosemide (RenalGuard group). The primary end point was an increase of ≥ 0.3 mg/dL in the serum creatinine concentration at 48 hours after the procedure. The secondary end points included serum cystatin C kinetics and rate of in-hospital dialysis. Contrast-induced acute kidney injury occurred in 16 of 146 patients in the RenalGuard group (11%) and in 30 of 146 patients in the control group (20.5%; odds ratio, 0.47; 95% confidence interval, 0.24 to 0.92). There were 142 patients (48.5%) with an estimated glomerular filtration rate ≤ 30 mL · min^{-1} · 1.73 and 149 patients (51.5%) with only a risk score ≥ 11. Subgroup analysis according to inclusion criteria showed a similarly lower risk of adverse events (estimated glomerular filtration rate ≤ 30 mL · min^{-1} · 1.73 m^{-2}: odds ratio, 0.44; risk score ≥ 11: odds ratio, 0.45; P for interaction=0.97). Changes in cystatin C at 24 hours (0.02 ± 0.32 versus -0.08 ± 0.26; $P=0.002$) and 48 hours (0.12 ± 0.42 versus 0.03 ± 0.31; $P=0.001$) and the rate of in-hospital dialysis (4.1% versus 0.7%; $P=0.056$) were higher in the control group.

Conclusion—RenalGuard therapy is superior to sodium bicarbonate and N-acetylcysteine in preventing contrast-induced acute kidney injury in high-risk patients.

Clinical Trial Registration—URL: http://www.clinicaltrial.gov. Unique identifier: NCT01098032.

(*Circulation*. 2011;124:00-00.)

Key Words: complications ■ contrast media ■ kidney ■ prevention

Contrast-induced acute kidney injury (CI-AKI) is a powerful predictor of unfavorable early and late outcomes.[1–3] Although still controversial,[4,5] several studies have shown the advantages of CI-AKI prophylaxis with N-acetylcysteine (NAC)[6] and sodium bicarbonate solution.[7,8] In the Renal Insufficiency After Contrast Media Administration Trial I (REMEDIAL I) trial, we demonstrated that the combined strategy of volume supplementation with sodium bicarbonate solution and NAC was superior to the administration of normal saline and NAC alone or a combination of normal saline, ascorbic acid, and NAC in preventing CI-AKI in patients at low to medium risk.[8] However, in high-risk patients, the rate of CI-AKI remains high.[3] Data from the Prevention of Radiocontrast Induced Nephropathy Clinical Evaluation (PRINCE) study indicate that increasing the urine flow rate (≥ 150 mL/h) reduces the toxic effect of contrast media (CM).[9] Currently, a forced diuresis regimen is usually achieved by administering high doses of furosemide. Theoretically, furosemide should protect the kidney by reducing the outer medullary hypoxia caused by CM by blocking the Na-K-2Cl transporter in the medullary thick ascending limb.[10] This approach, however, has actually been shown to

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From the Laboratory of Interventional Cardiology and Department of Cardiology, Clinica Mediterranea, Naples (C.B., G.V., A.F., B.G., B.R.); Laboratory of Interventional Cardiology IRCCS Multimedica, Milan (F.A.); Cardiovascular Research Centre, University of Ferrara, Ferrara (M.V.); Division of Cardiology, University of Modena-Reggio Emilia, Modena (G.M.S.); and Department of Cellular and Molecular Biology and Pathology, "Federico II" University of Naples (G.C.), Italy.

Correspondence to Carlo Briguori, MD, PhD, Interventional Cardiology, Clinica Mediterranea, Via Orazio, 2, I-80121, Naples, Italy. E-mail carlobriguori@clinicamediterranea.it

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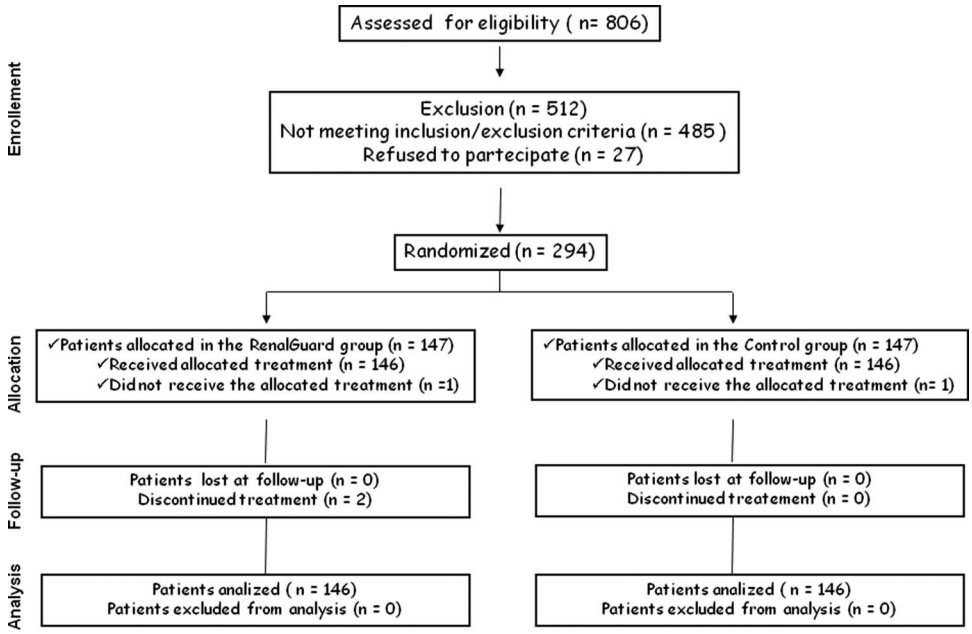

Figure 1. Diagram showing the flow of participants through each stage of the trial according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

be deleterious and to increase the rates of CI-AKI.[11] It has been suggested that the deleterious effect observed is a result of a negative fluid balance.[11,12] The availability of a device that would guide the physician in achieving high urine output while simultaneously balancing urine output and venous fluid infusion to prevent hypovolemia would be the ideal solution. Preliminary data suggest that the RenalGuard System may have these properties.[13]

Editorial see p ●●●
Clinical Perspective on p ●●●

Methods

Patient Population

This multicenter, randomized, investigator-driven study compared 2 different strategies to prevent CI-AKI in patients at high risk. The design of the REMEDIAL II trial has previously been reported.[14] Briefly, all consecutive patients with chronic kidney disease scheduled for coronary and/or peripheral angiography and/or angioplasty with an estimated glomerular filtration rate (eGFR) $\leq$30 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ and/or a risk score $\geq$11 were considered eligible for the study (Figure 1). The eGFR was calculated by applying the Levey-modified Modification of Diet in Renal Disease formula: $(186.3 \times \text{serum creatinine}^{-1.154}) \times (\text{age}^{-0.203}) \times (0.742$ if female).[15] Chronic kidney disease was defined as an eGFR <60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$. The risk score for predicting CI-AKI was calculated according to the following algorithm: hypotension (integer score 5), intra-aortic balloon pump support (integer score 5), congestive heart failure (integer score 4), age $>$75 years (integer score 4), diabetes mellitus (integer score 3), eGFR <60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ (integer score 2 to 6), preexisting anemia (integer score 3), and CM volume (integer score 1 for each 100 cm^3). The global scores $\leq$5, 6 to 10, 11 to 16, and $\geq$16 predict a CI-AKI risk of 7.5%, 14%, 26.1%, and 57.3%, respectively.[16]

Recruitment, Enrollment, and Allocation

All patients with chronic kidney disease scheduled for coronary and/or peripheral angiography/angioplasty from January 2009 to December 2010 were screened for inclusion/exclusion criteria (Figure 1). Exclusion criteria were acute myocardial infarction; acute pulmonary edema; cardiogenic shock; dialysis; multiple myeloma; administration of sodium bicarbonate, theophilline, dopamine, mannitol, and/or fenoldopam; recent ($\leq$48 hours) administration of iodinated CM; and current enrollment in any other study when enrollment in the REMEDIAL II would involve deviation from either protocol. All patients who met the inclusion/exclusion criteria and signed an informed consent were enrolled in the study. Patients were randomized according a computer-generated randomization list. The REMEDIAL II trial was conducted in 4 interventional cardiology centers in Italy according to the principles of the Declaration of Helsinki[17] and Good Clinical Practice[18] and has been approved by our ethics committees. The trial was registered with http://www.clinicaltrial.gov (trial identifier: NCT01098032).

Protocol

After enrollment, patients were randomly assigned to either the control group or the RenalGuard group (Figure 1). Both therapies were instituted before and after administration of the contrast agent. The left ventricular end-diastolic pressure was measured by a pigtail catheter at the beginning of the procedure.

Control Group

Patients allocated to this group received 154 mEq/L sodium bicarbonate in dextrose and H_2O, according to the protocol reported by Merten et al.[7] The initial intravenous bolus was 3 mL/kg per hour for at least 1 hour before contrast injection. Then, all patients received the same fluid at a rate of 1 mL/kg per hour during contrast exposure and for 6 hours after the procedure. All patients enrolled in this group received NAC (Fluimucil, Zambon Group SpA, Milan, Italy) orally at a dose of 1200 mg twice daily the day before and the day of administration of the contrast agent (for a total of 2 days).[19] In this group, an additional NAC dose (1200 mg diluted in 100 mL normal saline) was administered intravenously during the procedure. The total NAC dose was $\geq$6 g.

RenalGuard Group

Patients enrolled in this group were treated by hydration with normal saline plus NAC controlled by the RenalGuard system (PLC Medical Systems, Inc, Franklin, MA). The characteristics of this system have previously been reported.[14] This RenalGuard system includes a closed-loop fluid management system, a high-volume fluid pump, a

Table 1. Clinical Characteristics of the Patients Enrolled in the 2 Groups

	Control Group (n=146)	RenalGuard Group (n=146)
Age, y	75±9	76±8
Male, n (%)	103 (70.5)	88 (60.5)
Weight, kg	78±15	77±14
Height, m	1.65±0.7	1.65±0.7
Body mass index, kg/m^2	29±5	28±5
Blood pressure, mm Hg		
Systolic	152±27	152±27
Diastolic	78±10	77±13
Mean	103±13	102±15
LV ejection fraction, %	48±10	46±11
LV end-diastolic pressure, mm Hg	14±7	14±7
LV dysfunction and/or unstable hemodynamic conditions, n (%)	41 (28)	42 (29)
LV ejection fraction, %	36±8	36±10
LV ejection fraction ≤30%, n (%)	20 (13.5)	22 (15)
Systemic hypertension, n (%)	144 (98)	143 (98)
Diabetes mellitus, n (%)	104 (71)	101 (69)
Peripheral chronic artery disease, n (%)	27 (18.5)	28 (19)
Drugs, n (%)		
ACE inhibitor	67 (46)	70 (48)
Calcium channel blocker	44 (30)	36 (25)
Angiotensin II receptor inhibitor	45 (31)	42 (29)
Diuretics	85 (58)	93 (64)
β-blockers	88 (60)	92 (63)
Statins	111 (76)	108 (74)
Procedure performed, n (%)		
Coronary angiography	60 (41)	51 (35)
PCI	58 (40)	71 (49)
Coronary angiography and ad hoc PCI	17 (12)	11 (7.5)
Peripheral procedure	11 (6)	13 (9)
Volume of contrast media, mL	145±79	135±76
Contrast ratio >1, n (%)	35 (24%)	28 (19)

LV indicates left ventricular; ACE, angiotensin-converting enzyme; and PCI, percutaneous coronary intervention.

Table 2. Clinical Characteristics of the Patients Enrolled in the 2 Groups

	Control Group (n=146)	RenalGuard Group (n=146)
Serum creatinine, median (range), mg/dL	1.79 (1.15–3.85)	1.80 (1.15–4.78)
eGFR, mL[·]min^{-1}·1.73 m^{-2}	32±7	32±9
Contrast nephropathy risk score	12±2	12±3
≤5, n (%)	3 (2)	2 (1.5)
≥6–10, n (%)	18 (13)	27 (19)
≥11–15, n (%)	103 (72.5)	95 (67)
≥16, n (%)	18 (12.5)	17 (12)
Serum urea nitrogen, mg/dL		
Baseline	78±31	80±35
After 48 h	70±30	71±35
Serum sodium, mEq/L		
Baseline	140±5	140±3
After 2 h	140±5	141±4
After 6 h	139±5	140±5
After 24 h	139±3	141±5
After 48 h	139±6	140±5
Serum potassium, mEq/L		
Baseline	4.7±0.7	4.6±0.7
After 2 h	4.4±0.7	4.1±0.7
After 6 h	4.4±0.6	4.2±0.6
After 24 h	4.3±0.6	4.1±0.6
After 48 h	4.3±0.6	4.2±0.6
Serum magnesium, mg/dL*		
Baseline		1.91±0.4
After 2 h		1.71±0.4
After 6 h		1.72±0.4
After 24 h		1.76±0.4
After 48 h		1.83±0.4

eGFR indicates estimated glomerular filtration rate.
*Serum magnesium was measured in 137 patients.

high-accuracy dual weight measuring system, motion-detection artifact reduction, a single-use intravenous set and urine collection system that interfaces with a standard Foley catheter, real-time display of urine and replacement fluid volume, timely alerts to drain the urine bag or to replace the hydration fluid bag, and safety features such as automatic air and occlusion detection. An initial bolus (priming) of 250 mL was infused over 30 minutes (preprocedural phase). In the presence of left ventricular dysfunction (ejection fraction ≤30% as assessed by 2-dimensional echocardiography) and/or unstable hemodynamic conditions (recent [<7 days] pulmonary edema or acute heart failure), priming was reduced to ≤150 mL. After the priming, furosemide (0.25 mg/kg) was administered intravenously to achieve an optimal urine flow of ≥300 mL/h. As soon as the urine flow reached the target value, the patient was moved into the catheterization laboratory, and the procedure was started (procedural phase). Controlled hydration by the RenalGuard system continued during the procedure and for 4 hours after the procedure (postprocedural phase). Urine flow was monitored and maintained at the target value throughout the procedure and during the next 4 hours. Additional furosemide doses were allowed in instances when there was a decrease in urine flow below the target value. In the RenalGuard group, NAC was administered only intravenously (1500 mg in 1 L saline) during the 3 phases (preprocedural, intraprocedural, and postprocedural) of the RenalGuard therapy. The conventional oral regimen was not used in the RenalGuard group because this is part of the conventional prophylactic approach.

Biomarkers of Kidney Function

Serum creatinine (sCr), serum cystatin C (sCyC), blood urea nitrogen, sodium, and potassium were measured the day before the procedure and at 2, 6, 12, 24, and 48 hours and 1 week after administration of the contrast agent. Additional measurements were performed in all instances when there was a deterioration of baseline renal function. In the RenalGuard group, magnesium was also dosed the day before and at 2, 6, 24, and 48 hours after the procedure (Dimension Clinical Chemistry System, Siemens Healthcare Diagnostics Inc, Newark, NJ). Urinary pH was measured at the time of enrollment and during treatment (in the control group, after infusion of the bolus when the patient spontaneously voided; in the RenalGuard group, soon after the optimal urine flow was achieved).

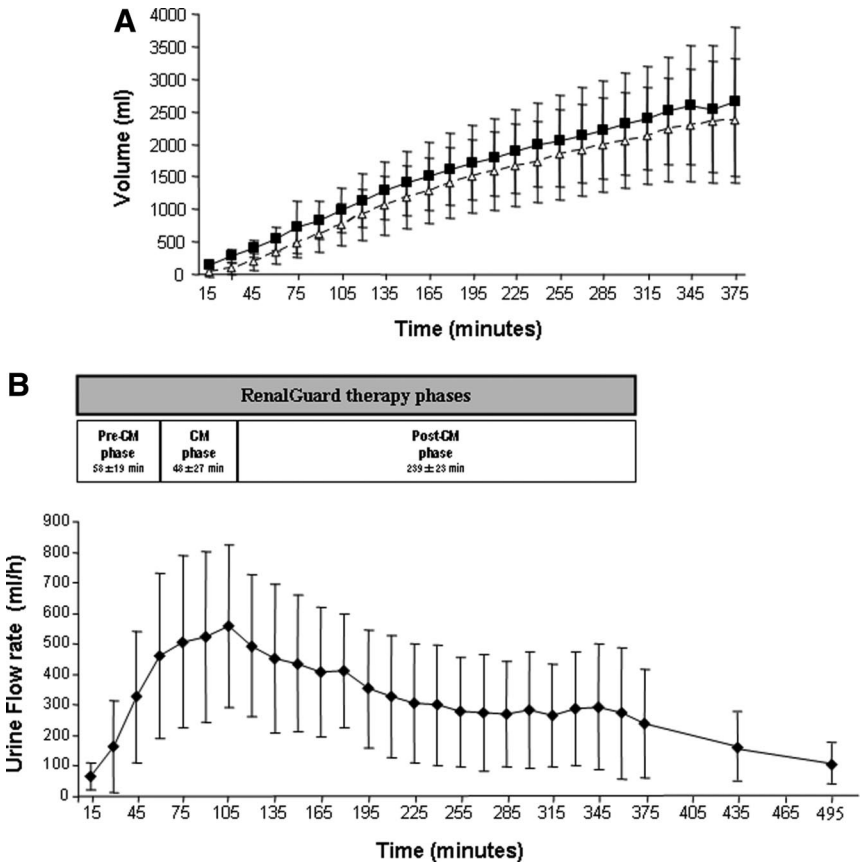

Figure 2. A, Temporally matched fluid replacement during treatment by using the RenalGuard system (continuous line indicates infusion; dashed line, urine). **B**, Mean urine flow in the RenalGuard group. Urine output (mL/h) was recorded every 15 minutes during RenalGuard therapy and every hour after RenalGuard interruption. Pre-CM phase indicates precontrast media exposure or preprocedural time; CM phase, contrast media exposure or intraprocedural time; and post-CM phase, postcontrast media or postprocedural time.

Contrast Agents

Iodixanol (Visipaque, GE; a nonionic, iso-osmolar (290 mOsm per 1 kg water) contrast agent was used in all patients.

Study End Points

The primary outcome measure was the development of CI-AKI, defined as an increase in sCr concentration ≥0.3 mg/dL above the baseline value at 48 hours after administration of CM or the need for dialysis.[20] Secondary end points reported here are an increase in sCr concentration ≥25% and ≥0.5 mg/dL at 48 hours after CM exposure, changes in the sCyC concentration at 24 and 48 hours after contrast exposure, the rate of acute renal failure requiring dialysis (defined as a decrease in renal function necessitating acute hemodialysis, ultrafiltration, or peritoneal dialysis within the first 5 days after intervention), and the rate of in-hospital and 1-month major adverse events. Major adverse events were considered to be death, renal failure requiring dialysis, and acute pulmonary edema. The severity of AKI was also assessed according to the Acute Kidney Injury Network criteria: stage 1, an sCr increase of ≥0.3 mg/dL from baseline or ≥1.5 to 1.9 times baseline; stage 2, an sCr increase of ≥2.0 to 2.9 times baseline; and stage 3, an sCr increase of ≥3.0 times baseline or the need for dialysis.[20]

Data Collection and Monitoring

Patient demographic details, medical history, current medication, eGFR, risk score for CI-AKI, and left ventricular ejection fraction were recorded at baseline. Total hydration volume administered according to the prophylaxis and total urine volume were recorded. The preprocedural sCr level was considered to be that before the initiation of any prophylaxis. All adverse events were recorded on the case report form, and the data coordinating center was informed by facsimile within 72 hours of any events. Serious adverse events and any other safety issues were reviewed by an independent Data Monitoring and Safety Committee. All events were adjudicated by a Clinical Events Committee, and members were blinded to treatment assignment.

Statistical Analysis

The treatment assignment between the 2 groups was determined by randomization in a 1:1 ratio. To ensure that almost equal numbers of patients receive each of the 2 treatments, a randomization block of 4 was used (Plan Procedure of SAS, version 8.2). The sample size was selected to demonstrate a reduction in the primary end point of CI-AKI from 25% in the control group to 10% in the RenalGuard group.[1,3,16,21,22] With the use of a 2-sided χ^2 test with a significance

Table 3. Characteristics of Patients Who Developed Acute Pulmonary Edema

Patient	Group	Age, y	Sex	LVEF, %	LVEDP, mm Hg	GFR, mL[·]min^{-1}·1.73 m^{-2}	SBP, mm Hg	Risk Score	Contrast Volume, mL	CI-AKI
1	Control	61	M	42	14	40	110	12	200	Yes
2	RenalGuard	80	F	55	12	35	120	15	250	No
3	RenalGuard	86	F	45	12	36	130	12	150	No
4	RenalGuard	81	F	43	13	35	120	13	250	No

LVEF indicates left ventricular ejection fraction; LVEDP, left ventricular end-diastolic pressure; GFR, glomerular filtration rate; SBP, systolic blood pressure before the procedure; and CI-AKI, contrast-induced acute kidney injury.

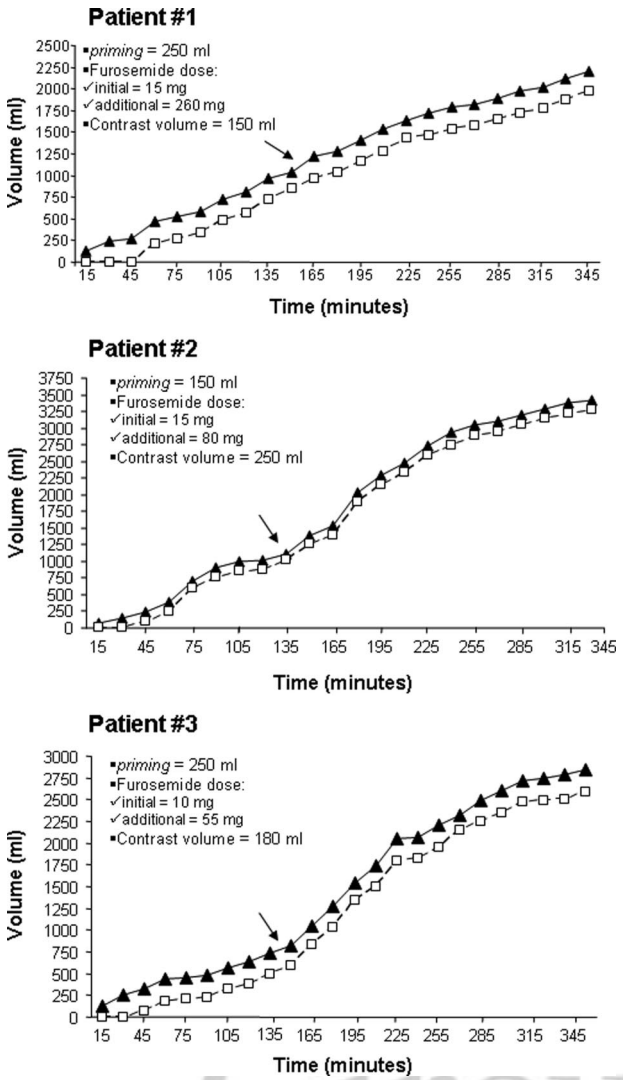

Figure 3. Fluid match in the 3 patients who developed acute pulmonary edema in the RenalGuard group. Pulmonary edema (arrow) occurred in all instances soon after the end of the coronary procedure. ▲ Indicates infusion volume; □, urine volume.

level of 0.05, a total of at least 266 randomized patients (133 in each arm) provided the study 90% power.

Continuous variables are given as mean±SD or median and first and third quartiles when appropriate. The Student *t* test and the nonparametric Mann-Whitney tests were used to determine differences between mean values for normally and nonnormally distributed variables, respectively. Categorical variables were reported as percentage and were analyzed by either the χ^2 or Fisher exact test as appropriate. To test the impact of prophylactic regimen (as defined by the 2 groups of treatment) on rate of CI-AKI, we used repeated measures ANOVA models after transforming sCr and sCyC levels into a natural logarithm (to overcome the problem of nonnormal distribution). In the ANOVA model, we considered the treatment strategy (as defined in the control group and RenalGuard group), time period, and time×treatment strategy interaction as fixed effects and patients as a random effect. Values of $P<0.05$ were considered significant throughout the analysis. Data were analyzed with SPSS 13.0 (SPSS Inc, Chicago, IL) for Windows.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Patient Population

Two enrolled patients did not undergo the scheduled treatment because of fever (n=1 in the control group) and gastrointestinal bleeding (n=1 in the RenalGuard group; Figure 1). The clinical and biochemical characteristics were well matched between the 2 groups (Tables 1 and 2). There were 142 patients (48.5%) with an eGFR ≤30 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ regardless of their risk score (68 in the control group and 75 in the RenalGuard group), whereas 149 patients (51.5%) had only a risk score ≥11 (78 in the control group and 71 in the RenalGuard group; $P=0.41$). The mean eGFR in the subgroup who met only the risk score criterion was 38±8 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ (quartiles 1 to 3, 33–50 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$).

Prophylaxis Regimen

The total volume of intravenous hydration associated with the treatment regimen was higher in the RenalGuard group (2312 mL [quartiles 1 to 3, 1928 to 2999 mL] versus 1438 mL [quartiles 1 to 3, 1390 to 1487 mL]; $P<0.001$). In the RenalGuard group, the priming volume was 250 mL (quartiles 1 to 3, 200 to 250 mL), whereas the furosemide dose to reach the target urine flow was 14±8 mg (quartiles 1 to 3, 0 to 50 mg). In the 42 patients with left ventricular dysfunction and/or unstable hemodynamic conditions, priming volume was 150 mL (quartiles 1 to 3, 150 to 200 mL). In the RenalGuard group, we observed highly accurate, temporally matched fluid replacement during the treatment (Figure 2A), and the mean urine flow was 352±131 mL/h (quartiles 1 to 3, 99 to 778 mL/h; Figure 2B). The target urine flow was reached in the 93% of patients (mean value, 416±119 mL/h), whereas in the remaining 7%, it was constantly below the target during the treatment (mean, 177±48 mL/h). In 13 patients (9%), the target urine flow was reached and maintained after the priming bolus alone without the need for any furosemide administration. On the contrary, additional doses of furosemide (25±35 mg [quartiles 1 to 3, 5 to 260 mg]) were necessary during the treatment in 42.5% of patients owing to the occurrence of urine flow reduction below the target value or pulmonary edema. The length of RenalGuard therapy was on average 5 hours 75 minutes (range, 3 to 9 hours). The preprocedural phase (ie, the time needed to reach the target urine flow rate) was 58±19 minutes (quartiles 1 to 3, 30 to 120 minutes); the intraprocedural time was 48±27 minutes (quartiles 1 to 3, 15 to 150 minutes); and the postprocedural time was 239±23 minutes (quartiles 1 to 3, 135 to 265 minutes; Figure 2B). Urine pH increased significantly in the control group (5.4±0.4 to 6.0±0.6; $P<0.001$), whereas it remained unchanged in the RenalGuard group (5.5±0.6 to 5.5±0.5; $P=0.38$). The NAC dose was higher in the control group than in the RenalGuard group (6.0±0.5 versus 4.5±0.9; $P<0.001$).

Pulmonary edema occurred in 3 patients (2.1%) in the RenalGuard group versus 1 patient (0.7%) in the control group ($P=0.62$). In all instances, pulmonary edema occurred after the coronary procedure. The characteristics of these 4 patients are shown in Table 3 and Figure 3. Four patients

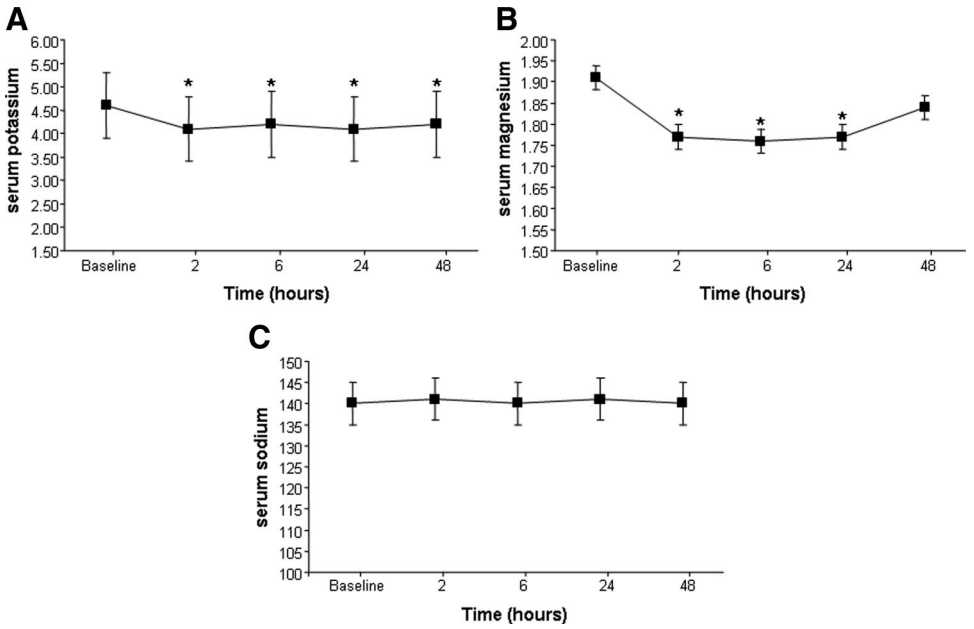

Figure 4. Serum electrolytes changes in the RenalGuard group, **A**, Potassium; **B**, magnesium; **C**, sodium. *$P<0.05$ vs baseline.

(2.7%) in the RenalGuard group experienced pain on micturition caused by the Foley catheter; in 1 patient, it was necessary to interrupt the RenalGuard therapy prematurely at 2.5 hours after the procedure. Changes in serum electrolytes in the RenalGuard group are shown in Figure 4. Asymptomatic hypokalemia (serum potassium <3.5 mEq/L) occurred in 12 patients (8.2%) in the control group and 11 patients (7.5%) in the RenalGuard group (Table 2). Potassium replacement occurred in 3 patients (2.1%) in the control group and in 6 patients (4.1%) in the RenalGuard group ($P=0.50$). Hypomagnesemia (serum magnesium <1.7 mg/dL) occurred in 16 patients (11.5%) in the RenalGuard group; none of them, however, had severe (<1.0 mg/dL) hypomagnesemia. No patients developed hypernatremia.

Contrast-Induced Acute Kidney Injury

The sCr kinetic in the 2 groups is given in Figure 5. As Figure 6A shows, CI-AKI was lower in the RenalGuard group (11%) than in the control group (20.5%). Subgroup analysis according to inclusion criteria (ie, eGFR ≤ 30 mL · min^{-1} · 1.73 m^{-2} and risk score ≥ 11) showed a similarly lower risk of adverse events compared with the control group (Figure 6B). The distribution of different cutoffs of sCr increase at 48 hours is given in Table 4. In the RenalGuard group, 8 of the 16 patients (50%) who developed CI-AKI had a mean urine flow rate $\geq$300 mL/h during the treatment period. Furthermore, 11 of these patients (75%) had a mean urine flow rate $\geq$150 mL/h.

The majority of patients in the 2 groups had a mild (stage 1) AKI (control group, 23 of 30 patients [77%] versus RenalGuard group, 15 of 16]94%[); more severe (stage 2 and 3) damage occurred more often in the control group (7 of 30 patients [23%] versus 1 of 16 patients [6%]; $P=0.14$). The rate of in-hospital renal failure requiring dialysis occurred in 6 patients in the control group (4.1%) compared with 1 patient in the RenalGuard group (0.7%; $P=0.056$; odds ratio, 0.16; 95% confidence interval, 0.02 to 1.13).

Values of sCyC were available for 137 patients in each group. Values of sCyC increased significantly more in the control group than in the RenalGuard group (Figure 7). The distribution of different cutoffs of sCyC increase at 24 and 48 hours is given in Table 4.

Length of in-hospital stay (from admission to discharge) was similar in the 2 groups (control group, 6.7±6.7 days versus RenalGuard group, 7.2±7.1 days; $P=0.39$). On the contrary, length of in-hospital stay (from admission to discharge) was longer in patients who developed CI-AKI (10±7 versus 6.5±6.7 days; $P=0.008$). The 1-month major adverse

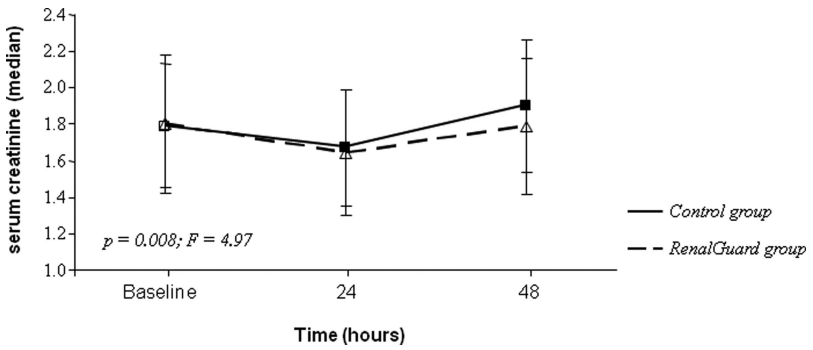

Figure 5. Serum creatinine concentration at baseline and 24 and 48 hours after contrast media administration in the control (continuous line) and RenalGuard (dashed line) groups. $P=0.008$; $F=4.97$ by repeated measures ANOVA.

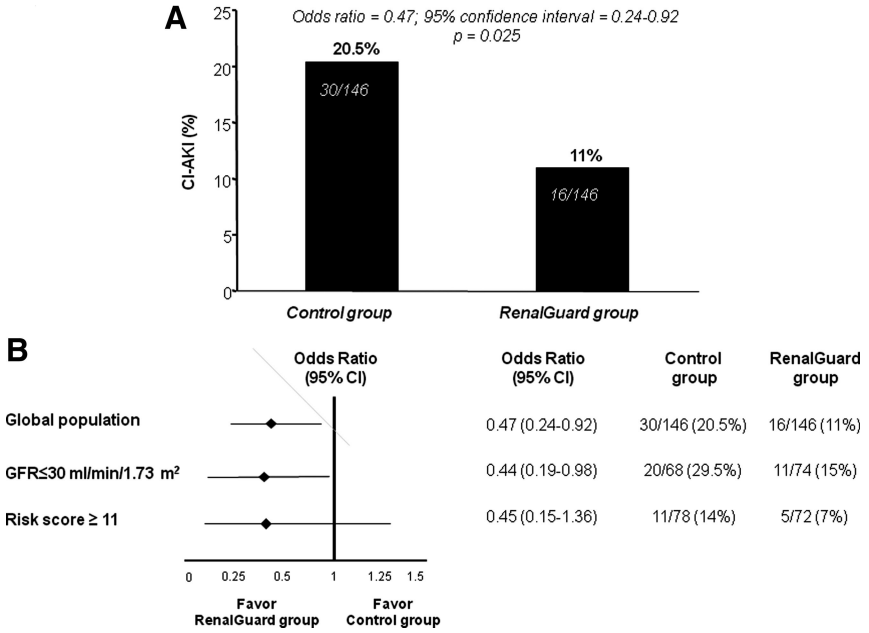

Figure 6. Incidence of contrast-induced acute kidney injury (CI-AKI) in the control and RenalGuard groups. **A**, All enrolled patients; **B**, patients stratified according to enrollment criteria: estimated glomerular filtration rate (eGFR) ≤30 mL · min^{-1} · 1.73 m^{-2} regardless of the risk score and risk score ≥11 alone with eGFR >30 mL · min^{-1} · 1.73 m^{-2}.

event rate was 9.6% (14 of 146) in the control group versus 6.8% (10 of 146) in the RenalGuard group (P=0.52; Table 5). All 8 patients who needed dialysis within 1 month had developed CI-AKI. Furthermore, the 1-month death rate was higher (although not statistically significant) in patients who developed CI-AKI (3 of 46 [6.5%] versus 9 of 246 [3.6%]; P=0.41).

Discussion

The main results of the REMEDIAL II trial are that the RenalGuard therapy (hydration with saline and NAC at a high dose plus a low dose of furosemide controlled by the RenalGuard system) is superior to the combination of sodium bicarbonate solution and NAC at a high dose in preventing CI-AKI in patients with GFR ≤30 mL · min^{-1} · 1.73 m^{-2} and/or a risk score ≥11 and that the majority of patients (93%) in the RenalGuard group reached the target urine flow rate ≥300 mL/h with a limited furosemide dose and without significant impairment in electrolytes balance.

Prophylactic Strategies for Contrast-Induced Acute Kidney Injury

The present trial compares 2 different approaches for preventing CI-AKI: controlled forced diuresis and conventional hydration with sodium bicarbonate solution. In both strategies, a high dose of NAC was also administered. Although the effectiveness of NAC in preventing CI-AKI is still controversial, its antioxidant and antiapoptotic properties may have a clinically appreciable effect in high-risk patients.[23–25]

Data from the PRINCE study indicate that increasing the urine flow rate (≥150 mL/h) reduces the toxic effect of CM.[9] Indeed, a secondary analysis of the PRINCE study demonstrated that no patient with a mean urine flow rate >150 mL/h developed acute renal failure with the need for dialysis. The high urine flow rate may reduce the incidence of CI-AKI via a combination of its known physiological effects,[26,27] including a lower concentration of CM in the kidneys, a more rapid transit of CM through the kidneys, less overall exposure to toxic CM, a potential reduction of oxygen consumption in the medulla, and maintenance of flow in the renal tubules and collecting ducts, which reduces sludging and precipitation of CM in tubular cells. Preclinical testing in a canine model supported the ability of matched hydration to blunt the decrease in renal function after CM exposure.[28] However, concerns regarding both volume overload and high furosemide dose have precluded attempts to confirm this hypothesis in the clinical setting until now. Indeed, previous studies that included hydration and forced diuresis did not always show favorable outcomes.[11] The major reasons were the lack of adequate matching between hydration and urine flow[29] and the high diuretic dose used, potentially forcing diuresis too drastically.[30]

The RenalGuard System, with its matched fluid replacement capability, enables the physician to achieve high urine output safely with a low furosemide dose by maintaining the intravascular volume and minimizing the risk of overhydration or underhydration.[13,31] We observed highly accurate, temporally matched fluid replacement during the treatment (Figure 2A). In the pilot clinical trial, a 250-mL bolus of saline, along with the administration of up to 0.5 mg/kg furosemide, was used to create a high urine rate, and matched replacement helped maintain high urine output (620±400 mL/h) without the risk of overhydration or underhydration.[13] The protective action of the sodium bicarbonate solution in preventing CI-AKI has not been determined. The higher amount of HCO_3^- in the proximal convoluted tubule may buffer the higher amount of H^+ as a result of cellular hypoxia and/or facilitate Na^+ reabsorption through the electrogenic Na^+/HCO_3^- cotrasposter.[32] In addition, differences in tubuloglomerular feedback activation related to characteristic intrarenal hormonal environments created by different sodium salt solutions may have a role.[33]

In the present study, we demonstrated that the approach of controlled, forced diuresis with RenalGuard therapy is more

Table 4. Distribution of the Changes in Serum Creatinine and Cystatin C Levels in the 2 Groups

	Control Group (n=146)	RenalGuard Group (n=146)	*P*
Changes in creatinine at 48 hours			
Absolute difference from baseline, mg/dL	0.14±0.46	−0.05±0.32	<0.001
Increase ≥25%, n (%)	19 (13)	4 (2.7)	
Increase ≥50%, n (%)	11 (7.5)	1 (0.7)	
Increase ≥0.5 mg/dL, n (%)	22 (15)	9 (6)	
Changes in cystatin C at 24 h*			
Absolute difference from baseline, mg/dL	0.02±0.32	−0.08±0.26	0.002
Increase ≥0.3 mg/dL, n (%)	21 (15.5)	11 (8.5)	
Increase ≥10%, n (%)	33 (24)	22 (16)	
Increase ≥15%, n (%)	23 (17)	17 (12)	
Increase ≥25%, n (%)	14 (10)	5 (3.5)	
Changes in cystatin C a 48 h*			
Absolute difference from baseline, mg/dL	0.12±0.42	−0.0±0.3	0.001
Increase ≥0.3 mg/dL, n (%)	29 (21)	16 (12)	
Increase ≥10%, n (%)	47 (34)	29 (22)	
Increase ≥15%, n (%)	35 (25.5)	21 (16)	
Increase ≥25%, n (%)	23 (17)	11 (8.5)	

*Serum cystatin C values were available in 137 patients in each group.

effective in preventing CI-AKI in high-risk patients. In the RenalGuard group, we observed a 53% relative risk reduction rate compared with the control group. Subgroup analysis according to inclusion criteria (ie, eGFR ≤30 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ and risk score ≥11) showed a similarly lower risk of adverse events compared with the controls. The beneficial effect was also documented by a lower severity of kidney damage, a lower rate of in-hospital dialysis, and a smaller increase in sCyC in the RenalGuard group than in the control group. Cystatin C is a marker of renal function that is superior to sCr in detecting both chronic and acute changes in GFR.[34,35]

Urine Flow Rate and Side Effects

In the RenalGuard group, 8 of the 16 patients (50%) who developed CI-AKI had a mean urine flow rate ≥300 mL/h during the treatment period. Furthermore, 11 of those patients (75%) had a mean urine flow rate ≥150 mL/h. These data indicate that the beneficial effect may be due to furosemide. By blocking the Na-K-2Cl transporter in the medullary thick ascending limb, furosemide reduces outer medullary hypoxia caused by CM.[10] In addition, in this subset of patients, additional strategies (other than increasing urine flow rate) should be attributed to RenalGuard therapy in the prevention of CI-AKI. Plus, the extremely sensitive definition of CI-AKI used in this trial did not exclude the possibility that there were non–CM-related causes for the increase in sCr.

Table 5. Major Adverse Events at 1 Month in the 2 Groups

	Control Group (n=146), n (%)	RenalGuard Group (n=146), n (%)	*P*
Cumulative major adverse events	14 (9.6)	10 (6.8)	0.52
Death	6 (4.1)	6 (4.1)	1.00
Dialysis	7 (4.8)	1 (0.7)	0.031
Acute pulmonary edema	1 (0.7)	3 (2.1)	0.62

The high urine flow rate obtained in the present study may raise concerns regarding the potential hazards of hypovolemia and impairment in electrolyte balance. However, no clinically significant changes in electrolyte balance were documented, and the highly accurate, temporally matched fluid replacement observed reduced the risk of hypovolemia. On the contrary, we observed a slightly higher rate of pulmonary edema in the RenalGuard group. The reported rate of pulmonary edema in patients treated by saline infusion for the prevention of CI-AKI ranges from 0% to 11%; the highest rate has been reported in high-risk patients[21] such as those enrolled in the present trial. We observed a perfect temporally matched fluid replacement even in the 3 patients who developed acute pulmonary edema. Interestingly, all patients experienced clinical signs of pulmonary edema after the coronary intervention, suggesting a potential role of the volume of CM. These data support the concept that the suggested priming volume (250 mL) should be reduced not only in patients with left ventricular dysfunction and/or unstable hemodynamic conditions (as we did in the present study) but also when the expected final volume of CM is higher than recommended. The larger volume infused in the RenalGuard group and variations of extracellular or intracellular volume expansion affected by infusion of the 2 different sodium solutions could be responsible for this side effect. It has been demonstrated that short-term infusion of similar volumes of various sodium solutions (like NaCl or $NaHCO_3$) determines

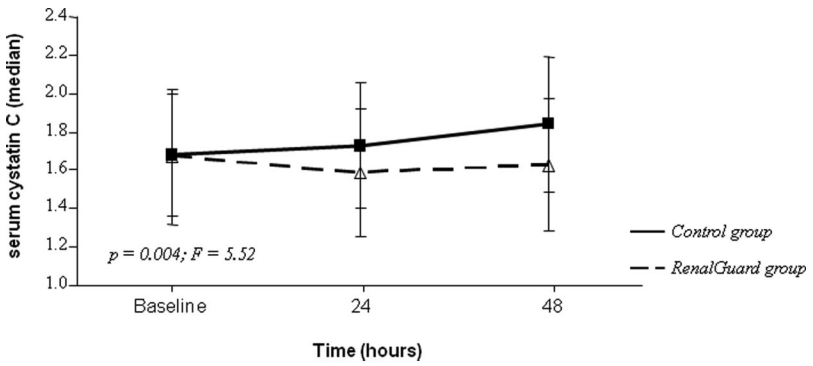

Figure 7. Serum cystatin C concentration at baseline and 24 and 48 hours after contrast media administration in the control (continuous line) and RenalGuard (dashed line) groups. *P*=0.004; *F*=5.52 by repeated measures ANOVA.

a similar degree of extracellular volume expansion.[33,36] Experimental studies showed that an equal infusion of chloride and nonchloride sodium salts resulted in a greater GFR increase for the chloride- but not for the nonchloride-expanded animals.[33] This is due to inhibition of the tubuloglomerular feedback in the chloride sodium salt group.[33]

Study Limitations

We performed an open-label study because blinding of both the patient and the operator was not feasible. The study was powered on CI-AKI (ie, an increase ≥0.3 mg/dL of sCr concentration within 48 hours) but not on hard clinical end points (namely dialysis and death); this may explain the lack of differences between groups in respect to hard clinical outcomes. However, CI-AKI predicts poor clinical outcome and therefore is accepted as a surrogate marker. In addition, assessment of sCyC overcomes the limitation of sCr as a marker of kidney damage. The larger NAC exposure in the control group might provide an advantage to this group over the RenalGuard group; this reinforces the better prophylactic effectiveness of the RenalGuard therapy. However, in the control group, NAC was administered mostly orally, whereas in the RenalGuard group, NAC was administered only intravenously. Because of the limited bioavailability of the oral form, it may be that the intravenous administration of NAC is more effective in preventing kidney damage. Finally, the results of the present study refer to patients with an eGFR ≤ 30 mL $\cdot$ min^{-1} $\cdot$ 1.73 m^{-2} and/or risk score ≥11. This subset represents ≈30% of all patients with chronic kidney disease assessed for eligibility during the study period. In this subgroup of patients, the effectiveness of hemofiltration has been reported.[21] However, the applicability of this approach to current clinical practice is unclear. Hemofiltration is expensive and logistically cumbersome, and its effectiveness compared with other less expensive strategies is not well established.[37]

Conclusions

RenalGuard therapy, including hydration with normal saline plus high doses of NAC in combination with a limited (0.25 mg/kg) dose of furosemide, seems to be an effective renoprotective strategy for patients at high risk for CI-AKI. The preliminary results of the Matched Hydration Compared to Standard Hydration for Contrast-Induced Nephrophaty Prevention (MYTHOS) trial support the effectiveness of the RenalGuard system also in patients with less severe chronic kidney disease (ie, eGFR <60 mL $\cdot$ min^{-1} $\cdot$ 1.73 m^{-2}). Indeed, the rate of CI-AKI was 16% in the group treated with standard hydration and 5% in the RenalGuard group.[31] Additional studies are warranted to define the role of RenalGuard therapy in preventing CI-AKI, taking into account both safety and cost-effectiveness.

Disclosures

None.

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CLINICAL PERSPECTIVE

The use of the RenalGuard System to create high urine output and fluid balancing may be beneficial in preventing contrast-induced acute kidney injury (CI-AKI). Patients with an estimated glomerular filtration rate ≤ 30 mL $\cdot$ min^{-1} $\cdot$ 1.73 m^{-2} and/or a risk score ≥ 11 were randomly assigned to sodium bicarbonate solution and N-acetylcysteine (control group) or the RenalGuard therapy, ie, hydration with saline and N-acetylcysteine controlled by the RenalGuard System and furosemide (RenalGuard group). Contrast-induced acute kidney injury (defined as an increase of ≥ 0.3 mg/dL in the serum creatinine concentration at 48 hours after the procedure) occurred in 16 of 146 patients in the RenalGuard group (11%) and in 30 of 146 patients in the control group (20.5%; $P=0.025$; odds ratio, 0.47; 95% confidence interval, 0.24 to 0.92). Serum cystatin C values ($P=0.004$; $F=5.52$ by ANOVA model) and the rate of in-hospital dialysis (4.1% versus 0.7%; $P=0.056$) were higher in the control group. RenalGuard therapy is superior to sodium bicarbonate and N-acetylcysteine in preventing contrast-induced acute kidney injury in high-risk patients. The present study supports that concept that increasing the urine flow rate reduces the toxic effect of contrast media. The RenalGuard system is helpful in guiding the physician in achieving high urine output (≥ 300 mL/h) while simultaneously balancing urine output and venous fluid infusion to prevent hypovolemia.