Editorial

Minimizing the Renal Toxicity of Iodinated Contrast

Peter A. McCullough, MD, MPH; Sherezade Khambatta, DO, MHA; Ayad Jazrawi, MD

A substantial proportion of adults with coronary disease are at risk for contrast-induced acute kidney injury (CI-AKI), manifested primarily by underlying chronic kidney disease, defined as an estimated glomerular filtration rate <60 mL $\cdot$ min^{-1} $\cdot$ /1.73^{-2}.[1] Although patients commonly understand that they have heart disease, studies have shown that $<10\%$ of those with chronic kidney disease are actually aware of this problem; thus, if not emphasized by the cardiologist during the consent before angiography, CI-AKI may come as a surprise to patients and their families after the procedure.[2–4] All forms of intravascular iodinated contrast are very water soluble, freely filtered by the glomerulus, and avidly taken up by renal tubular cells in the loop of Henle, and are retained in patients with chronic kidney disease within tubular cells and the peritubular space for ≈7 days where there is direct oxidative cellular damage, sloughing of renal tubular cells and brush border material, and acute tubular dysfunction.[5] Thus, the interest in reducing CI-AKI and its translation, if any, into improved clinical outcomes after angiography and coronary intervention have long been of interest among interventional cardiologists.

Articles see p 1250 and p 1260

In the current issue of *Circulation* are reports from 2 randomized trials using very different approaches in an attempt to reduce CK-AKI. The Acetylcysteine for Contrast-Induced Nephropathy (ACT) Trial Investigators[6] present the largest randomized, placebo-controlled trial to date of short-term, oral *N*-aceytlcysteine 1200 mg twice a day given before and after angiography. In convincing fashion, this high dose of *N*-aceytlcysteine did not reduce rates of CK-AKI (12.7% for both groups) as assessed with a single postprocedural creatinine value at ≈58 hours after contrast exposure. The trial recruited moderate-risk subjects (estimated glomerular filtration rate, ≈69 mL $\cdot$ min^{-1} $\cdot$ /1.73^{-2}; ≈60% with diabetes mellitus; 100 cm^3 of contrast) and was internally consistent, with no significant differences in primary or alternative definitions of CI-AKI or clinical outcomes. The implications of this adequately powered, well-conducted clinical trial are clear: The short-term use of *N*-aceytlcysteine for the prevention of CI-AKI in clinical practice should be abandoned. For researchers, this trial should invoke a check-down on all the reasons for neutral findings, including reconsideration of the therapeutic agent, dose, duration, and measurement of end points. *N*-acetylcysteine has favorable renal hemodynamic effects, acts as a relatively weak antioxidant, and therefore remains an attractive therapeutic target.[7] Future CI-AKI trials should consider longer treatment periods, more extensive collection of biomarkers, and relevant clinical end points.

The second trial reported in this issue is the Renal Insufficiency Following Contrast Media Administration (REMEDIAL II) trial, which, in high-risk subjects (estimated glomerular filtration rate, ≈32 mL $\cdot$ min^{-1} $\cdot$ /1.73^{-2}; ≈70% with diabetes mellitus; ≈140 cm^3 of contrast) tested a strategy of forced diuresis using large volumes of intravenous crystalloid and low-dose loop diuretic combined with a device (RenalGuard, PLC Medical, Franklin, MA) that controls an intake/output matching algorithm and induces supraphysiological urine flow rates.[7] With this strategy, subjects randomized to the device achieved a urine flow rate of ≈350 mL/min compared with an unspecified but expected <150 mL/h in the control group. Using 2 different biomarkers (creatinine and cystatin C) measured at multiple time points out to 7 days, the investigators showed that there were lower rates of CI-AKI (11.0% versus 20.5%; relative risk reduction, 63%; $P=0.025$) and clinical events in the experimental arm. This prevention strategy theoretically works to reduce contrast exposure and reuptake by renal tubular cells and to accelerate its urinary elimination. This trial could have been improved with an attempt to measure the radiographic degree of residual contrast in the kidneys and the quantity of contrast removed by urinary losses.[8,9] If these 2 measures were consistent with the biochemical results, then the therapeutic concept would have been solidified. Considering these shortcomings, the authors and investigators should be congratulated on completing a difficult protocol, addressing safety concerns and logistical difficulties, and bringing a relatively clear result to the clinical and research community. For very high-risk patients, forced diuresis appears to have merit conceptually and is worthy of consideration in a large, definitive-outcomes trial.

In summary, the ACT trial will influence clinical practice by dissuading interventional cardiologists and other operators from the routine use of short-term *N*-aceytlcysteine and stimulate researchers to test antioxidants for much longer durations of therapy to match the time iodinated contrast is present in the renal tubular cells and peritubular space. The REMEDIAL II trial should encourage investigators to consider reducing nephrotoxicity by reducing the transit time and opportunity for tubular uptake of contrast using forced diuresis in patients with severe baseline chronic kidney disease. The forced diuresis approach should be balanced by

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the St. John Providence Health System, Providence Hospital and Medical Center, Southfield; Providence Park Heart Institute, Novi; and St. John Hospital and Medical Center, Detroit, MI.

Correspondence to Peter A. McCullough, MD, MPH, FACC, FACP, FAHA, FCCP, Consultant Cardiologist, Chief Academic and Scientific Officer, St. John Providence Health System, Providence Park Heart Institute, 47601 Grand River Ave, Ste B-125, Novi, MI 48374. E-mail peteramccullough@gmail.com

(*Circulation*. 2011;124:1210-1211.)

***Circulation* is available at http://circ.ahajournals.org**
DOI: 10.1161/CIRCULATIONAHA.111.054502

the risks of precipitating pulmonary edema or electrolyte shifts with this high-volume/high-output strategy. Finally, future research can be enhanced by creative measures giving insights into mechanism of benefit, by using complementary modalities, and of course by the power of large-scale trials that give valid and definitive results that change clinical practice.[10]

Disclosures

None.

References

1. McCullough PA. Beyond serum creatinine: defining the patient with renal insufficiency and why? *Rev Cardiovasc Med*. 2003;4(suppl 1):S2–S6.
2. Saab G, Whaley-Connell AT, McCullough PA, Bakris GL. CKD awareness in the United States: the Kidney Early Evaluation Program (KEEP). *Am J Kidney Dis*. 2008;52:382–383.
3. Whaley-Connell, Saab G, Szpunar S, Stevens L, Shlipak M, Bomback A, Tamura MK, McFarlane S, Li S, Chen SC, Collins A, Norris K, Bakris G, McCullough PA; KEEP Investigators. Disease state awareness, kidney disease, and relationship to ESRD and death. Presented at: National Kidney Foundation 2011 Spring Clinical Meetings; April 24–30, 2011; Las Vegas, NV.
4. Agrawal V, Ghosh AK, Barnes MA, McCullough PA. Awareness and knowledge of clinical practice guidelines for CKD among internal medicine residents: a national online survey. *Am J Kidney Dis*. 2008;52:1061–1069.
5. McCullough PA. Radiocontrast-induced acute kidney injury. *Nephron Physiol*. 2008;109:61–72.
6. ACT Investigators. Acetylcysteine for prevention of renal outcomes in patients undergoing coronary and peripheral vascular angiography: main results from the Randomized Acetylcysteine for Contrast-Induced Nephropathy Trial (ACT). *Circulation*. 2011;124:1250–1259.
7. Brigouri C, Visconti G, Focaccio A, Airoldi F, Valgimigli M, Sangiorgi GM, Golia B, Ricciardelli B, Condorelli G; for the REMEDIAL II Investigators. Renal Insufficiency After Contrast Media Administration Trial II (REMEDIAL II): RenalGuard system in high-risk patients for contrast-induced acute kidney injury. *Circulation*. 2011;124:1260–1269.
8. Older RA, Korobkin M, Cleeve DM, Schaaf R, Thompson W. Contrast-induced acute renal failure: persistent nephrogram as clue to early detection. *AJR Am J Roentgenol*. 1980;134:339–342.
9. Love L, Johnson MS, Bresler ME, Nelson JE, Olson MC, Flisak ME. The persistent computed tomography nephrogram: its significance in the diagnosis of contrast-associated nephrotoxicity. *Br J Radiol*. 1994;67:951–957.
10. McCullough PA. Multimodality prevention of contrast-induced acute kidney injury. *Am J Kidney Dis*. 2008;51:169–172.

KEY WORDS Editorials ■ contrast media ■ kidney diseases ■ renal insufficiency

Acetylcysteine for Prevention of Renal Outcomes in Patients Undergoing Coronary and Peripheral Vascular Angiography

Main Results From the Randomized Acetylcysteine for Contrast-Induced Nephropathy Trial (ACT)

ACT Investigators*

Background—It remains uncertain whether acetylcysteine prevents contrast-induced acute kidney injury.

Methods and Results—We randomly assigned 2308 patients undergoing an intravascular angiographic procedure with at least 1 risk factor for contrast-induced acute kidney injury (age >70 years, renal failure, diabetes mellitus, heart failure, or hypotension) to acetylcysteine 1200 mg or placebo. The study drugs were administered orally twice daily for 2 doses before and 2 doses after the procedure. The allocation was concealed (central Web-based randomization). All analysis followed the intention-to-treat principle. The incidence of contrast-induced acute kidney injury (primary end point) was 12.7% in the acetylcysteine group and 12.7% in the control group (relative risk, 1.00; 95% confidence interval, 0.81 to 1.25; $P=0.97$). A combined end point of mortality or need for dialysis at 30 days was also similar in both groups (2.2% and 2.3%, respectively; hazard ratio, 0.97; 95% confidence interval, 0.56 to 1.69; $P=0.92$). Consistent effects were observed in all subgroups analyzed, including those with renal impairment.

Conclusions—In this large randomized trial, we found that acetylcysteine does not reduce the risk of contrast-induced acute kidney injury or other clinically relevant outcomes in at-risk patients undergoing coronary and peripheral vascular angiography.

Clinical Trial Registration—http://www.clinicaltrials.gov. Unique identifier: NCT00736866.

(*Circulation*. 2011;124:1250-1259.)

Key Words: acute kidney injury ■ coronary angiogram ■ contrast media ■ angioplasty ■ acetylcysteine

Contrast-induced acute kidney injury represents a serious complication of procedures requiring administration of iodinated contrast media and is associated with the need for dialysis, prolonged hospitalization,[1–3] increased costs, and mortality.[4,5]

Editorial see p 1210
Clinical Perspective on p 1259

Acetylcysteine may prevent contrast-induced acute kidney injury by diminishing direct oxidative stress and by improving renal hemodynamics.[6–8] It also represents a safe, inexpensive, and easily administered intervention. Since the first randomized trial testing acetylcysteine for the prevention of contrast-induced acute kidney injury was published,[9] several trials were completed and reached inconsistent results.[10] Such studies are limited by low statistical power (the median study size considering all previous trials was 80 patients), and most failed to meet quality standards such as allocation concealment, blinding, and intention-to-treat analysis.[10] Systematic reviews have found high heterogeneity across studies, precluding definitive conclusions regarding the efficacy of acetylcysteine.[10–16] Current guidelines disagree on whether acetylcysteine should be recommended for high-risk patients, although all recognize that more data are required.[17–20]

The conflicting results of previous evidence have left clinicians uncertain about the effectiveness of acetylcysteine, and several specialists highlighted the need for a large-scale trial to inform clinical practice.[13,21,22] To address this issue, we conducted the Acetylcysteine for Contrast-Induced Nephropathy Trial (ACT), a multicenter randomized trial of acetylcysteine in patients at risk for contrast-induced acute kidney injury undergoing angiography.

Methods

Trial Design

ACT was an academic pragmatic randomized (concealed) controlled trial of acetylcysteine versus placebo in patients at risk for contrast-

Received April 19, 2011; accepted June 28, 2011.

*A complete list of the members of the ACT Investigators appears in the Acknowledgments at the end of the article.

From Research Institute, Hospital do Coração, São Paulo, Brazil. See Acknowledgments for a complete list of affiliations and locations.

The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.111.038943/-/DC1.

Correspondence to Dr Otavio Berwanger, Research Institute, Hospital do Coração (HCor), Rua Abílio Soares 250, 12th Floor, CEP: 04005–000, São Paulo SP, Brazil. E-mail oberwanger@hcor.com.br

Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.111.038943**

induced acute kidney injury undergoing an intravascular angiographic procedure conducted in 46 sites in Brazil. Participants, healthcare staff, data collectors, and outcome assessors were blinded to whether patients received acetylcysteine or placebo. All analyses followed the intention-to-treat principle. The trial was designed by the steering committee. A detailed description of the study design has been published previously,[23] and the trial was registered at http://www.clinicaltrials.gov (NCT00736866). The study was approved by the research ethics board of each participating institution.

Study Population

Patients undergoing coronary or peripheral arterial diagnostic intravascular angiography or percutaneous intervention were eligible for the trial if they had at least 1 risk factor for contrast-induced acute kidney injury: age >70 years, chronic renal failure (stable serum creatinine concentrations >132.6 μmol/L [1.5 mg/dL]), diabetes mellitus, clinical evidence of congestive heart failure, left ventricular ejection fraction <0.45, or hypotension. We chose the inclusion criteria on the basis of independent risk factors validated by previous observational studies.[24,25] We excluded patients on dialysis and those with ST-segment elevation myocardial infarction undergoing primary angioplasty (because they were unable to receive the study hydration protocol for at least 6 hours before the procedure). Women were excluded if they were pregnant, breastfeeding, or aged <45 years and did not use contraceptive methods.

Randomization

After providing written informed consent, patients were randomized in a 1:1 ratio to receive acetylcysteine or placebo. The allocation list was generated in random permuted blocks of variable size (4, 6, 8, or 10) and was stratified by site. To guarantee concealment of the allocation list, randomization was implemented through a 24-hour Web-based automated randomization system.

Study Interventions

The study drugs were packed in identical envelopes containing either 600 mg of oral powder acetylcysteine (Medley, Brazil) or placebo to be diluted in water. The powder and the solution were identical in appearance, taste, and smell. A dose of 1200 mg (2 envelopes) of acetylcysteine or placebo was administered orally every 12 hours, for 2 doses before and 2 doses after the procedure. All decisions about management of patients were at the discretion of the medical team, except that nontrial acetylcysteine was not allowed.

Hydration with 0.9% saline, 1 mL/kg per hour, from 6 to 12 hours before to 6 to 12 hours after angiography, was strongly recommended. However, changes in the total volume or speed of administration were permitted.

Study Procedures

Data were obtained at baseline, on the day of the angiography, and between 48 to 96 hours and at 30 days after angiography. Baseline data were collected immediately after randomization and before administration of hydration scheme and the study drugs. Data collected at baseline included demographic and clinical characteristics and the most recent serum creatinine level measured within the past 3 months under stable clinical conditions. On the day of the angiography, we collected data regarding the administration of the study drug, hydration scheme, and angiographic procedure. Between 48 to 96 hours after angiography, we assessed vital status, need for dialysis, need for another angiogram, and data regarding the administration of the study drugs and hydration and collected a blood sample for serum creatinine measurement. However, we strongly recommended to all investigators that the creatinine sample be collected within a 48- to 72-hour interval. Whenever >1 measurement was available during the period of 48 to 96 hours, the measure closer to 72 hours was used. We contacted the patients 30 days after the angiography to assess the need for dialysis and the vital status.

End Points

The primary end point was contrast-induced acute kidney injury, defined as a 25% elevation of serum creatinine above baseline between 48 and 96 hours after angiography. The secondary end points were as follows: a composite of death or need for dialysis in 48 to 96 hours and at 30 days; individual components of the composite outcome; elevation ≥44.2 μmol/L (0.5 mg/dL) in serum creatinine between 48 and 96 hours; cardiovascular deaths at 30 days; and other adverse events. Elevation ≥13.3 μmol/L (0.3 mg/dL) in serum creatinine, the Acute Kidney Injury Network criteria for acute kidney injury, was a post hoc defined end point.[26]

Trial Management

The coordinating center resources included procedures manuals, slide sets, and a study Web site. Trained investigators and study coordinators at each site collected the data using a Web-based system. Data quality control was guaranteed by automated data entry checks, weekly contact with investigators, on-site monitoring, and central statistical monitoring.[27] General feedback was provided at investigators' meetings and in periodic newsletters.

Sample Size

On the basis of a recent meta-analysis, we anticipated an incidence of contrast-induced acute kidney injury at 48 to 96 hours of ≈15%.[10] To detect a 30% relative risk reduction, with 90% statistical power and a 2-tailed α of 5%, we sought to include 2300 patients.

Statistical Analysis

All analyses were performed on an intention-to-treat basis, and no postrandomization exclusions were performed. Differences in discrete variables were evaluated by the χ^2 test. Continuous variables with skewed distributions were analyzed with the Wilcoxon rank sum test. The results of comparisons of proportions are presented as relative risks and their respective 95% confidence intervals (CIs). Secondary outcomes evaluated 30 days after randomization were analyzed with unadjusted Cox proportional hazards regression. The composite outcome death or need for dialysis was presented as Kaplan-Meier curves. Missing values were not imputed.

A subgroup effect was inferred when the χ^2 test for homogeneity of effects was statistically significant. The following prespecified subgroups were analyzed: age >70 or ≤70 years, gender, patients with or without previous renal failure (serum creatinine >132.6 μmol/L [1.5 mg/dL]), presence of diabetes mellitus, and volume of contrast ≥140 mL. Subgroups were defined post hoc according to the following: time of measurement of creatinine after angiography, presence of acute coronary syndrome, type of contrast, and estimated glomerular filtration rate.

We conducted a prespecified random-effects meta-analysis to evaluate the results of the ACT in the context of previous randomized controlled trials of acetylcysteine versus placebo for preventing contrast-induced acute kidney injury (see additional methods in the online-only Data Supplement).[28] Because several systematic reviews addressing the same question were published to date, we screened references from previous reviews. This strategy was complemented by a comprehensive search on MEDLINE (2008 to present). The terms included in the electronic search were *contrast-induced nephropathy* combined with a sensitive strategy for the identification of randomized controlled trials.[29] We placed no language or publication status restrictions. We screened reference lists of all available primary studies and review articles to identify additional relevant citations. We found high heterogeneity between included trials. Thus, in an attempt to explain the high heterogeneity between trials, as a post hoc decision, we conducted stratified analyses according to prespecified methodological characteristics.

Statistical analyses were performed with the use of STATA/SE 10.0 (STATA Corp LP, College Station, TX) and SPSS release 16.0.2 (SPSS Inc, Chicago, IL).

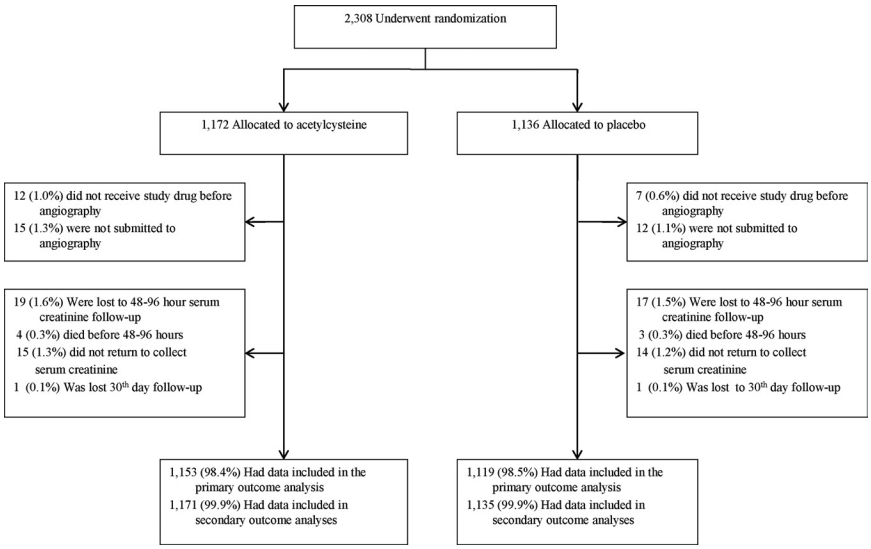

Figure 1. Randomization, study drug adherence, and follow-up of the study patients.

Results

Study Participants

Between September 2008 and July 2010, a total of 2308 patients were enrolled in 46 sites in Brazil: 1172 patients were allocated to acetylcysteine and 1136 to placebo (Figure 1). A follow-up serum creatinine was not collected in 19 patients (1.6%) in the acetylcysteine group and in 17 patients (1.5%) in the placebo group. Information for outcomes at 30 days was available for all but 2 patients (99.9% with complete follow-up).

The baseline characteristics were well balanced between the groups (Table 1). The most common reasons for inclusion were diabetes mellitus, which was present in 1395 patients (60.4%), and age >70 years in 1202 patients (52.1%). Approximately half of the patients (1138) had an estimated creatinine clearance <60 mL/min (1 mL/s), and 35.4% of the sample was included during an acute coronary syndrome episode.

Compliance With Study Protocol and Characteristics of Angiography

From all of the included patients, 67.2% underwent diagnostic coronary angiographies, 28.8% were submitted to percutaneous coronary interventions, and 2.8% were submitted to peripheral vascular angiography (Table 2). Twenty-seven patients (1.2%) had their angiography cancelled after randomization but were kept in the analysis according to the intention-to-treat principle. Low-osmolarity contrast medium was the most common type of contrast used (74.7% of the cases). In approximately half of the included patients, the volume of contrast administered was >100 mL.

Compliance with all 4 study drug doses was >95%, and <1% of the patients did not receive the study drugs before angiography (Figure 1). Ninety-eight percent of the patients received intravenous hydration before and 98.0% after the procedure (Table 2). The median duration of hydration was 6 hours before and after angiography for both groups.

The mean times between angiography and follow-up serum creatinine sampling were 57.6±16.9 and 58.2±16.9 hours for the acetylcysteine and placebo groups (P=0.48), respectively. For most patients (76.4%), serum creatinine was collected between 48 and 72 hours after angiography (Table 2).

End Points

The primary end point occurred in 147 of 1153 patients (12.7%) in the acetylcysteine group and in 142 of 1119 patients (12.7%) in the placebo group (relative risk, 1.00; 95% CI, 0.81 to 1.25; P=0.97) (Table 3). Results were similar when only patients ultimately submitted to angiography were considered: 144 of 1142 (12.6%) and 140 of 1111 (12.6%) patients in the acetylcysteine and placebo groups, respectively (relative risk, 1.00; 95% CI, 0.81 to 1.24; P=0.99). Elevation of ≥44.2 μmol/L (0.5 mg/dL) in creatinine after the procedure was similar between groups (relative risk, 1.04; 95% CI, 0.69 to 1.57; P=0.85). Doubling of creatinine was also similar in both groups (relative risk, 0.74; 95% CI, 0.36 to 1.52; P=0.41).

The incidence of the composite outcome death or need for dialysis at 30 days was 2.2% in the acetylcysteine group and 2.3% in the placebo group (hazard ratio, 0.97; 95% CI, 0.56 to 1.69; P=0.92) (Table 3 and Figure 2). The incidence of the composite outcome death, need for dialysis, or doubling in serum creatinine, as well as the incidence of the individual components of this composite outcome, was not statistically different between the acetylcysteine and placebo groups. Cardiovascular deaths at 30 days were similar between the experimental and control groups (hazard ratio, 0.99; 95% CI, 0.51 to 1.90; P=0.97). There was also no difference between groups for outcomes defined post hoc.

Subgroup Analysis

Effects on Patients With Impaired Renal Function

There was no effect of acetylcysteine in the 367 patients with baseline serum creatinine >132.6 μmol/L (1.5 mg/dL) (acetylcysteine group: 12/188 and placebo group: 10/179; P=0.75 for homogeneity of effects) or in the 823 patients with estimated glomerular filtration rate between 30 and 60 mL/min per 1.73 m^2 (acetylcysteine group: 30/425 and

Table 1. Baseline Characteristics of Patients

Characteristic	Acetylcysteine (n=1172)	Placebo (n=1136)
Female sex, No. (%)	445 (38.0)	447 (39.3)
Age, mean±SD, y	68.0±10.4	68.1±10.4
Patients fulfilling inclusion criteria		
Serum creatinine >132.6 μmol/L (1.5 mg/dL), No. (%)	180 (15.4)	182 (16.0)
Diabetes mellitus, No. (%)	717 (61.2)	678 (59.7)
Known heart failure, No. (%)	116 (9.9)	104 (9.2)
Hypotension, No. (%)	3 (0.3)	2 (0.2)
Age >70 y, No. (%)	601 (51.3)	601 (52.9)
Acute coronary syndrome, No. (%)	419 (35.8)	397 (34.9)
History of hypertension, No. (%)	1,014 (86.5)	976 (85.9)
Previous medication		
Use of NSAIDs >7 d, No. (%)	63 (5.4)	59 (5.2)
Use of ACE inhibitor, No. (%)	698 (59.6)	661 (58.2)
Use of diuretics, No. (%)	442 (37.7)	401 (35.3)
Use of metformin, No. (%)	362 (30.9)	336 (29.6)
Serum creatinine, mg/dL	1.2±0.5	1.2±0.5
Estimated creatinine clearance, mL/min*		
Mean±SD	67.6±31.4	67.7±32.1
<30 mL/min, No. (%)	68 (5.8)	63 (5.5)
30 to 60 mL/min, No. (%)	515 (43.9)	492 (43.3)
>60 mL/min, No. (%)	589 (50.3)	581 (51.2)
Estimated glomerular filtration rate, mL/min per 1.73 m^2†		
Mean±SD	69.3±28.7	69.0±27.9
<30 mL/min, No. (%)	58 (4.9)	50 (4.4)
30 to 60 mL/min, No. (%)	428 (36.5)	404 (35.6)
>60 mL/min, No. (%)	686 (58.5)	682 (60.0)
Weight, mean±SD, kg	73.1±13.9	73.3±14.7

NSAID indicates nonsteroidal anti-inflammatory drug; ACE, angiotensin-converting enzyme. There was no statistically significant difference for baseline characteristics.

*Creatinine clearance estimated by the Cockcroft-Gault formula.

†Glomerular filtration rate estimated by the abbreviated Modification of Diet in Renal Disease study equation.

placebo group: 27/398) or <30 mL/min per 1.73 m^2 (acetylcysteine group: 6/56 and placebo group: 3/48; $P=0.73$ for homogeneity of effects), as shown in Figure 3.

Effects on Other Subgroups

The neutral effect of acetylcysteine on the risk of contrast-induced acute kidney injury was also consistent in those with or without diabetes mellitus ($P=0.42$) and across other subgroups such as patients aged >70 or ≤70 years ($P=0.52$), male or female patients ($P=0.55$), or exposure to high (≥140 mL) or low (<140 mL) volumes of contrast media ($P=0.79$), as shown in Figure 3. There was no effect of acetylcysteine in the subgroup of patients who had serum creatinine collected within 48 to 72 hours after angiography or in the subgroup in which serum creatinine was collected between 72 and 96 hours ($P=0.36$).

Table 2. Procedure Characteristics, Protocol Adequacy, and Hydration Scheme

Characteristic	Acetylcysteine (n=1172)	Placebo (n=1136)	*P*
Procedure, No. of patients/total No. (%)			0.79
Peripheral vascular angiography	32 (2.7)	32 (2.8)	
Coronary diagnostic angiography	778 (66.4)	774 (68.1)	
Percutaneous coronary intervention	347 (29.6)	318 (28.0)	
Not submitted to angiography	15 (1.3)	12 (1.1)	
Adherence to study drug, No. of patients/total No. (%)			
Dose 1	1160 (99.0)	1128 (99.3)	0.28
Dose 2	1136 (96.9)	1099 (96.7)	0.61
Dose 3	1129 (96.3)	1090 (95.9)	0.71
Dose 4	1120 (95.5)	1076 (94.7)	0.39
Hydration before procedure, No. of patients/total No. (%)			
NaCl or bicarbonate	1147 (97.9)	1119 (98.5)	0.25
NaCl 0.9%, 1 mL/kg per hour for 6 h	552 (47.1)	540 (47.5)	0.83
NaCl 0.9%, any scheme	1090 (93.0)	1071 (94.3)	0.21
NaCl 0.45%	3 (0.2)	0 (0.0)	0.25*
Bicarbonate 0.9%	60 (5.1)	52 (4.6)	0.55
Duration of hydration before procedure, h			
Median (interquartile range)	6 (4–6)	6 (4–6)	0.32
Hydration after procedure, No. of patients/total No. (%)			
NaCl or bicarbonate	1145 (97.7)	1115 (98.2)	0.53
NaCl 0.9%, 1 mL/kg per hour for 6 h	814 (69.4)	792 (69.7)	0.92
NaCl 0.9%, any scheme	1129 (96.3)	1100 (96.8)	0.58
NaCl 0.45%	1 (0.08)	0 (0)	1.00*
Bicarbonate 0.9%	66 (5.6)	62 (5.5)	0.85
Duration of hydration after procedure, h			
Median (interquartile range)	6 (6–6)	6 (6–6)	0.71
Contrast type, No. (%)†			0.86
High osmolarity	253 (21.9)	256 (22.8)	
Low osmolarity	869 (75.1)	836 (74.4)	
Iso-osmolar	35 (3.0)	32 (2.8)	
Contrast volume, mL			
Median (interquartile range)	100 (70–130)	100 (70–130)	0.66
Additional angiography within 48–96 h after first procedure, No. (%)	38 (3.2)	47 (4.1)	0.25

(*Continued*)

Table 2. Continued

Characteristic	Acetylcysteine (n=1172)	Placebo (n=1136)	P
Timing of serum creatinine sampling after angiography, No. (%)‡			0.87
48 to ≤72 h	876 (76.3)	851 (76.6)	
72 to 96 h	272 (23.7)	260 (23.4)	

*Fisher exact test.

†In the acetylcysteine and placebo groups, 1157 and 1124 patients, respectively, were ultimately submitted to angiography. These are the denominators for type of contrast.

‡Serum creatinine after angiography was available for 1148 and 1111 patients in the acetylcysteine and placebo groups, respectively.

Adverse Events

The incidence of other serious adverse events was 1.3% in the acetylcysteine group and 2.2% in the placebo group ($P=0.09$) (Table I in the online-only Data Supplement). There was no difference between the study groups for any other adverse events, except that vomiting was less common in the acetylcysteine than in the placebo group (0.3% and 1.2%, respectively; $P=0.02$).

Updated Meta-Analysis

We identified 46 randomized controlled trials comparing acetylcysteine with placebo (or no acetylcysteine) in patients undergoing cardiac or peripheral angiography (Table II in the online-only Data Supplement). One study was excluded from our meta-analyses because no cases of contrast-induced acute kidney injury were observed in either the treatment or control group.[30] There was important heterogeneity between studies ($P<0.0001$; $I^2=59\%$). Therefore, we did not combine the results of all studies but instead attempted to identify the sources of heterogeneity by stratifying the analyses according to methodological characteristics of the trials.

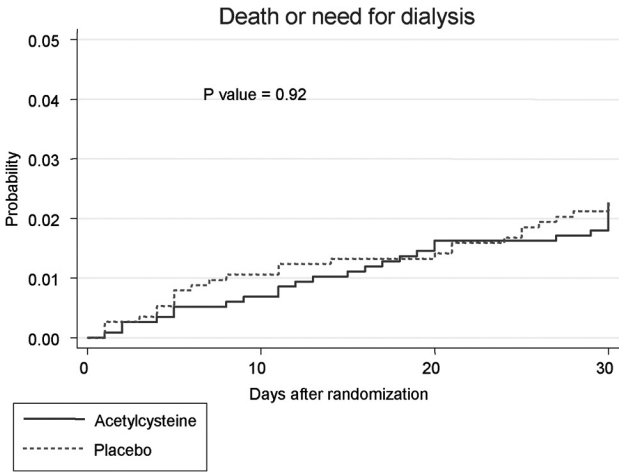

Figure 2. Probability of death or need for dialysis from the day of randomization (day 0) to day 30 among patients in the acetylcysteine and placebo groups.

The pooled relative risk in studies with unclear or inadequate allocation concealment was 0.59 (95% CI, 0.43 to 0.82), with substantial heterogeneity across trials ($I^2=57\%$), whereas in studies with allocation concealment, the effect estimate (relative risk, 1.01; 95% CI, 0.75 to 1.37) was similar to that found in our study, with no remaining heterogeneity ($I^2=0\%$) (Figure 4). Meta-analyses stratified according to adequacy of all methodological characteristics (allocation concealment, double blinding, and intention-to-treat analysis) revealed a similar pattern. The pooled relative risk for low-quality studies was 0.63 (95% CI, 0.47 to 0.85; $I^2=56\%$) and for studies meeting all 3 methodological criteria was 1.05 (95% CI, 0.73 to 1.53; $I^2=0\%$).

Discussion

In this large randomized trial, acetylcysteine did not reduce the incidence of contrast-induced acute kidney injury. Acetylcysteine also did not show statistically sig-

Table 3. End Points

Outcomes	Acetylcysteine	Placebo	Relative Risk (95% CI)	P
Primary end point, No. of events/total No. (%)				
Contrast-induced acute kidney injury	147/1153 (12.7)	142/1119 (12.7)	1.00 (0.81–1.25)	0.97
Other end points, No. of events/total No. (%)				
End points in 48 to 96 h				
Doubling in serum creatinine	13/1153 (1.1)	17/1119 (1.5)	0.74 (0.36–1.52)	0.41
Elevation ≥44.2 μmol/L (0.5 mg/dL) in serum creatinine	45/1153 (3.9)	42/1119 (3.8)	1.04 (0.69–1.57)	0.85
Elevation ≥13.3 μmol/L (0.3 mg/dL) in serum creatinine	140/1153 (12.1)	123/1119 (11.0)	1.10 (0.88–1.39)	0.39
End points at 30 d				
Deaths or need for dialysis*	26/1171 (2.2)	26/1135 (2.3)	0.97 (0.56–1.69)	0.92
Death, need for dialysis, or doubling in serum creatinine	38/1171 (3.2)	41/1135 (3.6)	0.90 (0.58–1.39)	0.63
Deaths*	23/1171 (2.0)	24/1135 (2.1)	0.97 (0.54–1.73)	0.92
Need for dialysis*	3/1171 (0.3)	3/1135 (0.3)	0.87 (0.17–4.35)	0.86
Cardiovascular deaths*	18/1171 (1.5)	18/1135 (1.6)	0.99 (0.51–1.90)	0.97

CI indicates confidence interval.

*Results are hazard ratios with 95% CI and P values obtained by Cox regression.

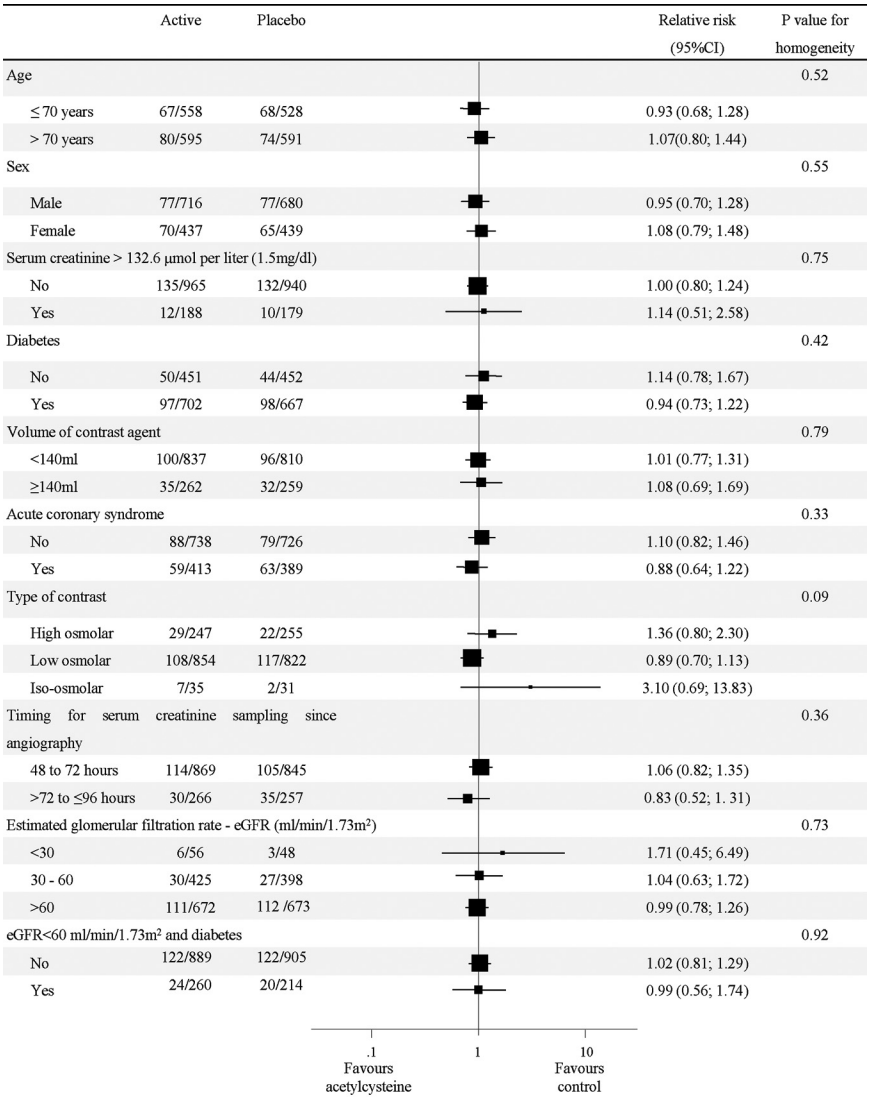

Figure 3. Effect of acetylcysteine on contrast-induced acute kidney injury according to subgroup. CI indicates confidence interval; eGFR, estimated glomerular filtration rate.

nificant beneficial effects on other end points such as all-cause mortality and need for dialysis at 30 days. These results were consistent among all subgroups evaluated, including higher-risk patients such as those with renal failure, those with diabetes mellitus, and those who received the largest amounts of contrast.

Several strengths of the ACT reinforce our findings. It represents the largest trial testing the effects of acetylcysteine for the prevention of contrast-induced acute kidney injury conducted to date. Although the incidence of contrast-induced acute kidney injury observed in the control group (12.7%) was somewhat lower than anticipated in our sample size calculation (15%), still the ACT would have adequate statistical power (84%) to detect a 30% decrease in the risk of contrast-induced acute kidney injury. We sought to ensure adequate methodological quality by using concealed random-

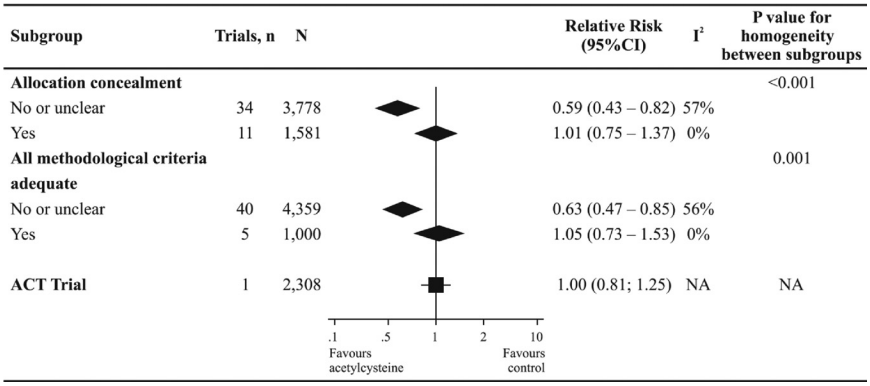

Figure 4. Meta-analyses of randomized controlled trials of acetylcysteine for preventing contrast-induced acute kidney injury stratified according to methodological criteria and the Acetylcysteine for Contrast-Induced Nephropathy Trial (ACT) main result. I^2 represents the percentage of total variation across studies due to heterogeneity rather than chance. We considered all methodological criteria adequate when a trial had allocation concealment and was blinded and the analysis followed the intention-to-treat principle. CI indicates confidence interval; NA, not applicable.

ization; blinding patients, investigators, caregivers, and outcome assessors; analyzing data according to the intention-to-treat principle; and by having >98% of patients with complete follow-up data. We tested a high dose of acetylcysteine because previous evidence suggested that a dose of 1200 mg twice daily may be superior to a dose of 600 mg twice daily.[16,31] Compliance to the study drugs was >95%, and cointerventions were well balanced between the groups. We used different methods to guarantee data quality including on-site monitoring, central statistical monitoring of the data, and data collection through a Web-based electronic data capture system.

More than 40 acetylcysteine trials have been completed in the past 10 years and have reached inconsistent results. One plausible explanation for the contradictory findings may be related to methodological quality.[11,12,15] In this regard, our meta-analysis of smaller high-quality studies published before the ACT found neutral effects of acetylcysteine for the prevention of contrast-induced acute kidney injury with no heterogeneity between studies. On the other hand, the meta-analysis of trials with inadequate methodology suggested a beneficial effect of this intervention but with important between-trial heterogeneity. These results are in accordance with previous empirical evidence suggesting that trials with inadequate or unclear concealment of allocation or unclear description on blinding tend to overestimate the treatment effects.[32,33] The ACT confirms the findings of smaller high-quality studies and, together with them, provides consistent evidence to support the lack of effect of acetylcysteine for the prevention of contrast-induced acute kidney injury.

Differences between the ACT and previous studies should be noted. Although some trials have enrolled only patients with renal failure, our trial sought to test the effects of acetylcysteine over a broader population at risk for contrast-induced acute kidney injury.[17–19] In this regard, besides renal failure, our patients were selected on the basis of other well-established independent risk factors such as age >70 years, diabetes mellitus, and heart failure.[2,3,24,25] The adoption of such broad inclusion criteria did not result in a low-risk population, as indicated by an overall incidence of contrast-induced acute kidney injury close to 13%, which was consistent among subgroups and similar to the incidence of previous trials, as shown in a previous systematic review.[10] Moreover, patients with diabetes mellitus or with renal impairment represented >70% of our sample, and approximately half of our patients had a creatinine clearance <60 mL/min (1 mL/s). Thus, our higher-risk subgroups had a larger sample size representation than the previous studies. Finally, we did not find evidence of a subgroup effect in higher-risk patients. In particular, there was no effect of acetylcysteine in the subgroup of 367 patients with baseline serum creatinine >132.6 μmol/L (1.5 mg/dL) or in the subgroups with estimated glomerular filtration rate <60 mL/min per 1.73 m^2 (total of 927 patients). Although the power to draw definitive conclusions for any of the subgroups is low, in all subgroups the results were very consistent. Therefore, it is unlikely that a beneficial effect exists for any subgroup. Although most of the previous studies tested oral acetylcysteine, as we did in the ACT, some employed intravenous formulations.[34–36] Even so, it is unlikely that the choice of intravenous instead of oral administration of acetylcysteine would influence our results. In this sense, the largest study using intravenous acetylcysteine also reached neutral results.[36]

Our trial has limitations. First, we did not observe a large number of events that allowed us to assess the effects of acetylcysteine on end points such as mortality and need for dialysis. However, despite the wide CIs, the point estimates for these outcomes showed neutral effects of acetylcysteine. Second, we used creatinine as our marker of kidney injury, and some recent publications suggest that newer markers such as cystatin C are more reliable for detecting contrast-induced acute kidney injury.[37,38] Nevertheless, results based on creatinine measures were consistent with those observed for other clinical end points. Additionally, a cystatin C ACT substudy involving >150 patients has now been completed, and the results should be available soon. Third, the median volume of contrast used was low (100 mL), and previous studies demonstrated an association between contrast volume and risk of contrast-induced acute kidney injury.[2,24] However, we found no evidence of a subgroup effect in patients who received >140 mL of contrast. Fourth, cointerventions other than hydration were at the discretion of the attending physician. Nevertheless, they were well balanced between groups. Fifth, we used a definition for contrast-induced acute kidney injury (25% elevation of serum creatinine from baseline) that may have high sensitivity but lack specificity. However, this definition has been used by most trials in the field.[13] Furthermore, previous studies demonstrated that even such minor increases predict a higher mortality and morbidity.[2,5] In addition, we found no effect of acetylcysteine when considering other definitions of contrast-induced acute kidney injury, such as a 100% or a 44.2-μmol/L (0.5-mg/dL) increase in serum creatinine, although the incidence of contrast-induced acute kidney injury and the study power are smaller with those definitions.

Studies have demonstrated persistence of contrast media up to 7 days after angiography in patients with contrast-induced acute kidney injury.[39,40] In this study, patients received acetylcysteine every 12 hours, 2 doses before and 2 doses after angiography. Thus, it may be suggested this was not a long enough duration of therapy. Nonetheless, we believe that extending acetylcysteine therapy would not change the results of our trial because the peak of renal dysfunction occurs shortly after angiography (2 to 5 days), with fast normalization after it.[41,42] Furthermore, previous trials that suggested acetylcysteine to be effective administered the drug for only up to 48 hours after angiography.[9,34,43]

In conclusion, our trial showed that acetylcysteine did not result in a lower incidence of contrast-induced acute kidney injury or other renal outcomes. On the basis of our results, we do not recommend routine use of acetylcysteine for patients undergoing angiography. These findings have important implications for clinical practice and may prevent unnecessary procedure delays and health expenditures associated with the administration of acetylcysteine.

Acknowledgments

We are indebted to all of the study coordinators, investigators, and patients who participated in the ACT. Participants in the ACT are as follows: **Writing Committee:** From Research Institute, Hospital do Coração, São Paulo, Brazil: Otávio Berwanger, Alexandre B. Cavalcanti, Amanda G.M.R. Sousa, Anna M. Buehler, Alessandra A. Kodama, Mariana T. Carballo, Vitor O. Carvalho, Celso Amodeo, Leda D. Lotaif, José Eduardo Sousa. From Instituto Dante Pazzanese de Cardiologia. São Paulo, Brazil: Amanda G.M.R. Sousa. **Statistical Analyses:** Mariana T. Carballo, Elivane S. Victor. **Trial Steering Committee:** Otávio Berwanger (chair), Alexandre B. Cavalcanti, Amanda G.M.R. Sousa, José Eduardo Sousa, Celso Amodeo, Leda D. Lotaif. **Trial Management Team:** Otávio Berwanger (chief investigator), Alexandre B. Cavalcanti (project manager), Anna M. Buehler (project manager), Mariana T. Carballo (statistician), Alessandra A. Kodama (data management), Eliana Santucci (research coordinator), Carlos E. S. Cardoso (data management), Dalmo da Silva (data management), Adailton L. Mendes (senior computer programmer), José Lobato (chief computer programmer). **Investigator Sites:** *Associação Hospital de Bauru*, Bauru, São Paulo: G. Prates, H. Yokoyama, P. Almeida, C. Pessoa; *Cardiocenter Hospital Santa Paula,* João Pessoa, Paraíba: H. Martins, M. Lopes, M. Barros; *Fundação Pública Estadual Hospital Gaspar Vianna*, Belém, Pará: H. Reis, C. Cordeiro; *Hospital Bandeirantes,* São Paulo: H. Castello, M. Cantarelli, S. Ferreira; *Hospital Barra Dor*, Rio de Janeiro: C. Mattos, M. Rati, C. Medeiros; *Hospital Beneficência Portuguesa*, São Paulo: J.A. Mangione, M.F. Mauro, S.A. Cristóvão, N.M. Carnieto, L.C. Rocha, D.F. Maksud, C. Barbosa; *Hospital Cardiologico Constantini*, Curitiba, Paraná: C. Costantini, S. Tarbine, M. Santos, C. Ortiz, A. Souza; *Hospital Copa Dor*, Rio de Janeiro: C. Mattos, L. Duarte; *Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo*, Ribeirão Preto, São Paulo: J. Marin Neto, G. Figueiredo, D. Lemos, F. Braga, G. Novaes, F. Oliveira, M. Tonani; *Hospital das Clínicas da Faculdade Federal de Pernambuco*, Recife, Pernambuco: E. Victor Filho, E. Rocha; *Hospital de Terapia Intensiva HTI*, Teresina, Piauí: P. Nunes, A. Sá Filho, I. Lima; *Hospital do Coração de Juiz de Fora*, Juiz de Fora, Minas Gerais: A. Muniz, J. Loures, A. Abraão; *Hospital do Coração de São Paulo*, São Paulo: J. Sousa, A. Moreira; *Hospital do Coração do Brasil*, Brasília, Distrito Federal: E. Araújo, L. Sousa, A. Fonseca; *Hospital Escola Álvaro Alvim*, Campos, Rio de Janeiro: J. Soares, C. Cunha; *Hospital Felício Rocho*, Belo Horizonte, Minas Gerais: J. Saad, F. Câmara, E. Falcheto; *Hospital Maternidade e Pronto Socorro Santa Lúcia*, Poços de Caldas, Minas Gerais: R. Bergo, F.T.C. Dall'Orto, R. Almeida, R. Mendes; *Hospital Moinhos de Vento*, Porto Alegre, Rio Grande do Sul: M. Wainstein, J. Ribeiro, C. Teixeira; *Hospital Quinta Dor*, Rio de Janeiro: C. Mattos; *Hospital Regional do Sul de Minas*, Varginha, Minas Gerais: F. Cunha; F.T.C. Dall'Orto, J. Lisboa, D. Osugui; *Hospital Samaritano*, São Paulo: F. Stella, J. Almeida, A. Stella, F. Assunção, S. Souza, J. Malachia, P. Buononato; *Hospital Santa Catarina*, Blumenau, Santa Catarina: D. Zappi, M. Linhares, M. Junckes; *Hospital Santa Helena São Francisco Cardio Vida*, Aparecida de Goiânia, Goiás: J. Guimarães, D. Araújo Filho; *Hospital Santa Lucinda*, Sorocaba, São Paulo: J. Maiello, E. Seixas; *Hospital Santa Marcelina*, São Paulo: B. Almeida, B. Janella, M. Almeida; *Hospital São José do Avaí*, Itaperuna, Rio de Janeiro: A. Silva, A. Marco, A. Teixeira, J. Pinto; *Hospital SOS Cardio*, Florianópolis, Santa Catarina: L. São Thiago, L. Giuliano, F. Aranha, D. Arante; *Hospital UDI*, São Luís, Maranhão: M. Barbosa, F. Aguiar Filho, C. Gama; *Hospital Universitário São José*, Belo Horizonte, Minas Gerais: C. Arêas, M. Lacerda, I. Freitas, F.T.C. Dall'Orto; *INCOR Hemocardio*, Natal, Rio Grande do Norte: L.A. Oliveira, I.R. Oliveira, F. Pinheiro, C. Amaral; *INCORPI Hospital Fornecedores de Cana*, Piracicaba, São Paulo: L. Gubolino, P. Teixeirense, J.F. Toledo; *Instituto Dante Pazzanese de Cardiologia*, São Paulo: A. Sousa, F. Feres, M. Centemero, J.R. Costa, V. Esteves, J. Polacini, R. Viana; *Instituto de Cardiologia*, São José, Santa Catarina: L. São Thiago, L. Giuliano, M. Antunes, R. Conceição; *Instituto de Cardiologia RGS Fundação Universitária de Cardiologia*, Porto Alegre, Rio Grande do Sul: A. Azmus, A. Quadros; *Instituto de Clínicas e Cirurgia de Juiz de Fora Hospital Monte Sinai*, Juiz de Fora, Minas Gerais: G. Ramalho, R. Santos; *Instituto de Moléstias Cardiovasculares*, São José do Rio Preto, São Paulo: P. Garzon, D. Faria, C. Queirantes, P. Galeazzi, V. Cavallini, R. Carvalho; *Instituto do Coração do Triângulo Mineiro*, Uberlândia, Minas Gerais: R. Botelho, C. Rosa, M. Seabra, A. Pereira, S. Reis, V. Pereira, S. Cunha, P. Vitor; *Instituto do Coração de Taguatinga Hospital Anchieta*, Taguatinga, Distrito Federal: P. Motta, E. Osterne, F. X Souza, V. Motta, M.S. Heleno, K.M. Ramalho; *Instituto Nacional de Cardiologia Laranjeiras*, Rio de Janeiro: H. Cramer, B. Santos Júnior, B. Tura, D. Cook, D. Justen; *Natal Hospital Center*, Natal, Rio Grande do Norte: M. Paiva, E. Czochra, K.C. Potengi, F. Pinheiro; *Santa Casa de Limeira*, Limeira, São Paulo: P. Teixeirense, J.F. Toledo, L. Gubolino; *Santa Casa de Marília*, Marília, São Paulo: A. Labrunie, P. Andrade, M. Tebet; *Santa Casa de Misericórdia de Juiz de Fora*, Juiz de Fora, Minas Gerais: A. Muniz, J. Loures, A. Abraão, M.S. Vankeulen, N.J. Pedroso, *Santa Casa de Porto Alegre*, Porto Alegre, Rio Grande do Sul: G. Nunes, A. Oliveira, C. Roehrig, I. Colnaghi; *Santa Casa de São Paulo*, São Paulo: F. Stella, M. Candeias, L. Scatamburlo, V. Kloth; *UNISUL Hospital Socimed*, Tubarão, Santa Catarina: S. Abreu, J. Lima.

Sources of Funding

The ACT is funded by the Brazilian Ministry of Health (Programa Hospitais de Excelencia a Serviço do SUS). The sponsor had no role in analysis, study design, or decision to publish these results.

Disclosures

None.

References

1. Parfrey PS, Griffiths SM, Barrett BJ, Paul MD, Genge M, Withers J, Farid N, McManamon PJ. Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency, or both: a prospective controlled study. *N Engl J Med*. 1989;320:143–149.
2. McCullough PA, Wolyn R, Rocher LL, Levin RN, O'Neill WW. Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. *Am J Med*. 1997;103:368–375.
3. Dangas G, Iakovou I, Nikolsky E, Aymong ED, Mintz GS, Kipshidze NN, Lansky AJ, Moussa I, Stone GW, Moses JW, Leon MB, Mehran R. Contrast-induced nephropathy after percutaneous coronary interventions in relation to chronic kidney disease and hemodynamic variables. *Am J Cardiol*. 2005;95:13–19.
4. McCullough PA, Stacul F, Becker CR, Adam A, Lameire N, Tumlin JA, Davidson CJ. Contrast-Induced Nephropathy (CIN) Consensus Working Panel: executive summary. *Rev Cardiovasc Med*. 2006;7:177–197.
5. Rihal CS, Textor SC, Grill DE, Berger PB, Ting HH, Best PJ, Singh M, Bell MR, Barsness GW, Mathew V, Garratt KN, Holmes DR Jr. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation*. 2002;105:2259–2264.
6. Drager LF, Andrade L, Barros de Toledo JF, Laurindo FR, Machado Cesar LA, Seguro AC. Renal effects of N-acetylcysteine in patients at risk for contrast nephropathy: decrease in oxidant stress-mediated renal tubular injury. *Nephrol Dial Transplant*. 2004;19:1803–1807.
7. Lopez BL, Snyder JW, Birenbaum DS, Ma XI. N-Acetylcysteine enhances endothelium-dependent vasorelaxation in the isolated rat mesenteric artery. *Ann Emerg Med*. 1998;32:405–410.
8. Heyman SN, Rosen S, Khamaisi M, Idee JM, Rosenberger C. Reactive oxygen species and the pathogenesis of radiocontrast-induced nephropathy. *Invest Radiol*. 2010;45:188–195.
9. Tepel M, van der Giet M, Schwarzfeld C, Laufer U, Liermann D, Zidek W. Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. *N Engl J Med*. 2000;343:180–184.
10. Kelly AM, Dwamena B, Cronin P, Bernstein SJ, Carlos RC. Meta-analysis: effectiveness of drugs for preventing contrast-induced nephropathy. *Ann Intern Med*. 2008;148:284–294.
11. Nallamothu BK, Shojania KG, Saint S, Hofer TP, Humes HD, Moscucci M, Bates ER. Is acetylcysteine effective in preventing contrast-related nephropathy? A meta-analysis. *Am J Med*. 2004;117:938–947.

12. Bagshaw SM, McAlister FA, Manns BJ, Ghali WA. Acetylcysteine in the prevention of contrast-induced nephropathy: a case study of the pitfalls in the evolution of evidence. *Arch Intern Med*. 2006;166:161–166.
13. Pannu N, Wiebe N, Tonelli M. Prophylaxis strategies for contrast-induced nephropathy. *JAMA*. 2006;295:2765–2779.
14. Zagler A, Azadpour M, Mercado C, Hennekens CH. N-Acetylcysteine and contrast-induced nephropathy: a meta-analysis of 13 randomized trials. *Am Heart J*. 2006;151:140–145.
15. Gonzales DA, Norsworthy KJ, Kern SJ, Banks S, Sieving PC, Star RA, Natanson C, Danner RL. A meta-analysis of N-acetylcysteine in contrast-induced nephrotoxicity: unsupervised clustering to resolve heterogeneity. *BMC Med*. 2007;5:32.
16. Trivedi H, Daram S, Szabo A, Bartorelli AL, Marenzi G. High-dose N-acetylcysteine for the prevention of contrast-induced nephropathy. *Am J Med*. 2009;122:874–815.
17. Benko A, Fraser-Hill M, Magner P, Capusten B, Barrett B, Myers A, Owen RJ. Canadian Association of Radiologists: consensus guidelines for the prevention of contrast-induced nephropathy. *Can Assoc Radiol J*. 2007;58:79–87.
18. Smith SC Jr, Feldman TE, Hirshfeld JW Jr, Jacobs AK, Kern MJ, King SB III, Morrison DA, O'Neill WW, Schaff HV, Whitlow PL, Williams DO, Antman EM, Smith SC Jr, Adams CD, Anderson JL, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Jacobs AK, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). *J Am Coll Cardiol*. 2006;47:1–121.
19. Wijns W, Kolh P, Danchin N, Di MC, Falk V, Folliguet T, Garg S, Huber K, James S, Knuuti J, Lopez-Sendon J, Marco J, Menicanti L, Ostojic M, Piepoli MF, Pirlet C, Pomar JL, Reifart N, Ribichini FL, Schalij MJ, Sergeant P, Serruys PW, Silber S, Sousa UM, Taggart D, Vahanian A, Auricchio A, Bax J, Ceconi C, Dean V, Filippatos G, Funck-Brentano C, Hobbs R, Kearney P, McDonagh T, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Vardas PE, Widimsky P, Kolh P, Alfieri O, Dunning J, Elia S, Kappetein P, Lockowandt U, Sarris G, Vouhe P, Kearney P, von Segesser L, Agewall S, Aladashvili A, Alexopoulos D, Antunes MJ, Atalar E, Brutel dlR, Doganov A, Eha J, Fajadet J, Ferreira R, Garot J, Halcox J, Hasin Y, Janssens S, Kervinen K, Laufer G, Legrand V, Nashef SA, Neumann FJ, Niemela K, Nihoyannopoulos P, Noc M, Piek JJ, Pirk J, Rozenman Y, Sabate M, Starc R, Thielmann M, Wheatley DJ, Windecker S, Zembala M. Guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2010;31:2501–2555.
20. Stacul F, Adam A, Becker CR, Davidson C, Lameire N, McCullough PA, Tumlin J. Strategies to reduce the risk of contrast-induced nephropathy. *Am J Cardiol*. 2006;98:59–77.
21. Caixeta A, Mehran R. Evidence-based management of patients undergoing PCI: contrast-induced acute kidney injury. *Catheter Cardiovasc Interv*. 2010;75:15–20.
22. Tepel M, Aspelin P, Lameire N. Contrast-induced nephropathy: a clinical and evidence-based approach. *Circulation*. 2006;113:1799–1806.
23. Costa E, Reis H, de Assis GM, Cardoso GL, Barbosa MM, de Aguiar Filho FA, Gama CA, Silva MG, Aguiar BM, Ferreira MG, Feitosa GS, Victor Filho E, Rocha EB, Paiva MS, Czochra ER, Oliveira LA, de Oliveira IR, Pinheiro F, Dourado GO, Luna Filho AL, Pacheco A, Nunes PM, de Sá Filho AP, Martins HC, Lopes MA, Barros MA, Mattos C, Neves MA, Medeiros CR, Mattos C, Duarte L, Mattos C, Cramer H, Santos B Jr, Tura BR, Rodrigues CV, Terreiro LA, Alves MA, Soares JS, da Cunha CC, da Silva AC, Barcelos AM, Teixeira MA, Pinto JS, Saad JA, Mandil A, Falcheto E, Arêas CA, Dall'Orto FT, Freitas IF, Botelho RV, Seabra MD, Rosa CA, Pereira AD, Reis SS, Pereira VJ, Cunha SM, Ramalho GM, dos Santos RR, Muniz AJ, Loures JB, Amorim T, Muniz AJ, Loures JB, Abraão AC, Padilha RM, Sousa JE, Sousa AG, Moreira AC, Sousa AG, Feres F, Centemero M, Costa R, Esteves V, Almeida BO, Janella BL, Almeida MC, Stella FP, Almeida JD, Kloth VR, Mangione JA, Mauro MF, Tallo F, Santos DJ, Castello H, Cantarelli MJ, Baradel S, Stella FP, das Candeias MO, Kloth VR, Maiello JR, Seixas EA, Teixerense PT, de Toledo JF, Gubolino LA, Prates GJ, Yokoyama H, de Almeida P, Pessoa CM, Machado NC, Garzon PG, Antonângelo AF, Galeazzi PB, Queirantes CS, Cavalini VH, Labrunie A, de Andrade PB, Tebet MA, Devito FS, Farias CE, Nicolela EL Jr, Passos HM, Rubio P, Gubolino LA, Teixerense PT, de Toledo JF, Nunes GL, Roehrig C, de Oliveira AT, Wainstein MV, Ribeiro JP, Teixeira C, Atallah TN, Gomes C, Morelli H, Costantini CR, Tarbine SG, Santos MF, Ortiz CC, de Souza AB, Pecoits-Filho R, Koppe G, Hoffman PD, Faria Neto JR, Wang R, Cury C, Stadler N, Nercolini DC, Zanuzzi C, Bueno RR, Guerios EE, Tarastchuk JC, Peixoto ML, Labrunie A, de Andrade PB, Tebet MA, Thiago LE, Giuliano LC, Aranha FG, Misiak M, Thiago LE, Giuliano LC, Antunes MH, da Conceição RS, Abreu SM, Preve JC, Guimarães JS, de Araújo Filho D, Araújo EC, de Sousa LN, Fonseca AG, da Motta PA, Osterne EC, Da Motta VP, Zimmermann AC. Rationale, design, and baseline characteristics of the Acetylcystein for Contrast-Induced nephropaThy (ACT) Trial: a pragmatic randomized controlled trial to evaluate the efficacy of acetylcysteine for the prevention of contrast-induced nephropathy. *Trials*. 2009;10:38.
24. Bartholomew BA, Harjai KJ, Dukkipati S, Boura JA, Yerkey MW, Glazier S, Grines CL, O'Neill WW. Impact of nephropathy after percutaneous coronary intervention and a method for risk stratification. *Am J Cardiol*. 2004;93:1515–1519.
25. Mehran R, Aymong ED, Nikolsky E, Lasic Z, Iakovou I, Fahy M, Mintz GS, Lansky AJ, Moses JW, Stone GW, Leon MB, Dangas G. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. *J Am Coll Cardiol*. 2004;44:1393–1399.
26. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care*. 2007;11:31.
27. Buyse M, George SL, Evans S, Geller NL, Ranstam J, Scherrer B, Lesaffre E, Murray G, Edler L, Hutton J, Colton T, Lachenbruch P, Verma BL. The role of biostatistics in the prevention, detection and treatment of fraud in clinical trials. *Stat Med*. 1999;18:3435–3451.
28. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177–188.
29. Lefebvre C, Manheimer E, Glanville J; on behalf of Cochrane Information Retrieval Methods Group. Chapter 6: Searching for studies. In: Higgins JP, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester, UK: John Willey & Sons Ltd.; 2008.
30. Kotlyar E, Keogh AM, Thavapalachandran S, Allada CS, Sharp J, Dias L, Muller D. Prehydration alone is sufficient to prevent contrast-induced nephropathy after day-only angiography procedures: a randomised controlled trial. *Heart Lung Circ*. 2005;14:245–251.
31. Briguori C, Colombo A, Violante A, Balestrieri P, Manganelli F, Paolo EP, Golia B, Lepore S, Riviezzo G, Scarpato P, Focaccio A, Librera M, Bonizzoni E, Ricciardelli B. Standard vs double dose of N-acetylcysteine to prevent contrast agent associated nephrotoxicity. *Eur Heart J*. 2004;25:206–211.
32. Juni P, Altman DG, Egger M. Systematic reviews in health care: assessing the quality of controlled clinical trials. *BMJ*. 2001;323:42–46.
33. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA*. 1995;273:408–412.
34. Marenzi G, Assanelli E, Marana I, Lauri G, Campodonico J, Grazi M, De MM, Galli S, Fabbiocchi F, Montorsi P, Veglia F, Bartorelli AL. N-Acetylcysteine and contrast-induced nephropathy in primary angioplasty. *N Engl J Med*. 2006;354:2773–2782.
35. Thiele H, Hildebrand L, Schirdewahn C, Eitel I, Adams V, Fuernau G, Erbs S, Linke A, Diederich KW, Nowak M, Desch S, Gutberlet M, Schuler G. Impact of high-dose N-acetylcysteine versus placebo on contrast-induced nephropathy and myocardial reperfusion injury in unselected patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: the LIPSIA-N-ACC (Prospective, Single-Blind, Placebo-Controlled, Randomized Leipzig Immediate PercutaneouS Coronary Intervention Acute Myocardial Infarction N-ACC) Trial. *J Am Coll Cardiol*. 2010;55:2201–2209.
36. Webb JG, Pate GE, Humphries KH, Buller CE, Shalansky S, Al SA, Sutander A, Williams T, Fox RS, Levin A. A randomized controlled trial of intravenous N-acetylcysteine for the prevention of contrast-induced nephropathy after cardiac catheterization: lack of effect. *Am Heart J*. 2004;148:422–429.
37. Herget-Rosenthal S, Marggraf G, Husing J, Goring F, Pietruck F, Janssen O, Philipp T, Kribben A. Early detection of acute renal failure by serum cystatin C. *Kidney Int*. 2004;66:1115–1122.
38. Hoffmann U, Fischereder M, Kruger B, Drobnik W, Kramer BK. The value of N-acetylcysteine in the prevention of radiocontrast agent-

induced nephropathy seems questionable. *J Am Soc Nephrol*. 2004;15:407–410.
39. D'Elia JA, Gleason RE, Alday M, Malarick C, Godley K, Warram J, Kaldany A, Weinrauch LA. Nephrotoxicity from angiographic contrast material: a prospective study. *Am J Med*. 1982;72:719–725.
40. Jakobsen JA, Berg KJ, Kjaersgaard P, Kolmannskog F, Nordal KP, Nossen JO, Rootwelt K. Angiography with nonionic x-ray contrast media in severe chronic renal failure: renal function and contrast retention. *Nephron*. 1996;73:549–556.
41. Gleeson TG, Bulugahapitiya S. Contrast-induced nephropathy. *AJR Am J Roentgenol*. 2004;183:1673–1689.
42. Rudnick MR, Berns JS, Cohen RM, Goldfarb S. Nephrotoxic risks of renal angiography: contrast media-associated nephrotoxicity and atheroembolism: a critical review. *Am J Kidney Dis*. 1994;24:713–727.
43. Kay J, Chow WH, Chan TM, Lo SK, Kwok OH, Yip A, Fan K, Lee CH, Lam WF. Acetylcysteine for prevention of acute deterioration of renal function following elective coronary angiography and intervention: a randomized controlled trial. *JAMA*. 2003;289:553–558.

CLINICAL PERSPECTIVE

Contrast-induced acute kidney injury is associated with the need for dialysis, prolonged hospitalization, and mortality. Its incidence in patients with risk factors (kidney failure, diabetes mellitus, or advanced age) varies between 9% and 38%. Previous acetylcysteine trials had substantial risk of bias and were underpowered. We conducted a randomized trial of acetylcysteine versus placebo in 2308 patients at risk for contrast-induced acute kidney injury (age >70 years, renal failure, diabetes mellitus, heart failure, or hypotension) undergoing an intravascular angiographic procedure. Allocation was concealed; patients, health staff, and outcome assessors were blinded, and analysis followed the intention-to-treat principle. We administered 1200 mg of acetylcysteine or placebo every 12 hours, twice before and twice after the angiography. We found no effect of acetylcysteine on contrast-induced acute kidney injury, the primary end point (12.7% vs 12.7% in the acetylcysteine and placebo groups, respectively; relative risk, 1.00; 95% confidence interval, 0.81 to 1.25; $P=0.97$). There was also no effect on any of the secondary outcomes or for any subgroup. We conducted a meta-analysis to assess the results of the Acetylcysteine for Contrast-Induced Nephropathy Trial in the context of 45 trials on the same subject and found a huge variation in the effect on contrast-induced acute kidney injury, although those with adequate methodological criteria did not show any clinical benefit of acetylcysteine. In conclusion, our trial, the largest conducted to date, showed that acetylcysteine is ineffective to prevent contrast-induced acute kidney injury. Therefore, we do not recommend routine use of acetylcysteine for patients undergoing angiography.

Supplemental Material

Methods for the Updated Meta-Analysis

Eligibility Criteria

We included randomized placebo-controlled trials that evaluated pharmacological interventions N-Acetylcysteine to prevent contrast-induced acute kidney injury (CI-AKI) in patients undergoing diagnostic and therapeutic coronary or peripheral angiography. Trials were eligible regardless of their publication status, language or primary objectives. We excluded: trials that did not evaluate the number of patients with CI-AKI, duplicate publications or sub studies of included trials.

Search Strategy

Since many systematic reviews on CI-AKI prevention methods were published to date, as a starting point, we decided to screen references from previous reviews. This strategy was complemented by a comprehensive search on MEDLINE/PubMed version (2008 to the present). We placed no language or publication status restrictions. We screened reference lists of all available primary studies and review articles to identify additional relevant citations. The search results were uploaded into a reference management program (Reference Manager 12.0).

The terms included in the electronic search were "Contrast-induced nephropathy" combined with a sensitive strategy for the identification of randomized controlled trials.[1]

Assessment of Study Eligibility

We screened all citations (i.e., titles and abstracts) identified in our search. Screeners (A.B.C. and O.B.) only excluded citations if it was clear that the article was not a report of a randomized controlled trial or the trial did not include a pharmacological intervention to prevent CIN as an experimental intervention. We obtained the full text article of all citations selected to undergo full review in the screening process. Individuals then determined eligibility of these full text articles. All

screening and eligibility decisions were conducted by two independent reviewers, and disagreements were resolved by third party adjudication.

Data collection

Two reviewers (A.B.C. and O.B.) independently extracted data from all trials that fulfilled our eligibility criteria. Disagreements were settled by a third reviewer.

We extracted the following descriptive data from all eligible trials: first author or study name, year of publication, patient population, treatment and control interventions, definition of CI-AKI and the number of patients randomized to the treatment and control groups, as well as the number of patients who had CI-AKI in each group.

Quality Assessment

We assessed the methodological quality of the trials by evaluating the original reports, the trial protocols (when published) and through attempted contact of the authors. We assessed the following risk of bias domains:

Allocation concealment

- Adequate (A): Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study.
- Unclear (B): Randomisation stated but no information on method used is available.
- Inadequate (C): Method of randomisation used such as alternate medical record numbers or unsealed envelopes; any information in the study that indicated that investigators or participants could influence intervention group.

Blinding

- Blinding of investigators: Yes/no/not stated/ Unclear or inadequate (if the study was described as double blind, but the method of blinding was not described or is not compatible with blinding).
- Blinding of participants: Yes/no/not stated/ Unclear or inadequate (if the study was described as double blind, but the method of blinding was not described or is not compatible with blinding).
- Blinding of outcome assessors: Yes/no/not stated/ Unclear or inadequate (if the study was described as double blind, but the method of blinding was not described or is not compatible with blinding).

Intention-to-treat

- Yes: Specifically reported by authors that intention-to-treat analysis was undertaken and this was confirmed on study assessment.
- Yes: Not stated but confirmed on study assessment.

- No: Not reported and lack of intention-to-treat analysis confirmed on study assessment.(Patients who were randomised were not included in the analysis because they did not receive the study intervention, they withdrew from the study or were not included because of protocol violation).
- No: Stated but not confirmed upon study assessment.
- Not stated.

* Obs.: Our evaluation will be independent of authors' claim of ITT analysis, i.e., a study might be considered by us as analyzed according to ITT principle even if there is no such statement as long as we confirme that on study assessment. The opposite is also true, if a study is reported as being ITT but we might consider it not to be ITT depending on our evaluation.

Statistical Analysis

CI-AKI from all included RCTs was combined to estimate the pooled risk ratio (RR) with 95% confidence interval (CI) using a random-effects model.[2] The presence of heterogeneity across studies was evaluated using I^2 statistics and standard Chi^2 tests for homogeneity for each outcome analysis.[3] An I^2 value represents the percentage of total variation across studies due to heterogeneity rather than chance. We conducted the analyses using Stata 11.0 (College Station, Texas, USA) and RevMan 5.1 (Cochrane Collaboration, Oxford, UK).

Supplemental Table 1. **Adverse Events. ***

	Acetylcysteine	**Placebo**	**Relative risk (CI 95%)**	**p**
	No. of events / total no. (%)			
Any Serious adverse events†	15/1172 (1.3)	25/1136 (2.2)	0.58 (0.31; 1.10)	0.09
Any Adverse Events	89/1172 (7.6)	80/1136 (7.0)	1.08 (0.81; 1.44)	0.61
Chest pain	25/1172 (2.1)	14/1122 (1.2)	1.73 (0.90; 3.31)	0.09
Dyspnea	19/1172 (1.6)	13/1123 (1.1)	1.42 (0.70; 2.85)	0.33
Nausea	8/1172 (0.7)	15/1136 (1.2)	0.52 (0.22; 1.21)	0.12
Vomit	4/1172 (0.3)	14/1136 (1.2)	0.28 (0.09; 0.84)	0.02
Diarrhea	7/1172 (0.6)	6/1136 (0.5)	1.13 (0.38; 3.35)	0.82

* CI denotes Confidence Interval.

† Includes stroke, myocardial infarction, pneumonia, sepsis and acute pulmonary edema.

Supplemental Table 2. **Summary of results and study quality characteristics of randomized controlled trials evaluating acetylcysteine for preventing contrast-induced nephropathy in patients undergoing invasive angiography.**

Study	Year	Acetylcysteine		Control		Allocation concealment	Double-blind	Intention-to-treat analysis
		no. of events	total no.	no. of events	total no.			
Allaqaband[5]	2002	8	45	6	40	Not reported	No	No
Amini[6]	2009	5	45	6	42	Yes	Yes	Yes
Azmus[7]	2005	14	196	17	201	Not reported	Yes	No
Baker[8]	2003	2	41	8	39	Not reported	No	Yes
Baskurt[9]	2009	7	73	5	72	Not reported	No	Yes
Briguori[10]	2002	6	92	10	91	Not reported	No	No
Carbonell[11]	2007	11	107	11	109	Yes	Yes	Yes
Carbonell[12]	2010	2	39	10	42	Not reported	Yes	No
Castini[13]	2010	9	53	7	51	Not reported	No	Yes
Coyle[14]	2006	6	68	1	69	No	No	No
Diaz-Sandoval[15]	2002	2	25	13	29	Yes	Yes	No
Drager[16]	2004	1	13	2	11	Not reported	Yes	No
Durham[17]	2002	10	38	9	41	Not reported	No	No
Efrati[18]	2003	0	24	2	25	Not reported	Yes	No
El Mahmoud[19]	2003	3	60	2	60	Not reported	No	No
Ferrario[20]	2009	8	99	6	101	Yes	Yes	Yes
Fung[21]	2004	8	46	6	45	Yes	No	Yes
Goldenberg[22]	2004	4	41	3	39	Yes	Yes	No
Gomes[23]	2005	8	77	8	79	Yes	Yes	No
Gulel[24]	2005	3	25	2	25	Not reported	No	No
Heng[25]	2008	2	28	3	32	Not reported	Yes	No
Kay[26]	2003	4	102	12	98	Not reported	Yes	No
Kefer[27]	2003	2	53	3	51	No	No	No
Kim[28]	2010	3	80	7	86	Not reported	No	Yes
Kimmel[29]	2008	1	19	2	17	Not reported	Yes	Yes
Kinbara[30]	2009	0	15	4	15	Not reported	No	Yes

Kotlyar[31]	2005	0	41	0	19	Yes	No	No
Lawlor[32]	2007	2	25	2	25	Yes	Yes	Yes
Loutrianakis[33]	2003	6	24	3	23	Not reported	Not reported	Not reported
MacNeill[34]	2003	1	21	7	22	Not reported	Yes	No
Marenzi[35]	2006	17	235	39	119	Not reported	No	No
Miner[36]	2004	9	89	18	22	Not reported	Yes	Yes
Moore[37]	2006	3	11	0	9	Not reported	No	Yes
Namgung[38]	2005	4	25	10	23	No	No	No
Ochoa[39]	2004	3	36	11	44	Not reported	Yes	Yes
Oldemeyer[40]	2003	4	49	3	47	Not reported	Yes	No
Rashid[41]	2004	3	46	3	48	Yes	Yes	No
Reinecke[42]	2007	6	114	7	115	Not reported	Not reported	Yes
Sadat[43]	2010	1	21	3	19	Not reported	No	Yes
Sandhu[44]	2006	3	53	0	53	Yes	No	No
Seyon[45]	2007	1	20	2	20	No	Yes	Yes
Shyu[46]	2002	2	60	15	61	Not reported	No	No
Sinha[47]	2004	5	35	6	35	No	No	No
Thiele[48]	2010	18	123	25	126	Not reported	No	Yes
Vallero[49]	2002	4	47	4	53	Not reported	No	Not reported
Webb[50]	2004	25	220	24	227	Yes	Yes	Yes

References

(1) Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: The Cochrane Collaboration, editor. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.0.0 (Updated February 2008) ed. 2008.

(2) DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7:177-188.

(3) Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.

(4) DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7:177-188.

(5) Allaqaband S, Tumuluri R, Malik AM, Gupta A, Volkert P, Shalev Y, Bajwa TK. Prospective randomized study of N-acetylcysteine, fenoldopam, and saline for prevention of radiocontrast-induced nephropathy. Catheter Cardiovasc Interv. 2002;57:279-283.

(6) Amini M, Salarifar M, Amirbaigloo A, Masoudkabir F, Esfahani F. N-acetylcysteine does not prevent contrast-induced nephropathy after cardiac catheterization in patients with diabetes mellitus and chronic kidney disease: a randomized clinical trial. Trials. 2009;10:45.

(7) Azmus AD, Gottschall C, Manica A, Manica J, Duro K, Frey M, Bulcão L, Lima C. Effectiveness of acetylcysteine in prevention of contrast nephropathy. J Invasive Cardiol. 2005;17:80-84.

(8) Baker CS, Wragg A, Kumar S, De PR, Baker LR, Knight CJ. A rapid protocol for the prevention of contrast-induced renal dysfunction: the RAPPID study. J Am Coll Cardiol. 2003;41:2114-2118.

(9) Baskurt M, Okcun B, Abaci O, Dogan GM, Kilickesmez K, Ozkan AA, Ersanli M, Gurmen T. N-acetylcysteine versus N-acetylcysteine + theophylline for the prevention of contrast nephropathy. Eur J Clin Invest. 2009;39:793-799.

(10) Briguori C, Manganelli F, Scarpato P, Elia PP, Golia B, Riviezzo G, Lepore S, Librera M, Villari B, Colombo A, Ricciardelli B. Acetylcysteine and contrast agent-associated nephrotoxicity. J Am Coll Cardiol. 2002;40:298-303.

(11) Carbonell N, Blasco M, Sanjuán R, Pérez-Sancho E, Sanchis J, Insa L, Bodí V, Núñez J, García-Ramón R, Miguel A. Intravenous N-acetylcysteine for preventing contrast-induced nephropathy: a randomised trial. Int J Cardiol. 2007;115:57-62.

(12) Carbonell N, Sanjuan R, Blasco M, Jorda A, Miguel A. N-acetylcysteine: short-term clinical benefits after coronary angiography in high-risk renal patients. Rev Esp Cardiol. 2010;63:12-19.

(13) Castini D, Lucreziotti S, Bosotti L, Salerno Uriarte D, Sponzilli C, Verzoni A, Lombardi F. Prevention of contrast-induced nephropathy: a single center randomized study. Clin Cardiol. 2010;33:E63-E68.

(14) Coyle LC, Rodriguez A, Jeschke RE, Simon-Lee A, Abbott KC, Taylor AJ. Acetylcysteine In Diabetes (AID): a randomized study of acetylcysteine for the prevention of contrast nephropathy in diabetics. Am Heart J. 2006;151:1032-1012.

(15) Diaz-Sandoval LJ, Kosowsky BD, Losordo DW. Acetylcysteine to prevent angiography-related renal tissue injury (the APART trial). Am J Cardiol. 2002;89:356-358.

(16) Drager LF, Andrade L, Barros de Toledo JF, Laurindo FR, Machado Cesar LA, Seguro AC. Renal effects of N-acetylcysteine in patients at risk for contrast nephropathy: decrease in oxidant stress-mediated renal tubular injury. Nephrol Dial Transplant. 2004;19:1803-1807.

(17) Durham JD, Caputo C, Dokko J, Zaharakis T, Pahlavan M, Keltz J, Dutka P, Marzo K, Maesaka JK, Fishbane S. A randomized controlled trial of N-acetylcysteine to prevent contrast nephropathy in cardiac angiography. Kidney Int. 2002;62:2202-2207.

(18) Efrati S, Dishy V, Averbukh M, Blatt A, Krakover R, Weisgarten J, Morrow JD, Stein MC, Golik A. The effect of N-acetylcysteine on renal function, nitric oxide, and oxidative stress after angiography. Kidney Int. 2003;64:2182-2187.

(19) El Mahmoud R, Le Feuvre C, Le Quan Sang KH, Helft G, Beygui F, Batisse JP, Metzger JP. [Absence of nephro-protective effect of acetylcysteine in patients with chronic renal failure investigated by coronary angiography]. Arch Mal Coeur Vaiss. 2003;96:1157-1161.

(20) Ferrario F, Barone MT, Landoni G, Genderini A, Heidemperger M, Trezzi M, Piccaluga E, Danna P, Scorza D. Acetylcysteine and non-ionic isosmolar contrast-induced nephropathy--a randomized controlled study. Nephrol Dial Transplant. 2009;24:3103-3107.

(21) Fung JW, Szeto CC, Chan WW, Kum LC, Chan AK, Wong JT, Wu EB, Yip GW, Chan JY, Yu CM, Woo KS, Sanderson JE. Effect of N-acetylcysteine for prevention of contrast nephropathy in patients with moderate to severe renal insufficiency: a randomized trial. Am J Kidney Dis. 2004;43:801-808.

(22) Goldenberg I, Shechter M, Matetzky S, Jonas M, Adam M, Pres H, Elian D, Agranat O, Schwammenthal E, Guetta V. Oral acetylcysteine as an adjunct to saline hydration for the prevention of contrast-induced nephropathy following coronary angiography. A randomized controlled trial and review of the current literature. Eur Heart J. 2004;25:212-218.

(23) Gomes VO, Poli de Figueredo CE, Caramori P, Lasevitch R, Bodanese LC, Araújo A, Röedel AP, Caramori AP, Brito FS Jr, Bezerra HG, Nery P, Brizolara A. N-acetylcysteine does not prevent contrast induced nephropathy after cardiac catheterisation with an ionic low osmolality contrast medium: a multicentre clinical trial. Heart. 2005;91:774-778.

(24) Gulel O, Keles T, Eraslan H, Aydogdu S, Diker E, Ulusoy V. Prophylactic acetylcysteine usage for prevention of contrast nephropathy after coronary angiography. J Cardiovasc Pharmacol. 2005;46:464-467.

(25) Heng AE, Cellarier E, Aublet-Cuvelier B, Decalf V, Motreff P, Marcaggi X, Deteix P, Souweine B. Is treatment with N-acetylcysteine to prevent contrast-induced nephropathy when using bicarbonate hydration out of date? Clin Nephrol. 2008;70:475-484.

(26) Kay J, Chow WH, Chan TM, Lo SK, Kwok OH, Yip A, Fan K, Lee CH, Lam WF. Acetylcysteine for prevention of acute deterioration of renal function following elective coronary angiography and intervention: a randomized controlled trial. JAMA. 2003 ;289:553-558.

(27) Kefer JM, Hanet CE, Boitte S, Wilmotte L, De KM. Acetylcysteine, coronary procedure and prevention of contrast-induced worsening of renal function: which benefit for which patient? Acta Cardiol. 2003;58:555-560.

(28) Kim BJ, Sung KC, Kim BS, Kang JH, Lee KB, Kim H, Lee MH. Effect of N-acetylcysteine on cystatin C-based renal function after elective coronary angiography (ENABLE Study): a prospective, randomized trial. Int J Cardiol. 2010;138:239-245.

(29) Kimmel M, Butscheid M, Brenner S, Kuhlmann U, Klotz U, Alscher DM. Improved estimation of glomerular filtration rate by serum cystatin C in preventing contrast induced nephropathy by N-acetylcysteine or zinc--preliminary results. Nephrol Dial Transplant. 2008;23:1241-1245.

(30) Kinbara T, Hayano T, Ohtani N, Furutani Y, Moritani K, Matsuzaki M. Efficacy of N-acetylcysteine and aminophylline in preventing contrast-induced nephropathy. J Cardiol. 2010;55:174-179.

(31) Kotlyar E, Keogh AM, Thavapalachandran S, Allada CS, Sharp J, Dias L, Muller D. Prehydration alone is sufficient to prevent contrast-induced nephropathy after day-only angiography procedures--a randomised controlled trial. Heart Lung Circ. 2005;14:245-451.

(32) Lawlor DK, Moist L, DeRose G, Harris KA, Lovell MB, Kribs SW, Elliot J, Forbes TL. Prevention of contrast-induced nephropathy in vascular surgery patients. Ann Vasc Surg. 2007;21:593-597.

(33) Loutrianakis E, Stella D, Hussain A et al. Randomized comparison of fenoldopam and N-acetylcysteine to saline in the prevention of radiocontrast induced nephropathy. J Am Coll Cardiol. 41, 327A. 2010.
Ref Type: Abstract

(34) MacNeill BD, Harding SA, Bazari H, Patton KK, Colon-Hernadez P, DeJoseph D, Jang IK. Prophylaxis of contrast-induced nephropathy in patients undergoing coronary angiography. Catheter Cardiovasc Interv. 2003;60:458-461.

(35) Marenzi G, Assanelli E, Marana I, Lauri G, Campodonico J, Grazi M, De Metrio M, Galli S, Fabbiocchi F, Montorsi P, Veglia F, Bartorelli AL. N-acetylcysteine and contrast-induced nephropathy in primary angioplasty. N Engl J Med. 2006;354:2773-2782.

(36) Miner SE, Dzavik V, Nguyen-Ho P, Richardson R, Mitchell J, Atchison D, Seidelin P, Daly P, Ross J, McLaughlin PR, Ing D, Lewycky P, Barolet A, Schwartz L. N-acetylcysteine reduces contrast-associated nephropathy but not clinical events during long-term follow-up. Am Heart J. 2004;148:690-695.

(37) Moore NN, Lapsley M, Norden AG, Firth JD, Gaunt ME, Varty K, Boyle JR. Does N-acetylcysteine prevent contrast-induced nephropathy during endovascular AAA repair? A randomized controlled pilot study. J Endovasc Ther. 2006;13:660-666.

(38) Nangung J, Doh JH, Lee SY, Lee WR. Effect of N acetylcysteine in the prevention of contrast induced nephropathy after coronary angiography. In: Abstracts of the 10th Annual Interventional Vascular Therapeutics Angioplasty Summit - Transcatheter Cardiovascular Therapeutics Asia Pacific Symposium. April 28-30, 2005, Seoul, Korea. Am J Cardiol. 95, 1A-83A. 2005.
Ref Type: Abstract

(39) Ochoa A, Pellizzon G, Addala S, Grines C, Isayenko Y, Boura J, Rempinski D, O'Neill W, Kahn J. Abbreviated dosing of N-acetylcysteine prevents contrast-induced nephropathy after elective and urgent coronary angiography and intervention. J Interv Cardiol. 2004;17:159-165.

(40) Oldemeyer JB, Biddle WP, Wurdeman RL, Mooss AN, Cichowski E, Hilleman DE. Acetylcysteine in the prevention of contrast-induced nephropathy after coronary angiography. Am Heart J. 2003;146:E23.

(41) Rashid ST, Salman M, Myint F, Baker DM, Agarwal S, Sweny P, Hamilton G. Prevention of contrast-induced nephropathy in vascular patients undergoing angiography: a randomized controlled trial of intravenous N-acetylcysteine. J Vasc Surg. 2004;40:1136-1141.

(42) Reinecke H, Fobker M, Wellmann J, Becke B, Fleiter J, Heitmeyer C, Breithardt G, Hense HW, Schaefer RM. A randomized controlled trial comparing hydration therapy to additional hemodialysis or N-acetylcysteine for the prevention of contrast medium-induced nephropathy: the Dialysis-versus-Diuresis (DVD) Trial. Clin Res Cardiol. 2007;96:130-139.

(43) Sadat U, Walsh SR, Norden AG, Gillard JH, Boyle JR. Does Oral N-Acetylcysteine Reduce Contrast-Induced Renal Injury in Patients With Peripheral Arterial Disease Undergoing Peripheral Angiography? A Randomized-Controlled Study. Angiology. 2011; 62:225-230.

(44) Sandhu C, Belli AM, Oliveira DB. The role of N-acetylcysteine in the prevention of contrast-induced nephrotoxicity. Cardiovasc Intervent Radiol. 2006;29:344-347.

(45) Seyon RA, Jensen LA, Ferguson IA, Williams RG. Efficacy of N-acetylcysteine and hydration versus placebo and hydration in decreasing contrast-induced renal dysfunction in patients undergoing coronary angiography with or without concomitant percutaneous coronary intervention. Heart Lung. 2007;36:195-204.

(46) Shyu KG, Cheng JJ, Kuan P. Acetylcysteine protects against acute renal damage in patients with abnormal renal function undergoing a coronary procedure. J Am Coll Cardiol. 2002;40:1383-1388.

(47) Sinha SK, Berry WA, Bueti J, Junaid A, Fine A, Krahn J. The prevention of radiocontrast-induced nephropathy trial (print): a prospective, double-blind, randomized, controlled trial of iso-osmolar versus low-osmolar radiocontrast in combination with N-acetylcysteine versus placebo [Abstract]. Presented at the American Heart Association Scientific Sessions, New Orleans, Louisiana, 7-10 November 2004. Ref Type: Abstract

(48) Thiele H, Hildebrand L, Schirdewahn C, Eitel I, Adams V, Fuernau G, Erbs S, Linke A, Diederich KW, Nowak M, Desch S, Gutberlet M, Schuler G. Impact of high-dose N-acetylcysteine versus placebo on contrast-induced nephropathy and myocardial reperfusion injury in unselected patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. The LIPSIA-N-ACC (Prospective, Single-Blind, Placebo-Controlled, Randomized Leipzig Immediate PercutaneouS Coronary Intervention Acute Myocardial Infarction N-ACC) Trial. J Am Coll Cardiol. 2010;55:2201-2219.

(49) Vallero A, Cesano G, Pozzato M, Garbo R, Minelli M, Quarello F, Formica M. [Contrast nephropathy in cardiac procedures: no advantages with prophylactic use of N-acetylcysteine (NAC)]. G Ital Nefrol. 2002;19:529-533.

(50) Webb JG, Pate GE, Humphries KH, Buller CE, Shalansky S, Al Shamari A, Sutander A, Williams T, Fox RS, Levin A. A randomized controlled trial of intravenous N-acetylcysteine for the prevention of contrast-induced nephropathy after cardiac catheterization: lack of effect. *Am* Heart J. 2004 ;148:422-429.

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 $\leq$30 mL · min^{-1} · 1.73 m^{-2} and/or a risk score $\geq$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 $\geq$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 $\leq$30 mL · min^{-1} · 1.73 and 149 patients (51.5%) with only a risk score $\geq$11. Subgroup analysis according to inclusion criteria showed a similarly lower risk of adverse events (estimated glomerular filtration rate $\leq$30 mL · min^{-1} · 1.73 m^{-2}: odds ratio, 0.44; risk score $\geq$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;124:1260-1269.)

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

Received March 8, 2011; accepted July 7, 2011.

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

Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.111.030759**

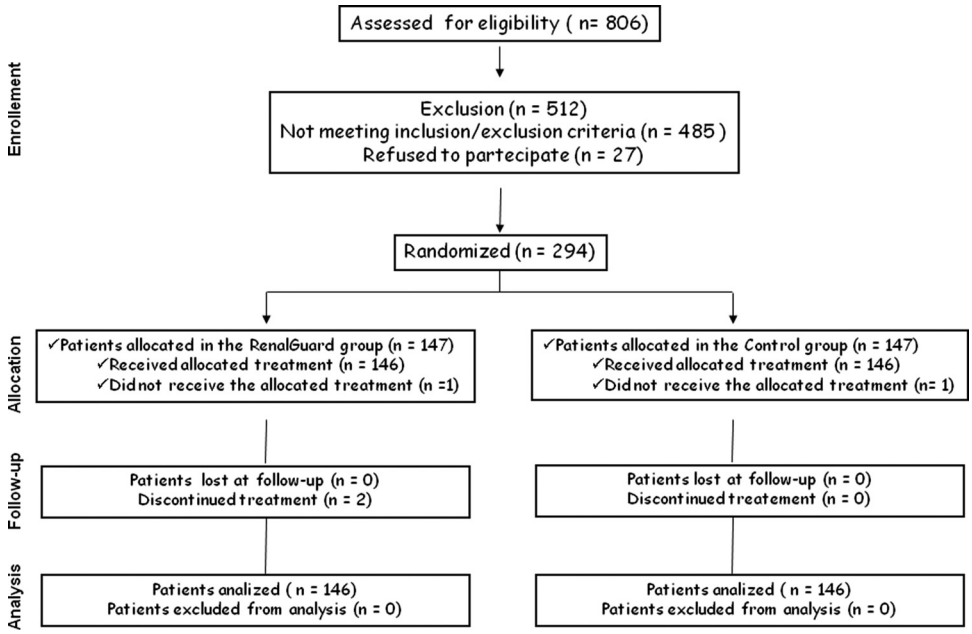

Figure 1. Diagram showing the flow of participants through each stage of the trial according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

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 1210
Clinical Perspective on p 1269

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).

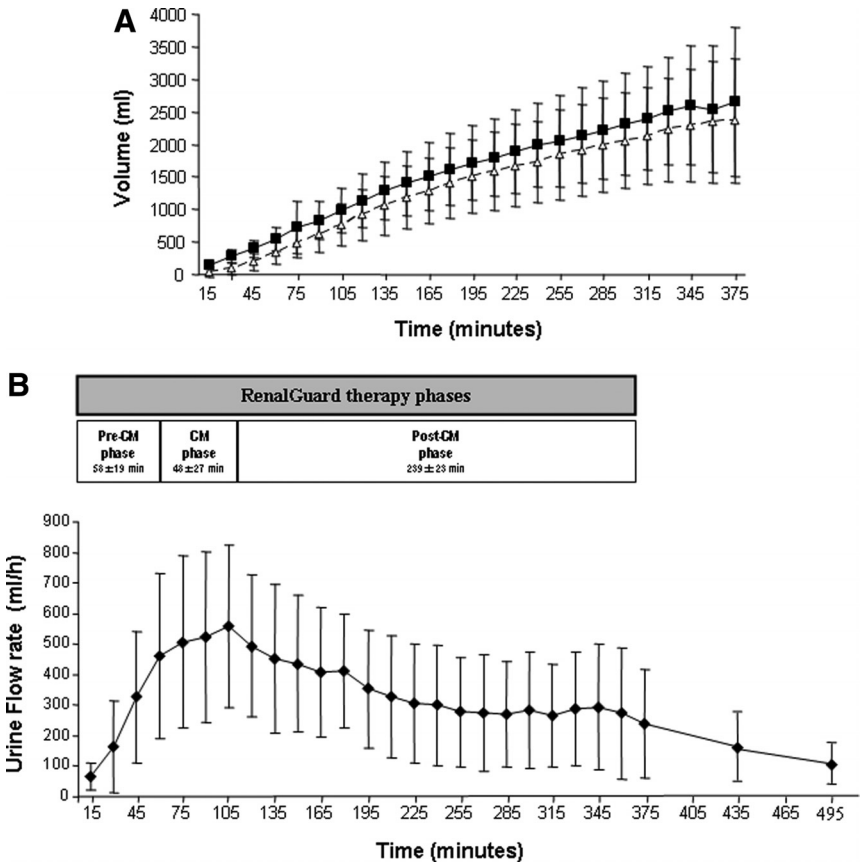

Figure 2. A, Temporally matched fluid replacement during treatment by using the RenalGuard system (continuous line indicates infusion; dashed line, urine). **B**, Mean urine flow in the RenalGuard group. Urine output (mL/h) was recorded every 15 minutes during RenalGuard therapy and every hour after 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.

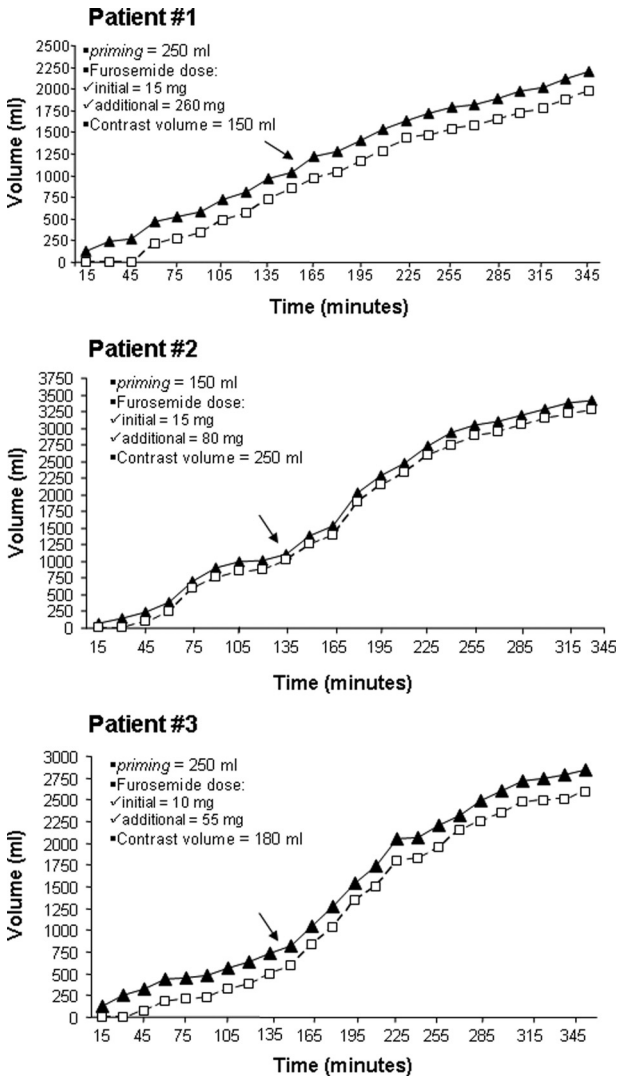

Figure 3. Fluid match in the 3 patients who developed acute pulmonary edema in the RenalGuard group. Pulmonary edema (arrow) occurred in all instances soon after the end of the coronary procedure. ▲ Indicates infusion volume; □, urine volume.

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

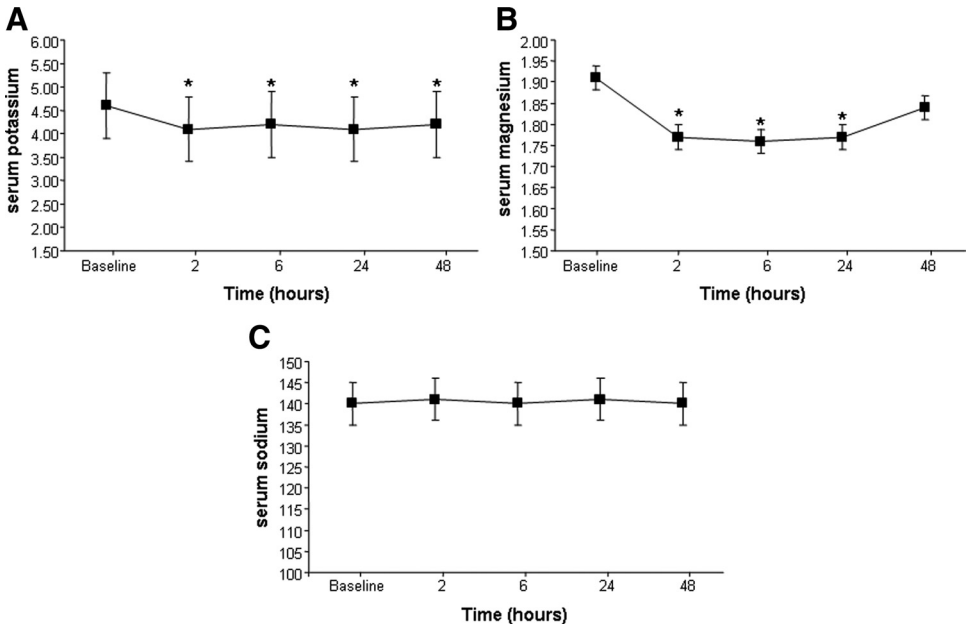

Figure 4. Serum electrolytes changes in the RenalGuard group, **A**, Potassium; **B**, magnesium; **C**, sodium. *$P<0.05$ vs baseline.

(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

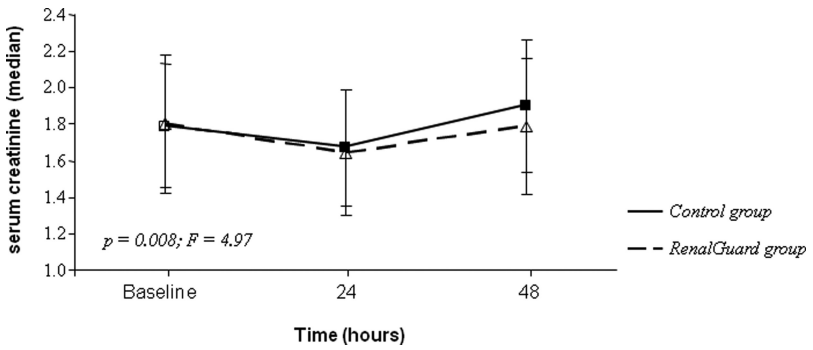

Figure 5. Serum creatinine concentration at baseline and 24 and 48 hours after contrast media administration in the control (continuous line) and RenalGuard (dashed line) groups. $P=0.008$; $F=4.97$ by repeated measures ANOVA.

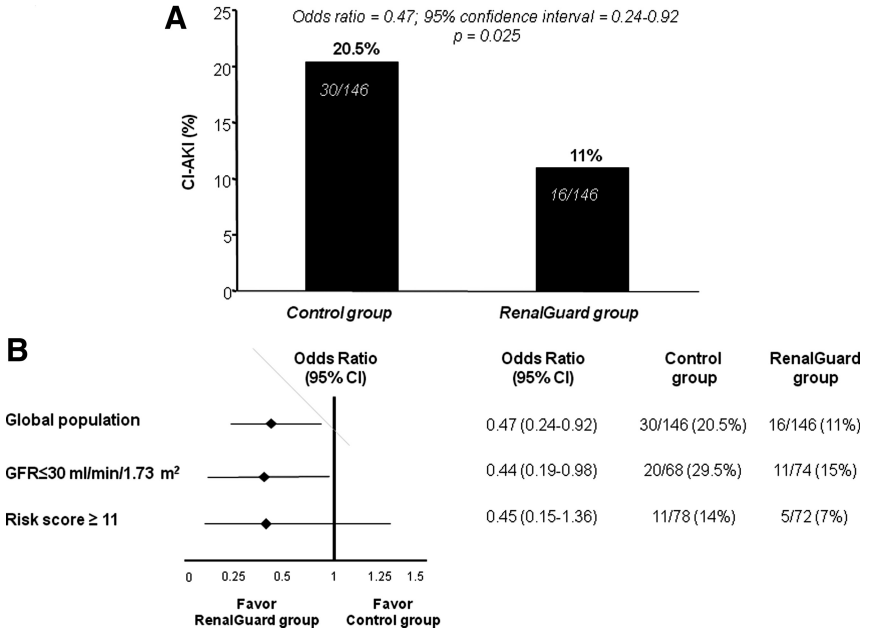

Figure 6. Incidence of contrast-induced acute kidney injury (CI-AKI) in the control and RenalGuard groups. **A**, All enrolled patients; **B**, patients stratified according to enrollment criteria: estimated glomerular filtration rate (eGFR) $\leq$30 mL · min^{-1} · 1.73 m^{-2} regardless of the risk score and risk score $\geq$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 $\leq$30 mL · min^{-1} · 1.73 m^{-2} and/or a risk score $\geq$11 and that the majority of patients (93%) in the RenalGuard group reached the target urine flow rate $\geq$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 ($\geq$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

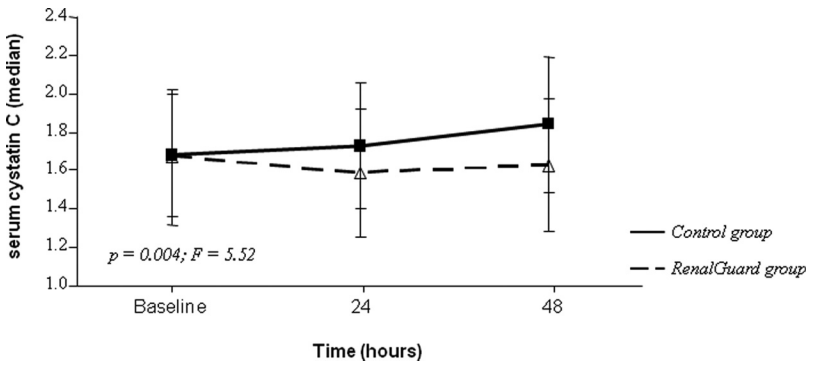

Figure 7. Serum cystatin C concentration at baseline and 24 and 48 hours after contrast media administration in the control (continuous line) and RenalGuard (dashed line) groups. $P=0.004$; $F=5.52$ by repeated measures ANOVA.

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.

References

1. McCullough PA. Contrast-induced acute kidney injury. *J Am Coll Cardiol*. 2008;51:1419–1428.
2. Solomon RJ, Mehran R, Natarajan MK, Doucet S, Katholi RE, Staniloae CS, Sharma SK, Labinaz M, Gelormini JL, Barrett BJ. Contrast-induced nephropathy and long-term adverse events: Cause and effect? *Clin J Am Soc Nephrol*. 2009;4:1162–1169.
3. Briguori C, Visconti G, Rivera NV, Focaccio A, Golia B, Giannone R, Castaldo D, De Micco F, Ricciardelli B, Colombo A. Cystatin C and contrast-induced acute kidney injury. *Circulation*. 2010;121:2117–2122.
4. ACT Investigators. Rationale, design, and baseline characteristics of the Acetylcystein for Contrast-Induced Nephropathy (ACT) trial: a pragmatic randomized controlled trial to evaluate the efficacy of acetylcysteine for the prevention of contrast-induced nephropathy. *Trials*. 2009;10:38.
5. Brar SS, Shen AY, Jorgensen MB, Kotlewski A, Aharonian VJ, Desai N, Ree M, Shah AI, Burchette RJ. Sodium bicarbonate vs sodium chloride for the prevention of contrast medium-induced nephropathy in patients undergoing coronary angiography: a randomized trial. *JAMA*. 2008;300:1038–1046.
6. Trivedi H, Daram S, Szabo A, Bartorelli AL, Marenzi G. High-dose N-acetylcysteine for the prevention of contrast-induced nephropathy. *Am J Med.* 2009;122:874.e9–874.e15.
7. Merten GJ, Burgess WP, Gray LV, Holleman JH, Roush TS, Kowalchuk GJ, Bersin RM, Van Moore A, Simonton CA 3rd, Rittase RA, Norton HJ, Kennedy TP. Prevention of contrast-induced nephropathy with sodium bicarbonate: a randomized controlled trial. *JAMA*. 2004;291:2328–2334.
8. Briguori C, Airoldi F, D'Andrea D, Bonizzoni E, Morici N, Focaccio A, Michev I, Montorfano M, Carlino M, Cosgrave J, Ricciardelli B, Colombo A. Renal Insufficiency Following Contrast Media Administration Trial (REMEDIAL): a randomized comparison of 3 preventive strategies. *Circulation*. 2007;115:1211–1217.
9. Stevens MA, McCullough PA, Tobin KJ, Speck JP, Westveer DC, Guido-Allen DA, Timmis GC, O'Neill WW. A prospective randomized trial of prevention measures in patients at high risk for contrast nephropathy: results of the P.R.I.N.C.E. Study: Prevention of Radiocontrast Induced Nephropathy Clinical Evaluation. *J Am Coll Cardiol*. 1999;33:403–411.
10. Liss P, Nygren A, Ulfendahl HR, Erikson U. Effect of furosemide or mannitol before injection of a non-ionic contrast medium on intrarenal oxygen tension. *Adv Exp Med Biol*. 1999;471:353–359.
11. Solomon R, Werner C, Mann D, D'Elia J, Silva P. Effects of saline, mannitol, and furosemide to prevent acute decreases in renal function induced by radiocontrast agents. *N Engl J Med*. 1994;331:1416–1420.
12. Weinstein JM, Heyman S, Brezis M. Potential deleterious effect of furosemide in radiocontrast nephropathy. *Nephron*. 1992;62:413–415.
13. Resnic FS, Davidson C, Zelman R, Dixon SR, Rudko R, Dorval JF. Prevention of contrast induced nephropathy using high volume matched diuresis using the RenalGuard System: first-in-man study [abstract]. *J Am Coll Cardiol*. 2009;53:A36.
14. Briguori C, Visconti G, Ricciardelli B, Condorelli G. Renal Insufficiency Following Contrast Media Administration Trial II (REMEDIAL II): RenalGuard system in high-risk patients for contrast-induced acute kidney injury: rationale and design. *EuroIntervention*. 2011;6:1117–1122.
15. KDOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis*. 2002;39:S1–266.
16. Mehran R, Aymong ED, Nikolsky E, Lasic Z, Iakovou I, Fahy M, Mintz GS, Lansky AJ, Moses JW, Stone GW, Leon MB, Dangas G. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. *J Am Coll Cardiol*. 2004;44:1393–1399.
17. Declaration of Helsinki. Ethical principles for medical research involving human subjects. *J Indian Med Assoc* 2009;107:403–405.
18. Anello C, O'Neill RT, Dubey S. Multicentre trials: a US regulatory perspective. *Stat Methods Med Res*. 2005;14:303–318.
19. Briguori C, Colombo A, Violante A, Balestrieri P, Manganelli F, Paolo Elia P, Golia B, Lepore S, Riviezzo G, Scarpato P, Focaccio A, Librera M, Bonizzoni E, Ricciardelli B. Standard vs double dose of n-acetylcysteine to prevent contrast agent associated nephrotoxicity. *Eur Heart J*. 2004;25:206–211.
20. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care*. 2007;11:R31.
21. Marenzi G, Marana I, Lauri G, Assanelli E, Grazi M, Campodonico J, Trabattoni D, Fabbiocchi F, Montorsi P, Bartorelli AL. The prevention of radiocontrast-agent-induced nephropathy by hemofiltration. *N Engl J Med*. 2003;349:1333–1340.

22. Tepel M, Aspelin P, Lameire N. Contrast-induced nephropathy: a clinical and evidence-based approach. *Circulation*. 2006;113:1799–1806.
23. Marenzi G, Assanelli E, Marana I, Lauri G, Campodonico J, Grazi M, De Metrio M, Galli S, Fabbiocchi F, Montorsi P, Veglia F, Bartorelli AL. N-acetylcysteine and contrast-induced nephropathy in primary angioplasty. *N Engl J Med*. 2006;354:2773–2782.
24. Briguori C, Quintavalle C, De Micco F, Condorelli G. Nephrotoxicity of contrast media and protective effects of acetylcysteine. *Arch Toxicol*. 2010;85:165–73.
25. Romano G, Briguori C, Quintavalle C, Zanca C, Rivera NV, Colombo A, Condorelli G. Contrast agents and renal cell apoptosis. *Eur Heart J*. 2008;29:2569–2576.
26. Persson PB, Hansell P, Liss P. Pathophysiology of contrast medium-induced nephropathy. *Kidney Int*. 2005;68:14–22.
27. Tumlin J, Stacul F, Adam A, Becker CR, Davidson C, Lameire N, McCullough PA. Pathophysiology of contrast-induced nephropathy. *Am J Cardiol* 2006;98:14K–20K.
28. Levin HR, Gelfand M, Wang J. Contrast-induced nephropathy is completely prevented by high volume diuresis with matched replacement of intravascular volume. *Cardiovasc Revasc Med*. 2007;8:123.
29. Dussol B, Morange S, Loundoun A, Auquier P, Berland Y. A randomized trial of saline hydration to prevent contrast nephropathy in chronic renal failure patients. *Nephrol Dial Transplant*. 2006;21:2120–2126.
30. Majumdar SR, Kjellstrand CM, Tymchak WJ, Hervas-Malo M, Taylor DA, Teo KK. Forced euvolemic diuresis with mannitol and furosemide for prevention of contrast-induced nephropathy in patients with CKD undergoing coronary angiography: a randomized controlled trial. *Am J Kidney Dis*. 2009;54:602–609.
31. Bartorelli AL, Ferrari C, Trabattoni D, Teruzzi G, Marana I, Assanelli E, Gatto P, Marenzi G. Furosemide-induced diuresis with matched hydration compared to standard hydration for contrast-induced nephropathy prevention: preliminary results of the MYTHOS trial. *J Am Coll Cardiol*. 2010;56:B77.
32. Boron WF. Acid-base transport by the renal proximal tubule. *J Am Soc Nephrol*. 2006;17:2368–2382.
33. Wesson DE. Glomerular filtration effects of acute volume expansion: importance of chloride. *Kidney Int*. 1987;32:238–245.
34. Dharnidharka VR, Kwon C, Stevens G. Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis. *Am J Kidney Dis*. 2002;40:221–226.
35. Newman DJ, Thakkar H, Edwards RG, Wilkie M, White T, Grubb AO, Price CP. Serum cystatin c measured by automated immunoassay: a more sensitive marker of changes in GFR than serum creatinine. *Kidney Int*. 1995;47:312–318.
36. Moore LC, Yarimizu S, Schubert G, Weber PC, Schnermann J. Dynamics of tubuloglomerular feedback adaptation to acute and chronic changes in body fluid volume. *Pflugers Arch*. 1980;387:39–45.
37. Klarenbach SW, Pannu N, Tonelli MA, Manns BJ. Cost-effectiveness of hemofiltration to prevent contrast nephropathy in patients with chronic kidney disease. *Crit Care Med*. 2006;34:1044–1051.

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.