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

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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)

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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.

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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]

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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-

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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).

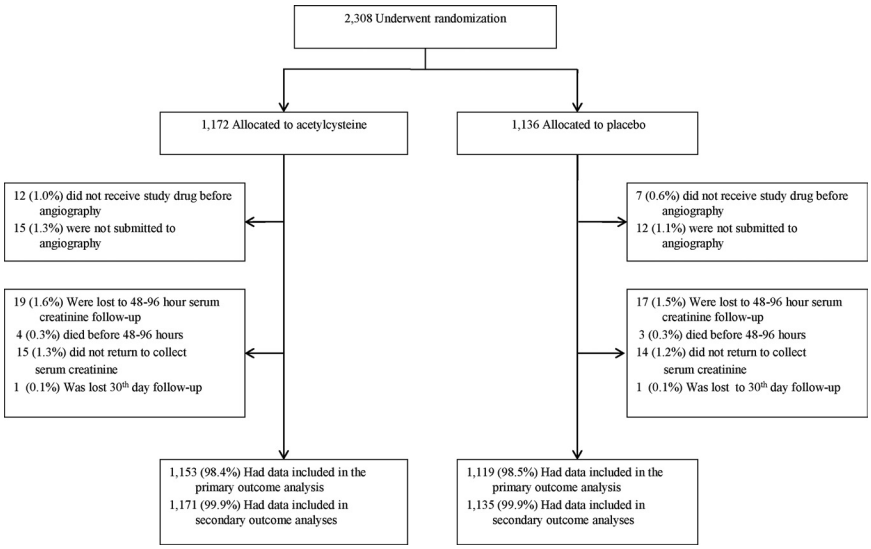

Figure 1. Randomization, study drug adherence, and follow-up of the study patients.

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.

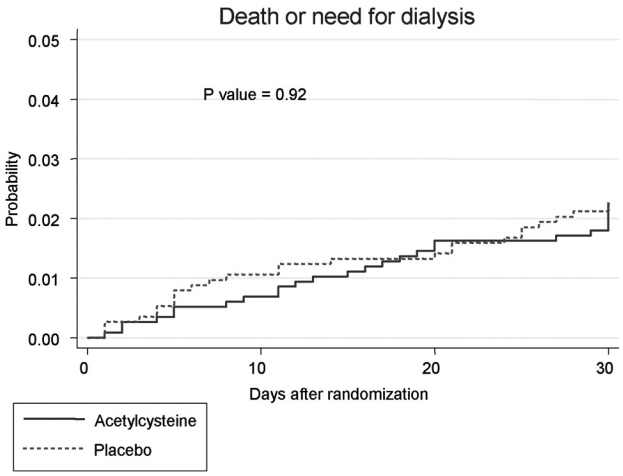

Figure 2. Probability of death or need for dialysis from the day of randomization (day 0) to day 30 among patients in the acetylcysteine and placebo groups.

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.

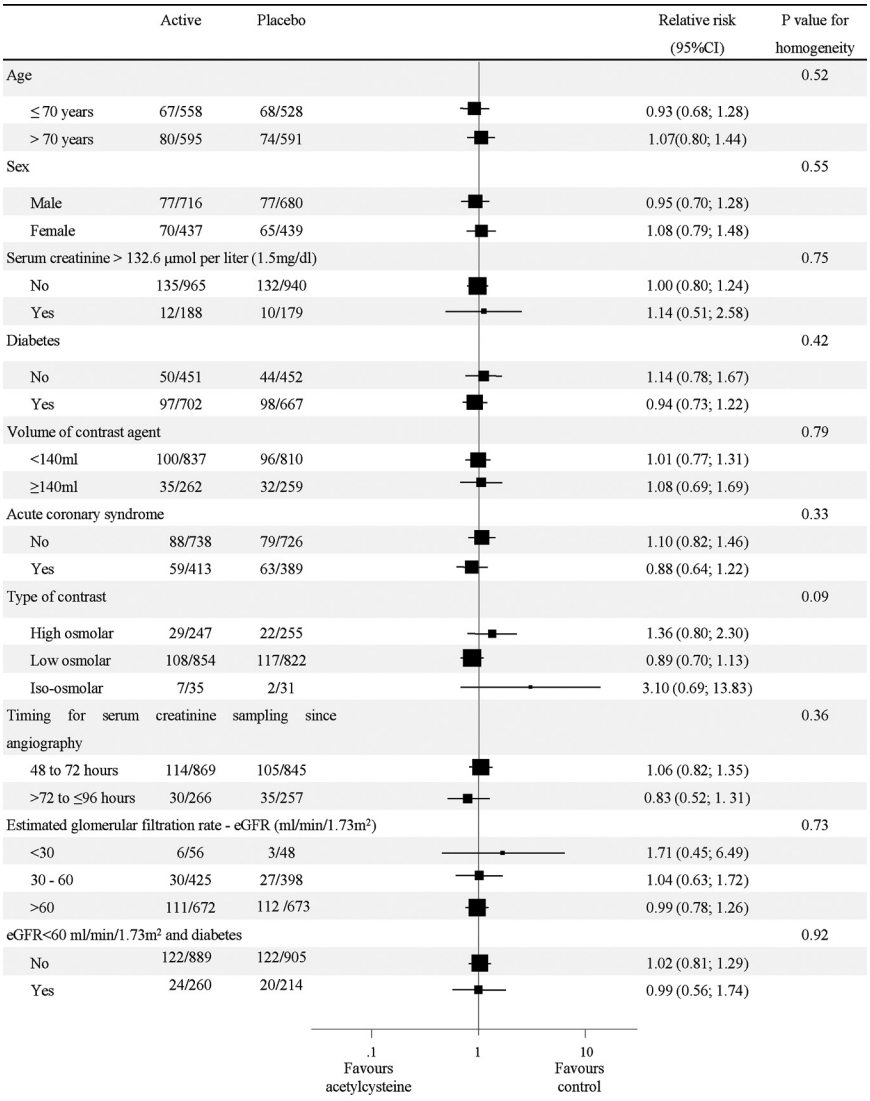

Figure 3. Effect of acetylcysteine on contrast-induced acute kidney injury according to subgroup. CI indicates confidence interval; eGFR, estimated glomerular filtration rate.

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-

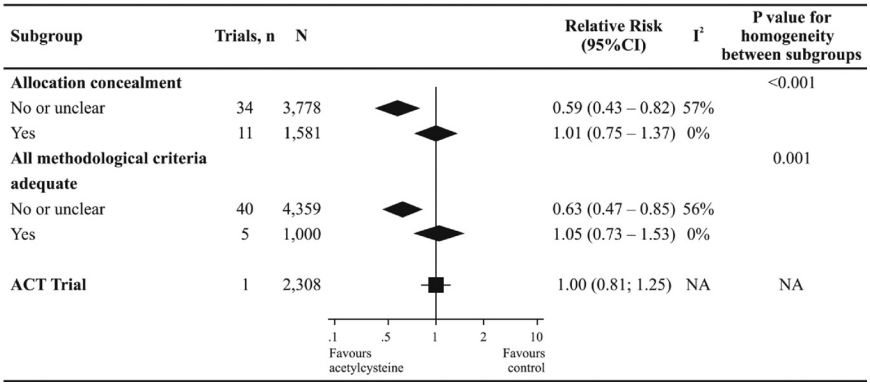

Figure 4. Meta-analyses of randomized controlled trials of acetylcysteine for preventing contrast-induced acute kidney injury stratified according to methodological criteria and the Acetylcysteine for Contrast-Induced Nephropathy Trial (ACT) main result. I^2 represents the percentage of total variation 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.

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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

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