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Acetylcysteine and Contrast Agent-Associated Nephrotoxicity

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OBJECTIVES Prophylactic acetylcysteine along with hydration seems to be better than hydration alone in preventing the reduction in renal function induced by a contrast dye.

BACKGROUND Contrast media can lead to acute renal failure that may occasionally require hemodialysis.

METHODS One hundred eighty-three consecutive patients with impairment of renal function, undergoing coronary and/or peripheral angiography and/or angioplasty, were randomly assigned to receive 0.45% saline intravenously and acetylcysteine (600 mg orally twice daily; group A, n = 92) or 0.45% saline intravenously alone (group B, n = 91) before and after nonionic, low-osmolality contrast dye administration.

RESULTS The baseline serum creatinine concentrations were similar (1.5 ± 0.4 mg/dl in group A vs. 1.5 ± 0.4 mg/dl in group B; p = 0.37). An increase of ≥25% in the baseline creatinine level 48 h after the procedure occurred in 6 (6.5%) of 92 patients in group A and in 10 (11%) of 91 patients in group B (p = 0.22). In the subgroup with a low (<140 ml) contrast dose, renal function deterioration occurred in 5 (8.5%) of 60 patients in group B and in 0 of 60 patients in group A (p = 0.02; odds ratio [OR] 0.44, 95% confidence interval [CI] 0.35 to 0.54). In the subgroup with a high contrast dose, no difference was found (5/31 vs. 6/32 patients, p = 0.78). By multivariate analysis, the amount of contrast agent, but not the treatment strategy, was a predictor of the occurrence of contrast dye–associated nephrotoxicity (OR 2.58, 95% CI 1.1 to 4.9; p = 0.035).

CONCLUSIONS In patients with reduced renal function undergoing angiography and/or angioplasty, the amount of contrast agent, but not the administration of prophylactic acetylcysteine, was a predictor of renal function deterioration. Prophylactic acetylcysteine might provide better protection than hydration alone, only when a small volume of contrast agent is used. (J Am Coll Cardiol 2002;40:298–303) © 2002 by the American College of Cardiology Foundation

Radiocontrast media can lead to a reversible form of acute renal failure that begins soon after contrast dye administration and that is generally benign (1). However, especially in high-risk patients, transient dialysis may be required. This renal failure requiring dialysis after a coronary intervention is associated with poor outcomes, including 40% in-hospital mortality and 19% two-year survival (2–4). The mechanism by which contrast-induced renal failure occurs is not well known. The two major theories, based largely on studies in experimental animals, are renal vasoconstriction, possibly mediated by an alteration in nitric oxide and/or endothelin, and direct toxic effects of the contrast agents (5–10).

The ability to more effectively prevent contrast-associated nephrotoxicity in high-risk patients will result in significant public health benefits by reducing in-hospital mortality, the hospital stay and the need for dialysis. Periprocedural hydration (11) and the use of a small amount of low-osmolality contrast agent (12–15) are generally considered worldwide in patients at risk of contrast-associated nephrotoxicity. Recently, Tepel et al. (16) reported that *N*-acetylcysteine along with hydration is more effective than hydration alone in preventing contrast-associated nephrotoxicity in patients with chronic renal insufficiency treated with an intravenous contrast dye. In the present study, we sought to demonstrate the efficacy of such a strategy in patients with impairment of renal function who were referred to our institution for coronary and/or peripheral angiography and/or angioplasty.

METHODS

Patient group. From September 2000, 183 consecutive patients with impairment of renal function (serum creatinine concentration >1.2 mg/dl and/or estimated creatinine clearance <70 ml/min) were referred to our institution to undergo elective coronary and/or peripheral angiography and/or angioplasty. Patients were randomly assigned to receive the antioxidant acetylcysteine and intravenous saline before and after administration of the contrast agent (group A) or saline alone (group B). Acetylcysteine was given orally at a dose of 600 mg twice daily, on the day before and on the day of administration of the contrast agent, for a total of two days. Saline (0.45%) was given intravenously at a rate of 1 ml/kg body weight per hour for 12 h before and 12 h after administration of the contrast agent (11). Iopromide (Ultravist-370, 0.769 mg/ml, 370 mg iodine/ml; Schering, Berlin, Germany), a nonionic, low-osmolality contrast agent, was used. None of the patients received theophylline,

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Abbreviations and Acronyms

CI = confidence interval
CrCl = creatinine clearance
OR = odds ratio
PCI = percutaneous coronary intervention
ROC = receiver operating characteristic

dopamine, mannitol or furosemide during the study. Serum creatinine and urea nitrogen levels were measured immediately before and 48 h after administration of the contrast agent; further measurements were performed in all cases of contrast-associated nephrotoxicity. Creatinine clearance (CrCl) was calculated by applying the Cockcroft-Gault formula to the baseline serum creatinine level: CrCl = ([140 − age] × weight/serum creatinine × 72), with female gender adjustment: $CrCl_{female}$ = CrCl × 0.85 (17). Proteinuria was determined by urinalysis (immunometric assay, NycoCard U-Albumin, Axus-Schiled PoCAS, Oslo, Norway) the day before contrast agent administration (18). Proteinuria is traditionally divided into microalbuminuria and macroalbuminuria. Microalbuminuria is defined as a protein excretion of 30 to 300 mg/24 h. Macroalbuminuria is defined as a protein excretion of >300 mg/24 h. An early contrast agent-induced reduction in renal function was defined as an increase in the serum creatinine concentration of ≥25% of the baseline value at 48 h or the need for dialysis after administration of the contrast media (8,15). Acute renal failure requiring dialysis was defined as a decrease in renal function necessitating immediate hemodialysis, ultrafiltration or peritoneal dialysis in the first five days after the intervention. The local ethics committee approved the study protocol, and all patients gave written, informed consent.

Statistical analysis. Continuous variables are given as the mean value ± SD. The unpaired Student *t* test was performed to determine differences between mean values for continuous variables, as appropriate. Creatinine and proteinuria concentrations were not normally distributed; therefore, the nonparametric Wilcoxon and Mann-Whitney *U* tests assessed intragroup and intergroup differences, respectively. Categorical variables were analyzed by the chi-square test. Changes in the serum creatinine concentration from baseline between groups were tested by two-way repeated measures analysis of variance, with the treatment strategy (as defined in groups A and B), time period and time × treatment strategy interaction as fixed effects and patient as a random effect. Receiver operating characteristic (ROC) curve analysis was performed to establish the value of the contrast volume most predictive of an early contrast agent-induced reduction in renal function. Multiple logistic regression was performed with the early contrast agent-induced reduction in renal function as the dependent variable. The treatment strategy (as defined in groups A and B) and the amount of contrast dye were entered into the multivariable model to test for independent effects. Probability values <0.05 were considered significant. Data were analyzed with SPSS for Windows, release 10.0 (SPSS Inc., Chicago, Illinois).

Table 1. Clinical Characteristics of the Two Subgroups

	Group A (n = 92)	Group B (n = 91)	p Value
Age (yrs)	64 ± 9	64 ± 9	0.97
Male gender	77 (84%)	81 (89%)	0.35
Body mass index (g/m²)	28 ± 5	28 ± 4	0.95
Blood pressure (mm Hg)			
Systolic	133 ± 16	130 ± 18	0.27
Diastolic	79 ± 8	77 ± 8	0.25
Mean	71 ± 16	72 ± 21	0.55
Left ventricular ejection fraction (%)	51 ± 13	54 ± 12	0.16
Hypertension	66 (72%)	65 (72%)	0.46
Diabetes mellitus	40 (43%)	29 (32.5%)	0.10
Hypercholesterolemia	138 (52%)	97 (56%)	0.70
Coronary artery disease	82 (89%)	80 (88%)	0.69
Single-vessel	25 (30.5%)	19 (23.8%)	
Double-vessel	21 (25.6%)	26 (32.5%)	
Triple-vessel	36 (43.9%)	35 (43.7%)	

Data are presented as the mean value ± SD or number (%) of patients.

RESULTS

Clinical characteristics. The clinical and biochemical characteristics of the patients in the two groups are shown in Tables 1 and 2. One hundred three patients underwent coronary angiography, with an eventual (ad-hoc) percutaneous coronary intervention (PCI) in 22 of the patients. Fifty-six patients underwent elective PCI. The remaining 11 patients had angiography for peripheral artery disease.

Amount of contrast agent. The amount of contrast agent administered was similar between the two groups (194 ± 127 ml in group A vs. 200 ± 144 ml in group B; p = 0.80). Of note, the amount of contrast dye was significantly higher in patients who had ad-hoc PCI (347 ± 182 ml vs. 321 ± 125 ml for PCI alone, 135 ± 72 ml for coronary angiography alone and 114 ± 43 ml for peripheral angiography; p < 0.001).

Table 2. Biochemical Characteristics of the Two Subgroups

	Group A (n = 92)	Group B (n = 91)	p Value
Serum creatinine (mg/dl)			
Baseline	1.52 ± 0.43	1.54 ± 0.36	0.37
After 48 h	1.48 ± 0.36	1.53 ± 0.45	0.55
Clearance creatinine (ml/min)	56 ± 22	54 ± 16	0.82
Proteinuria (mg/24 h)	214 ± 433	110 ± 142	0.40
Macroalbuminuria* (mg/24 h)	12.5%	13%	0.94
Serum urea nitrogen (mg/dl)	56 ± 22	54 ± 16	0.66
Serum sodium (mEq/l)	142 ± 4	142 ± 4	0.84
Serum potassium (mEq/l)	4.8 ± 0.6	4.8 ± 0.5	0.86
Drugs assumed			
ACE inhibitors	52 (56.5%)	60 (55%)	0.84
Calcium antagonists	33 (36.2%)	42 (38.4%)	0.92
AT-II antagonists	12 (13%)	8 (7%)	0.21
Diuretics	31 (33.7%)	42 (38%)	0.57

*Protein excretion >300 mg/24 h. Data are presented as the mean value ± SD or number (%) of patients.
ACE = angiotensin-converting enzyme; AT-II = angiotensin II.

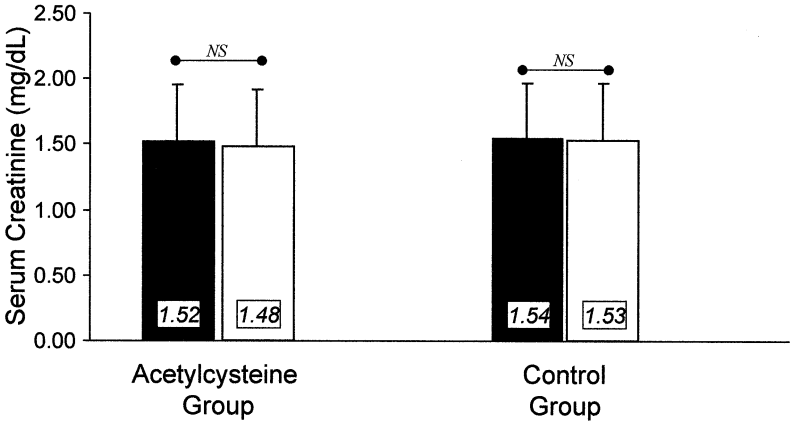

Figure 1. Serum creatinine concentration at baseline **(solid bar)** and at 48 h **(open bar)** after contrast dye administration in patients treated with acetylcysteine and hydration (Acetylcysteine Group) and in those treated with hydration alone (Control Group). **Brackets** represent the standard deviation. There was no statistically significant interaction between the changes in the serum creatinine concentration from baseline and the treatment strategy ($F = 0.026$, $p = 0.87$) by the two-way analysis of variance for repeated measures.

Contrast agent-associated nephrotoxicity. The mean serum creatinine concentration for all patients was 1.52 ± 0.40 mg/dl (range 1.25 to 4.84 mg/dl). In group A, the mean serum creatinine concentration decreased from 1.52 ± 0.43 mg/dl (range 1.25 to 4.84) to 1.48 ± 0.36 mg/dl 48 h after contrast agent administration (Fig. 1). In group B, the mean serum creatinine concentration decreased from 1.54 ± 0.36 mg/dl (range 1.26 to 3.20) to 1.53 ± 0.46 mg/dl (Fig. 1). There was no statistically significant interaction between the changes in serum creatinine concentration from baseline and the treatment strategy ($F = 0.026$, $p = 0.87$) (Fig. 1).

Acute contrast agent-associated nephrotoxicity occurred in 6 (6.5%) of 92 patients in group A and in 10 (11%) of 91 patients in group B ($p = 0.22$). Renal failure requiring temporary dialysis occurred in only one patient in group B (1.1%).

The amount of contrast agent, even thought slightly higher in group A, was not statistically different in the 16 patients of the two groups who had contrast agent-associated nephrotoxicity (348 ± 159 ml in group A and 192 ± 115 ml in group B; $p = 0.15$). We found a significant, direct correlation between the absolute change in serum creatinine concentration and the amount of contrast agent in group A only ($r = 0.42$, $p < 0.001$) (Fig. 2), but not in group B ($r = 0.07$, $p = 0.59$). By ROC analysis, we identified a contrast media volume ≥140 ml as the best cutoff value to predict the occurrence of contrast-associated nephrotoxicity (sensitivity 89%, specificity 55%). In the subgroup with a small (<140 ml) contrast dose, significant renal function deterioration occurred in 5 (8.5%) of 60 patients in group B and in none in group A ($p = 0.020$; odds ratio [OR] 0.44, 95% confidence interval [CI] 0.35 to 0.54). In the subgroup with a high (≥140 ml) contrast dose, the event occurred in 5 (16%) of 31 patients in group B and in 6 (18.8%) of 32 patients in group A ($p = 0.78$). Proteinuria levels and the macroalbuminuria rate were similar in patients with and without contrast-associated nephrotoxicity (138 ± 123 mg/24 h vs. 163 ± 318 mg/24 h, $p = 0.66$; and 13% vs. 12.5%, $p = 0.94$, respectively).

A baseline serum creatinine concentration above 1.8 mg/dl occurred in 31 patients (34%) in group A and in 33 patients (36%) in group B ($p = 0.27$). Among these patients, two in group A (6.5%) and six in group B (18%) had an early contrast agent-induced reduction in renal function ($p = 0.16$). Importantly, among the subgroup of patients who received a low amount of contrast agent (13/31 in group A and 16/33 in group B; $p = 0.6$), none of the 13 patients in group A had acute renal function impairment, although this complication occurred in 4 (25%) of the 16 patients in group B ($p = 0.049$; OR 0.75, 95% CI 0.56 to 0.99). In contrast, there was no significant difference when a high volume of contrast dye was administered (2/18 in group A vs. 2/17 in group B; $p = 0.15$).

By logistic regression analysis, the amount of contrast agent administered (OR 2.58, 95% CI 1.1 to 4.9; $p = 0.035$), but not the treatment strategy (as defined in groups A and B) (OR 0.6, 95% CI 0.18 to 2.02; $p = 0.41$), was a predictor of acute renal function deterioration.

DISCUSSION

Radiographic contrast media account for 10% of all causes of hospital-acquired acute renal failure and represent the third most common cause of in-hospital renal function deterioration after decreased renal perfusion and postoperative renal insufficiency (19). Persistent renal failure is rare and has been described primarily with far-advanced underlying disease (2–4). The in-hospital mortality rate in patients developing renal insufficiency is directly related to the magnitude of the increase in the serum creatinine concentration (2–4). The mortality rate ranges from 3.8% with an increase in serum creatinine of 0.5 to 0.9 mg/dl to 64% with an increase of >3.0 mg/dl (20). The ability to more effectively prevent contrast-associated nephrotoxicity in high-risk patients will provide significant public health

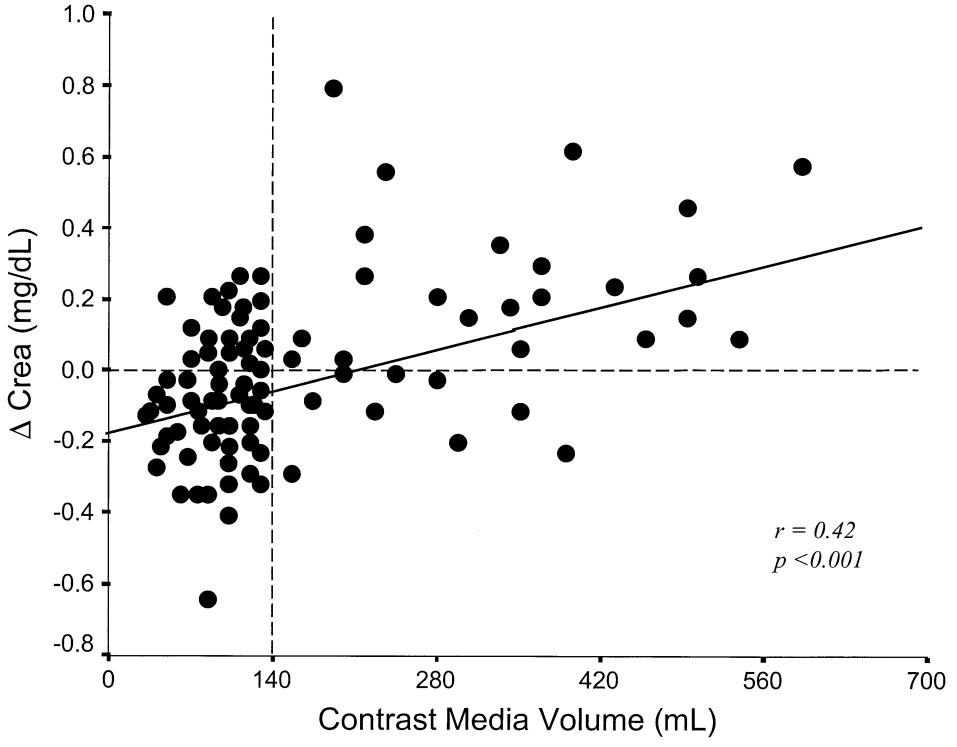

Figure 2. Change in creatinine concentration (ΔCrea) from baseline, plotted as a function of the amount of contrast dye administered in the acetylcysteine group. The **horizontal dashed line** represents ΔCrea = 0; the **vertical dashed line** represents the cutoff value (140 ml) for small and large amounts of contrast dye.

benefits as we reduce the in-hospital mortality rates, hospital stay and need for dialysis.

The main results of the present study are: 1) the most important predictor of contrast dye-associated nephrotoxicity is the amount of contrast dye administered; and 2) prophylactic administration of saline and acetylcysteine might be more effective than saline alone in preventing contrast-associated nephrotoxicity only when a small (<140 ml) amount of a nonionic, low-osmolality contrast dye is used.

Previous studies on prevention of contrast-associated nephrotoxicity. Optimal therapy to prevent contrast-associated nephrotoxicity remains uncertain. Trials of prophylactic measures in humans have evaluated hydration strategies, furosemide, mannitol, dopamine, calcium-channel blocks and atrial natriuretic peptide (11,21–25). In general, all of the previous prevention trials have shown no consistent benefit, and in some cases, a deleterious effect was seen with the use of dopamine (21,25), mannitol (22), forced diuresis (22), atrial natriuretic peptide (24) or aminophylline (23,25) for contrast-associated nephrotoxicity. Solomon et al. (11) showed in a randomized trial that saline hydration is more effective than saline plus furosemide or mannitol in preventing an increase in the postprocedural serum creatinine level. Therefore, at present, only periprocedural hydration (11) and the use of a low-osmolality contrast agent (12–15) are universally considered in patients at high risk of contrast-associated nephropathy.

Acetylcysteine and contrast-associated nephrotoxicity. Considerable enthusiasm has resulted from the preliminary study by Tepel et al. (16) of acetylcysteine in patients with chronic renal failure receiving intravenous contrast dye. The study included 83 patients with a creatinine plasma level ≥1.2 mg/dl (and/or clearance <50 ml/h) who were undergoing computed tomography with a constant dose of 75 ml iopromide, a nonionic, low-osmolality contrast agent. These patients were randomly treated with hydration plus placebo (n = 45) or hydration plus acetylcysteine (600 mg orally twice daily) before and after administration of the contrast agent. Ten (12%) of the 83 patients had an increase of at least 0.5 mg/dl in the serum creatinine concentration 48 h after administration of the contrast agent: 1 (2%) of the 41 patients in the acetylcysteine group and 9 (21%) of the 42 patients in the control group ($p = 0.01$, relative risk = 0.1, 95% CI 0.02 to 0.9). In the acetylcysteine group, the mean serum creatinine concentration decreased significantly ($p < 0.001$) from 2.5 ± 1.3 mg/dl to 2.1 ± 1.3 mg/dl at 48 h after the administration of the contrast medium, whereas in the control group, the mean serum creatinine concentration increased nonsignificantly ($p = 0.18$) from 2.4 ± 1.3 mg/dl to 2.6 ± 1.5 mg/dl.

In our study, we did not find any significant effect on the occurrence of contrast-associated nephrotoxicity with acetylcysteine treatment. In fact, the occurrence of an increase of at least 25% of the baseline level in the serum creatinine concentration 48 h after administration of the contrast agent

was as follows: 6 (6.5%) of the 92 patients in the acetylcysteine group and 10 (11%) of the 91 patients in the control group ($p = 0.22$). The discordance between our study and Tepel et al. study (16) may be explained by the differences in the amount of contrast dye used and in the baseline level of renal function. In the study by Tepel et al. (16), a constant, low (75 ml) dose of contrast agent was administered. In contrast, in our study, the amount of contrast dye used was variable because of the different type of examination. Importantly, in accordance with Tepel et al. (16), we found a significant benefit of acetylcysteine administration only in the subgroup of patients receiving a small (<140 ml) amount of contrast dye. Therefore, it may be that acetylcysteine has a protective effect against contrast-associated nephrotoxicity only when a low amount of contrast dye is administered. Furthermore, the baseline mean creatinine level was higher in the study by Tepel et al. (16) (2.4 ± 1.3 mg/dl) than in ours. Some data exist that identify the baseline level of renal function as a predictor of contrast-induced nephrotoxicity (26).

Potential mechanisms of acetylcysteine's protective effect. The mechanism by which contrast-induced renal failure occurs is not well understood. The two major theories, based largely on studies in experimental animals, are renal vasoconstriction and direct toxic effects of the contrast agents (5–10). Renal vasoconstriction occurs relatively commonly; it is mediated in part by contrast-induced release of endothelin and adenosine, by alterations in nitric oxide and by the high osmolality of the contrast agent (5–8). The toxic renal damage may cause tubular injury, leading to the generation of oxygen free radicals, which are considered as important modulators of renal blood flow and the glomerular filtration rate (9,10,27,28).

N-acetylcysteine, a reduced thiol, is a precursor of L-cysteine and may serve as a precursor for glutathione synthesis. *N*-acetylcysteine improves endothelium-dependent vasomotion in the coronary and peripheral circulation (28) and is a potent antioxidant that may scavenge a wide variety of oxygen-derived free radicals (28–30). The ability of *N*-acetylcysteine to increase intracellular and extracellular glutathione might be a crucial factor in protecting renal tissue in contrast-induced damage (29). Therefore, acetylcysteine may be capable to preventing contrast-associated nephrotoxicity by both improving renal hemodynamic and preventing direct oxidative tissue damage.

Role of the amount of contrast dye. There is a debate whether the quantity of the contrast agent predicts the degree of renal dysfunction. Some studies have reported no relationship between the amount of contrast material and the occurrence of renal function deterioration, whereas others have suggested a direct correlation (31,32). There is, however, a general consensus on the use of a small dose of contrast dye, and the avoidance of repetitive, closely spaced studies represents one of the most important recommendations to prevent contrast-associated nephrotoxicity (13–15). A low dose has been variably defined as <70 ml, <125 ml or <5 ml/kg (to a maximum of 300 ml), divided by the plasma creatinine concentration (12). McCullough et al. (4) found that no patient who received <100 ml of contrast dye required dialysis after contrast exposure. In the present study, the amount of contrast agent administered was an independent predictor of the occurrence of contrast dye-associated nephrotoxicity. The main dose for coronary angiography is 130 ml and that for PCI is 191 ml (33). We identified a volume of 140 ml as the best cutoff value for predicting the occurrence of contrast media-associated nephrotoxicity. These data emphasize the necessity for limiting the amount of contrast dye used when dealing with patients with impaired renal function. In particular, the avoidance of repetitive, closely spaced studies and the ad-hoc PCI, favoring a staged, or two-step, procedure, may represent an important strategy to prevent contrast-associated nephrotoxicity in high-risk patients.

Study limitations. Serum creatinine was only measured after 48 h. Therefore, we may have missed a later increase in serum creatinine in some patients who did not have renal function deterioration within 48 h of their procedure. Our positive finding—that is, the effectiveness of the combination of oral acetylcysteine along with hydration only with a small amount of contrast media—is based on a post-hoc analysis of a small group of patients. Our results need to be verified in a larger group of patients with more severe baseline renal insufficiency.

Conclusions. In patients with reduced renal function undergoing angiography and/or angioplasty, the amount of contrast agent, but not the prophylactic acetylcysteine treatment, is a predictor of acute renal function deterioration. Prophylactic acetylcysteine might provide better protection than hydration alone, only when a small volume of contrast agent is used.

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