Editor's Capsule Summary

What is already known on this topic

Except for intravenous saline solution administration, little consensus exists about strategies to reduce contrast-induced nephropathy.

What question this study addressed

Does N-acetylcysteine in addition to saline solution administered to patients undergoing intravenous contrast computed tomography (CT) in the emergency department (ED) reduce the rate of contrast-induced nephropathy above that of saline solution administration alone?

What this study adds to our knowledge

N-acetylcysteine did not reduce the rate of contrast-induced nephropathy in the 357-patient target population, but the volume of saline solution infusion was associated with a decrease in contrast-induced nephropathy.

How this is relevant to clinical practice

N-acetylcysteine is not needed as an adjunct to reduce contrast-induced nephropathy among most ED patients undergoing contrast CT, but higher-volume fluid administration was useful.

emergency department (ED) patients are particularly limited because most contrast-induced nephropathy studies enroll either stable outpatients or patients undergoing emergency cardiac catheterization, neither of which may be representative of emergency patients undergoing CT.

Goals of This Investigation

Given these uncertainties, we sought to study the role of N-acetylcysteine in the prevention of contrast-induced nephropathy in emergency CT by performing a randomized, double-blind, placebo-controlled trial testing the hypothesis that intravenous N-acetylcysteine plus saline solution is superior to intravenous saline solution alone.

MATERIALS AND METHODS

Study Design and Setting

This was a randomized, double-blind, placebo-controlled trial conducted in the EDs at 2 tertiary care, urban university hospitals: Beth Israel Deaconess Medical Center in Boston, MA (adult census >50,000 visits/year), and Carolinas Medical Center in Charlotte, NC (adult census >100,000 visits/year). Randomization was stratified both by study site and whether the clinician intended to use sodium bicarbonate infusion.

Selection of Participants

Patients were eligible for the study if they were undergoing emergency contrast-enhanced CT of the chest, abdomen, or pelvis as part of clinical care, were aged 18 years or older, were willing to have a serum creatinine level measured 48 to 72 hours after CT scan, and had 1 or more risk factors suggesting an elevated risk of contrast-induced nephropathy: preexisting renal dysfunction (creatinine level 1.4 mg/dL or higher or estimated glomerular filtration rate of less than 60 mL/minute per 1.73 m^2),[45] diabetes mellitus, hypertension being treated with antihypertensive medications, coronary artery disease, use of nephrotoxic drugs (cyclosporine A, aminoglycosides, amphotericin, cisplatin, or nonsteroidal anti-inflammatory drugs), liver disease, congestive heart failure (active or by history), older age (65 years of age or older), and anemia (hematocrit level less than 30%). Patients were excluded if they were unable or unwilling to provide written informed consent, had end-stage renal disease currently undergoing regular peritoneal or hemodialysis, were pregnant, had a known allergy to N-acetylcysteine, were judged by the treating physicians to be clinically unstable (30 minute delay for infusion of study medication or placebo was contraindicated), or were being treated with N-acetylcysteine as part of their clinical care. Patients were enrolled primarily during day and evening hours.

Interventions

Patients in the treatment group received 3 g of N-acetylcysteine in 500 mL normal saline solution during 30 minutes before contrast administration. After contrast administration, patients received a continuous infusion of 200 mg of N-acetylcysteine per hour, administered as an infusion of 67 mL per hour of a solution of 3 g of N-acetylcysteine diluted to a total volume of 1,000 mL with normal saline solution. Patients in the placebo group received 500 mL of normal saline solution during 30 minutes before contrast administration and a continuous infusion of 67 mL per hour of normal saline solution after contrast administration. Patients in both arms received the postcontrast infusion (N-acetylcysteine or saline solution) for a minimum of 2 hours. Then, the postcontrast infusion was stopped when one of the following occurred: the patient was discharged from the ED, the post-CT infusion was stopped at the discretion of the clinical team caring for the patient, the patient was discharged from the hospital, or 24 hours elapsed. The postcontrast infusion was also discontinued with the development of any of the following adverse reactions considered severe enough to require discontinuation of the study infusion: symptomatic hypotension requiring treatment, altered mental status, respiratory distress, pulmonary edema, oropharyngeal edema or bronchospasm requiring treatment, severe urticaria or patient discomfort, or any other event considered severe enough by the clinical team treating the patient to require discontinuation. In such cases, treatment allocation was also unblinded at the request of the clinical team treating the patient. We also recorded and report the development of any new symptoms that occurred temporally

with the study infusion (N-acetylcysteine or placebo), regardless of the need to discontinue the infusion.

Outcome Measures

The primary outcome of contrast-induced nephropathy was defined a priori as an increase in serum creatinine level of greater than or equal to 0.5 mg/dL or an increase of 25% above baseline, a commonly used definition.[4,5,28,46] The primary outcome was measured by the change in serum creatinine level from the pre-radiocontrast baseline to the serum creatinine level measured 48 to 72 hours after radiocontrast administration.

Baseline serum creatinine level was measured with a serum sample drawn before radiocontrast administration. To obtain the follow-up sample, inpatients underwent phlebotomy in the hospital; outpatients underwent phlebotomy either by returning to the hospital or during a home visit from an outpatient phlebotomist, with the exception of 1 patient whose blood was drawn at a commercial laboratory.

Secondary outcomes included moderate renal injury (defined as a 100% increase in serum creatinine level) or severe renal failure necessitating renal replacement therapy (peritoneal or hemodialysis). We performed a follow-up telephone call to identify patients who had clinically significant renal injury beyond the 72-hour period.

Anticipating that patients would receive variable amounts of intravenous crystalloid as part of their clinical care in the emergency setting, we abstracted from the chart and recorded the volume of intravenous crystalloid administered within 24 hours of enrollment. We also planned a subanalysis to test the hypothesis that intravenous crystalloid decreases the incidence of contrast-induced nephropathy in a volume-dependent fashion.

Similarly, we also anticipated that patients may receive 1 or more literature-derived prophylactic treatments (such as intravenous fluids) for contrast-induced nephropathy. These clinician-initiated treatments were not excluded by the protocol. We recorded the use of these treatments and these data for inclusion in the planned multivariate analysis.

Sodium bicarbonate is one of the most common clinician-initiated treatments utilized to prevent contrast-induced nephropathy in the emergency setting. To address this potential source of confounding, we used blocked randomization. Although the decision to use sodium bicarbonate was left to the treating physician, if it was used we recommended a standardized dose of 132 mEq sodium bicarbonate in 1 L of 5% dextrose prepared by removing 150 mL of fluid from a 1-L bag of 5% dextrose in water and adding 3 ampules of 8.4% sodium bicarbonate (44 mEq sodium bicarbonate/50 mL solution). We recommended that this solution be infused at 3 mL/kg per hour for 1 hour before radiocontrast administration and then at 1 mL/kg per hour for the 6 hours after contrast administration. A similar (but not identical) regimen has been described previously[47] and is consistent with clinician-initiated treatment protocols available at both institutions.

Finally, because preexisting renal dysfunction is consistently identified as a strong risk factor for contrast-induced nephropathy in other settings, we also planned a subanalysis of patients with a precontrast serum creatinine level 1.4 mg/dL or higher or estimated glomerular filtration rate of less than 60 mL/minute per 1.73 m^2.

Primary Data Analysis

Wald 95% confidence intervals (CIs) for the difference in proportions were used to compare the proportion of patients with contrast-induced nephropathy between study groups. Exclusion of zero in the 95% CI for the difference in proportions is analogous to finding a statistically significant difference between the randomized groups. Logistic regression was performed to compare randomized groups while controlling for important potential confounders. After univariate analysis, we chose a 4-variable model that included age as a summary patient variable, congestive heart failure because there was an uneven distribution during randomization, and intravenous fluids because of its significant association with the primary outcome. Odds ratios are reported, along with their 95% CIs. Data analysis was performed with SAS (version 9.2; SAS Institute, Inc., Cary, NC).

Because the volume of intravenous fluid administration could not be predicted at the outset of treatment in the emergency care setting, we could not adjust our randomization method for it. Instead, to assess the robustness of our hypothesis that increased fluids were associated with a decreased probability of developing contrast-induced nephropathy (and to further guard against unmeasured confounding), we performed a propensity score analysis. We assessed the association of possible confounders with the dependent categorical variable of receiving greater than or equal to 1 L of fluids to create the propensity score. We then calculated the propensity score adjusted odds ratio for the relationship between intravenous fluids (per liter) and the development of contrast-induced nephropathy and compared it with the nonpropensity adjusted odds ratio.

Because the study inclusion criteria included only patients with at least 1 literature-derived risk factor for contrast-induced nephropathy, we initially estimated that the rate of contrast-induced nephropathy would be 20%. We powered the study to find a 50% relative reduction in the rate of contrast-induced nephropathy. To find a 10% absolute risk reduction (50% relative risk reduction) with α=.05 and 90% power, assuming a 20% overall prevalence of contrast-induced nephropathy in the control group and a 10% dropout (lost to follow-up) rate, we initially estimated that we would need 294 patients in each arm (588 patients total) and defined the sample size as 600 patients. At the first interim analysis, the study was repowered to 800 patients at the request of the data and safety monitoring board because of a lower-than-projected event rate of 12% in the control group. Assuming the same 50% relative risk reduction with a 10% dropout rate, with α=0.05 and 80% power (reduced from 90%), the revised estimate called for 784 patients. The sample size was therefore reset to 800 patients.

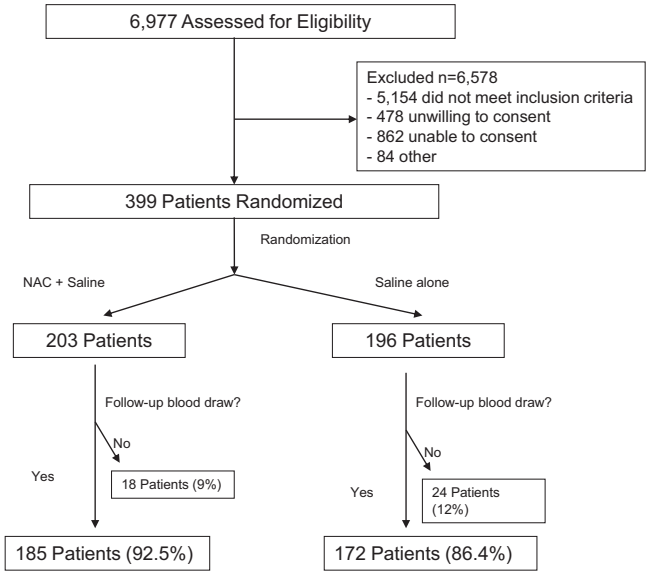


Figure 1. Consort diagram for patient enrollment. *NAC,* N-Acetylcysteine.

We used O'Brien-Fleming stopping criteria for efficacy, with 3 planned interim analyses. In the original analysis plan, significance was defined as follows: 200 patients, $P=0.00058$; 400 patients, $P=0.01506$; and 600 patients, $P=0.04715$. For the revised analysis, we retained the 3 interim analyses with a plan to conduct these at 200 patients, 400 patients, and 800 patients, retaining the same efficacy stopping criteria as above. Stopping for futility or harm was defined at the discretion of the data and safety monitoring board.

The study was approved by the institutional review boards at Beth Israel Deaconess Medical Center and Carolinas Medical Center. All patients enrolled in the study gave written, informed consent. A single data and safety monitoring board was convened to perform a planned analysis of clinical outcomes, morbidity, and mortality at regular intervals of 200 patients.

RESULTS

The study was halted for futility at the second interim analysis by the data and safety monitoring board. The recommendation of the board was that because there was not a strong enough trend toward efficacy, and because the incidence of outcomes was much lower than anticipated, further enrollments would not likely result in an ability to reject the null hypothesis.

Characteristics of Study Subjects

We screened a total of 6,977 patients and enrolled 399 patients in the study (Figure 1), of whom 357 (89.4%) completed a second blood draw to determine outcome and were included in the study. The population was well matched between the treatment and control groups in terms of age, demographics, comorbidities, exposure to contrast agent, and initial renal function (Tables 1 and 2). The baseline serum creatinine level was 1.0 mg/dL (SD 0.3) in both treatment and control groups. The only imbalance in baseline factors was congestive heart failure, which occurred in 4% of the treatment group and 9% of the control group. Both treatment and control groups received moderate intravenous fluid administration in the ED (1,402 [971] versus 1,378 [1,021] mL) (Table 1).

Main Results

The overall rate of contrast-induced nephropathy was 26 of 357 (7.3%). One additional patient who did not have an initial change in creatinine level had detectable renal injury identified during the follow-up telephone call. There were 18 patients in the experimental group (9%) and 24 patients in the control group (12%) who did not complete their second blood draw and were not included in the analysis. The rate of contrast-induced nephropathy in the treatment group of N-acetylcysteine plus saline solution was similar to that of the saline solution alone group (14/185 [7.6%] versus 12/172 [7.0%], for a risk difference of 0.6% [−4.8% to 6.0%]). The absolute change in creatinine level was −0.050 (0.25) versus −0.025 (0.23) (mean difference in groups of 0.025; 95% CI −0.025 to 0.075) (Table 3). Only 1 patient overall (in the N-acetylcysteine plus saline solution group) developed moderate kidney injury, defined as a 100% increase in creatinine level. No patient required renal replacement therapy within the follow-up period.

There were few adverse events, which were self-limited and balanced evenly between the treatment and control groups (Table 4). The adverse reaction was severe enough to require discontinuation of the infusion in only 2 patients (both in the N-acetylcysteine plus saline solution group). No patient developed a severe adverse reaction resulting in death, injury, or prolonged hospitalization.

The total volume of fluid administered in the ED was the only covariate that had an independent association with the reduction of the rate of contrast-induced nephropathy. Although fluid administration in both groups was similar (Figure 2), the rate of contrast-induced nephropathy in patients who received less than 1 L of intravenous fluids was 19 of 147 (12.9%) compared with 7 of 210 (3.3%) in those who received 1 L or more of intravenous fluids, for a risk difference of 9.6% (3.7% to 15.5%) (Figure 3). Our final adjusted model demonstrated that N-acetylcysteine, age, and congestive heart failure did not have a statistically significant association with the development of contrast-induced nephropathy, whereas there was a 69% risk reduction (OR 0.41; 95% CI 0.21 to 0.80) per liter of intravenous fluids administered (Table 5). The c-statistic for model accuracy was 0.67, indicating only a moderate predictive ability for the model. Preexisting renal dysfunction, defined in this study as a creatinine level of 1.4 mg/dL or higher or estimated glomerular filtration rate of less than 60 mL/minute per 1.73 m^2, was not significantly associated with an increased risk of contrast-induced nephropathy.

Because we did not randomize by fluid volume administered, we performed a propensity score adjustment analysis for the

Table 1. Demographics, use of sodium bicarbonate and total fluids by randomized group.*

Parameter	N-Acetylcysteine, N=200	Placebo, N=199
Age, mean (SD) [median; minimum-maximum], y	61.5 (15.3) [62; 28–95]	59.7 (15.9) [59; 18–94]
Sex		
Male	76 (38)	86 (43)
Female	124 (62)	113 (57)
Race		
White	137 (69)	142 (71)
White/Hispanic	1 (1)	0
Black	50 (25)	47 (24)
Asian	1 (1)	2 (1)
Other	11 (6)	8 (4)
Congestive heart failure	7 (4)	18 (9)
CRI, baseline	8 (4)	10 (5)
Coronary artery disease	36 (18)	33 (17)
Myocardial infarction	15 (8)	12 (6)
Diabetes†	65 (33)	64 (32)
Mild DM	51 (26)	48 (24)
Major DM	10 (5)	13 (7)
Hypertension	153 (77)	148 (74)
Liver disease‡	17 (9)	17 (9)
Mild liver disease	8 (4)	5 (3)
Major liver disease	8 (4)	10 (5)
Peripheral vascular disease	7 (4)	5 (3)
Stroke	9 (5)	9 (5)
Reactive airway disease	31 (16)	27 (14)
COPD	14 (7)	13 (7)
Asthma	22 (11)	16 (8)
Malignancy	30 (15)	34 (17)
Solid tumor, no metastasis	20 (10)	14 (7)
Solid tumor, with metastasis	6 (3)	9 (5)
Leukemia or lymphoma	1 (1)	3 (2)
Sodium bicarbonate pretreatment	8 (4.00)	8 (4.02)
Type of IV contrast	193	193
Isovue	12 (6)	13 (7)
Optiray	176 (91)	175 (91)
Visipaque	5 (3)	5 (3)
Volume (in mL) of contrast infused, mean (SD) [median; minimum-maximum]	113.11 (22.95) [130; 65–200]	115.24 (21.06) [130; 25–160]
Total IV fluids plus bolus (in mL) given to administer study medication, mean (SD) [median; minimum-maximum]	1,402 (971) [1,500; 0–5,500]	1,378 (1,021) [1,325; 500–7,100]

IV, Intravenous; *CRI*, Chronic Renal Insufficiency; *DM*, Diabetes Mellitus; *COPD*, Chronic Obstructive Pulmonary Disease.
*Data are presented as No. (%) unless otherwise indicated.
†Major DM is defined as diabetes with the presence of end-organ damage (retinopathy, neuropathy, nephropathy).
‡Minor liver disease is liver disease without ongoing damage (eg, chronic hepatitis C infection); major liver disease is liver disease with ongoing dysfunction or damage (eg, cirrhosis, ascites).

Table 2. Infusion of CT dye and pre- and poststudy CT dye infusion of study medication.

CT Dye and Study Medication Started	N-Acetylcysteine, N=200	Placebo, N=199
Pre-CT dye study medication administered, No. (%)		
Full bolus administered before CT	187 (94)	184 (94)
Bolus not received	6 (3)	3 (2)
Bolus interrupted	5 (3)	4 (2)
Full bolus received after CT	2 (1)	5 (3)
CT dye administered, No. (%)	190 (97)	194 (97)
Postbolus study medication infusion, mean (SD) [median; minimum-maximum], mL	627 (543) [469; 0–1,750]	700 (576) [700; 0–1,650]

tendency to administer more than 1 L of intravenous fluids. We found that 3 factors were associated with reduced fluid administration: age (P=.02), black race (P=.07), and congestive heart failure (P=.05). These factors were used to create a propensity score. After adjusting for our derived propensity score for receiving less than 1 L of fluids, a significant relationship persisted between the amount of fluids administered and the development of contrast-induced

Table 3. Outcomes by randomized group.

Outcome	N-Acetylcysteine, N=185	Placebo, N=172	Mean Difference, (95% CI)*
Baseline creatinine level, mean (SD) [median; minimum-maximum]	1.00 (0.28) [0.9; 0.5 to 1.9]	0.99 (0.27) [0.9; 0.5 to 1.8]	−0.01 (−0.07 to 0.04)
Follow-up creatinine level, mean (SD) [median; minimum-maximum]	0.95 (0.29) [0.9; 0.4 to 2.8]	0.96 (0.31) [0.9; 0.4 to 2.9]	0.01 (−0.05 to 0.07)
Change in creatinine level (follow-up to baseline), mean (SD) [median; minimum-maximum]	−0.050 (0.252) [0; –1.1 to 1.7]	−0.025 (0.227) [0; –1.0 to 1.3]	0.025 (−0.025 to 0.075)
Percentage change in creatinine level, mean (SD) [median; minimum-maximum]	−2.7 (23.4) [0; –61.1 to 154.5]	−1.3 (19.8) [0; –58.9 to 81.3]	1.5 (−3.0 to 6.0)
Increased by 0.5 mg/dL or 25%, No. (%)	14 (7.6)	12 (7.0)	0.6 (−4.8 to 6.0)

*Satterthwaite 95% CIs for the mean difference between groups are summarized for the continuous variables. Wald 95% CIs are reported for the risk difference between groups for the categorical variables.

Table 4. Comparison of adverse events by group.

	No. (%)	
Adverse Event	N-Acetylcysteine, N=200	Placebo, N=199
Itching	1	2 (1.0)
Flushing	3 (1.5)	3 (1.5)
Rash	1 (0.5)	0
Hypotension	0	0
Wheezing	0	1 (0.5)
Nausea	4 (2.0)	4 (2.0)
Vomiting	1 (0.5)	3 (1.5)
Other	3 (2.5)	4 (2.0)

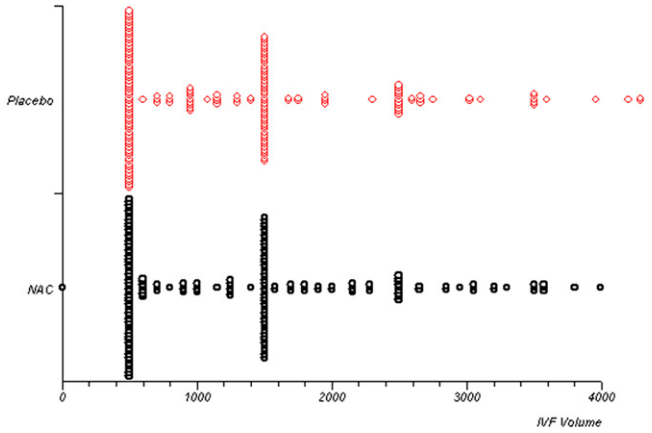


Figure 2. Intravenous fluid administration in placebo (saline solution only) and experimental (N-acetylcysteine plus saline solution) groups. Each circle represents 1 patient. Intravenous fluid volume in milliliters.

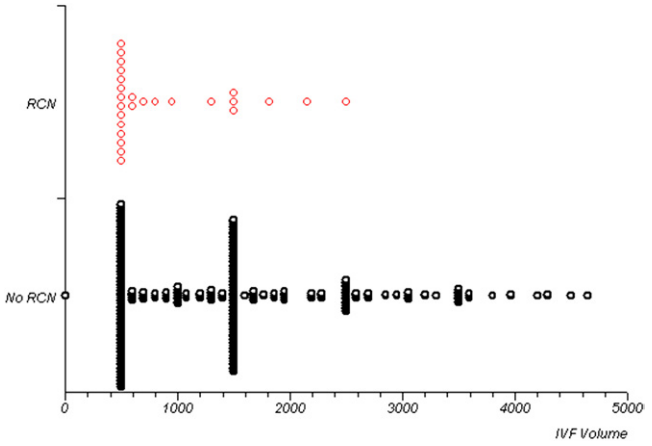


Figure 3. Intravenous fluid administration in contrast-induced nephropathy and noncontrast-induced nephropathy groups. Each circle represents 1 patient. Intravenous fluid volume in milliliters.

Table 5. Final adjusted logistic regression model for the development of contrast-induced nephropathy.

Characteristic	OR	95% CI
Age, in deciles	1.0	0.77–1.30
CHF	1.9	0.48–7.11
IVF, per liter	0.41	0.21–0.80
N-acetylcysteine treatment	1.2	0.51–2.66

CHF, Congestive heart failure.
The c-statistic for the model accuracy was 0.67, and the Hosmer-Lemeshow goodness-of-fit statistic was P=.046, with a χ^2 of 7.72 and df=8.

nephropathy (OR per liter of fluids 0.42; 95% CI 0.21 to 0.82), which was nearly identical to the relationship in our original model without propensity adjustment.

We performed a subgroup analysis on the 87 patients with serum creatinine levels greater than 1.2 mg/dL, a cutoff used in a previous study.[22] In this subgroup, contrast-induced nephropathy occurred in 0% (0/47) of patients treated with N-acetylcysteine plus saline solution and in 7.5% (3/40) of patients treated with saline solution alone, for a risk difference of −7.5% (−15.7% to 0.7%).

LIMITATIONS

Our results were obtained in patients considered to be at relatively low risk for contrast-induced nephropathy and should not be extended to patients who might be at higher risk for it. We purposefully chose our population as we did because previous work has suggested that an elevated serum creatinine

level alone might not identify patients at risk for contrast-induced nephropathy in the emergency setting.[19,23] Our low-risk population had only a 7% incidence of contrast-induced nephropathy by our definition, which was far lower than our initial estimate of 20%, leaving us underpowered to definitively reject our hypothesis. Additionally, we had no patients who developed renal failure, so we cannot comment on this patient-oriented outcome. Thus, although we found no evidence of benefit in our study, it is possible that a much larger study or one with a higher-risk population would yield a different conclusion.

Our study allowed for heterogeneity with respect to total treatment dosages and fluid volumes. In clinical practice, patients treated in an emergency setting may be available for treatment for only a few hours (if discharged) or up to several days (if admitted), and treatments initiated in the emergency setting may be stopped at any time by the admitting service. As such, we believe that our methodology best reflects actual emergency practice and highlights the nationally and internationally recognized need for setting-specific studies.[48]

Serum creatinine level has been criticized as a marker for renal function or injury in contrast-induced nephropathy studies. We chose it to measure the primary outcome of contrast-induced nephropathy for two reasons. First, a change in the level remains the standard for defining contrast-induced nephropathy and other causes of acute kidney injury.

Second, although other markers such as cystatin C, neutrophil gelatinase-associated lipocalcin, or kidney injury molecule 1[49] show some promise as alternatives to serum creatinine, these markers are currently experimental and not available in the clinical setting. At the same time, the inherent limitations of serum creatinine level are particularly important in studies of N-acetylcysteine because there are data demonstrating direct and indirect effects of N-acetylcysteine administration on creatinine measurement and metabolism.[50,51] However, the anticipated nontherapeutic effect of N-acetylcysteine would have increased the likelihood of observing a positive treatment effect, which we did not observe. Furthermore, the effect of N-acetylcysteine on creatinine measurements and metabolism remains highly contested.[50,51]

We report the association between fluid administration and a reduction in contrast-induced nephropathy. This is a finding that is observational, and although we have attempted to address confounding through modeling, including a propensity score analysis, we acknowledge the threat of residual confounding because we did not experimentally assign the administration of fluid. Specifically, despite the multivariate methods, patients who received less fluid may have been sicker (eg, suffered from congestive heart failure), explaining why they received less fluids and have a higher rate of contrast-induced nephropathy.

DISCUSSION

We did not find evidence of benefit in using N-acetylcysteine in addition to intravenous normal saline solution to prevent contrast-induced nephropathy in ED patients undergoing CT imaging with contrast, but we did find a strong association between the degree of fluid administration in the ED and a decrease in the rate of contrast-induced nephropathy. The incidence of contrast-induced nephropathy in our population was low overall (7%), and no patients developed renal failure; thus, these findings are directly generalizable only to a similar low-risk population. The finding of an association between the degree of fluid administration and decreased rate of contrast-induced nephropathy are provocative, but fluid administration was not assigned in an experimental fashion, so this finding should be interpreted in this context.

Unlike many previous studies of both N-acetylcysteine[36-44] and intravenous fluids[24-27] to prevent contrast-induced nephropathy, this study enrolled only emergency CT patients. This is a critical aspect of any study aimed at assessing emergency treatments because commonly accepted approaches to problems outside of the emergency setting may not be applicable to emergency patients. Traditional cardiac risk factors, for example, may have limited ability to risk-stratify patients who present to the ED with chest pain.[52]

Our inability to find a benefit with N-acetylcysteine differs from the result of another, smaller study of emergency CT patients who received 0.45% saline solution and were randomized to no N-acetylcysteine or 900 mg of intravenous N-acetylcysteine both before and after the procedure.[22] The rate of contrast-induced nephropathy, based on serum creatinine level, was 21% in the saline solution only group versus 5% in the N-acetylcysteine plus saline solution group ($P<.03$); there was no difference in contrast-induced nephropathy rates according to cystatin C measurements. That study used 0.45% saline solution rather than 0.9% saline solution for intravenous fluid administration, an important consideration in that 0.9% saline solution appears to be a superior fluid with respect to the prevention of contrast-induced nephropathy.[25]

Our study also differed in baseline serum creatinine values. The previous study required a baseline serum creatinine level greater than 1.2 mg/dL as an enrollment criterion, whereas we had no creatinine minimum. A subgroup analysis of the 87 patients in our study with baseline serum creatinine values greater than 1.2 mg/dL found a lower point estimate for the rate of contrast-induced nephropathy in the N-acetylcysteine plus saline solution group versus the saline solution only group (0% versus 7.5%; risk difference −7.5%; 95% CI −15.6% to 0.7%); however, this subgroup was underpowered for meaningful interpretation. We believe that the specific question of the utility of N-acetylcysteine in patients with mild to moderately increased creatinine levels who undergo ED contrast-enhanced CT deserves further study.

Our data showed a significant, independent association between moderate intravenous fluid administration and a reduction in the rate of contrast-induced nephropathy. Those receiving less than 1 L of fluids developed contrast-induced nephropathy at a rate of 12.9%, versus 3.3% in those who received 1 L or more (risk difference 9.6%; 3.7% to 15.5%).

Although not surprising given the findings of fluid administration in non-ED studies using infusion rates on the order of 1 mL/kg per hour,[24-27] our study supports the concept of moderate fluid administration as a means to reduce the rate of contrast-induced nephropathy specifically in patients undergoing emergency CT.

The only imbalance in baseline factors in our study was congestive heart failure, which occurred in 4% of the treatment group and 9% of the control group. This may have led to a different approach to treatment (eg, less aggressive fluid resuscitation in the congestive heart failure patients in the control group) or a higher propensity to develop contrast-induced nephropathy because of comorbid burden, although it is hard to draw definitive conclusions.

In our study, N-acetylcysteine was safe and associated with a very low rate of adverse events that was similar to that of placebo (Table 4). The adverse event rate of intravenous N-acetylcysteine administered for acetaminophen poisoning varies considerably, ranging from 3.7% to 66% in several studies.[48-51] We used a lower loading dose than these studies (3 g during 30 minutes versus 150 mg/kg during 15 to 60 minutes); we also used a placebo group, whereas many previous studies were observational.

Although we used a common definition of contrast-induced nephropathy (an increase in serum creatinine level of at least 0.5 mg/dL or an increase in serum creatinine level of at least 25% above baseline), the clinical importance of this definition is not entirely clear. For example, in our population of 26 patients who developed contrast-induced nephropathy by this criterion, none subsequently required renal replacement therapy.

In a population of ED patients undergoing contrast-enhanced CT, we found a relatively low rate of contrast-induced nephropathy (7%), and none of these patients developed renal failure. In this population, we were unable to demonstrate that N-acetylcysteine with saline solution was more effective than saline solution alone in preventing contrast-induced nephropathy after emergency contrast-enhanced CT in a low-risk population but found that the administration of 1 L of intravenous fluid or more was associated with a marked decrease in the rate of contrast-induced nephropathy.

Supervising editor: Robert D. Welch, MD, MS

Author affiliations: From the Department of Emergency Medicine (Traub, Tang, O'Connor, Shapiro) and the Center for Vascular Biology (Nelson), Beth Israel Deaconess Medical Center, Boston, MA; the Department of Emergency Medicine, Mayo Clinic Arizona, Phoenix, AZ (Traub); the Mayo Clinic College of Medicine, Rochester, MN (Traub); Indiana University School of Medicine, Indianapolis, IN (Mitchell); University of Mississippi Medical Center, Jackson, MS (Jones); Technomics Research, Minneapolis, Minnesota (Shapiro); the Department of Critical Care, University of Pittsburgh School of Medicine, Pittsburgh, PA (Shapiro); and Harvard Medical School, Boston, MA (Shapiro).

Author contributions: SJT and NIS conceived the study, designed the trial, and obtained research funding. SJT, NIS, AM and AEJ oversaw the the conduct of the trial and data collection. JO and AT were responsible for patient recruitment and data management. JK provided advice regarding study design and data analysis. SJT drafted the manuscript, and all authors contributed substantially to its final form. SJT takes responsibility for the paper as a whole.

Funding and support: By *Annals* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). The authors have stated that this study was sponsored through an investigator-initiated grant from Cumberland Pharmaceuticals. Other than the research grant, no conflict of interest exists.

Publication dates: Received for publication November 8, 2012. Revisions received January 27, 2013, and March 22, 2013. Accepted for publication April 12, 2013.

Address for correspondence: Stephen J. Traub, MD, E-mail traub.stephen@mayo.edu.

REFERENCES

1. Wong PC, Li Z, Guo J, et al. Pathophysiology of contrast-induced nephropathy. *Int J Cardiol*. 2012;158:186-192.
2. Maliborski A, Zukowski P, Nowicki G, et al. Contrast-induced nephropathy—a review of current literature and guidelines. *Med Sci Monit*. 2011;17:RA199-204.
3. Nash K, Hafeez A, Hou S. Hospital-acquired renal insufficiency. *Am J Kidney Dis*. 2002;39:930-936.
4. Dangas G, Iakovou I, Nikolsky E, et al. Contrast-induced nephropathy after percutaneous coronary interventions in relation to chronic kidney disease and hemodynamic variables. *Am J Cardiol*. 2005;95:13-19.
5. Solomon RJ, Mehran R, Natarajan MK, et al. Contrast-induced nephropathy and long-term adverse events: cause and effect? *Clin J Am Soc Nephrol*. 2009;4:1162-1169.
6. Rihal CS, Textor SC, Grill DE, et al. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation*. 2002;105:2259-2264.
7. McCullough PA, Wolyn R, Rocher LL, et al. Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. *Am J Med*. 1997;103:368-375.
8. Gupta R, Gurm HS, Bhatt DL, et al. Renal failure after percutaneous coronary intervention is associated with high mortality. *Catheter Cardiovasc Interv*. 2005;64:442-448.
9. Kocher KE, Meurer WJ, Fazel R, et al. National trends in use of computed tomography in the emergency department. *Ann Emerg Med*. 2011;58:452-462.e453.
10. National Hospital Ambulatory Medical Care Survey: 2008 emergency department summary tables. Available at: http://wwwcdcgov/nchs/data/ahcd/nhamcs_emergency/nhamcsed2008pdf. Accessed March 18, 2012.
11. Krol AL, Dzialowski I, Roy J, et al. Incidence of radiocontrast nephropathy in patients undergoing acute stroke computed tomography angiography. *Stroke*. 2007;38:2364-2366.
12. Hopyan JJ, Gladstone DJ, Mallia G, et al. Renal safety of CT angiography and perfusion imaging in the emergency evaluation of acute stroke. *AJNR Am J Neuroradiol*. 2008;29:1826-1830.
13. Dittrich R, Akdeniz S, Kloska SP, et al. Low rate of contrast-induced nephropathy after CT perfusion and CT angiography in acute stroke patients. *J Neurol*. 2007;254:1491-1497.

14. Tremblay LN, Tien H, Hamilton P, et al. Risk and benefit of intravenous contrast in trauma patients with an elevated serum creatinine. *J Trauma*. 2005;59:1162-1166; discussion 1166-1167.
15. Hipp A, Desai S, Lopez C, et al. The incidence of contrast-induced nephropathy in trauma patients. *Eur J Emerg Med*. 2008;15:134-139.
16. McGillicuddy EA, Schuster KM, Kaplan LJ, et al. Contrast-induced nephropathy in elderly trauma patients. *J Trauma*. 2010;68:294-297.
17. Kulvatunyou N, Rhee PM, Carter SN, et al. Defining incidence and outcome of contrast-induced nephropathy among trauma: is it overhyped? *Am Surg*. 2011;77:686-689.
18. Kim KS, Kim K, Hwang SS, et al. Risk stratification nomogram for nephropathy after abdominal contrast-enhanced computed tomography. *Am J Emerg Med*. 2011;29:412-417.
19. Mitchell AM, Kline JA. Contrast nephropathy following computed tomography angiography of the chest for pulmonary embolism in the emergency department. *J Thromb Haemost*. 2007;5:50-54.
20. Kooiman J, Klok FA, Mos IC, et al. Incidence and predictors of contrast-induced nephropathy following CT-angiography for clinically suspected acute pulmonary embolism. *J Thromb Haemost*. 2010;8:409-411.
21. Mitchell AM, Jones AE, Tumlin JA, et al. Incidence of contrast-induced nephropathy after contrast-enhanced computed tomography in the outpatient setting. *Clin J Am Soc Nephrol*. 2010;5:4-9.
22. Poletti PA, Saudan P, Platon A, et al. I.v. N-acetylcysteine and emergency CT: use of serum creatinine and cystatin C as markers of radiocontrast nephrotoxicity. *AJR Am J Roentgenol*. 2007;189:687-692.
23. Traub SJ, Kellum JA, Tang A. et al. Risk factors for radiocontrast nephropathy after emergency department contrast-enhanced computerized tomography. *Acad Emerg Med*. 2013;20:40-45.
24. Solomon R, Werner C, Mann D, et al. 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.
25. Mueller C, Buerkle G, Buettner HJ, et al. Prevention of contrast media-associated nephropathy: randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty. *Arch Intern Med*. 2002;162:329-336.
26. Trivedi HS, Moore H, Nasr S, et al. A randomized prospective trial to assess the role of saline hydration on the development of contrast nephrotoxicity. *Nephron Clin Pract*. 2003;93:C29-34.
27. Krasuski RA, Beard BM, Geoghagan JD, et al. Optimal timing of hydration to erase contrast-associated nephropathy: the OTHER CAN study. *J Invasive Cardiol*. 2003;15:699-702.
28. Mehran R, Aymong ED, Nikolsky E, et al. 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.
29. Ozcan EE, Guneri S, Akdeniz B, et al. Sodium bicarbonate, N-acetylcysteine, and saline for prevention of radiocontrast-induced nephropathy. A comparison of 3 regimens for protecting contrast-induced nephropathy in patients undergoing coronary procedures. A single-center prospective controlled trial. *Am Heart J*. 2007;154:539-544.
30. Brar SS, Shen AY, Jorgensen MB, et al. 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.
31. Vasheghani-Farahani A, Sadigh G, Kassaian SE, et al. Sodium bicarbonate plus isotonic saline versus saline for prevention of contrast-induced nephropathy in patients undergoing coronary angiography: a randomized controlled trial. *Am J Kidney Dis*. 2009;54:610-618.
32. Joannidis M, Schmid M, Wiedermann CJ. Prevention of contrast media-induced nephropathy by isotonic sodium bicarbonate: a meta-analysis. *Wien Klin Wochenschr*. 2008;120:742-748.
33. Meier P, Ko DT, Tamura A, et al. Sodium bicarbonate-based hydration prevents contrast-induced nephropathy: a meta-analysis. *BMC Med*. 2009;7:23.
34. Brar SS, Hiremath S, Dangas G, et al. Sodium bicarbonate for the prevention of contrast induced-acute kidney injury: a systematic review and meta-analysis. *Clin J Am Soc Nephrol*. 2009;4:1584-1592.
35. Hoste EA, De Waele JJ, Gevaert SA, et al. Sodium bicarbonate for prevention of contrast-induced acute kidney injury: a systematic review and meta-analysis. *Nephrol Dial Transplant*. 2010;25:747-758.
36. Tepel M, van der Giet M, Schwarzfeld C, et al. Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. *N Engl J Med*. 2000;343:180-184.
37. Sar F, Saler T, Ecebay A, et al. The efficacy of n-acetylcysteine in preventing contrast-induced nephropathy in type 2 diabetic patients without nephropathy. *J Nephrol*. 2010;23:478-482.
38. Koc F, Ozdemir K, Kaya MG, et al. Intravenous N-acetylcysteine plus high-dose hydration versus high-dose hydration and standard hydration for the prevention of contrast-induced nephropathy: CASIS-A multicenter prospective controlled trial. *Int J Cardiol*. 2012;155:418-423.
39. Marenzi G, Assanelli E, Marana I, et al. N-acetylcysteine and contrast-induced nephropathy in primary angioplasty. *N Engl J Med*. 2006;354:2773-2782.
40. Webb JG, Pate GE, Humphries KH, et al. 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.
41. Thiele H, Hildebrand L, Schirdewahn C, et al. 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.
42. Droppa M, Desch S, Blase P, et al. Impact of N-acetylcysteine on contrast-induced nephropathy defined by cystatin C in patients with ST-elevation myocardial infarction undergoing primary angioplasty. *Clin Res Cardiol*. 2011;100:1037-1043.
43. Berwanger O, Cavalcanti AB, Sousa AM, et al. 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.
44. Jaffery Z, Verma A, White CJ, et al. A randomized trial of intravenous N-acetylcysteine to prevent contrast induced nephropathy in acute coronary syndromes. *Catheter Cardiovasc Interv*. 2011.
45. Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med*. 1999;130:461-470.
46. Conen D, Buerkle G, Perruchoud AP, et al. Hypertension is an independent risk factor for contrast nephropathy after percutaneous coronary intervention. *Int J Cardiol*. 2006;110:237-241.

47. Merten GJ, Burgess WP, Gray LV, et al. Prevention of contrast-induced nephropathy with sodium bicarbonate: a randomized controlled trial. *JAMA*. 2004;291:2328-2334.
48. Goldfarb S, McCullough PA, McDermott J, et al. Contrast-induced acute kidney injury: specialty-specific protocols for interventional radiology, diagnostic computed tomography radiology, and interventional cardiology. *Mayo Clin Proc*. 2009; 84:170-179.
49. Waring WS, Moonie A. Earlier recognition of nephrotoxicity using novel biomarkers of acute kidney injury. *Clin Toxicol (Phila)*. 2011; 49:720-728.
50. Toprak O. Interactions between serum creatinine, volume status, N-acetylcysteine, and contrast-induced nephropathy. *Ren Fail*. 2006;28:265-266.
51. Hoffmann U, Fischereder M, Kruger B, et al. The value of N-acetylcysteine in the prevention of radiocontrast-agent induced nephropathy seems questionable. *J Am Soc Neprhol*. 2004;15: 407-410.
52. Jayes RL Jr, Beshansky JR, D'Agostino RB, et al. Do patients' coronary risk factor reports predict acute cardiac ischemia in the emergency department? A multicenter study. *J Clin Epidemiol*. 1992;45:621-626.

The LOGISTIC Procedure

Model Information	
Data Set	WORK.STATA_DATA2
Response Variable	chg_creat_cat
Number of Response Levels	2
Model	binary logit
Optimization Technique	Fisher's scoring

Number of Observations Read	399
Number of Observations Used	357

Response Profile		
Ordered Value	**chg_creat_cat**	**Total Frequency**
1	1	26
2	0	331

Probability modeled is chg_creat_cat=1.

Note: 42 observations were deleted due to missing values for the response or explanatory variables.

Class Level Information		
Class	**Value**	**Design Variables**
treatment	**N-Acetylcysteine**	1
	Placebo	-1
histheartfailure	**-1**	1
	0	-1

The LOGISTIC Procedure

Model Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics		
Criterion	**Intercept Only**	**Intercept and Covariates**
AIC	188.280	185.400
SC	192.158	204.788
-2 Log L	186.280	175.400

Testing Global Null Hypothesis: BETA=0			
Test	**Chi-Square**	**DF**	**Pr > ChiSq**
Likelihood Ratio	10.8803	4	0.0279
Score	8.8345	4	0.0654
Wald	8.1275	4	0.0870

Type 3 Analysis of Effects			
Effect	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
new_age	1	0.0013	0.9711
histheartfailure	1	0.8026	0.3703
tot_vol_oct29	1	6.8343	0.0089
treatment	1	0.1383	0.7100

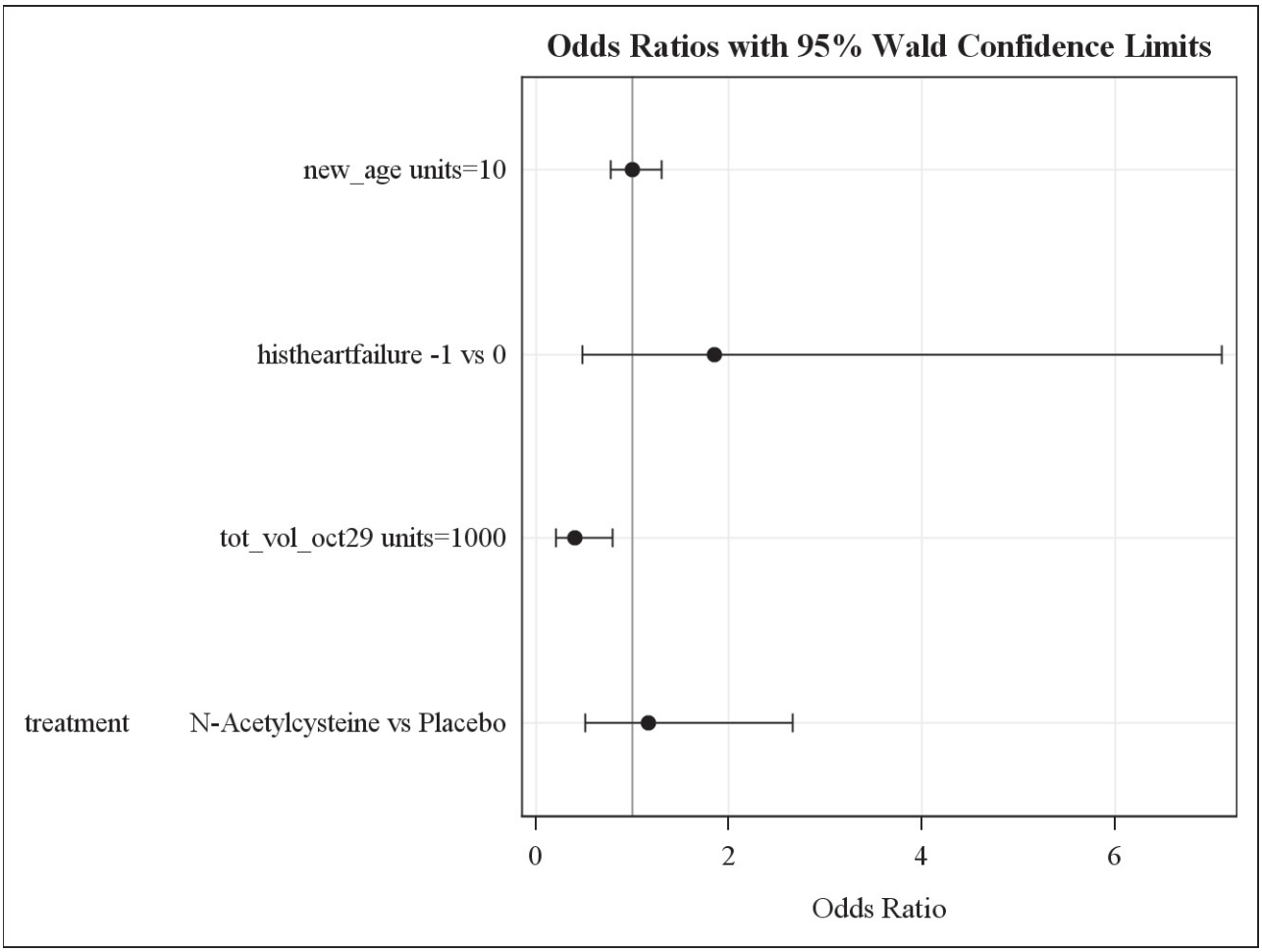
The LOGISTIC Procedure

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept		1	-1.3216	1.0046	1.7307	0.1883
new_age		1	0.000485	0.0134	0.0013	0.9711
histheartfailure	**-1**	1	0.3076	0.3434	0.8026	0.3703
tot_vol_oct29		1	-0.00090	0.000344	6.8343	0.0089
treatment	**N-Acetylcysteine**	1	0.0780	0.2097	0.1383	0.7100

Association of Predicted Probabilities and Observed Responses			
Percent Concordant	64.9	**Somers' D**	0.348
Percent Discordant	30.2	**Gamma**	0.366
Percent Tied	4.9	**Tau-a**	0.047
Pairs	8606	**c**	0.674

Odds Ratio Estimates and Wald Confidence Intervals				
Effect	**Unit**	**Estimate**	**95% Confidence Limits**	
new_age	10.0000	1.005	0.773	1.307
histheartfailure -1 vs 0	1.0000	1.850	0.482	7.107
tot_vol_oct29	1000.0	0.406	0.207	0.798
treatment N-Acetylcysteine vs Placebo	1.0000	1.169	0.514	2.659

The LOGISTIC Procedure



The LOGISTIC Procedure

Partition for the Hosmer and Lemeshow Test					
		chg_creat_cat = 1		chg_creat_cat = 0	
Group	Total	Observed	Expected	Observed	Expected
1	36	0	0.36	36	35.64
2	36	2	0.84	34	35.16
3	35	1	1.51	34	33.49
4	37	0	1.81	37	35.19
5	36	2	1.93	34	34.07
6	36	4	2.62	32	33.38
7	37	6	3.85	31	33.15
8	36	4	3.92	32	32.08
9	36	2	4.39	34	31.61
10	32	5	4.76	27	27.24

Hosmer and Lemeshow Goodness-of-Fit Test		
Chi-Square	DF	Pr > ChiSq
7.7193	8	0.4614

The Propensity Model

Appendix 2: Summary of Propensity Score Modeling

- Table 1 provides the distributional summary and comparisons for the selected baseline parameters included in the propensity model. Please note that none of the parameters differ significantly between groups.
- Table 2 provides the results of the propensity model.
    - Three (3) of the factors are significant or very nearly significant with regard to a relationship with the probability that a patient would have received 1 or more liters of fluid. These factors are age (p=0.0224), race=black (p=0.0675) and congestive heart failure (p=0.0502).
    - The resultant c-statistic or area under the receiver operating characteristic curve = 0.616 for the model.
    - In a study reviewed by FDA, the cut-off used to determine whether or not two observational groups were comparable was as follows:
        - If the c-statistic < 0.60 the groups were well balanced and no adjustment by propensity score was necessary.
        - If the c-statistic ≥ 0.60 and there was sufficient overlap between the propensity score distributions by group. Insufficient overlap is evidenced by propensity score quintiles that contain no fewer than 5 subjects in each group. In this case, propensity score adjustment is adequate.
        - The groups are not comparable if insufficient overlap exists.
    - The results for this study show that the groups are comparable with propensity score adjustment.
        - Note the c-statistic just barely crosses the boundary.
        - Note that the there is a lot of overlap between the propensity score distributions as evidenced by Table 3 & 4 and Figure 1.
- Even after propensity score adjustment, a significant relationship exists between fluid administration and development of RCN. In fact, the adjusted odds ratio and 95% confidence interval is nearly identical to the model presented in the manuscript which adjusts for age, CHF and NAC treatment.

The Propensity Model

Table 1 Checking for Balance in Important Risk Factors Among Patients Who Received Less Than 1 Liter of Fluids vs. Those Who Received 1 Liter or More of Fluids and Complete Follow-up

Parameter	Mean ± SD (Median) Min – Max or # (%)		p-value*
	< 1 Liter N=147	≥ 1 Liter N=210	
Age	62 ± 16 (62) 22 – 95	59 ± 15 (59) 18 – 94	0.0870
Race = Black	29% (43/147)	22% (47/210)	0.1730
CRI – baseline	4% (6/147)	6% (12/210)	0.6252
Congestive Heart Failure	9% (13/147)	5% (10/210)	0.1309
Coronary Artery Disease	18% (27/147)	19% (39/210)	1.000
Diabetes	33% (49/147)	31% (65/210)	0.6461
COPD	5% (8/147)	9% (19/210)	0.2285

*Fisher's Exact Test for categorical variables and Wilcoxon Two Sample Test for continuous variables.

Table 2 Results for Propensity Model

Parameter	Wald Chi-Square	p-value
Age	5.2115	0.0224
Race = Black	3.3439	0.0675
CRI – Baseline	1.9462	0.1630
Congestive Heart Failure	3.8335	0.0502
Coronary Artery Disease	0.1648	0.6848
Diabetes	0.6676	0.4139
COPD	2.4588	0.1169
C-statistic	0.616	

Table 3 Propensity Score Distribution

Group	N	Mean ± SD	Median [IQR]	Min – Max
≥ 1 Liter	210	0.604 ± 0.096	0.607 [0.545, 0.665]	0.307 – 0.827
< 1 Liter	147	0.566 ± 0.095	0.572 [0.514, 0.630]	0.213 – 0.766

The Propensity Model

Table 4 Number of Patients in Each Quintile by Fluids Group

Group	Q1	Q2	Q3	Q4	Q5
≥ 1 Liter	35 (17%)	34 (16%)	44 (21%)	43 (20%)	54 (26%)
< 1 Liter	37 (25%)	36 (24%)	29 (20%)	27 (18%)	18 (12%)

The Propensity Model

Figure 1 Histogram for Propensity Score for Patients with Less Than 1 L of Fluids (Bottom Panel) and Greater than 1 Liter of Fluids (Top Panel)

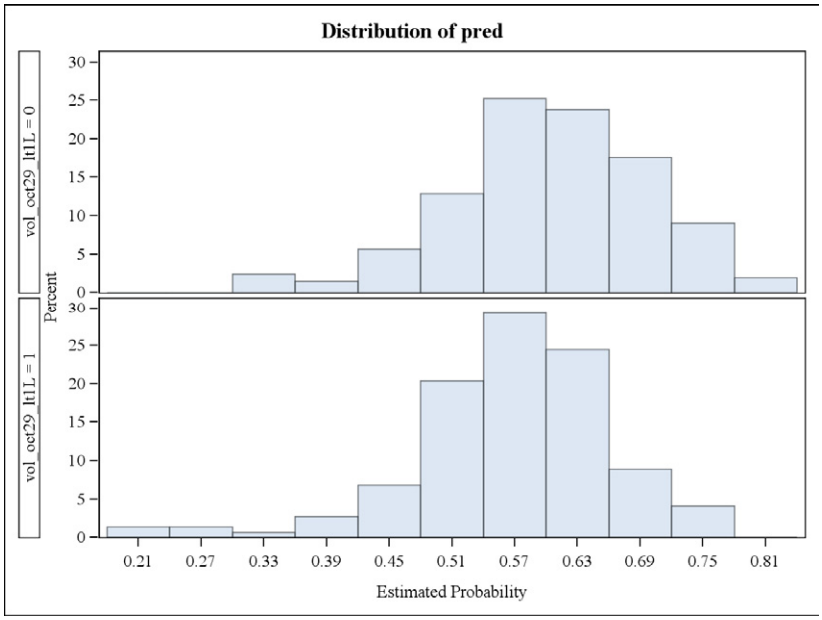


Table 5 Propensity Score Adjusted Odds Ratio for IVF Fluids

	Propensity Score Adjusted Odds Ratio	95% CI	p-value
IVF (per liter)	0.42	(0.21, 0.82)	0.0111

The Propensity Model

Model Information	
Data Set	WORK.STATA_DATA2
Response Variable	vol_oct29_lt1L
Number of Response Levels	2
Model	binary logit
Optimization Technique	Fisher's scoring

Number of Observations Read	357
Number of Observations Used	357

Response Profile		
Ordered Value	**vol_oct29_lt1L**	**Total Frequency**
1	0	210
2	1	147

Probability modeled is vol_oct29_lt1L=0.

Model Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

The Propensity Model

Model Fit Statistics		
Criterion	Intercept Only	Intercept and Covariates
AIC	485.731	485.545
SC	489.609	516.567
-2 Log L	483.731	469.545

Testing Global Null Hypothesis: BETA=0			
Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	14.1859	7	0.0480
Score	13.9304	7	0.0524
Wald	13.1526	7	0.0685

The Propensity Model

Analysis of Maximum Likelihood Estimates					
Parameter	**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept	1	1.5834	0.5183	9.3343	0.0022
new_age	1	-0.0180	0.00787	5.2115	0.0224
black	1	-0.4745	0.2595	3.3439	0.0675
histcri	1	-0.7765	0.5566	1.9462	0.1630
histheartfailure	1	0.9774	0.4992	3.8335	0.0502
histcad	1	-0.1233	0.3036	0.1648	0.6848
histdiabetes	1	0.1988	0.2433	0.6676	0.4139
histcopd	1	-0.7333	0.4677	2.4588	0.1169

Odds Ratio Estimates			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
new_age	0.982	0.967	0.997
black	0.622	0.374	1.035
histcri	0.460	0.155	1.369
histheartfailure	2.658	0.999	7.070
histcad	0.884	0.488	1.603
histdiabetes	1.220	0.757	1.965
histcopd	0.480	0.192	1.201

The Propensity Model

Hosmer and Lemeshow Goodness-of-Fit Test		
Chi-Square	DF	Pr > ChiSq
8.2018	8	0.4140

The Logistic Model Adjusted by Propensity Score
Dependent variable is CIN
Independent Variables are fluid group and propensity score

The LOGISTIC Procedure

Model Information		
Data Set	WORK.PRED	Predicted Values and Diagnostic Statistics
Response Variable	chg_creat_cat	
Number of Response Levels	2	
Model	binary logit	
Optimization Technique	Fisher's scoring	

Number of Observations Read	357
Number of Observations Used	357

Response Profile		
Ordered Value	**chg_creat_cat**	**Total Frequency**
1	1	26
2	0	331

Probability modeled is chg_creat_cat=1.

The Logistic Model Adjusted by Propensity Score
Dependent variable is CIN
Independent Variables are fluid group and propensity score

The LOGISTIC Procedure

Model Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics		
Criterion	Intercept Only	Intercept and Covariates
AIC	188.280	181.512
SC	192.158	193.145
-2 Log L	186.280	175.512

Testing Global Null Hypothesis: BETA=0			
Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	10.7680	2	0.0046
Score	8.5963	2	0.0136
Wald	7.9875	2	0.0184

The Logistic Model Adjusted by Propensity Score
Dependent variable is CIN
Independent Variables are fluid group and propensity score

The LOGISTIC
Procedure

Analysis of Maximum Likelihood Estimates					
Parameter	**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept	1	-0.5478	1.1886	0.2124	0.6449
pred	1	-1.7771	2.0762	0.7326	0.3920
tot_vol_oct29	1	-0.00087	0.000344	6.4483	0.0111

Association of Predicted Probabilities and Observed Responses			
Percent Concordant	65.8	**Somers' D**	0.331
Percent Discordant	32.7	**Gamma**	0.336
Percent Tied	1.4	**Tau-a**	0.045
Pairs	8606	**c**	0.665

Odds Ratio Estimates and Wald Confidence Intervals				
Effect	**Unit**	**Estimate**	**95% Confidence Limits**	
tot_vol_oct29	1000.0	0.418	0.213	0.819

The Logistic Model Adjusted by Propensity Score
Dependent variable is CIN
Independent Variables are fluid group and propensity score

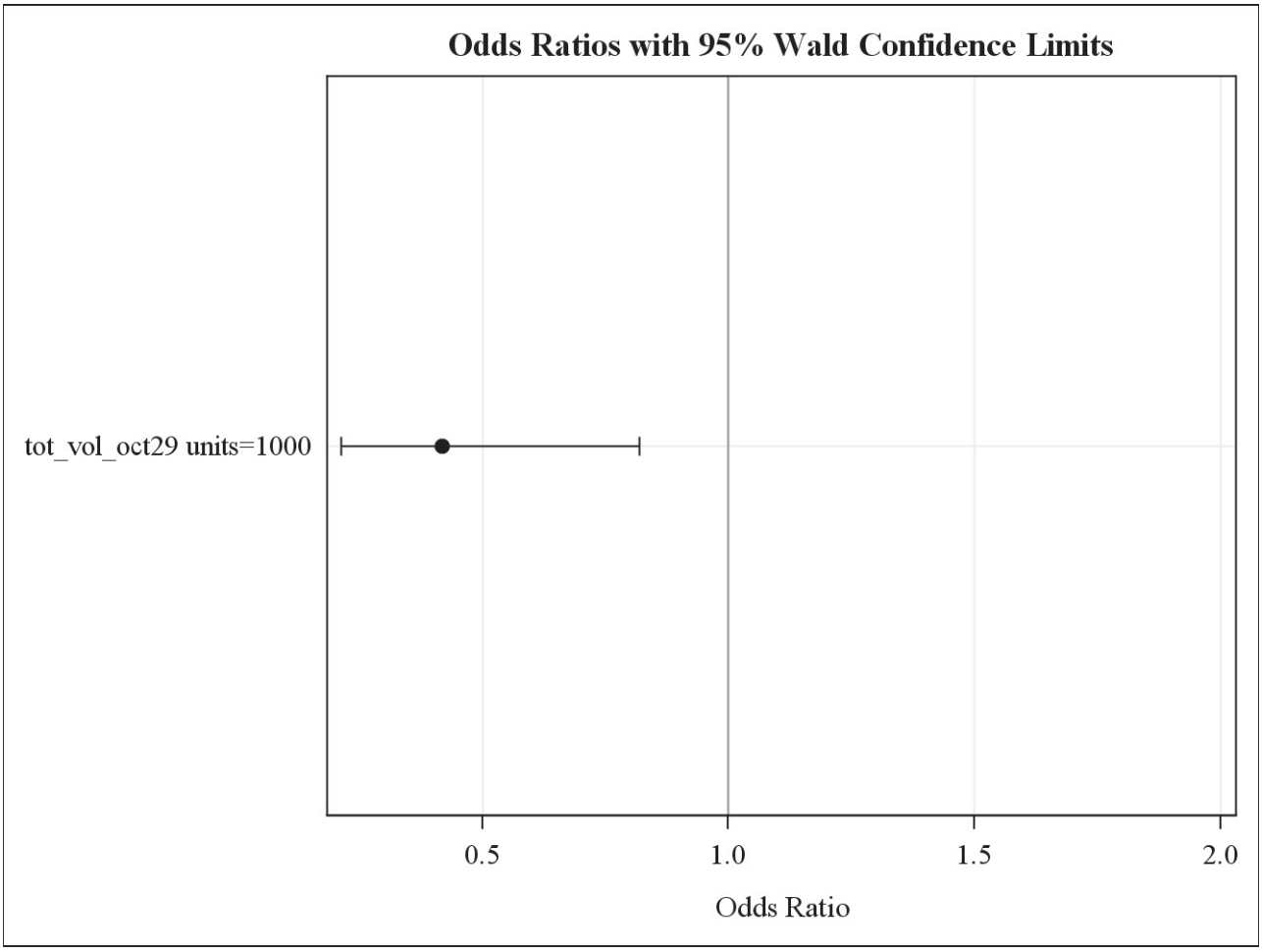
The LOGISTIC Procedure

Partition for the Hosmer and Lemeshow Test					
Group	Total	chg_creat_cat = 1		chg_creat_cat = 0	
		Observed	Expected	Observed	Expected
1	36	0	0.37	36	35.63
2	36	2	0.85	34	35.15
3	36	1	1.43	35	34.57
4	36	1	1.76	35	34.24
5	36	1	2.01	35	33.99
6	36	2	2.63	34	33.37
7	36	7	3.59	29	32.41
8	36	6	4.04	30	31.96
9	36	3	4.46	33	31.54
10	33	3	4.86	30	28.14

Hosmer and Lemeshow Goodness-of-Fit Test		
Chi-Square	DF	Pr > ChiSq
9.2289	8	0.3234

The Logistic Model Adjusted by Propensity Score
Dependent variable is CIN
Independent Variables are fluid group and propensity score

The LOGISTIC
Procedure



SAS Output for Table 3

The UNIVARIATE Procedure
Variable: pred (Estimated Probability)
vol_oct29_lt1L = 0

Moments			
N	210	**Sum Weights**	210
Mean	0.60398058	**Sum Observations**	126.835922
Std Deviation	0.09642989	**Variance**	0.00929872
Skewness	-0.4280574	**Kurtosis**	0.4242143
Uncorrected SS	78.5498671	**Corrected SS**	1.94343329
Coeff Variation	15.9657271	**Std Error Mean**	0.00665429

Basic Statistical Measures			
Location		**Variability**	
Mean	0.603981	**Std Deviation**	0.09643
Median	0.606560	**Variance**	0.00930
Mode	0.636154	**Range**	0.51959
		Interquartile Range	0.11983

SAS Output for Table 3

The UNIVARIATE Procedure
Variable: pred (Estimated Probability)
vol_oct29_lt1L = 0

Tests for Location: Mu0=0				
Test	**Statistic**		**p Value**	
Student's t	**t**	90.76553	**Pr > |t|**	<.0001
Sign	**M**	105	**Pr >= |M|**	<.0001
Signed Rank	**S**	11077.5	**Pr >= |S|**	<.0001

Quantiles (Definition 5)	
Quantile	**Estimate**
100% Max	0.826592
99%	0.793466
95%	0.755404
90%	0.728493
75% Q3	0.664753
50% Median	0.606560
25% Q1	0.544923
10%	0.491393
5%	0.440192

SAS Output for Table 3

The UNIVARIATE Procedure
Variable: pred (Estimated Probability)
vol_oct29_lt1L = 0

Quantiles (Definition 5)	
Quantile	**Estimate**
1%	0.328620
0% Min	0.307003

Extreme Observations			
Lowest		**Highest**	
Value	**Obs**	**Value**	**Obs**
0.307003	306	0.778171	357
0.326450	182	0.791696	128
0.328620	313	0.793466	219
0.345697	235	0.804841	31
0.358230	159	0.826592	51

SAS Output for Table 3

The UNIVARIATE Procedure
Variable: pred (Estimated Probability)
vol_oct29_lt1L = 1

Moments			
N	147	**Sum Weights**	147
Mean	0.56574202	**Sum Observations**	83.1640769
Std Deviation	0.09476413	**Variance**	0.00898024
Skewness	-0.9212356	**Kurtosis**	2.17152993
Uncorrected SS	48.3605278	**Corrected SS**	1.311115
Coeff Variation	16.7504133	**Std Error Mean**	0.00781601

Basic Statistical Measures			
Location		**Variability**	
Mean	0.565742	**Std Deviation**	0.09476
Median	0.571766	**Variance**	0.00898
Mode	0.593619	**Range**	0.55348
		Interquartile Range	0.11649

Note: The mode displayed is the smallest of 4 modes with a count of 3.

SAS Output for Table 3

The UNIVARIATE Procedure
Variable: pred (Estimated Probability)
vol_oct29_lt1L = 1

Tests for Location: Mu0=0				
Test	**Statistic**		**p Value**	
Student's t	**t**	72.38243	**Pr > |t|**	<.0001
Sign	**M**	73.5	**Pr >= |M|**	<.0001
Signed Rank	**S**	5439	**Pr >= |S|**	<.0001

Quantiles (Definition 5)	
Quantile	**Estimate**
100% Max	0.766363
99%	0.752549
95%	0.707296
90%	0.668747
75% Q3	0.630330
50% Median	0.571766
25% Q1	0.513838
10%	0.459744
5%	0.400522
1%	0.231511
0% Min	0.212879

SAS Output for Table 3

The UNIVARIATE Procedure
Variable: pred (Estimated Probability)
vol_oct29_lt1L = 1

Extreme Observations			
Lowest		**Highest**	
Value	**Obs**	**Value**	**Obs**
0.212879	178	0.732653	338
0.231511	252	0.741680	343
0.258077	155	0.741876	311
0.298652	184	0.752549	240
0.350262	180	0.766363	355