

Prevention, Incidence, and Outcomes of Contrast-Induced Acute Kidney Injury

Steven D. Weisbord, MD, MSc; Maria K. Mor, PhD; Abby L. Resnick, MA; Kathryn C. Hartwig, MA; Ali F. Sonel, MD; Michael J. Fine, MD, MSc; Paul M. Palevsky, MD

Background: Little is known about whether health care providers (physicians) implement preventive care for contrast-induced acute kidney injury (CIAKI). The objectives of our prospective cohort study were (1) to assess provider use of preventive strategies for CIAKI, (2) to determine the incidence of CIAKI, and (3) to examine the association of CIAKI with adverse outcomes at 30 days, including death, need for dialysis, and hospital admission.

Methods: We prospectively identified patients with estimated glomerular filtration rates less than 60 mL/min/1.73 m² undergoing procedures with intravascular radiocontrast agents and recorded the use of intravenous fluids and *N*-acetylcysteine and the discontinuation of nonsteroidal anti-inflammatory medications. We measured postprocedure serum creatinine levels to quantify the incidence of CIAKI and tracked 30-day mortality and need for dialysis or hospitalization to evaluate the association of CIAKI with these outcomes.

Results: Preprocedure and postprocedure intravenous fluids were administered to 264 of 660 study patients

(40.0%), more commonly with coronary angiography than with computed tomography (91.2% vs 16.6%, $P < .001$). *N*-acetylcysteine was administered to 39.2% of patients, while only 6.8% of patients using nonsteroidal anti-inflammatory drugs were instructed to discontinue the medication. In a propensity analysis, the use of intravenous fluids was associated with a reduced rate of CIAKI. The incidence of CIAKI was lowest following computed tomography (range, 0.0%-10.9%) and was highest following noncoronary angiography (range, 1.9%-34.0%). Eleven patients (1.7%) died, 1 patient (0.2%) required dialysis, and 83 patients (12.6%) were hospitalized; however, CIAKI was not independently associated with hospital admission or death.

Conclusions: Strategies to prevent CIAKI are implemented nonuniformly. Although biochemical evidence of CIAKI is relatively common, clinically significant CIAKI is rare. These findings should help health care providers focus the use of preventive care on the highest-risk patients and have important implications for future clinical trials.

Arch Intern Med. 2008;168(12):1325-1332

Author Affiliations: Center for Health Equity Research and Promotion (Drs Weisbord, Mor, Sonel, and Fine and Mss Resnick and Hartwig) and Renal Section, Medical Specialty Service Line (Drs Weisbord and Palevsky and Ms Hartwig), Veterans Affairs Pittsburgh Healthcare System; and Renal-Electrolyte Division (Drs Weisbord and Palevsky) and Division of General Internal Medicine (Dr Fine), Department of Medicine, School of Medicine, and Department of Biostatistics, Graduate School of Public Health (Dr Mor), University of Pittsburgh, Pittsburgh, Pennsylvania.

CONTRAST-INDUCED ACUTE kidney injury (CIAKI), which has been found to be associated with increased mortality risk and medical resource use, is unique in that it is iatrogenic, its risk factors are well-known, and its timing is predictable.¹⁻⁴ As a result, it is a condition that is potentially amenable to preventive care. Several clinical trials have identified interventions that reduce the risk for CIAKI in high-risk patients.⁵⁻⁷ The administration of preprocedure and postprocedure intravenous (IV) fluid has been shown to be beneficial, and isotonic fluid offers greater protection than hypotonic fluid.^{5,7} Although expert consensus on the benefit of *N*-acetylcysteine has not been reached, findings from some trials suggest that this agent decreases the incidence of CIAKI, and the use of *N*-acetylcysteine has become common at many institutions.^{8,9} Animal studies¹⁰⁻¹² have demonstrated that

nonsteroidal anti-inflammatory drugs (NSAIDs) increase the risk for renal injury from radiocontrast agent administration, leading to recommendations to discontinue these medications before the intravascular administration of an iodinated radiocontrast agent.

Despite evidence that these measures mitigate the risk for CIAKI, little is known about whether health care providers (physicians) routinely implement these preventive strategies in patients at increased risk for this condition. Prior analyses demonstrated potential underutilization of preventive care, although these observations were limited in scope and were drawn from retrospectively collected data.¹³ Moreover, little is known about the associations of the type of procedure (ie, computed tomography [CT], coronary angiography, and noncoronary angiography) with the use of preventive care and with outcomes following CIAKI. The objectives of our prospective cohort study

were (1) to assess provider use of preventive strategies for CIAKI, (2) to determine the incidence of CIAKI, and (3) to examine the association of CIAKI with adverse outcomes at 30 days, including death, need for dialysis, and hospital admission.

METHODS

PATIENT POPULATION

We conducted a prospective observational cohort study of patients undergoing procedures involving the administration of intravascular iodinated radiocontrast agents at the Veterans Affairs (VA) Pittsburgh Healthcare System between February 1, 2005, and July 31, 2006. We identified all subjects scheduled to undergo CT with IV radiocontrast, coronary angiography, or noncoronary angiography in the inpatient or outpatient setting before the procedure. We recorded the serum creatinine (SCr) level measured most proximate to and within 60 days of the procedure and calculated patients' baseline estimated glomerular filtration rate (eGFR) using the 4-variable Modification of Diet in Renal Disease study equation.¹⁴ Patients at the VA Pittsburgh Healthcare System are recommended to have SCr levels measured within 2 months before receiving an intravascular radiocontrast agent, which allowed us to identify patients' baseline kidney function. We recruited only those patients whose most proximate preprocedure eGFR value was less than 60 mL/min/1.73 m². To enroll subjects for whom there was sufficient time for health care providers to implement preventive care, we excluded patients undergoing emergent coronary angiography for ST-elevation myocardial infarction or emergent CT for the diagnosis of acute pulmonary embolism or ruptured aortic aneurysm. We also excluded individuals receiving chronic dialysis and those unable to provide informed consent based on the need for mechanical ventilation assistance. To limit the study to patients whose principal risk factor for acute kidney injury was a radiocontrast agent, we excluded subjects receiving IV vasopressor or inotropic medications and hospitalized patients with documented systolic blood pressure less than 90 mm Hg at the time of the procedure. For patients willing to participate and to comply with a follow-up SCr measurement at 48 to 96 hours after the procedure, informed consent was obtained.

BASELINE DATA COLLECTION

At the time of the procedure, we collected demographic data from participants and asked about the use of NSAIDs other than once-daily aspirin. We asked patients taking these agents if they were instructed to discontinue the medication before the procedure and, if so, whether they complied. The study coordinator (K.C.H.) also asked patients whether they were instructed to increase their oral fluid intake before the procedure and, if so, by how much. We recorded the type and volume of radiocontrast media administered, immediate complications associated with the procedure, and treatment location at the time of the procedure (hospital, outpatient setting, or long-term care facility). For patients undergoing outpatient procedures, an SCr level was measured at a VA laboratory 48 to 96 hours following the procedure. Although our goal was to have this test performed approximately 48 hours after all outpatient procedures, we extended this window to 96 hours because VA laboratory facilities are closed on weekends. For inpatients, we ordered a 48-hour postprocedure SCr measurement but recorded all postprocedure SCr values.

Using the electronic health record, we recorded patients' medications and comorbid medical conditions and assessed

the use of the following preventive interventions for CIAKI: (1) administration of IV fluids before and after the procedure, including the type, rate, and duration; (2) administration of *N*-acetylcysteine before administration of the radiocontrast agent; and (3) discontinuation of NSAIDs before the procedure.

FOLLOW-UP DATA COLLECTION

To evaluate longer-term outcomes, we conducted 30-day post-procedure electronic medical record reviews and telephone interviews to determine patients' vital status, need for postprocedure dialysis, and hospital admissions not immediately following the index radiographic procedure. We also recorded whether hospital admissions were because of renal failure.

STATISTICAL ANALYSIS

We report our results for the overall patient population and by the 3 procedure types (ie, CT, coronary angiography, and noncoronary angiography). All categorical data are reported as percentages, while continuous data are presented as mean (SD) or as median (interquartile range) as appropriate. Differences in demographic and clinical variables by procedure type were assessed using analysis of variance, Fisher exact test, and Kruskal-Wallis test as appropriate. To describe the use of preventive care, we report the proportion of patients who received preprocedure and/or postprocedure IV fluids and the proportion of patients who received isotonic fluid. We also report the proportion of patients administered *N*-acetylcysteine, the proportion of patients prescribed NSAIDs, and, among subjects who reported taking prescribed or over-the-counter NSAIDs, the proportion in whom these medications were discontinued.

We assessed the incidence of CIAKI using 3 non-mutually exclusive relative increments in the SCr level from baseline ($\geq 25\%$, $\geq 50\%$, and $\geq 100\%$) and 3 non-mutually exclusive absolute changes in SCr levels from baseline (≥ 0.25 , ≥ 0.5 , and ≥ 1.0 mg/dL) (to convert SCr levels to micromoles per liter, multiply by 88.4). Among hospitalized patients with multiple post-procedure SCr measurements, the development of CIAKI was based on the maximal increase in SCr level within 96 hours.

Although our study was not designed or powered to examine the protective effect of preventive care, we explored univariate associations of IV fluid administration, *N*-acetylcysteine use, and discontinuation of NSAIDs with the development of CIAKI using Fisher exact test. To account for clinical differences between patients who did and did not receive preventive strategies, we generated propensity scores using logistic regression models that predicted the use of each preventive measure. Patients were stratified by quintiles of the propensity score, and only those quintiles with adequate overlap between treated and non-treated patients were used in the analyses. Multivariate logistic regression analysis was used to assess the associations of the 3 preventive interventions with the development of CIAKI, adjusting for propensity score. For these analyses, we used 2 definitions of CIAKI as the dependent variable, an increase in SCr level of at least 0.5 mg/dL and an increase of at least 25%, as these have been the most commonly used definitions in prior studies. Unadjusted associations of CIAKI with mortality, need for dialysis, and hospitalization were assessed using Fisher exact test for each of the 6 definitions. Because of the low incidence of death, we used exact logistic regression analysis to examine the associations of CIAKI with mortality, adjusting for confounders that were found to have a univariate association ($P \leq .10$) with this outcome. Two-sided $P < .05$ was considered to represent statistical significance. All analyses were conducted using commercially available statistical software (STATA version 9; StataCorp LP, College Station, Texas). The institutional re-

view board at the VA Pittsburgh Healthcare System approved all study procedures.

RESULTS

PATIENT AND PROCEDURE CHARACTERISTICS

We screened 11 410 patients undergoing radiographic procedures, of whom 1884 (16.5%) were scheduled to receive an intravascular radiocontrast agent and had a baseline eGFR less than 60 mL/min/1.73 m². Of these, 324 met exclusion criteria (17.2%), and 900 did not receive an intravascular radiocontrast agent, declined to participate, or were unavailable for recruitment, resulting in a study population of 660 patients (**Figure 1**). All 660 patients had baseline SCr levels measured within 60 days of the procedure, 440 had this test within 3 days before the procedure (66.7%), and 477 had this test within 7 days before the procedure (72.3%). Four hundred twenty-one patients (63.8%) underwent CT, 181 patients (27.4%) underwent coronary angiography, and 58 patients (8.8%) underwent noncoronary angiography. The mean age was 69 years, the median baseline eGFR was 52 mL/min/1.73 m², and 95.5% were men. Iso-osmolar radiocontrast (Iodixanol; GE Healthcare, Princeton, New Jersey), which is the primary agent used in patients with reduced eGFR at the VA Pittsburgh Healthcare System, was administered to 568 patients, and a low-osmolar radiocontrast agent (Iohexol, GE Healthcare) was administered to 92 patients (**Table 1**).

USE OF PREVENTIVE CARE

Overall, 282 patients (42.7%) received preprocedure IV fluids, 317 (48.0%) received postprocedure IV fluids, and 264 (40.0%) received both (more commonly with coronary angiography than with CT [91.2% vs 16.6%, $P < .001$]) (**Figure 2**). Isotonic fluid was administered to 83.7% of patients who received preprocedure fluids and to 62.5% of patients who received postprocedure fluids. Hospitalized patients and those undergoing coronary angiography were most likely to receive IV fluids (**Table 2**). One hundred thirty-two patients (20.0%) reported being told to increase their preprocedure oral fluid intake, and 103 patients (78.0%) described complying with this recommendation.

N-acetylcysteine was administered to 259 patients (39.2%), most commonly those undergoing coronary angiography; however, there was no standard protocol in place for the administration of *N*-acetylcysteine. Overall, 67 patients (10.2%) were prescribed NSAIDs, 44 patients (6.7%) reported taking these medications, yet only 3 (6.8%) of those who reported taking NSAIDs were instructed to discontinue the medication, all of whom were undergoing coronary angiography.

INCIDENCE OF CIAKI

Postprocedure SCr level was measured in 585 patients (88.6%), of whom 546 patients (93.3%) completed

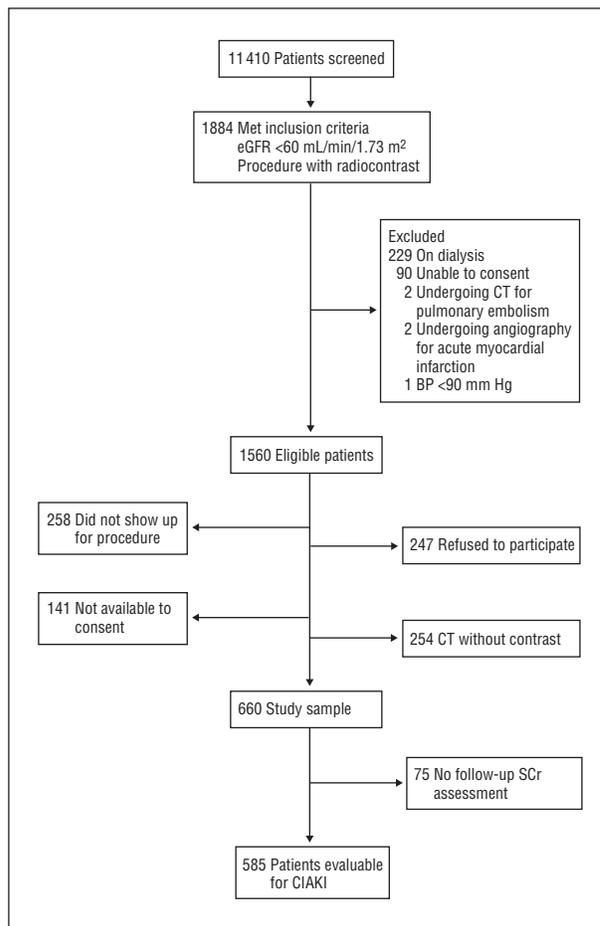


Figure 1. Patient recruitment. BP indicates blood pressure; CIAKI, contrast-induced acute kidney injury; CT, computed tomography; eGFR, estimated glomerular filtration rate; SCr, serum creatinine.

this test within 96 hours, while 39 patients (6.7%) had their SCr level measured on postprocedure day 5. These 39 patients were included in our assessment of CIAKI, as sensitivity analyses that excluded these subjects did not alter the study results. The incidence of CIAKI ranged from 0.2% to 7.7% based on relative increases in SCr levels of at least 100% to at least 25%, respectively, and from 0.7% to 13.3% with absolute changes in SCr levels of at least 1.0 mg/dL to at least 0.25 mg/dL, respectively (**Table 3**). Although the incidence of CIAKI was highest following noncoronary angiography and was lowest with CT, adjustment for baseline eGFR rendered these differences non-statistically significant (data not shown).

30-DAY OUTCOMES

We collected 30-day outcome data by electronic medical record review for all 660 patients and were able to contact 427 patients (64.7%) for follow-up telephone interview. Eleven patients (1.7%) had died, 10 of whom had undergone CT and 1 of whom had undergone coronary angiography. Three of these 11 patients (27.3%) had developed CIAKI based on an increase in SCr level

Table 1. Baseline Patient Characteristics by Radiographic Procedure

Characteristic	Overall (N=660)	Computed Tomography (n=421)	Coronary Angiography (n=181)	Noncoronary Angiography (n=58)	P Value ^a
Age, mean (SD), y	69 (10)	69 (10)	67 (9)	70 (10)	.06
Male sex, %	95	96	93	100	.09
Race/ethnicity, %					
White	90	91	91	86	.29
African American	7	7	6	14	
Other	2	2	3	0	
Location at time of procedure, %					<.001
Inpatient	29	25	34	34	
Ambulatory	68	70	66	66	
Long-term care	3	5	0	0	
Comorbidities, %					
Diabetes mellitus	45	41	51	62	.002
Liver disease	12	14	5	14	.003
Congestive heart failure	20	16	27	28	.003
Peripheral vascular disease	19	13	20	59	<.001
Cerebrovascular disease	14	11	16	36	<.001
Baseline renal function					
Serum creatinine level, median (interquartile range), mg/dL	1.4 (1.3-1.6)	1.4 (1.3-1.5)	1.4 (1.3-1.9)	1.6 (1.4-1.9)	<.001
Estimated glomerular filtration rate, mL/min/1.73 m ² , %					
Median (interquartile range)	52 (47-56)	53 (48-57)	52 (44-56)	46 (36-54)	<.001
30-59	97	100	96	84	<.001
15-29	2	0	3	7	
<15	1	0	1	9	
Radiocontrast, %					
Low-osmolar contrast	14	14	16	0	.001
Iso-osmolar contrast	86	86	84	100	
Volume contrast, median (interquartile range), mL	140 (100-150)	150 (100-150)	78 (60-120)	83 (50-150)	<.001
Prescribed medications, %					
Nonsteroidal anti-inflammatory drugs	10	10	12	9	.60
Loop diuretics	27	24	30	34	.11
Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers	46	38	62	55	<.001

^aSimultaneously tests for differences between any of the 3 procedures.

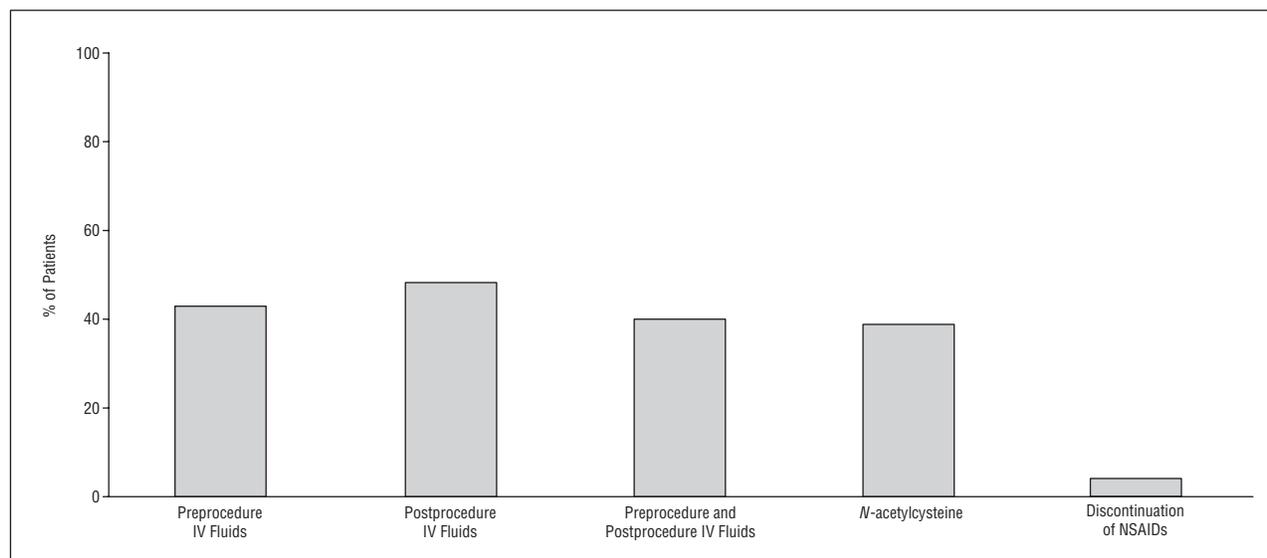


Figure 2. Use of preventive care for contrast-induced acute kidney injury. IV indicates intravenous; NSAIDs, nonsteroidal anti-inflammatory drugs.

of at least 25% or at least 0.5 mg/dL. Only 1 patient (0.2%) required dialysis, and 83 patients (12.6%) were hospitalized within 30 days but not immediately fol-

lowing the index procedure. Only 1 hospital admission was related to renal failure but occurred in a patient who had not developed CIAKI.

Table 2. Use of Preventive Care by Type of Radiographic Procedure

Variable	Overall (N=660)	Computed Tomography (n=421)	Coronary Angiography (n=181)	Noncoronary Angiography (n=58)	P Value ^a
Preprocedure intravenous fluids					
Overall use, % ^b	43	20	92	55	<.001
Isotonic sodium chloride	13	13	15	14	.60
Isotonic sodium bicarbonate	23	5	64	24	<.001
Hypotonic sodium chloride	7	2	13	17	<.001
Volume, median (interquartile range), mL	368 (250-900)	900 (300-1200)	258 (213-450)	740 (300-960)	<.001
Postprocedure intravenous fluids					
Overall use, % ^b	48	22	98	85	<.001
Isotonic sodium chloride	13	14	9	15	.21
Isotonic sodium bicarbonate	17	4	41	43	<.001
Hypotonic sodium chloride	18	4	48	27	<.001
Volume, median (interquartile range), mL	450 (450-900)	900 (500-1200)	450 (450-450)	900 (600-1200)	<.001
<i>N</i> -acetylcysteine use, %	39	17	84	59	<.001
Discontinued nonsteroidal anti-inflammatory drugs, % ^c	7	0	2103

Abbreviation: ellipsis, not applicable.

^aSimultaneously tests for differences between any of the 3 procedures.

^bSum of patients receiving each form of intravenous fluid may not equal overall use as patients may have received more than 1 type of intravenous fluid.

^cProportion of patients who reported taking nonsteroidal anti-inflammatory drugs in whom medication was discontinued.

Table 3. Incidence of Contrast-Induced Acute Kidney Injury (CIAKI) by Type of Radiographic Procedure

CIAKI Definition Based on Change in Serum Creatinine Level	Overall (n=585)	Computed Tomography (n=367)	Coronary Angiography (n=165)	Noncoronary Angiography (n=53)	P Value ^a
%					
≥25	7.7	6.5	8.5	13.2	.19
≥50	1.2	0.5	1.2	5.7	.02
≥100	0.2	0.0	0.0	1.9	.09
mg/dL					
≥0.25	13.3	10.9	12.1	34.0	<.001
≥0.5	5.3	3.5	6.1	15.1	.004
≥1.0	0.7	0.3	0.6	3.8	.04

SI conversion factor: To convert serum creatinine levels to micromoles per liter, multiply by 88.4.

^aSimultaneously tests for differences between any of the 3 procedures.

Table 4. Associations of Preventive Care With Contrast-Induced Acute Kidney Injury (CIAKI)

CIAKI Definition Based on Change in Serum Creatinine Level	Odds Ratio (95% Confidence Interval)			
	Intravenous Fluids		<i>N</i> -acetylcysteine	
	Unadjusted	Adjusted ^a	Unadjusted	Adjusted ^a
≥25%	1.4 (0.8-2.6)	0.7 (0.3-1.5)	2.1 (1.1-3.9)	1.8 (0.8-4.1)
≥0.5 mg/dL	1.2 (0.6-2.5)	0.4 (0.2-1.0)	2.8 (1.3-6.0)	1.6 (0.6-4.3)

SI conversion factor: To convert serum creatinine levels to micromoles per liter, multiply by 88.4.

^aAdjusted for propensity score.

ASSOCIATIONS OF PREVENTIVE CARE, CIAKI, AND 30-DAY OUTCOMES

In univariate analyses, the use of preprocedure and postprocedure IV fluid was not associated with a lower incidence of CIAKI. Analyses that adjusted for propensity scores estimated a protective effect of IV fluid, although this effect was statistically significant for only 1 definition of CIAKI,

an increase in SCr level of at least 0.5 mg/dL (**Table 4**). Patients who received *N*-acetylcysteine were more likely to develop CIAKI than those who did not receive this agent, although propensity score adjustment rendered these differences nonstatistically significant. Discontinuation of NSAIDs was not associated with a lower rate of CIAKI, yet the few patients in whom these medications were discontinued significantly limited this analysis.

Table 5. Associations of Contrast-Induced Acute Kidney Injury (CIAKI) With Mortality^a

CIAKI Definition Based on Change in Serum Creatinine Level	Odds Ratio (95% Confidence Interval)	
	Unadjusted	Adjusted ^b
%		
≥25	5.4 (0.9-24.7)	3.9 (0.6-20.3)
≥50
≥100
mg/dL		
≥0.25	2.8 (0.5-12.8)	2.6 (0.4-3.0)
≥0.5	8.3 (1.3-38.8)	7.0 (1.0-40.1)
≥1.0

SI conversion factor: To convert serum creatinine levels to micromoles per liter, multiply by 88.4.

^aEllipsis indicates not calculable because of no deaths based on definitions used.

^bAdjusted for location at time of procedure and for cerebrovascular disease.

Contrast-induced acute kidney injury defined by a rise in SCr level of at least 0.5 mg/dL was associated with an increased risk for mortality in univariate analyses, although adjustment for cerebrovascular disease and status at the time of the procedure (hospitalized vs outpatient), which were each associated with an increased risk for death, rendered this association nonstatistically significant. The wide confidence intervals of these odds ratios reflected the small number of deaths (**Table 5**). In sensitivity analyses using a composite definition of CIAKI based on an increase in SCr level of at least 25% or at least 0.5 mg/dL, which has been a commonly used definition in past trials, CIAKI had no statistically significant association with mortality in univariate or adjusted analyses (data not shown). There was a marginally statistically significant univariate association of CIAKI defined by a rise in SCr level of at least 0.5 mg/dL with need for dialysis ($P=.05$), although these analyses were limited by so few patients who required renal replacement therapy. CIAKI was not associated with hospital readmission in univariate or covariate adjusted analyses (data not shown).

COMMENT

In this observational study of patients at increased risk for CIAKI undergoing contrast-enhanced radiographic procedures, preventive measures were implemented non-uniformly, with substantially greater use in hospitalized patients and in those undergoing coronary angiography. Although CIAKI occurred in a reasonable proportion of patients, adverse 30-day outcomes were uncommon. These findings should help direct the use of evidence-based preventive strategies to the highest-risk patients and have important implications for the design of future trials of CIAKI.

Intravascular volume expansion with isotonic fluid is arguably the most effective preventive intervention for CIAKI.^{11,12,15} We observed wide variation in the use and composition of IV fluid. More than 50% of patients failed

to receive any IV fluid, while hypotonic fluid use constituted 37.5% of postprocedure fluid administration overall. Health care providers may use hypotonic fluids in some patients for fear of precipitating heart failure with the administration of fluid containing higher concentrations of sodium. However, this is likely to be clinically appropriate in few patients. Efforts to increase the administration of IV isotonic fluids in the highest-risk patients will help further decrease the incidence of CIAKI.

We also found nonuniform administration of *N*-acetylcysteine and almost universal lack of discontinuation of NSAIDs. Given the considerable debate on the benefit of *N*-acetylcysteine therapy, the variable implementation of this treatment in the present study may reflect uncertainty in the medical community regarding the benefit of this agent.^{8,9,16} However, discontinuation of NSAIDs was infrequently performed, despite expert recommendations to stop these medications before administration of a radiocontrast agent.^{11,12} Given the frequency at which NSAIDs are consumed by the general population, routine discontinuation of these agents is a simple and safe strategy to reduce patients' risk for CIAKI.

Despite being less likely to receive preventive care, patients who underwent CT developed CIAKI less frequently than those who underwent angiography, particularly noncoronary procedures. This may be related to a higher baseline eGFR in these patients than in subjects who underwent noncoronary angiography. In fact, 254 patients who met initial inclusion criteria and were scheduled for CT with an IV radiocontrast agent underwent the procedure without vascular enhancement. This is likely reflective of decisions by radiologists to perform CT without an IV radiocontrast agent in higher-risk patients. Whether IV administration of a radiocontrast agent is less nephrotoxic than intra-arterial administration is an important clinical issue, as the provision of prophylactic IV fluid is considerably more challenging in subjects undergoing outpatient CT than in hospitalized patients or in those undergoing angiography. However, of 212 study patients who underwent outpatient CT and had a baseline eGFR of at least 45 mL/min/1.73 m², 5 patients (2.4%) experienced an increase in SCr level of at least 25%, 2 patients (0.9%) manifested a rise of at least 0.5 mg/dL, and none died. These findings suggest that the risk for clinically consequential CIAKI in patients with mild chronic kidney disease who are undergoing outpatient CT is low, even in the absence of preventive care. Given the practical and fiscal obstacles to routinely providing IV fluids to the majority of patients scheduled to undergo outpatient CT who are judged to be at risk for CIAKI, preventive protocols in the radiology setting should focus on those at highest risk. Moreover, future analyses should weigh the short-term benefits of avoiding an IV radiocontrast agent with the longer-term risks of underdiagnosis from lack of vascular enhancement.

We defined our patients as being at high risk for CIAKI based on a reduced baseline eGFR, yet few patients manifested robust elevations in SCr levels. Expert consensus panels have recommended, and many clinical trials have used, a baseline eGFR less than 60 mL/min/1.73 m² (or

creatinine clearance <60 mL/min) to categorize patients as high risk.^{6,12,17-21} Our findings indicate that patients with only mildly reduced eGFR are at low risk for CIAKI. The use of an eGFR less than 60 mL/min/1.73 m² as the threshold below which risk for CIAKI increases is consistent with the National Kidney Foundation's definition of chronic kidney disease.²² However, in many older patients, reduced eGFR calculated using the 4-variable Modification of Diet in Renal Disease study equation may be more a function of increased age than elevation in SCr level.¹⁴ Using an eGFR level less than 60 mL/min/1.73 m² to define increased risk may misclassify many patients with regard to true susceptibility for CIAKI.

Clinical trials have used small increments in SCr level to define CIAKI under the assumption that these changes are predictive of adverse outcomes.^{6,7,23-26} However, we found that adverse outcomes with CIAKI were uncommon. Although using small changes in SCr level as the primary end point in clinical trials allows for the enrollment of fewer patients and may inflate study "event rates," it has likely contributed to the proliferation of small trials of sodium bicarbonate and N-acetylcysteine with inadequate numbers of clinically meaningful events that have confused rather than informed clinical decision making.^{23,24,26} We conducted post-hoc analyses to estimate the sample size necessary to accurately evaluate the efficacy of a hypothetical intervention in reducing mortality from 1.7%, which was the rate observed in our study, to 0.85%. Considering an α level of .05 and 90% power, more than 3700 patients would be required in each study arm. For future trials, investigators should define patients as high risk based on more advanced baseline renal insufficiency and should consider including the need for dialysis, hospital length of stay, and death in sample size estimations to derive clinically meaningful data on the efficacy of preventive interventions.

There are certain limitations to this study. First, our findings are based on a small sample size and clinical events from a single site, which limits generalizability to the full spectrum of patients at risk for CIAKI. Second, in addition to enrolling many patients with only mildly reduced eGFR, we excluded subjects with hypotension and patients undergoing emergent procedures, rendering most of our study population at lower rather than higher risk for CIAKI. Third, variability in the timing of postprocedure SCr assessments and the inclusion of patients with postprocedure SCr measurements at 96 hours and longer could have affected the accuracy with which we identified cases of CIAKI. Fourth, there may have been a Hawthorne effect with respect to the use of preventive care. However, if present, this would suggest that preventive strategies are used even less uniformly elsewhere. Fifth, we were unable to contact a substantial number of patients by telephone for 30-day follow-up and cannot be certain that we captured all 30-day outcomes. However, the use of the VA integrated electronic health record, which records care delivered at all VA facilities, likely enabled us to identify most postprocedure events. Patients with lower baseline eGFR were more likely to receive IV fluids and N-acetylcysteine, suggesting that operator bias, in which health care providers are more likely to imple-

ment preventive care in higher-risk patients, may have masked the true beneficial effect of such care.

In conclusion, this study demonstrates nonuniform implementation of preventive care for CIAKI. Patients undergoing CT were least likely to receive preventive interventions but demonstrated the lowest rate of CIAKI. These findings will help health care providers determine which patients are the most likely to derive benefit from preventive measures. The low incidence of clinically consequential CIAKI is a novel observation that will help physicians and patients make informed decisions on the risks and benefits of radiocontrast administration and should assist investigators in designing adequately powered clinical trials to advance our understanding of how to most effectively prevent this iatrogenic condition in patients at greatest risk.

Accepted for Publication: January 13, 2008.

Correspondence: Steven D. Weisbord, MD, MSc, Center for Health Equity Research and Promotion, VA Pittsburgh Healthcare System, Mail Stop 111F-U, 7E Room 120, Pittsburgh, PA 15240 (weisbordsd@upmc.edu).

Author Contributions: *Study concept and design:* Weisbord, Hartwig, Fine, and Palevsky. *Acquisition of data:* Weisbord, Hartwig, and Sonel. *Analysis and interpretation of data:* Weisbord, Mor, Resnick, Hartwig, Sonel, Fine, and Palevsky. *Drafting of the manuscript:* Weisbord. *Critical revision of the manuscript for important intellectual content:* Mor, Resnick, Fine, and Palevsky. *Statistical analysis:* Weisbord, Mor, and Resnick. *Administrative, technical, and material support:* Hartwig. *Study supervision:* Sonel, Fine, and Palevsky.

Financial Disclosure: Dr Weisbord has received grant support from and has served on the speakers bureau of GE Healthcare.

Funding/Support: This study was supported by VA Health Services Research and Development Career Development Award RCD 03-176 and by a VA Stars and Stripes Competitive Pilot Project Fund award (Dr Weisbord); and by midcareer development award K24 AI001769 from the National Institute of Allergy and Infectious Diseases (Dr Fine).

REFERENCES

1. Hou SH, Bushinsky DA, Wish JB, Cohen JJ, Harrington JT. Hospital-acquired renal insufficiency: a prospective study. *Am J Med.* 1983;74(2):243-248.
2. McCullough PA, Wolyn R, Rocher LL, Levin RN, O'Neill WW. Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. *Am J Med.* 1997;103(5):368-375.
3. Rudnick MR, Berns JS, Cohen RM, Goldfarb S. Contrast media-associated nephrotoxicity. *Semin Nephrol.* 1997;17(1):15-26.
4. Weisbord SD, Chen H, Stone RA, et al. Associations of increases in serum creatinine with mortality and length of hospital stay after coronary angiography. *J Am Soc Nephrol.* 2006;17(10):2871-2877.
5. 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(3):329-336.
6. Solomon R, Werner C, Mann D, D'Elia J, Silva P. Effects of saline, mannitol, and furosemide to prevent acute decreases in renal function induced by radiocontrast agents. *N Engl J Med.* 1994;331(21):1416-1420.
7. 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(1):C29-C34.

8. Marenzi G, Assanelli E, Marana I, et al. *N*-acetylcysteine and contrast-induced nephropathy in primary angioplasty. *N Engl J Med*. 2006;354(26):2773-2782.
9. Shyu KG, Cheng JJ, Kuan P. Acetylcysteine protects against acute renal damage in patients with abnormal renal function undergoing a coronary procedure. *J Am Coll Cardiol*. 2002;40(8):1383-1388.
10. Agmon Y, Peleg H, Greenfeld Z, Rosen S, Brezis M. Nitric oxide and prostanoids protect the renal outer medulla from radiocontrast toxicity in the rat. *J Clin Invest*. 1994;94(3):1069-1075.
11. Stacul F, Adam A, Becker CR, et al. Strategies to reduce the risk of contrast-induced nephropathy. *Am J Cardiol*. 2006;98(6A):59K-77K.
12. Solomon R, Deray G. How to prevent contrast-induced nephropathy and manage risk patients: practical recommendations. *Kidney Int Suppl*. 2006;100(100):S51-S53.
13. Weisbord SD, Bruns FJ, Saul MI, Palevsky PM. Provider use of preventive strategies for radiocontrast nephropathy in high risk patients. *Nephron Clin Pract*. 2004;96(2):c56-c62.
14. Levey AS, Green T, Kusek JW, Beck GJ. A simplified equation to predict glomerular filtration rate from serum creatinine [abstract] *J Am Soc Nephrol*. 2000; 11:A0828.
15. Rudnick MR, Tumlin JA. Pathogenesis, clinical features, and diagnosis of radiocontrast media-induced acute kidney injury (acute renal failure). In: Rose BD, ed. *UpToDate*. Waltham, MA: UpToDate Inc; 2007.
16. Kay J, Chow WH, Chan TM, et al. Acetylcysteine for prevention of acute deterioration of renal function following elective coronary angiography and intervention: a randomized controlled trial. *JAMA*. 2003;289(5):553-558.
17. McCullough PA, Stacul F, Becker CR, et al. Contrast-Induced Nephropathy (CIN) Consensus Working Panel: executive summary. *Rev Cardiovasc Med*. 2006; 7(4):177-197.
18. Solomon RJ, Natarajan MK, Doucet S, et al; Investigators of the CARE Study. Cardiac Angiography in Renally Impaired Patients (CARE) study: a randomized double-blind trial of contrast-induced nephropathy in patients with chronic kidney disease. *Circulation*. 2007;115(25):3189-3196.
19. Jo SH, Youn TJ, Koo BK, et al. Renal toxicity evaluation and comparison between Visipaque (iodixanol) and Hexabrix (ioxaglate) in patients with renal insufficiency undergoing coronary angiography: the RECOVER study: a randomized controlled trial. *J Am Coll Cardiol*. 2006;48(5):924-930.
20. Aspelin P, Aubry P, Fransson SG, Strasser R, Willenbrock R, Berg KJ. Nephrotoxic effects in high-risk patients undergoing angiography. *N Engl J Med*. 2003; 348(6):491-499.
21. Barrett BJ, Katzberg RW, Thomsen HS, et al. Contrast-induced nephropathy in patients with chronic kidney disease undergoing computed tomography: a double-blind comparison of iodixanol and iopamidol [published correction appears in *Invest Radiol*. 2007;42(2):94]. *Invest Radiol*. 2006;41(11):815-821.
22. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis*. 2002; 39(2)(suppl 1):S1-S266.
23. Briguori C, Airolidi F, D'Andrea D, et al. Renal Insufficiency Following Contrast Media Administration Trial (REMEDIAL): a randomized comparison of 3 preventive strategies. *Circulation*. 2007;115(10):1211-1217.
24. Merten GJ, Burgess WP, Gray LV, et al. Prevention of contrast-induced nephropathy with sodium bicarbonate: a randomized controlled trial. *JAMA*. 2004;291(19):2328-2334.
25. Recio-Mayoral A, Chaparro M, Prado B, et al. The reno-protective effect of hydration with sodium bicarbonate plus *N*-acetylcysteine in patients undergoing emergency percutaneous coronary intervention: the RENO Study. *J Am Coll Cardiol*. 2007;49(12):1283-1288.
26. Tepel M, van der Giet M, Schwarzfeld C, Laufer U, Liermann D, Zidek W. Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. *N Engl J Med*. 2000;343(3):180-184.