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JAMA. 2008;300(9):1038-1046 (doi:10.1001/jama.300.9.1038)

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Sodium Bicarbonate vs Sodium Chloride for the Prevention of Contrast Medium–Induced Nephropathy in Patients Undergoing Coronary Angiography

A Randomized Trial

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CONTRAST MEDIUM–INDUCED NEPHROPATHY is a recognized complication of exposure to iodine contrast media. It is a common cause of renal failure associated with prolonged hospitalization, increased health care costs, and substantial morbidity and mortality.¹⁻³ The reported incidence of contrast-induced nephropathy ranges from 2% in low-risk populations to 50% in high-risk populations.³⁻⁵ Risk factors for development of this complication include chronic kidney disease, volume and type of contrast, and patient-related factors such as diabetes, congestive heart failure, advanced age, anemia, sex, and reduced effective circulating volume.^{2,6-9}

The mechanism of contrast medium–induced nephropathy remains unknown but may be related to renal vasoconstriction resulting in medullary ischemia or direct nephrotoxicity.^{10,11} In recent years, studies have investigated preventive therapies such as various plasma-expanding fluids, antioxidants (eg, *N*-acetylcysteine and ascorbic acid),

Context Sodium bicarbonate has been suggested as a possible strategy for prevention of contrast medium–induced nephropathy, a common cause of renal failure associated with prolonged hospitalization, increased health care costs, and substantial morbidity and mortality.

Objective To determine if sodium bicarbonate is superior to sodium chloride for preventing contrast medium–induced nephropathy in patients with moderate to severe chronic kidney dysfunction who are undergoing coronary angiography.

Design, Setting, and Patients Randomized, controlled, single-blind study conducted between January 2, 2006, and January 31, 2007, and enrolling 353 patients with stable renal disease who were undergoing coronary angiography at a single US center. Included patients were 18 years or older and had an estimated glomerular filtration rate of 60 mL/min per 1.73 m² or less and 1 or more of diabetes mellitus, history of congestive heart failure, hypertension, or age older than 75 years.

Interventions Patients were randomized to receive either sodium chloride (n=178) or sodium bicarbonate (n=175) administered at the same rate (3 mL/kg for 1 hour before coronary angiography, decreased to 1.5 mL/kg per hour during the procedure and for 4 hours after the completion of the procedure).

Main Outcome Measure The primary end point was a 25% or greater decrease in the estimated glomerular filtration rate on days 1 through 4 after contrast exposure.

Results Median patient age was 71 (interquartile range, 65-76) years, and 45% had diabetes mellitus. The groups were well matched for baseline characteristics. The primary end point was met in 13.3% of the sodium bicarbonate group and 14.6% of the sodium chloride group (relative risk, 0.94; 95% confidence interval, 0.55-1.60; *P*=.82). In patients randomized to receive sodium bicarbonate vs sodium chloride, the rates of death, dialysis, myocardial infarction, and cerebrovascular events did not differ significantly at 30 days (1.7% vs 1.7%, 0.6% vs 1.1%, 0.6% vs 0%, and 0% vs 2.2%, respectively) or at 30 days to 6 months (0.6% vs 2.3%, 0.6% vs 1.1%, 0.6% vs 2.3%, and 0.6% vs 1.7%, respectively) (*P*>.10 for all).

Conclusion The results of this study do not suggest that hydration with sodium bicarbonate is superior to hydration with sodium chloride for the prevention of contrast medium–induced nephropathy in patients with moderate to severe chronic kidney disease who are undergoing coronary angiography.

Trial Registration clinicaltrials.gov Identifier: NCT00312117

JAMA. 2008;300(9):1038-1046

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diuretics, dopamine, fenoldopam, and hemofiltration, with mixed results.¹²⁻²¹ Animal models of renal failure and one randomized clinical trial suggest that hy-

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dration with sodium bicarbonate may be an effective therapy for prevention of contrast-induced nephropathy.¹²⁻¹⁴ A proposed mechanism for this potentially protective effect is that alkalinizing the tubular urine with sodium bicarbonate infusion may attenuate free radical formation, leading to less oxidant injury and lower rates of contrast-induced nephropathy.

To evaluate the effect of sodium bicarbonate on the prevention of contrast medium-induced nephropathy, we performed a randomized, controlled, single-blind trial in a population with moderate to severe chronic kidney disease who were undergoing coronary angiography.

METHODS

Study Population

Between January 2, 2006, and January 31, 2007, all consecutive patients referred to the cardiac catheterization laboratory at the Kaiser Permanente Medical Center in Los Angeles, California, were screened to determine if they met the study criteria. The inclusion criteria were an estimated glomerular filtration rate (GFR) of 60 mL/min per 1.73 m² or less, age 18 years or older, and at least 1 of diabetes mellitus, history of congestive heart failure, hypertension (>140/90 mm Hg or treatment with an antihypertensive medication), or age older than 75 years. The estimated GFR was calculated using serum creatinine levels and the Modification of Diet in Renal Disease study equation ($186.3 \times \text{serum creatinine level}^{-1.154} \times \text{age}^{-0.203}$ [$\times 0.742$ if female]) and was adjusted for race by multiplying by 1.21 for patients self-identified as black.¹⁵

Exclusion criteria included inability to obtain consent, receipt of a sodium bicarbonate infusion prior to randomization, emergency cardiac catheterization, intra-aortic balloon counterpulsation, dialysis, exposure to radiographic contrast media within the preceding 2 days, allergy to radiographic contrast media, acutely decompensated congestive heart failure, severe valvular abnormality (eg, severe aortic stenosis or mitral regurgitation), single functioning kidney, history of kidney or heart

transplantation, and change in estimated GFR of 7.5% or more per day or a cumulative change of 15% or more over the prior 2 or more days.

Study Protocol

Eligible patients were randomly assigned in a 1:1 ratio to receive an infusion of either sodium chloride or sodium bicarbonate, stratified by diabetes status and *N*-acetylcysteine use. Diabetes mellitus was defined as any of the following: use of oral hypoglycemic agents or insulin, fasting plasma glucose levels greater than 126 mg/dL (to convert to mmol/L, multiply by 0.0555), or a random plasma glucose level of 200 mg/dL or greater. Repeat measurement of fasting or random plasma glucose levels on a subsequent day was used to confirm the diagnosis of diabetes. *N*-acetylcysteine use was defined as 600 mg twice daily for 2 days, starting the day prior to the index procedure. *N*-acetylcysteine use was at the discretion of the referring physician; if started, the 2-day course was completed.

Four computer-generated concealed randomization schedules, each using permuted blocks of 4, were created. When an eligible patient was enrolled, the research assistant used sealed opaque envelopes to allocate the patient to the next sequential randomization number.

The infusion protocol was identical for both fluid types. Infusion was begun 1 hour prior to the start of contrast administration at 3 mL/kg for 1 hour, decreased to 1.5 mL/kg per hour during the procedure and for 4 hours following completion of the procedure. For patients weighing more than 100 kg, the bolus and infusion rate were limited to those used for patients weighing 100 kg. The sodium bicarbonate solution was formulated by adding three 50-mL ampules of sodium bicarbonate (150 mEq of sodium) to 1 L of 5% dextrose with water. The sodium chloride solution used was commercially available 0.9% saline. Baseline serum creatinine levels were measured on the day of coronary angiography prior to hydration and contrast exposure. Patients were asked to have serum creatinine levels measured on days 1 and 2 post coronary angiography. If levels were not available for day

2, they were obtained on day 3. For all patients, serum creatinine levels were assessed until any increase in level resolved or reached a new baseline of renal function. All study participants received intra-arterial ioxilan (350 mg iodine/mL), a non-ionic, low-osmolar contrast medium.

The study was partially blinded. Patients were not told to which group they were randomized. Patient consents were obtained by 2 of the study investigators (N.D., M.R.) not involved in any of the procedures. The physicians performing the procedures were not blinded and theoretically could have determined a patient's assigned treatment by inspection of the fluid infused. However, laboratory personnel processing the samples had no knowledge of each patient's study assignment. The study was approved by the institutional review board of Kaiser Permanente Southern California; consecutive, eligible patients provided written informed consent.

Study End Points

The primary end point of a 25% or greater reduction in the estimated GFR was calculated using baseline rate obtained prior to the procedure and the lowest rate post-procedure on days 1 through 4. Secondary end points were a 25% or greater increase in the serum creatinine level, need for hemodialysis in the 30 days post-procedure, and 30-day all-cause mortality. All patients who developed contrast-induced nephropathy were asked to return in 2 to 8 weeks for repeat measurement of serum creatinine levels. The change in estimated GFR from baseline to 2 to 8 weeks post-angiography was calculated, with a difference of 25% or greater defined as persistent impairment of renal function.

The study protocol was amended to permit ascertainment of clinical events at 6 months from the index exposure to contrast. Clinical adverse events were reported at 30 days and at 30 days to 6 months. Clinical outcomes assessed included all-cause mortality, myocardial infarction, cerebrovascular accident, and dialysis. Myocardial infarction was defined according to the European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/

World Heart Federation consensus document²² and excluded periprocedural events related to the index procedure. Cerebrovascular accident was defined as either an ischemic or hemorrhagic stroke (neurologic deficit persisting for ≥ 24 hours) or transient ischemic attack (neurologic deficit persisting < 24 hours). All events were classified and confirmed by 2 investigators (A.Y.-J.S., A.I.S.) blinded to treatment assignment.

Data Collection and Management

Information on demographic characteristics and comorbid conditions was obtained from the patient and the medical record. Height, weight, and blood pressure were recorded from the initial nursing assessment. Race/ethnicity was self-reported by patients, using investigator-defined categories. Detailed medication history was obtained and included current use of *N*-acetylcysteine, β -blockers, angiotensin-converting en-

zyme inhibitors, angiotensin receptor blockers, statins, and diuretics. Recorded procedural data included contrast volume, procedure duration, left ventricular end-diastolic pressure (LVEDP), aortic systolic and diastolic blood pressures, number of stents implanted, and frequency of ad hoc percutaneous coronary intervention. Laboratory data collected prior to angiography included levels of fasting low-density and high-density lipoprotein cholesterol, glycated hemoglobin, hemoglobin, and serum creatinine.

Statistical Analysis

The primary end point was analyzed by the Cochran-Mantel-Haenszel method, using diabetes status and *N*-acetylcysteine use as the stratification variables. Continuous data are reported as mean (SD) or median (interquartile range) as appropriate. Categorical data are presented as absolute values and percentages. Baseline characteristics between the 2 groups were com-

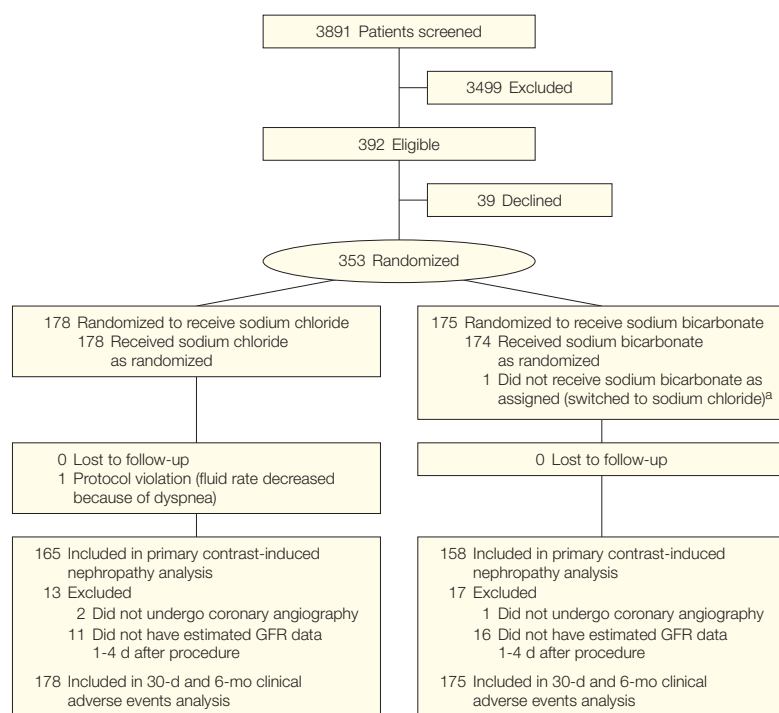
pared using the *t* test or Wilcoxon rank sum test for continuous variables and the χ^2 or Fisher exact test for categorical variables.

A multiple logistic regression model yielding odds ratios (ORs) and 95% confidence intervals (CIs) was used to identify predictors of contrast-induced nephropathy. The model included known risk factors (eg, age, diabetes, hypertension, congestive heart failure, contrast volume, anemia, and baseline renal function) and variables showing a univariate association ($P < .10$) with occurrence (eg, sex, acute coronary syndrome [ACS]). Clinically relevant interaction terms were sought; none were found to be significant. Model calibration was performed with the Hosmer-Lemeshow goodness-of-fit test, which was satisfied.

The study sample size was calculated on the basis of a power analysis assuming that 15% of the sodium chloride group and 5% of the sodium bicarbonate group would develop contrast-induced nephropathy. The predicted incidence in the sodium bicarbonate group was based in part on a study by Merten et al,¹⁴ while the 15% predicted incidence with sodium chloride has been observed in prior randomized trials.^{23,24} Four interim analyses were planned for review by the data and safety monitoring panel. Each interim analysis had prespecified stopping criteria, which were not met during the study. The 2-sided α for the first, second, third, and fourth (final) analyses were .00005, .004, .019, and .043, respectively. A χ^2 analysis adjusting for the interim analyses suggested that 290 patients with complete data would be required to detect a statistically significant difference, with a power of 80% and 2-sided α of .05. Comparisons of selected subgroups and persistent renal impairment were preplanned secondary analyses; however, the trial was adequately powered for the primary end point only.

All analyses were conducted by 2 authors (S.S.B., R.J.B.) using SAS version 9.1.3 (SAS Institute Inc, Cary, North Carolina). All tests were 2-tailed, with differences reported as significant if $P < .05$, and were not adjusted for multiple comparisons. The study

Figure. Study Flow



Reasons for exclusion were not tracked during the course of enrollment. GFR indicates glomerular filtration rate. ^aPatient was receiving an intravenous medication that was not compatible with sodium bicarbonate infusion. Additional intravenous access was not attainable; therefore, the fluid type was changed to sodium chloride administered at the protocol rate.

analysis was performed according to the intention-to-treat principle and included protocol violators.

RESULTS

Patient Population and Baseline Characteristics

Of 392 eligible patients, 353 agreed to be randomized and were assigned to receive either sodium chloride (n=178) or sodium bicarbonate (n=175) (FIGURE). Demographic, clinical, hemodynamic, and angiographic characteristics were well balanced between the treatment groups (TABLE 1). The median age for the full study cohort was 71 years; 65% were men. The frequency of diabetes and adequacy of control as assessed by glycosylated hemoglobin levels were similar between treatment groups, as were N-acetylcysteine use, contrast volume, and procedural duration. Hemodynamic parameters were obtained periprocedurally and included cuff and aortic systolic and diastolic blood pressures measured at the start of the procedure. Left ventricular end-diastolic pressure, a surrogate for intravascular volume status, was measured after coronary angiography was performed but prior to left ventriculography and found to be similar between the groups.

Contrast Medium-Induced Nephropathy

Overall, contrast-induced nephropathy assessed by estimated GFR occurred in 13.9% (45/323) of the patients. The group receiving sodium chloride hydration had a 14.6% (24/165) incidence vs 13.3% (21/158) in the sodium bicarbonate group, for a relative risk of 0.94 (95% CI, 0.55-1.60; $P=.82$). Other measures of contrast-induced nephropathy did not differ by treatment assignment (TABLE 2). Baseline estimated GFR and serum creatinine levels were similar between the groups. The absolute and percent change in the mean estimated GFR and serum creatinine levels were not significantly different between the treatment groups (TABLE 3). Contrast exposure, measured as grams of iodine divided by the baseline estimated GFR,

was calculated and found to be similar between the sodium chloride and sodium bicarbonate groups (1.4 [SD, 1.1] vs 1.3 [SD, 0.9], respectively; $P=.37$).

Nine patients randomized to receive sodium chloride and 11 patients to receive sodium bicarbonate had repeat contrast exposure or underwent

coronary artery bypass grafting prior to measurement of serum creatinine levels on day 2. Repeat contrast exposure was in the setting of percutaneous coronary intervention in all. No significant difference was observed in the incidence of contrast-induced nephropathy between treatment groups when

Table 1. Baseline Characteristics

Characteristic	Sodium Chloride (n = 178)	Sodium Bicarbonate (n = 175)	P Value
Age			
Median (IQR), y	71 (65-76)	71 (65-75)	.50
>75 y, No. (%)	49 (27.5)	43 (24.6)	.53
Women, No. (%)	62 (35.2)	66 (37.7)	.57
Black, No. (%)	18 (10.1)	14 (8.0)	.27
Medical history, No. (%)			
Prior CHF	52 (29.6)	44 (25.1)	.39
Prior MI	108 (61.4)	108 (61.7)	.84
Diabetes	81 (45.5)	76 (43.4)	.73
HbA _{1c} , mean (SD), %	7.3 (1.8)	7.3 (1.7)	.89
Lipids, median (IQR), mg/dL			
LDL-C	91 (73-113)	95 (81-112)	.20
HDL-C	40 (35-48)	40 (34-48)	.49
Blood pressure, mean (SD), mm Hg			
Cuff			
Systolic	148 (21)	148 (23)	.51
Diastolic	65 (13)	63 (14)	.06
Aortic			
Systolic	148 (28)	149 (27)	.56
Diastolic	66 (11)	65 (11)	.66
LVEDP	17 (7)	17 (8)	.96
LVEF, mean (SD), %	55 (16)	58 (13)	.13
Weight, mean (SD), kg	81 (19)	84 (21)	.14
Height, median (IQR), cm	168 (160-175)	170 (163-178)	.30
BMI, median (IQR) ^a	27.5 (24.7-31.8)	28.5 (25.5-32.3)	.26
Hemoglobin, mean (SD), g/dL	13.0 (1.8)	13.0 (1.7)	.82
Prior revascularization, No. (%)	115 (64.6)	114 (65.1)	.92
PCI, No. (%)	56 (31.5)	57 (32.6)	.87
No. of stents, mean (SD)	1.5 (1.0)	1.6 (0.9)	.38
Contrast volume, median (IQR), mL	137 (89-247)	126 (80-214)	.15
Iodine in contrast, median (IQR), g	48 (31-86)	44 (28-75)	.14
Procedure duration, median (IQR), min	37.5 (22.0-69.5)	33.0 (19.0-56.0)	.08
ACS, No. (%)	82 (46.1)	80 (45.7)	.95
Medication, No. (%)			
N-acetylcysteine	84 (47.2)	80 (45.7)	.82
β-Blocker	150 (84.3)	155 (88.6)	.24
ACE inhibitor	112 (62.9)	112 (64.0)	.83
Angiotensin receptor blocker	30 (16.9)	28 (16.0)	.57
Statin	146 (82.0)	142 (81.1)	.83
Diuretic	66 (37.1)	80 (45.7)	.09

Abbreviations: ACE, angiotensin-converting enzyme; ACS, acute coronary syndrome; BMI, body mass index; CHF, congestive heart failure; HbA_{1c}, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.

SI conversion factor: To convert LDL-C and HDL-C values to mmol/L, multiply by 0.0259.

^aCalculated as weight in kilograms divided by height in meters squared.

Table 2. Incidence of Contrast Medium-Induced Nephropathy

Measure	No. (%)		Absolute Difference (95% CI)	P Value ^a
	Sodium Chloride (n = 165)	Sodium Bicarbonate (n = 158)		
Estimated GFR, >25% decrease	24 (14.6)	21 (13.3)	1.3 (-6.3 to 8.8)	.75
Serum creatinine				
>25% increase	27 (16.4)	25 (15.8)	0.6 (-7.5 to 8.7)	>.99
>0.5-mg/dL increase	22 (13.3)	14 (8.9)	4.4 (-2.4 to 11.3)	.22
>25% or >0.5-mg/dL increase	30 (18.2)	26 (16.5)	1.7 (-6.5 to 10.0)	.78

Abbreviations: CI, confidence interval; GFR, glomerular filtration rate.

SI conversion factor: To convert serum creatinine values to $\mu\text{mol/L}$, multiply by 88.4.

^aBy Fisher exact test.

Table 3. Measures of Change in Renal Function^a

Measure	Mean (SD)		Absolute Difference	% Difference
	Before Contrast	After Contrast		
Sodium chloride				
Estimated GFR, mL/min per 1.73 m ²	48.3 (9.4)	46.1 (13.7)	-2.2 (9.4)	-5.2 (20.8)
Serum creatinine, mg/dL	1.49 (0.38)	1.64 (0.74)	0.16 (0.50)	9.3 (26.9)
Sodium bicarbonate				
Estimated GFR, mL/min per 1.73 m ²	47.7 (9.8)	44.7 (13.5)	-3.1 (9.5)	-6.6 (19.7)
Serum creatinine, mg/dL	1.49 (0.36)	1.66 (0.65)	0.17 (0.50)	11.0 (30.6)

Abbreviation: GFR, glomerular filtration rate.

SI conversion factor: To convert serum creatinine values to $\mu\text{mol/L}$, multiply by 88.4.

^aWithin-group comparisons were performed with the Wilcoxon signed rank test ($P < .01$ for all). Between-group comparisons were performed with the Wilcoxon rank sum test ($P > .20$ for all).

these patients were excluded from the primary analysis. The incidence in the sodium chloride group was 13.5% (21/156) vs 13.6% (20/147) in the sodium bicarbonate group, for a relative risk of 1.01 (95% CI, 0.57-1.79; $P = .97$).

Similar numbers of patients with severe renal dysfunction (estimated GFR ≤ 30 mL/min per 1.73 m²) were randomized to receive sodium chloride ($n = 11$) and sodium bicarbonate ($n = 10$) ($P = .90$). In this group, the incidence of contrast-induced nephropathy in the sodium chloride and sodium bicarbonate groups was 36.4% (4/11) and 20.0% (2/10), respectively ($P = .64$ by Fisher exact test). Selected subgroup analyses (TABLE 4) did not show any significant interactions between the treatment group and various baseline characteristics (Breslow-Day test for homogeneity, $P > .30$ for all variables tested).

A graded relationship was observed between LVEDP and the development of contrast-induced nephropathy. The incidence was 11.6% among those with

LVEDP greater than 20 mm Hg, 14.6% among those with LVEDP of 10 to 20 mm Hg, and 16.0% among those with LVEDP less than 10 mm Hg ($P = .42$ by Cochran-Armitage trend test).

Patients who developed contrast-induced nephropathy were asked to return in 2 to 8 weeks for measurement of serum creatinine levels to reassess extent of recovery. In the subset of patients developing nephropathy, we calculated the percentage with persistently impaired renal function, defined as a 25% or greater decrease in the estimated GFR at 2 to 8 weeks compared with baseline. Persistent renal impairment was observed in 20% in the sodium chloride group and 18% in the sodium bicarbonate group ($P = .99$).

Clinical Adverse Events

Clinical adverse events were recorded at 30 days and 6 months after the index coronary angiography. All randomized patients, including those excluded from the contrast-induced nephropathy analysis, were included

based on the intention-to-treat principle (TABLE 5). Mortality at 30 days was similar, with 3 deaths in each treatment group. Between 30 days and 6 months, there were an additional 4 deaths in the sodium chloride group and 1 in the sodium bicarbonate group. Cumulative mortality at 6 months in the sodium chloride and sodium bicarbonate groups was 3.9% and 2.3%, respectively ($P = .54$). Among the patients who developed nephropathy, cumulative 6-month mortality was 9.5% in the sodium chloride group and 10.0% in the sodium bicarbonate group ($P > .99$).

During the 6-month follow-up period, 6 patients started dialysis; 4 were randomized to receive sodium chloride and 2 to receive sodium bicarbonate. The mean age of these patients was 76 (SD, 11) years, 75% were men, and the mean baseline estimated GFR was 37 (SD, 9.1) mL/min per 1.73 m². Among the 6 patients who started dialysis, 4 developed contrast-induced nephropathy by the protocol definition. All 4 of these patients died by 6 months.

Risk Factors

The incidence of contrast-induced nephropathy was significantly higher in the patients who underwent angiography for ACS vs non-ACS indications (22.2% vs 7.3%, respectively; $P < .001$). In a multiple logistic regression model (C statistic, 0.78) for development of nephropathy, the OR for ACS to non-ACS status was 3.4 (95% CI, 1.6-7.2; $P = .002$) after adjustment for baseline estimated GFR and the following risk factors for contrast-induced nephropathy: age, sex, diabetes, hypertension, history of congestive heart failure, anemia, and contrast volume. When added to the above logistic regression model, N-acetylcysteine use was not a predictor of nephropathy ($P = .57$).

Other predictors of contrast-induced nephropathy from the logistic regression analysis included diabetes mellitus, female sex, and contrast volume. The incidence among patients with diabetes mellitus was 20.0%, vs 9.0% for those without diabetes ($P = .005$). The corre-

sponding adjusted OR from the above model was 2.14 (95% CI, 1.03-4.43; $P=.04$). Women were also observed to have a higher incidence compared with men (20.0% vs 10.6%, $P=.02$). The adjusted OR for women vs men was 2.15 (95% CI, 1.05-4.37; $P=.04$). Higher volumes of contrast media were also observed to increase incidence. For every 50 mL of contrast adminis-

tered, the odds of developing nephropathy increased by 14% (OR, 1.14; 95% CI, 1.00-1.29; $P=.05$). The interaction between sodium bicarbonate and *N*-acetylcysteine was found to be non-significant. The interaction between the observed predictors of nephropathy and sodium bicarbonate and *N*-acetylcysteine was also sought and found to be non-significant.

COMMENT

In this randomized controlled trial of patients with moderate to severe chronic kidney disease who were undergoing coronary angiography, no difference was observed in the incidence of contrast medium-induced nephropathy between patients receiving hydration with sodium chloride and those receiving sodium bicarbonate. The primary end point of a

Table 4. Incidence of Contrast Medium-Induced Nephropathy in Select Subgroups

Subgroup	No. (%)		Absolute Difference (95% CI)	P Value ^a
	Sodium Chloride	Sodium Bicarbonate		
Diabetes				
Yes	n = 77	n = 68		
Estimated GFR >25% decrease	15 (19.5)	14 (20.6)	-1.1 (-14.7 to 12.0)	>.99
Serum creatinine				
>25% increase	17 (22.1)	16 (23.5)	-1.4 (-15.1 to 12.2)	.86
>0.5-mg/dL increase	16 (20.8)	11 (16.2)	4.6 (-8.0 to 17.2)	.53
>25% or >0.5-mg/dL increase	16 (22.2)	16 (25.8)	-3.6 (-18.1 to 10.9)	.69
No	n = 88	n = 90		
Estimated GFR >25% decrease	9 (10.2)	7 (7.8)	2.4 (-6.0 to 10.9)	.61
Serum creatinine				
>25% increase	10 (11.4)	9 (10.0)	1.4 (-7.7 to 10.4)	.81
>0.5-mg/dL increase	6 (6.8)	3 (3.3)	3.5 (-3.0 to 9.9)	.33
>25% or >0.5-mg/dL increase	11 (12.5)	9 (10.0)	2.5 (-6.8 to 11.8)	.64
N-Acetylcysteine Use				
Yes	n = 78	n = 73		
Estimated GFR >25% decrease	14 (18.0)	13 (17.8)	0.2 (-12.1 to 12.4)	>.99
Serum creatinine				
>25% increase	13 (16.8)	15 (20.6)	-3.8 (-16.3 to 8.5)	.68
>0.5-mg/dL increase	13 (16.8)	10 (13.7)	3.1 (-8.5 to 14.4)	.66
>25% or >0.5-mg/dL increase	16 (20.5)	16 (21.9)	-1.4 (-14.5 to 11.7)	.85
No	n = 87	n = 85		
Estimated GFR >25% decrease	10 (11.5)	8 (9.4)	2.1 (-7.1 to 11.2)	.80
Serum creatinine				
>25% increase	14 (16.1)	10 (11.8)	4.3 (-6.0 to 14.7)	.51
>0.5-mg/dL increase	9 (10.3)	4 (4.7)	5.6 (-2.2 to 13.5)	.25
>25% or >0.5-mg/dL increase	14 (16.1)	10 (11.8)	4.3 (-6.0 to 14.7)	.51
Contrast Volume				
≤150 mL	n = 89	n = 90		
Estimated GFR >25% decrease	11 (12.4)	12 (13.3)	-0.9 (-10.8 to 8.8)	>.99
Serum creatinine				
>25% increase	14 (15.7)	15 (16.8)	-1.1 (-11.7 to 9.9)	>.99
>0.5-mg/dL increase	10 (11.2)	7 (7.8)	3.4 (-5.1 to 12.0)	.46
>25% or >0.5-mg/dL increase	15 (16.9)	16 (17.8)	-0.9 (-12.0 to 10.2)	>.99
>150 mL	n = 76	n = 68		
Estimated GFR >25% decrease	13 (17.1)	9 (13.2)	3.9 (-7.8 to 15.6)	.64
Serum creatinine				
>25% increase	13 (17.1)	10 (14.7)	2.4 (-9.5 to 14.3)	.82
>0.5-mg/dL increase	12 (15.8)	7 (10.3)	5.5 (-5.4 to 16.4)	.46
>25% or >0.5-mg/dL increase	15 (19.7)	10 (14.7)	5.0 (-7.3 to 17.3)	.51

Abbreviations: CI, confidence interval; GFR, glomerular filtration rate.

SI conversion factor: To convert serum creatinine values to $\mu\text{mol/L}$, multiply by 88.4.

^aBy Fisher exact test.

Table 5. Clinical Adverse Events in the Full Cohort (N = 353)

Outcome ^a	No. (%)		Absolute Difference (95% CI)	P Value ^a
	Sodium Chloride (n = 178)	Sodium Bicarbonate (n = 175)		
30 d				
All-cause mortality	3 (1.7)	3 (1.7)		
Myocardial infarction	0	1 (0.6)		
Dialysis	2 (1.1)	1 (0.6)		
CVA ^b	4 (2.2)	0		
Cumulative major adverse events ^c	8 (4.5)	4 (2.3)	2.2 (-1.6 to 6.0)	.38
30 d to 6 mo				
All-cause mortality	4 (2.3)	1 (0.6)		
Myocardial infarction	4 (2.3)	1 (0.6)		
Dialysis	2 (1.1)	1 (0.6)		
CVA ^b	3 (1.7)	1 (0.6)		
Cumulative major adverse events ^c	8 (4.6)	4 (2.3)	2.3 (-1.6 to 6.1)	.38
6 mo				
Cumulative mortality	7 (3.9)	4 (2.3)	1.7 (-2.0 to 5.3)	.54
Cumulative major adverse events ^c	16 (9.0)	8 (4.6)	4.4 (-0.8 to 9.6)	.14

Abbreviations: CI, confidence interval; CVA, cerebrovascular accident.

^aBy Fisher exact test.

^bStroke and transient ischemic attack.

^cAll-cause mortality, myocardial infarction, dialysis, and CVA.

25% or greater decrease in estimated GFR occurred in 14.6% of patients randomized to receive sodium chloride and in 13.3% to receive sodium bicarbonate. When measured as an absolute or percent increase in serum creatinine level, the incidence of nephropathy was not statistically different between the sodium chloride and sodium bicarbonate groups. The overall observed rates of contrast-induced nephropathy were similar to those reported in prior studies and meta-analyses of nonionic, low-osmolar contrast media.¹⁶⁻²⁰ The incidence observed with sodium bicarbonate infusion in the current study is comparable to that seen in the Cardiac Angiography in Renally Impaired Patients (CARE) trial.²³ In CARE, a randomized comparison of 2 contrast media, all study participants (n=414) received periprocedural hydration with sodium bicarbonate per the protocol described by Merten et al.¹⁴ The incidence of contrast-induced nephropathy was 10.6% in the group receiving sodium bicarbonate only and 11.9% in the group receiving sodium bicarbonate plus *N*-acetylcysteine. Similarly, use of *N*-acetylcysteine in the current study, in either the sodium chloride or the sodium bicarbonate groups, was not associated with less nephropathy.

Prior randomized trials of contrast-induced nephropathy have provided limited follow-up beyond the first several days following contrast exposure.^{14,18,24} Therefore, the correlates between development of nephropathy and clinical adverse events are derived primarily from cohort studies. In the current study, we report clinical adverse events at 30 days and 6 months after contrast exposure among all randomized patients, including those excluded from the contrast-induced nephropathy analysis. The 30-day mortality rate was similar between treatment groups. At 6 months, slightly more deaths occurred in the sodium chloride group, a difference that was not statistically significant. The overall mortality at 6 months was 3.1% among all randomized patients vs 9.8% among the patients developing contrast-induced nephropathy. The 30-day rates of clinical adverse events in the current study are similar to those reported in a prior randomized trial but lower than estimates reported in cohort studies.²⁰ The exclusion of very high-risk patient populations, such as those with cardiogenic shock and acute myocardial infarction, likely account in part for these differences.

The current study also enrolled patients with stable renal function. In registry studies it may be more difficult to identify patients with deteriorating renal function prior to contrast exposure, a group that also is likely to have a higher incidence of clinical adverse events. The progression to dialysis beyond the short term has not been characterized in prior randomized trials. Among all randomized patients, the incidence of dialysis at 6 months was 1.7%; however, among patients developing contrast-induced nephropathy the incidence was 9.8%. While the overall mortality of the patients undergoing dialysis at 6 months was 66.7%, it was 100% among patients developing nephropathy. While need for dialysis was a rare event overall, it portends a poor prognosis in the intermediate term after coronary angiography and contrast exposure.

The pathophysiology of contrast-induced nephropathy is complex and not well understood. Two commonly proposed mechanisms are renal vasoconstriction resulting in medullary ischemia and oxidant or free radical injury. Reported durations of renal vasoconstriction vary from less than 2 to more than 4 hours.^{10,25} Hydration may attenuate this adverse effect of contrast exposure by reducing renin activation and loss of nitric oxide, but the optimal duration and rate of hydration remain unknown.

The extent to which free radical injury accounts for contrast-induced nephropathy is also not known. Although the mechanism by which sodium bicarbonate might reduce nephropathy remains poorly defined, it has been postulated that sodium bicarbonate infusion may decrease generation of free radicals mediated by the Haber-Weiss reaction by increasing tubular pH, since the reaction is most active at lower pH levels.¹⁴ Sodium bicarbonate infusion also may scavenge the potent oxidant peroxynitrate, produced via a nitric oxide-mediated pathway.²⁶ However, the results of the current study suggest that there may be no significant difference between periprocedural hydration with sodium chloride or sodium bicarbon-

ate for the prevention of contrast-induced nephropathy.

The findings of the current study differ from those of 2 prior reports. In the study by Merten et al,¹⁴ contrast-induced nephropathy, defined as a 25% increase in serum creatinine level within 2 days of contrast exposure, occurred in 1.7% of 60 patients randomized to receive sodium bicarbonate and in 13.6% of 59 randomized to receive sodium chloride ($P=.02$). In the second study, the Renal Insufficiency Following Contrast Media Administration (REMEDIAL) trial,²⁴ a decrease in the incidence of contrast-induced nephropathy was observed with the combination of sodium bicarbonate infusion plus double-dose oral *N*-acetylcysteine. Both studies were limited by small sample sizes. An additional 1 or 2 events in the sodium bicarbonate group may have yielded nonconclusive results. The study by Merten et al was terminated after enrollment of 119 of the planned 260 patients. It has been noted that the *P* value for the difference in event rates was higher than expected for early termination of a trial.²⁷ Also, patients in the study by Merten et al received both intra-arterial and intravenous contrast. The risk of developing contrast-induced nephropathy in the former group may be greater.^{28,29}

The current study also differed slightly from the 2 prior studies in the hydration protocol. In the current study, postprocedure hydration was performed at 1.5 mg/kg per hour for 4 hours, compared with 1 mg/kg per hour for 6 hours in the prior studies. While the duration of hydration was slightly shorter in the current study, the volume administered was similar between all studies. Patients in the REMEDIAL trial and in the study by Merten et al had baseline estimated GFR values of 32 to 35 mL/min per 1.73 m² and 43 mL/min per 1.73 m², respectively, compared with 48 mL/min per 1.73 m² in the current study. It is possible that sodium bicarbonate may be more effective at lower levels of renal function. Also, each of these studies used different contrast media, and therefore the type of contrast medium is unlikely

to account for the observed differences. The current study and the study by Merten et al both used nonionic, low-osmolar contrast media (ioxilan [350 mg iodine/mL] and iopamidol [370 mg iodine/mL], respectively); in contrast, the REMEDIAL trial used iodixanol (320 mg iodine/mL), a nonionic, iso-osmolar medium.

No standardized definition of contrast-induced nephropathy has been established. In the current study we chose to use estimated GFR to estimate renal function and define contrast-induced nephropathy. The Kidney Disease Outcomes Quality Initiative guidelines from the National Kidney Foundation describe the use of estimated GFR as the best overall index of renal function.³⁰ The use of estimated GFR of 60 mL/min per 1.73 m² or less to identify patients at risk of nephropathy is also consistent with the recommendations of the Contrast-Induced Nephropathy Consensus Working Panel, which state that the risk of acute kidney injury is increased and of clinical importance in patients with chronic kidney disease below this level.³¹ At this estimated GFR, kidney damage is established and half or more of the kidney function in the adult is lost.³⁰ However, the use of estimated GFR to assess acute changes in renal function remains less well established. In the current study we choose to define contrast-induced nephropathy as a 25% change in renal function determined by estimated GFR. This degree of change is commonly used to define contrast-induced nephropathy by serum creatinine level. Among the variables used in the Modification of Diet in Renal Disease study equation, the only variable changing during the study period for repeat measures is serum creatinine level; age, sex, and race remain constant. Therefore, changes in estimated GFR largely parallel changes in serum creatinine level, as our results show.

Unlike patients in prior studies using sodium bicarbonate, those in the current study underwent a uniform procedure, diagnostic coronary angiography, with very similar rates of ad hoc percu-

taneous coronary intervention in both groups. Patients in the current study received only intra-arterially administered contrast, whereas some patients in prior studies received intravenously administered contrast. The groups in the current study were well matched, with procedure duration, contrast volume, and other contrast-induced nephropathy risk factors similar in both groups. Left ventricular end-diastolic pressure, a possible surrogate for volume status, was measured and similar between the treatment groups. The analysis was performed by the intention-to-treat principle and included all randomized patients in the clinical follow-up. Lastly, the study was adequately powered and met its enrollment goal.

Limitations

The primary study end point of contrast-induced nephropathy could not be determined in 11.9% of the study participants in whom serial measurements of serum creatinine levels were not available. These patients were asymptomatic as outpatients and cited transportation difficulties as the primary reason for not being able to return to the clinic for blood draws. The baseline characteristics of these patients were similar to those of patients with available follow-up assessment of creatinine levels. In a sensitivity analysis, the inclusion of these patients as either developing or not developing nephropathy did not change the principal results. Moreover, these patients were included in the analysis of clinical adverse events.

Second, the physicians performing cardiac catheterization were not blinded to each patient's treatment assignment. However, the procedure duration and contrast volume, which would likely reflect any biases in contrast administration, were similar between groups (median procedure duration: 37.5 vs 33.0 minutes, respectively; median contrast volume: 137 vs 126 mL). Laboratory personnel measuring the serum creatinine levels were blinded to the treatment status. Also, the intensity of follow-up was similar between

groups, and all randomized patients were included in the adverse events analysis.

Third, the study was performed at a single center, which potentially may limit the generalizability of the findings. Fourth, while the volume of fluid administered was similar for both treatment groups, the sodium content of the 2 intravenous fluids differed slightly. Normal saline (0.9% sodium chloride) has 154 mEq of sodium per liter; in contrast, the sodium bicarbonate solution had 130 mEq of sodium per liter. However, this formulation was similar to that used by Merten et al¹⁴ in the registry phase.

Conclusion

The results of this study do not suggest that hydration with sodium bicarbonate is superior to hydration with sodium chloride in patients with moderate to severe chronic kidney disease who are undergoing coronary angiography. The overall incidence of contrast-induced nephropathy among patients was 13.9% and did not differ by treatment assignment. The frequency of clinical adverse events did not significantly differ between groups. Any true difference between the hydration strategies is likely to be small and not clinically significant.

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Obtained funding: Brar, Shen, Jorgensen, Kotlewski, Aharonian.

Administrative, technical, or material support: Brar, Shen, Jorgensen, Kotlewski, Aharonian, Desai, Ree, Shah, Burchette.

Study supervision: Brar.

Financial Disclosures: None reported.

Funding/Support: This study was supported by Kaiser Permanente Southern California.

Role of the Sponsor: The administration of Kaiser Permanente had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript.

Additional Contributions: We thank Stephanie Tovar, MS (Kaiser Permanente), for her assistance with manuscript preparation and Ric Hyett, HCA, and Columbus Batiste, MD (Kaiser Permanente), for assistance with data collection. None of these individuals received financial compensation for their contributions.

REFERENCES

- Levy EM, Viscoli CM, Horwitz RI. The effect of acute renal failure on mortality: a cohort analysis. *JAMA*. 1996;275(19):1489-1494.
- Dangas G, Iakovou I, Nikolovsky E, et al. Contrast-induced nephropathy after percutaneous coronary interventions in relation to chronic kidney disease and hemodynamic variables. *Am J Cardiol*. 2005;95(1):13-19.
- Mehran R, Aymong ED, Nikolovsky 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(7):1393-1399.
- Nikolovsky E, Mehran R, Turcot D, et al. Impact of chronic kidney disease on prognosis of patients with diabetes mellitus treated with percutaneous coronary intervention. *Am J Cardiol*. 2004;94(3):300-305.
- Nikolovsky E, Aymong ED, Dangas G, Mehran R. Radiocontrast nephropathy: identifying the high-risk patient and the implications of exacerbating renal function. *Rev Cardiovasc Med*. 2003(4 suppl 1):S7-S14.
- Parfrey PS, Griffiths SM, Barrett BJ, et al. Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency, or both: a prospective controlled study. *N Engl J Med*. 1989;320(3):143-149.
- Manske CL, Sprafka JM, Strony JT, Wang Y. Contrast nephropathy in azotemic diabetic patients undergoing coronary angiography. *Am J Med*. 1990;89(5):615-620.
- Iakovou I, Dangas G, Mehran R, et al. Impact of gender on the incidence and outcome of contrast-induced nephropathy after percutaneous coronary intervention. *J Invasive Cardiol*. 2003;15(1):18-22.
- Nikolovsky E, Mehran R, Lasic Z, et al. Low hematocrit predicts contrast-induced nephropathy after percutaneous coronary interventions. *Kidney Int*. 2005;67(2):706-713.
- Russo D, Minutolo R, Cianciarus B, Memoli B, Conte G, De Nicola L. Early effects of contrast media on renal hemodynamics and tubular function in chronic renal failure. *J Am Soc Nephrol*. 1995;6(5):1451-1458.
- Katholi RE, Woods WTJ, Taylor GJ, et al. Oxygen free radicals and contrast nephropathy. *Am J Kidney Dis*. 1998;32(1):64-71.
- Sporer H, Lang F, Oberleithner H, Greger R, Deetjen P. Inefficacy of bicarbonate infusions on the course of postschaemic acute renal failure in the rat. *Eur J Clin Invest*. 1981;11(4):311-315.
- Atkins JL. Effect of sodium bicarbonate preloading on ischemic renal failure. *Nephron*. 1986;44(1):70-74.
- 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.
- Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. Modification of Diet in Renal Disease Study Group. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med*. 1999;130(6):461-470.
- 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.
- Rudnick MR, Goldfarb S, Wexler L, et al. Nephrotoxicity of ionic and nonionic contrast media in 1196 patients: a randomized trial: the Iohexol Cooperative Study. *Kidney Int*. 1995;47(1):254-261.
- Tepl 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.
- 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.
- Stone GW, McCullough PA, Tumlin JA, et al. Fenoldopam mesylate for the prevention of contrast-induced nephropathy: a randomized controlled trial. *JAMA*. 2003;290(17):2284-2291.
- Spargias K, Alexopoulos E, Kyrzopoulos S, et al. Ascorbic acid prevents contrast-mediated nephropathy in patients with renal dysfunction undergoing coronary angiography or intervention [published correction appears in *Circulation*. 2005;111(3):379]. *Circulation*. 2004;110(18):2837-2842.
- Thygesen K, Alpert JS, White HD; Joint ESC/ACC/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. *J Am Coll Cardiol*. 2007;50(22):2173-2195.
- Solomon RJ, Natarajan MK, Doucet S, et al. 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.
- Briguori C, Airoidi 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.
- Tumlin JA, Wang A, Murray PT, Mathur VS. Fenoldopam mesylate blocks reductions in renal plasma flow after radiocontrast dye infusion: a pilot trial in the prevention of contrast nephropathy. *Am Heart J*. 2002;143(5):894-903.
- Caulfield JL, Singh SP, Wishnok JS, Deen WM, Tannenbaum SR. Bicarbonate inhibits N-nitrosation in oxygenated nitric oxide solutions. *J Biol Chem*. 1996;271(42):25859-25863.
- Barrett BJ, Parfrey PS. Clinical practice: preventing nephropathy induced by contrast medium. *N Engl J Med*. 2006;354(4):379-386.
- Campbell DR, Flemming BK, Mason WF, Jackson SA, Hirsch DJ, MacDonald KJ. A comparative study of the nephrotoxicity of iohexol, iopamidol and ioxaglate in peripheral angiography. *Can Assoc Radiol J*. 1990;41(3):133-137.
- Moore RD, Steinberg EP, Powe NR, et al. Nephrotoxicity of high-osmolality versus low-osmolality contrast media: randomized clinical trial. *Radiology*. 1992;182(3):649-655.
- 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.
- McCullough PA, Adam A, Becker CR, et al. Risk prediction of contrast-induced nephropathy. *Am J Cardiol*. 2006;98(6A):27K-36K.