Sodium Bicarbonate Versus Isotonic Saline for the Prevention of Contrast-Induced Nephropathy in Patients With Diabetes Mellitus Undergoing Coronary Angiography and/or Intervention: A Multicenter Prospective Randomized Study

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Introduction: Contrast-induced nephropathy (CIN) is a leading cause of acute renal failure and affects mortality and morbidity. Although the incidence of CIN is quite low in the general population, CIN incidence is significantly increased in patients with diabetes mellitus (DM).

Objectives: We compared the efficacy of prophylactic use consisting of a saline infusion or a sodium bicarbonate infusion for the prevention of CIN in patients with DM.

Materials and Methods: A total of 195 DM patients who had unselected renal function were randomized into 2 groups: 101 patients were assigned to saline infusion, and 94 patients were assigned to bicarbonate infusion. The primary end point was the maximum increase in the serum creatinine (SCr) level, whereas the secondary end point was the development of CIN after the procedure.

Results: The maximum increase in SCr levels was significantly lower in the saline group than in the bicarbonate group: −0.03 mg/dL (IQR, −0.09 to 0.10 mg/dL) versus 0.02 mg/dL (IQR, −0.09 to 0.13 mg/dL) ($P = 0.014$). The rate of CIN was significantly lower in the saline group than in the bicarbonate group (5.9% vs 16%, $P = 0.024$). In the subset of study participants with a baseline creatinine clearance of less than 60 mL/min, the maximum increase in SCr levels was significantly lower, −0.08 mg/dL (IQR, −0.13 to −0.04 mg/dL), in the saline group than in the bicarbonate group, 0.03 mg/dL (IQR, −0.13 to 0.12 mg/dL) ($P = 0.004$).

Conclusions: The use of prophylactic hydration with isotonic saline before coronary procedures may decrease SCr levels and reduce the incidence of CIN in patients with DM with unselected renal functions to a greater extent than sodium bicarbonate can.

Key Words: contrast-induced nephropathy, diabetes mellitus, isotonic saline, sodium bicarbonate

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Contrast-induced nephropathy (CIN) is one of the major complications seen in patients who undergo coronary angiography and percutaneous coronary intervention (PCI).[1] Contrast-induced nephropathy is the third leading cause of acute renal failure in hospitalized patients. Previous studies have shown that patients who have CIN have increased risk of intrahospital mortality, increased treatment costs, and hospital stay.[2] Although the mechanism of CIN is unknown, one hypothesis is that medullar ischemia contributes to CIN by causing renal vasoconstriction and free radical injury.[3,4] Several protocols have been tested for the prevention of CIN, including hydration with isotonic or hypotonic saline as well as antioxidant molecules (*N*-acetylcysteine [NAC] and ascorbic acid), but conflicting results were obtained.[1,5–9] Recently, volume supplementation with sodium bicarbonate has been tested as a potential new treatment modality for preventing CIN: Sodium bicarbonate can decrease the formation of free oxygen radicals by increasing urine pH and by producing nefroprotection.[10,11] In several randomized studies, sodium bicarbonate plus hydration therapy was found to be more effective in preventing CIN than saline therapy was.[10,12] Although CIN incidence is quite low in the general population, the incidence of CIN and the need for transient hemodialysis are significantly increased in patients with preexisting renal disease, diabetes mellitus (DM), and particularly diabetic nephropathy.[5,6,13,14] Diabetic patients have a 20% CIN incidence, whereas nondiabetic patients have a 5.5% CIN incidence, and this incidence may increase to up to 40% in diabetic patients with renal impairment.[14–16]

The presented study was designed to compare the effects of sodium bicarbonate and isotonic saline on the prevention of CIN; a prospective randomized multicenter trial was performed in unselected patients with DM who were undergoing coronary angiography and/or PCI.

MATERIALS AND METHODS

Study Population

From May 2009 to June 2010, all patients who met the inclusion criteria and who were undergoing coronary angiography and/or PCI were placed in the study. An ethics committee approved the study, and informed consent was obtained from the patients. Diabetic patients who were admitted to the 3 separate clinics (those at Gaziosmanpasa University, Necmettin Erbakan University, and Erciyes University) and who underwent coronary angiography were randomized into bicarbonate or saline groups. In each clinic, a first patient was randomly selected through a draw, and other patients were assigned by turns. Thus,

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all groups in each clinic were equally distributed. The inclusion criteria were having DM and being at least 18 years old. Diabetes mellitus was described as any of the following: use of oral hypoglycemic agents or insulin, fasting plasma glucose levels greater than 126 mg/dL, or a random plasma glucose level of 200 mg/dL or greater. The exclusion criteria were contrast-agent hypersensitivity, pregnancy lactation, decompensated heart failure, pulmonary edema, severe renal impairment (defined as serum creatinine [SCr] ≥3.0 mg/dL), emergency procedures, and previous contrast agent administration within 7 days of study enrollment. Metformin and nonsteroidal anti-inflammatory drugs were ceased 48 hours before the procedure and re-initiated 48 hours after the procedure in patients who had not developed contrast nephropathy.

Study Protocol

Patients were randomized into equally sized study groups and given either an infusion of isotonic saline (saline group) or sodium bicarbonate (bicarbonate group). In all cases, the patients' demographic features, risk factors, and medications were recorded. Patients who were assigned to the isotonic saline group received 1-mL/kg per hour 0.9% sodium chloride for 12 hours before and 12 hours after the procedure.[13] The sodium bicarbonate solution was prepared by adding 154 mL of 1000-mEq/L sodium bicarbonate to 846 mL of 5% dextrose in water. Sodium bicarbonate (1 mL/kg per hour) was given to the patients 6 hours before and 6 hours after the procedure.[10] Echocardiography was used to evaluate all patients' left ventricular function before the procedure as well. In addition, coronary angiography and/or PCI were done via the femoral artery. Serum creatinine levels and urinary PH were measured the day before as well as 24 hours and 48 hours after administration of the contrast agent. Creatinine clearance (CrCl) was calculated using the Cockcroft-Gault formula.[17]

Study End Points

The primary end point was the maximum increase in the SCr level within 48 hours after the administration of the contrast media. The secondary end point was the development of CIN after the procedure. Contrast-induced nephropathy was defined as a baseline SCr of 25% or more and/or an absolute increase in SCr of 0.5 mg/dL or more 48 hours after the procedure.[18]

Subgroup Analysis

High-risk factors for CIN other than DM were used for the subgroup analysis. The following high-risk factors were chosen for the subgroup analysis: the presence of renal impairment (defined as a baseline CrCl of less than 60 mL/min), the use of high-dose contrast media (defined as >100 mL), reduced left ventricular systolic function (ejection fraction by echocardiography ≤40%), and advanced age (70 years or older).

Statistical Analysis

To calculate the necessary sample size, a standard difference of 0.17 mg/dL[11] in the primary end point of change in SCr level between baseline and 48 hours' follow-up was assumed for both the saline and bicarbonate groups. The standard deviation was 0.50; and consequently, the standardized effect size was calculated to be 0.34 (0.17/0.50). According to these calculations, a sample size of 93 patients per group would permit a 2-sided significance level of 5% and 90% power. Power analysis was performed using G-Power version 3.1.2.

Pearson χ^2 test and the Fisher exact test were used to compare the incidence of CIN and other categorical variables among the groups. Categorical variables were presented as counts and percentages. The Kolmogorov-Smirnov test was used to evaluate whether the distribution of variables was normal. The 2 independent sample *t* test or the Mann-Whitney *U* test was used to compare continuous variables between the 2 groups. Continuous variables were presented as mean (standard deviation [SD]) or as median (interquartile range [IQR]). $P < 0.05$ was considered to be statistically significant. Analyses were performed using commercially available software (PASW version 18, ID: 33478001 SPSS Inc, Chicago, IL).

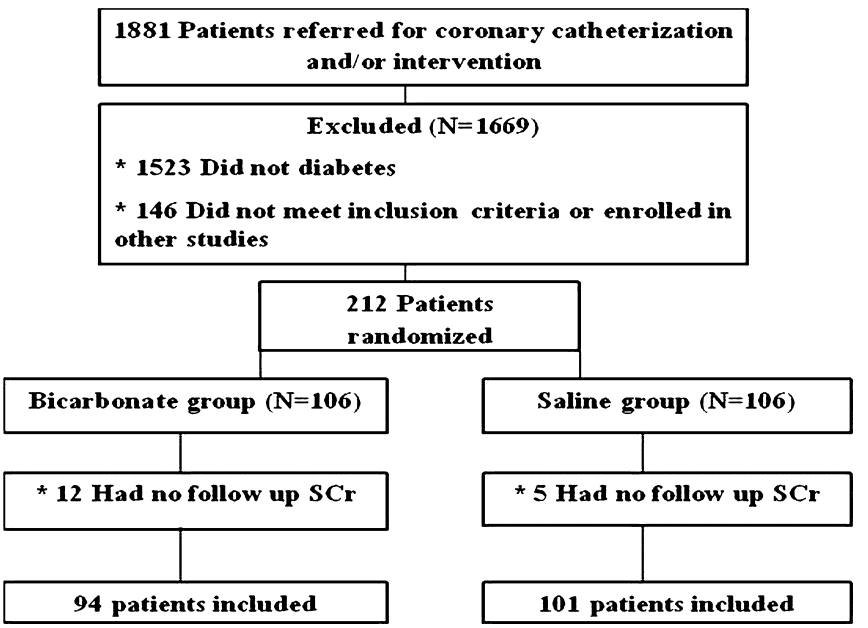

FIGURE 1. Patient flow.

RESULTS

Baseline Characteristics and Study Population

Of 1881 consecutive patients referred for coronary angiography and/or intervention, 212 were eligible for this study. A total of 17 patients, 5 patients in the saline group and 12 patients in the bicarbonate group, were not included in the study because their SCr levels were not monitored 48 hours after the procedure. Therefore, a total of 195 patients, including 101 patients in the saline group and 94 patients in the bicarbonate group, were used in the study (Fig. 1). The mean age was 62; and of the total 195 patients, 102 patients were men. The 2 treatment groups were similar with regard to baseline characteristics and medications (Table 1). At the end of the study, none of the patients required hemodialysis, and there were no adverse reactions other than CIN.

Study End Points

The baseline median SCr levels in both groups are presented in Table 2. The maximum increase in the SCr levels was significantly lower in the saline group than in the bicarbonate group, −0.03 mg/dL (IQR, −0.09 to 0.10 mg/dL) vs 0.02 mg/dL (IQR, −0.09 to 0.13 mg/dL), respectively (P = 0.014; Fig. 2). Contrast-induced nephropathy developed in 21 (10.8%) of the 195 patients. The rate of CIN was significantly lower in the saline group compared to the bicarbonate group (5.9% vs 16%, respectively; P = 0.024; Fig. 3). Urinary pH was significantly higher in the bicarbonate group than in the saline group (P = 0.002; Table 2).

Subgroup Analysis

Of the 195 patients, 46 patients (24%) were of advanced age, 41 patients (21%) had reduced left ventricular systolic function, 39 patients (20%) received a high-dose contrast agent, and 59 patients (30%) had renal impairment. In the group of patients with a baseline CrCl of less than 60 mL/min, the maximum increase in SCr levels was significantly lower in the saline group than in the bicarbonate group, −0.08 mg/dL (IQR, −0.13 to −0.04 mg/dL) compared with 0.03 mg/dL (IQR, −0.13 to 0.12 mg/dL), respectively (P = 0.004; Table 3). No other significant differences existed between the high-risk subgroups at the primary and secondary end points.

DISCUSSION

The main finding of the present study is that in patients with DM who are undergoing coronary angiography and/or PCI, prophylactic saline infusion significantly reduces the maximum increase in the SCr level and the rate of CIN compared with bicarbonate infusion. Furthermore, in patients with CrCl less than 60 mL/min, the maximum increase in the SCr level was significantly lower in the saline infusion group than in the bicarbonate infusion group.

TABLE 1. Baseline Characteristics of Study Groups

	Saline Group (n = 101)	Bicarbonate Group (n = 94)	*P*
Age, mean (SD), yrs	62 ± 9	62 ± 9	0.719
Age ≥70, n (%)	22 (22)	24 (26)	0.538
Male, n (%)	48 (48)	54 (58)	0.166
BMI, median (IQR), kg/m^2	28 (25–30)	28 (26–32)	0.082
LVEF, median (IQR), %	53 (45–60)	50 (44–60)	0.641
LVEF ≤40%, n (%)	20 (20)	21 (22)	0.664
HbA1c, median (IQR)	7.5 (6.6–8.9)	7.1 (6.6–8.3)	0.279
SBP, median (IQR), mm Hg	126 (111–135)	125 (110–140)	0.965
DBP, median (IQR), mm Hg	70 (65–80)	80 (70–82)	0.118
Hypertension, n (%)	61(60)	62 (66)	0.421
Current smoker, n (%)	26 (26)	31 (33)	0.267
Previous MI, n (%)	30 (30)	21 (22)	0.242
PCI performed, n (%)	33 (32)	23 (25)	0.245
Medications, n (%)			
ACEI or ARB	93 (92)	85 (90)	0.683
Nitrate	48 (48)	40 (43)	0.486
Calcium-channel blocker	9 (9)	13 (14)	0.278
β-blocker	86 (85)	76 (81)	0.424
Statin	79 (78)	67 (71)	0.264
Insulin	36 (36)	25 (27)	0.173
Metformin	33 (33)	36 (38)	0.412
Contrast administration			
Contrast dose, median (IQR)	90 (85–100)	90 (90–100)	0.275
Dose >100 mL, n (%)	22 (21)	18 (19)	0.774
CrCl, median (IQR), mL/min	74 (54–101)	78 (61–108)	0.115
CrCl <60 mL/min, n (%)	36 (36)	23 (25)	0.090

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; SD, standard deviation.

TABLE 2. Study End Points and Urine pH After 48 Hours of Administration of Contrast Agent

	Saline Group (n = 101)	Bicarbonate Group (n = 94)	*P*
SCr, median (IQR), mg/dL			
Baseline	1.0 (0.87–1.33)	1.0 (0.80–1.30)	0.147
Difference	−0.03 (−0.09 to 0.10]	0.02 (−0.09 to 0.13)	0.014
CIN, n (%)			
SCr ≥25%	6 (5.9)	15 (16)	0.024
SCr ≥0.5 mg/dL	1 (1)	2 (2.1)	0.610
Urine pH, median (IQR)			
Baseline	5.5 (5.0–6.0)	5.5 (5.0–6.0)	0.414
Difference	0 (−0.5 to 0.5)	0.5 (0–1.0)	0.002

Several strategies have been recommended for the prevention of CIN among patients undergoing coronary angiography and interventions using a contrast agent.[19] Hydration therapy may reduce medullar ischemia by decreasing the unfavorable effects of the contrast agent, such as renin activation and nitric oxide reduction.[11] Likewise, hydration therapy may reduce direct cell damage by diluting the contrast agent as it passes through the medullar tubules.[20] Sodium bicarbonate plus hydration may help to prevent CIN by reducing the production of free oxygen radicals by increasing tubular pH and by scavenging peroxynitrate generated from nitric oxide.[19] In previous studies, sodium bicarbonate was found to be beneficial in the prevention of CIN independent of clinical outcomes such as death, heart failure, and the need for renal replacement.[10,12,19,21,22] However, in recent studies, these findings were not confirmed, and sodium bicarbonate was not shown to be superior to saline for the prevention of CIN.[11,23,24] In this present study, saline's more positive effect may be due to the earlier initiation and larger volume of hydration in the saline group compared with the bicarbonate group. In the saline group, SCr levels obtained at the 48th hour were decreased compared with the baseline levels; however, an increase in the SCr levels occurred in the bicarbonate group. Hydration was initiated in the saline group 12 hours before the procedure and continued 12 hours after the procedure (a total of 24 hours); whereas in the bicarbonate group, hydration began 6 hours before the procedure and continued 6 hours after the procedure (a total of 12 hours). The results of this study are consistent with our previous study, coronary acetylcysteine study (CASIS).[25] In CASIS, SCr levels obtained after the 48th hour were decreased compared with the baseline levels in patients to whom were recommended *N*-acetylcysteine (NAC) plus high-dose hydration. In the previous literature, a detailed randomized study concerning the amount and starting time of hydration does not exist. However, in 2 small studies, hydration administration starting immediately before the contrast medium administration and continuing 12 hours after the procedure was compared to an intravenous hydration regimen starting at least 12 hours before the procedure. According to the results of both studies, hydration therapy initiated earlier is more favorable than therapy started later.[26,27] Another potential explanation for the finding that saline is more favorable than bicarbonate for the prevention of CIN is that our study population had better baseline renal functions than did those in some previous studies.[10,12,22] Sodium bicarbonate may be more effective in patients with significantly impaired renal functions.[11] In our study, the baseline median SCr level was 1.0 mg/dL (IQR, 0.80–1.30 mg/dL). Therefore, in our study, saline therapy might be more effective than bicarbonate treatment. The other possible explanation for the decreased efficacy of sodium bicarbonate prophylaxis in our study may be the pro-oxidant ability of bicarbonate in the presence of free oxygen radicals. The generation of free radicals is increased in DM, and bicarbonate may increase the formation of peroxymonocarbonate, which is a potent free radical generated by the coupling of bicarbonate with hydrogen peroxide.[15,28] The present study is the first study of bicarbonate use in patients with DM, according to the current

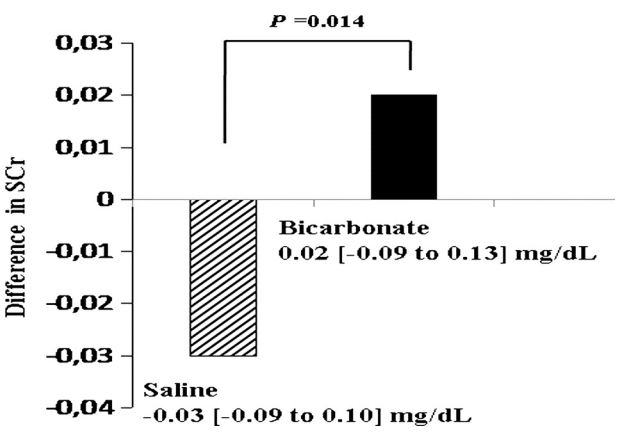

FIGURE 2. Difference of SCr after procedure.

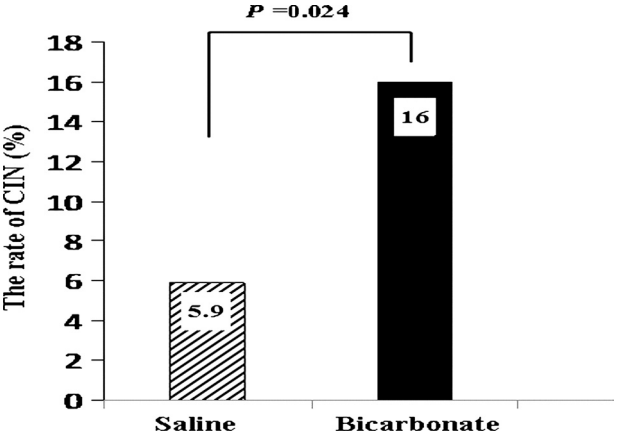

FIGURE 3. Rate of CIN in study groups.

TABLE 3. Subgroup Analysis of Differences Between Study Groups in Baseline SCr Level Changes and the Rate of CIN

	Saline Group (n = 101)	Bicarbonate Group (n = 94)	*P*
Age ≥70, n	22	24	
Baseline SCr, median (IQR), mg/dL	1.0 (0.95–1.31)	1.0 (0.80–1.33)	0.684
SCr difference, median (IQR), mg/dL	−0.06 (−0.09 to 0.0)	0.02 (−0.1 to 0.25)	0.190
CIN, n (%)	2 (9.1)	5 (20.8)	0.268
LVEF ≤40, n	20	21	
Baseline SCr, median (IQR), mg/dL	1.16 (0.97–1.53)	1.20 (0.88–1.33)	0.389
SCr difference, median (IQR), mg/dL	−0.06 (−0.11 to 0]	−0.07 (−0.1 to 0.1)	0.592
CIN, n (%)	0 (0)	2 (9.5)	0.157
Contrast agent dose >100 mL, n	21	18	
Baseline SCr, median (IQR), mg/dL	0.87 (0.8–1.1)	0.88 (0.7–1.04)	0.330
SCr difference, median (IQR), mg/dL	0 (−0.06 to 0.16)	0.11 (0–0.29)	0.093
CIN, n (%)	3 (14.3)	4 (22.2)	0.520
CrCl (baseline) <60 mL/min, n	36	23	
Baseline SCr, median (IQR), mg/dL	1.38 (1.15–1.67)	1.33 (1.23–1.56)	0.786
SCr difference, median (IQR), mg/dL	−0.08 (−0.13 to −0.04)	0.03 (−0.13 to 0.12)	0.004
CIN, n (%)	0 (0)	1 (4.3)	0.207

knowledge, and does not support bicarbonate use in these patients. Administration of NAC in the prevention of *CIN* may be an alternative treatment in patients with DM. *N*-acetylcysteine may prevent CIN by decreasing oxidative tissue damage and by improving renal hemodynamics.[5,13,14] Initial studies suggested a highly beneficial effect of NAC, therefore resulting in a trend for physicians to use NAC in procedures in which contrast agent must be administered.[1,5,29–31] However, a study population of Coyle et al.[32] was similar to ours, and no superior effect of NAC therapy was found over hydration therapy in diabetic patients.

Study Limitations

This study has certain limitations. First, the follow-up period was only 48 hours in this study. There are some studies that report that SCr levels peak 72 hours after a procedure using contrast agent and that the levels do not return to normal for up to 10 days.[12] However, this does not constitute a major problem because CIN develops within 24 hours after the procedure in most patients.[33] Second, contrast osmolality together with contrast amount are one of the affecting factors on CIN in diabetic patients. Low osmolar agent, iohexol, was found less related with CIN than high osmolar agents in diabetic patients in the previous studies.[15] Although in several studies, iso-osmolar agents were found to be protective than low osmolar agents in prevention of CIN in patients with DM,[34,35] there was no difference found between these agents in some studies.[36–39] In our study, low osmolar agent, iohexol, was preferred routinely in all included centers. Finally, the main limitation is that the time of initiation of hydration and the hydration volume were not the same for the saline and bicarbonate groups. However, there are different studies in the literature that compared saline and bicarbonate with different doses of hydration regimens.[23,38,40] Although optimal hydration strategy is not precisely described in the literature, 12 hours preprocedure and 12 hours postprocedure strategy of hydration therapy is the most preferred regimen in the literature.[2] In our previous study, CASIS, we have performed the same strategy of hydration therapy in the saline control group (250 individuals). Bicarbonate group was designed similarly with the longest hydration therapy reported by Ozcan et al.[10] Prophylactic bicarbonate therapy prevents free radical damage mainly by increasing urinary pH. Thus, less hydration of the saline group does not exactly depreciate the study. However, this conflict may be resolved in a different study of which the equal amount of fluid therapy will be used in diabetic patients.

CONCLUSION

This study evaluated, together with the results of previous studies, that isotonic saline and standard hydration therapy are thought to be a method more appropriate than other alternatives for the prevention of CIN in patients with DM. However, multicenter randomized studies with large study population will clarify this issue.

REFERENCES

1. 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.
2. Barrett BJ, Parfrey PS. Clinical practice. Preventing nephropathy induced by contrast medium. *N Engl J Med*. 2006;354:379–386.
3. Russo D, Minutolo R, Cianciaruso B, et al. Early effects of contrast media on renal hemodynamics and tubular function in chronic renal failure. *J Am Soc Nephrol*. 1995;6:1451–1458.
4. Katholi RE, Woods WT Jr, Taylor GJ, et al. Oxygen free radicals and contrast nephropathy. *Am J Kidney Dis*. 1998;32:64–71.
5. 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.
6. Briguori C, Airoldi F, D'Andrea D, et al. Renal Insufficiency Following Contrast Media Administration Trial (REMEDIAL): a randomized comparison of 3 preventive strategies. *Circulation*. 2007;115:1211–1277.
7. Mueller C, Buerkle G, Buettner HJ, et al. Prevention of contrast associated nephropathy. *Arch Intern Med*. 2002;162:329–336.
8. Kshirsagar AV, Poole C, Mottl A, et al. *N*-acetylcysteine for the prevention of radiocontrast induced nephropathy: a meta-analysis of prospective controlled trials. *J Am Soc Nephrol*. 2004;15:761–769.

9. Pannu N, Manns B, Lee H, et al. Systematic review of the impact of *N*-acetylcysteine on contrast nephropathy. *Kidney Int*. 2004; 65:1366–1374.
10. 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.
11. 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.
12. 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.
13. Jo SH, Koo BK, Park JS, et al. *N*-acetylcysteine versus ascorbic acid for preventing contrast-induced nephropathy in patients with renal insufficiency undergoing coronary angiography NASPI study—a prospective randomized controlled trial. *Am Heart J*. 2009; 157:576–583.
14. Pflueger A, Larson TS, Nath KA, et al. Role of adenosine in contrast media-induced acute renal failure in diabetes mellitus. *Mayo Clin Proc*. 2000;75:1275–1283.
15. Pflueger A, Abramowitz D, Calvin AD. Role of oxidative stress in contrast-induced acute kidney injury in diabetes mellitus. *Med Sci Monit*. 2009;15:125–136.
16. Barrett BJ, Parfrey PS, Vavasour HM, et al. Contrast nephropathy in patients with impaired renal function: high versus low osmolar media. *Kidney Int*. 1992;41:1274–1276.
17. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31–41.
18. Jo SH, Koo BK, Park JS, et al. Prevention of radiocontrast medium-induced nephropathy using short-term high-dose simvastatin in patients with renal insufficiency undergoing coronary angiography (PROMISS) trial—a randomized controlled study. *Am Heart J*. 2008;155:499.e1–449.e8.
19. Kunadian V, Zaman A, Spyridopoulos I, et al. Sodium bicarbonate for the prevention of contrast induced nephropathy: a meta-analysis of published clinical trials. *Eur J Radiol*. 2011l;79:48–55.
20. Weisbord SD, Palevsky PM. Prevention of contrast-induced nephropathy with volume expansion. *Clin J Am Soc Nephrol*. 2008;3:273–280.
21. Kanbay M, Covic A, Coca SG, et al. Sodium bicarbonate for the prevention of contrast-induced nephropathy: a meta-analysis of 17 randomized trials. *Int Urol Nephrol*. 2009;41:617–627.
22. Tamura A, Goto Y, Miyamoto K, et al. Efficacy of single-bolus administration of sodium bicarbonate to prevent contrast-induced nephropathy in patients with mild renal insufficiency undergoing an elective coronary procedure. *Am J Cardiol*. 2009;104:921–925.
23. Maioli M, Toso A, Leoncini M, et al. Sodium bicarbonate versus saline for the prevention of contrast-induced nephropathy in patients with renal dysfunction undergoing coronary angiography or intervention. *J Am Coll Cardiol*. 2008;52:599–604.
24. Lee SW, Kim WJ, Kim YH, et al. Preventive strategies of renal insufficiency in patients with diabetes undergoing intervention or arteriography (the PREVENT Trial). *Am J Cardiol*. 2011; 107:1447–1452.
25. 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.
26. 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.
27. Bader BD, Berger ED, Heede MB, et al. What is the best hydration regimen to prevent contrast media-induced nephrotoxicity? *Clin Nephrol*. 2004;62:1–7.
28. Richardson D, Regino C, Yao H, et al. Methionine oxidation by peroxymonocarbonate, a reactive oxygen species formed from CO_2/bicarbonate and hydrogen peroxide. *Free Radic Biol Med*. 2003;35:1538–1550.
29. Diaz-Sandoval LJ, Kosowsky BD, Losordo DW. Acetylcysteine to prevent angiography-related renal tissue injury (the APART trial). *Am J Cardiol*. 2002;89:356–358.
30. 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;40:1383–1388.
31. Briguori C, Colombo A, Violante A, et al. Standard vs double dose of *N*-acetylcysteine to prevent contrast agent-associated nephrotoxicity. *Eur Heart J*. 2004;25:206–211.
32. Coyle LC, Rodriguez A, Jeschke RE, et al. Acetylcysteine In Diabetes (AID): a randomized study of acetylcysteine for the prevention of contrast nephropathy in diabetics. *Am Heart J*. 2006;151:1032.e9–e12.
33. Goldenberg I, Matetzky S. Nephropathy induced by contrast media: pathogenesis, risk factors and preventive strategies. *CMAJ*. 2005;172:1461–1471.
34. Aspelin P, Fransson SG, Strasser R, et al. Nephrotoxicity in high-risk patients study of iso-osmolar and low-osmolar non-ionic contrast media study investigators. Nephrotoxic effects in high-risk patients undergoing angiography. *N Engl J Med*. 2003;348:491–499.
35. Chalmers N. Comparison of iodixanol and iohexol in renal impairment. Randomized controlled trial. *Br J Radiol*. 1999;72:701–703.
36. Liss P, Hansell P, Lagerqvist B. Renal failure in 57,925 patients undergoing coronary procedures using iso-osmolar or low-osmolar contrast media. *Kidney Int*. 2006;70:1811–1817.
37. Solomon R. The role of osmolality in the incidence of contrast-induced nephropathy: a systematic review of angiographic contrast media in high-risk patients. *Kidney Int*. 2005;68:2256–2263.
38. Solomon RJ, Doucet S, Sharma AK, 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;115:3189–3196.
39. Schmidt P, Pang D, Nykamp D, et al. *N*-Acetylcysteine and sodium bicarbonate versus *N*-acetylcysteine and standard hydration for the prevention of radiocontrast-induced nephropathy following coronary angiography. *Ann Pharmacother*. 2007;41:46–50.
40. Pakfetrat M, Nikoo MH, Malekmakan L, et al. A comparison of sodium bicarbonate infusion versus normal saline infusion and its combination with oral acetazolamide for prevention of contrast-induced nephropathy: a randomized, double-blind trial. *Int Urol Nephrol*. 2009;41:629–634.

