Meta-Analysis of Individual Patient Data of Sodium Bicarbonate and Sodium Chloride for All-Cause Mortality after Coronary Angiography

Jeremiah R. Brown, PhD, **Daniel M. Pearlman, MPH**, **Emily J. Marshall, MPH**, **Shama S. Alam, PhD**, **Todd A. MacKenzie, PhD**, **Alejandro Recio-Mayoral, MD**, **Vitor O. Gomes, MD, PhD**, **Bokyung Kim, MS**, **Lisette O. Jensen, MD, PhD**, **Christian Mueller, MD**, **Mauro Maioli, MD**, and **Richard J. Solomon, MD**

The Dartmouth Institute for Health Policy and Clinical Practice (Brown JR, MacKenzie TA, Marshall EJ, Alam SS, Pearlman DM, Kim B), Department of Medicine (Brown JR, MacKenzie TA) and Department of Community and Family Medicine (Brown JR, MacKenzie TA), Audrey and Theodor Geisel School of Medicine at Dartmouth, New Hampshire, United States; Division of Cardiology, Misericordia e Dolce Hospital, Prato, Italy (Maioli M); Department of Cardiology, Virgen Macarena University Hospital, Seville, Spain (Recio-Mayoral A) Hospital São Lucas, PUCRS, Porto Alegre, RS, Brazil (Gomes VO); Department of Cardiology, Odense University Hospital, Odense, Denmark (Jensen LO); Department of Cardiology, University Hospital Basel, Petersgraben, Switzerland (Mueller C); Fletcher Allen Health Care, University of Vermont School of Medicine, Vermont, United States (Solomon RJ).

Abstract

We sought to examine the relationship between sodium bicarbonate prophylaxis for contrast-associated nephropathy and mortality. We conducted an individual patient data meta-analysis from multiple randomized controlled trials. We obtained individual-patient datasets for 7 of 10 eligible trials (2292 of 2764 participants). For the remaining 3 trials, time-to-event data was imputed based on follow-up periods described in their original reports. We included all trials that compared peri-procedural intravenous sodium bicarbonate to peri-procedural intravenous sodium chloride in patients undergoing coronary angiography or other intra-arterial interventions. Included trials were determined by consensus according to predefined eligibility criteria. The primary outcome was all-cause mortality hazard, defined as time from randomization to death. In 10 trials with a total of

2764 participants, sodium bicarbonate was associated with lower mortality hazard than sodium chloride at 1 year (HR=0.61, 95% CI 0.41–0.89, p=0.011). While peri-procedural sodium bicarbonate was associated with a reduction in the incidence of contrast-associated nephropathy (RR=0.75, 95% CI 0.62–0.91, p=0.003), there exists a statistically significant interaction between the effect on mortality and the occurrence of contrast-associated nephropathy (HR=5.65, 95% CI 3.58–8.92, p<0.001) for up to 1-year mortality). Peri-procedural intravenous sodium bicarbonate seems to be associated with a reduction in long-term mortality in patients undergoing coronary angiography or other intra-arterial interventions.

Keywords

contrast-induced nephropathy; angiography; angioplasty; mortality

Introduction

Contrast-associated nephropathy (CAN) is an iatrogenic complication of routine radiography with iodinated contrast media.[1] Although the increase in serum creatinine is typically transient, CAN is associated with increased risks of mortality, major adverse cardiac events, and new onset or progression of chronic kidney disease.[2–4] Few prophylactic therapies have proven effective in prevention of CAN. Sodium chloride and sodium bicarbonate infusions before and after contrast exposure are considered by many to have the most robust supportive evidence base.[5] However, the impact of these therapies on the associated "downstream" adverse events has not been formally tested. In particular, the effects of sodium chloride or sodium bicarbonate on mortality have not been studied systematically. We sought to conduct a meta-analysis using the multiple randomized trials comparing intravenous sodium bicarbonate to sodium chloride for the prevention of CAN to determine if 1 therapy is more associated with a reduction in mortality or incidence of CAN. Because mortality is infrequent, we performed this meta-analysis using individual-patient-level data rather than study level data. This would allow for more precision in determining time to death and the relationship (if any) to CAN severity. We tested the null hypothesis that all-cause mortality hazards do not differ between patients randomized to peri-procedural sodium bicarbonate compared to peri-procedural sodium chloride. We also tested whether any differences in the incidence of death was accompanied by differences in the incidence of CAN in the same trials.

Methods

Potentially eligible trials were identified through standardized electronic database searches for journal articles or meeting abstracts, in any language, indexed within MEDLINE, Web of Science, and/or BIOSIS from inception until 12 June 2014 (Table e1). Reference lists of included trials and other content-relevant journal articles were reviewed manually.

Included trials were determined by consensus according to predefined eligibility criteria: (a) population: patients undergoing coronary angiography (b) intervention: intravenous isotonic sodium bicarbonate; (c) control: intravenous sodium chloride; (d) outcome: all-cause mortality—number and proportion of participants in both intervention and control arms; (e)

study design: double-blind, single-blind, or open-label randomized trials. 6 trials that reported zero deaths overall were excluded.

Individual-patient datasets were requested from authors of included trials, standardized, and aggregated into a single dataset. To verify accuracy, the number of deaths, CAN events, and participants in each arm were checked against original reports. As needed, we sought clarification from the relevant trialist; when data from the individual-patient dataset could not be reconciled with the original report for a trial, we used the former as the definitive data source. Variables consistently reported across trials were age, sex, history of diabetes mellitus, hypertension or congestive heart failure, left-ventricular ejection fraction, contrast volume administered, Mehran risk score, baseline serum creatinine concentration and estimated filtration rate, all-cause mortality, cause-of-death, CAN, and time from randomization to death or censor. For included trials that did not provide individual-patient datasets, time-to-event data was imputed based on the trial- or treatment-arm–specific follow-up periods specified in the original reports (Table e2). We performed sensitivity analyses to assess the influence of including such trials. The trials' original reports were used to abstract data on trial-level characteristics, including: eligibility criteria (as above), source (first author surname, year, PubMed identifier), design (blinding, parallel *vs.* factorial, ineligible trial arms, eligibility trial arms involving confounded comparisons), setting (single- *vs.* multi-center), procedure (coronary angiography, percutaneous coronary intervention), contrast medium (agent, ionicity, osmolality), fluid administration protocol (concentration, rate, dose, duration), inclusion criteria (renal insufficiency, none), and criteria used to define CAN (endpoint assessment, biomarker changes).

The primary outcome, all-cause mortality hazard (instantaneous mortality risk), was defined as the time from randomization to death or censorship, whichever occurred first. Participants alive and still being followed-up were censored at 1 year to analyze the primary outcome. The proportional hazard assumption was assessed to confirm that mortality hazards were generalizable from randomization to the endpoint. The secondary outcome, CAN risk, was defined according to the criteria provided within the original report of each trial. When more than 1 CAN outcome was reported, the primary outcome criteria were was preferentially used.

Survival functions were generated for sodium bicarbonate (intervention) and sodium chloride (control) arms based on time-to-event data in the pooled dataset using Kaplan-Meier methodology.[6] Primary outcome survival analysis was done using a 2-stage approach, as in earlier time-to-event individual-patient data meta-analyses.[7] In stage 1, primary outcome effect estimates were summarized as hazard ratios (HRs) and 95% confidence intervals (CIs) for each trial; these were calculated using nonparametric log-rank tests. In stage 2, trial-specific estimates were pooled in a meta-analysis using the Mantel-Haenszel fixed-effect model.[8] We completed sensitivity analyses to assess the influence of the statistical method chosen to do the survival analysis, using several alternative approaches. (See supplementary appendix).

Dr. Jeremiah Brown, Dr. Todd MacKenzie, and Daniel Pearlman analyzed the data. IRB approval was waived for this study because no patients were actively enrolled. We received a waiver from the Center for the Protection for Human Subjects (CPHS STUDY00029137).

Results

Results of systematic search and trial selection processes are summarized in the appendix (Figure e1). 10 trials (2764 participants) met eligibility criteria (Table 1).[9–18] We excluded 1 trial arm each from 2 of these trials—1, because participants did not receive any volume expansion infusion,[14] and another because participants received oral, not intravenous, sodium bicarbonate.[12] Both of these trials initially had 3 treatment arms. 2 of the 10 trials involved confounded comparisons, having compared pre-procedural and post-procedural sodium bicarbonate to only post-procedural sodium chloride[14,16] In contrast to the aforementioned excluded arms, these were consistent with eligibility criteria and therefore retained in the analyses. The influence of this decision on main outcome was assessed by sensitivity analyses (Table e3–e4).

Of participants in all trials used in this analysis, 69.3% were male. Administered dosages of sodium bicarbonate and sodium chloride varied across trials (Table 1). All were based on Merten protocol, which calls for a concentration of 154 mEq/L given at 3 mL/kg/h for 1 hour before the index procedure, and a rate of 1 mL/kg/h for 6 hours afterwards. Almost all trials involved protocol exceptions for participants with congestive heart failure, who received lower dosages than patients without congestive heart failure. Most trials did not report procedure duration data, and thus, intra-procedural dosages were unclear. Most trials used a single, non-ionic, low-osmolar or iso-osmolar contrast agent. 1 trial used an ionic contrast agent;[11] none used a high-osmolar agent. Renal function inclusion criteria is summarized in Table 1.

Individual-patient data on baseline characteristics were obtained for the majority of variables of interest from 7 of 10 trials and 2292 of 2764 participants.[9,11–14,16,17] Corresponding authors of 2 trials did not respond to emails requesting collaboration,[15,18] and a third was unable to participate because of data-sharing policy constraints.[10] Among the 7 trials providing individual-patient data, sodium bicarbonate and sodium chloride arms were well matched on baseline characteristics (Table 2). We analyzed aggregate data from original reports of the 3 remaining trials[10,15,18] to confirm those baseline characteristics were also balanced.

Survival analysis was based on all 10 included trials,[9–18] where time-to-event data was exact for 7 trials (2292 participants)[9,11–14,16,17] and imputed for 3 trials (472 participants).[10,15,18] Randomization to sodium bicarbonate was associated with decreased mortality hazard up to 1 year (HR=0.61, 95% CI 0.41–0.89, p=0.011, Figure 1). There was no significant heterogeneity for the summary estimate up to 1 year (p=0.50, I^2=0%; Figure 2). The results of additional sensitivity analyses are summarized in the supplementary material (Table e3). The leading documented cause-of-death in either arm was cardiovascular, though cause-of-death was unknown among a similar proportion of deaths that occurred (Table e5). Methods used to determine cause-of-death were non-standardized across all 10 trials.

Among the 10 included trials, the proportion of patients who developed CAN was lower among those randomized to sodium bicarbonate (155 [11%] of 1381) than those randomized to sodium chloride (207 [15%] of 1383): RR=0.75 (0.62–0.91), p=0.003 (Figure e2). There was no significant heterogeneity (p=0.07, I^2=44%; Figure e2). Sensitivity analysis based on a random-effects model yielded a similar effect size but attenuated its statistical significance: RR=0.72 (0.52–0.99), p=0.046 (Figure e2). The results of additional sensitivity analyses are summarized in the supplementary material (Table e4). Among the 7 individual-patient data trials, the proportion of patient deaths among those who developed CAN was 5- to 6-times higher than among participants who did not develop CAN up to 1 year post-randomization (p<0.00001; Figure e3).

Discussion

We report novel findings from an individual-patient data meta-analysis of randomized controlled trials (RCT) having compared peri-procedural volume expansion with intravenous sodium bicarbonate to that with intravenous sodium chloride for all-cause mortality. In the fixed-effect meta-analysis, patients undergoing coronary angiography, with or without percutaneous coronary intervention, who were randomized to sodium bicarbonate were an estimated 39% (11–59%) less likely to die at any point up to 1 year *vs.* those randomized to sodium chloride. The random-effects meta-analysis found a similar benefit up to 1 year.

Our findings are supported by a lack of heterogeneity across studies and statistical robustness through multiple sensitivity analyses that support validity of a potential protective relationship between sodium bicarbonate and mortality. Additionally, sensitivity analyses provide evidence that these effects are robust to multiple potential confounding variables. Evidence of the survival advantage associated with sodium bicarbonate up to 1 year was robust to 14 of 16 sensitivity analyses (p=0.04–0.009) (See supplementary appendix). Only 1 of 10 included trials yielded an effect estimate that favored sodium chloride for all-cause mortality hazard, and it was insignificant.[17]

Our study greatly expands current scientific evidence investigating sodium bicarbonate and mortality by conducting an individual-patient data meta-analysis among patients randomized to sodium bicarbonate or sodium chloride.[5,19] Jang and colleagues reported no significant reduction in mortality risk among patients randomized to sodium bicarbonate (10 [2%] of 539) *vs.* sodium chloride (20 [4%] of 543): odds ratio [OR]=0.49 (0.23–1.04), p=0.06 (fixed-effect model).[5] Jang's estimate is based on 8 deaths for the sodium chloride arm of Ueda and colleagues' trial, which had only 3 deaths.[18] Second, their estimate is based on only 5 of 10 trials included in this study.[10,13,15,16,18] In another meta-analyses, Kunadian and colleagues also found no significant difference between all-cause mortality risk among participants randomized to sodium bicarbonate (9 [2%] of 511) *vs.* sodium chloride (16 [3%] of 514): OR=0.60 (0.26–1.41) p=0.24 (random-effects model).[19] This estimate is subject to the same limitations of Jang's analysis. Kunadian's meta-analysis included only 4 of the 10 trials from this study.[10,13,15,16] Kunadian and colleagues also lack time-to-event data.

We also conducted a secondary analysis on CAN and found sodium bicarbonate (*vs.* sodium chloride) had an estimated 25% relative reduction in CAN risk in the fixed- and random-effects models. The accompanying CIs indicate a less than 5% chance that the patients prescribed sodium bicarbonate have any less than a 25% relative risk reduction in CAN, *vs.* those prescribed sodium chloride (Figure e2). These findings are consistent with study-level data meta-analyses comparing sodium bicarbonate and sodium chloride fluid administration for CAN risk (Table e6).

The mechanism of the effects of bicarbonate observed in these 10 trials is speculative. Ischemia-reperfusion can induce oxidative stress mediated apoptosis of kidney cells and cardiac myocytes.[20][21] Acidosis exacerbates generation of reactive oxygen species and areas of ischemia are typically more acidic than non-ischemic areas.[22] Furthermore, contrast media is not oxygenated and the bolus into the coronary vascular bed in particular may therefore create further ischemia and oxidative stress leading to cardiac myocyte apoptosis.[23] We hypothesize that peri-procedural fluid administration with intravenous sodium bicarbonate confers its associated survival advantage by attenuating oxidative injury-mediated endothelial dysfunction[24,25] and reducing counter-regulatory repair capacity[26] of both the kidneys and the heart. Sodium bicarbonate therapy might be useful in critical situations and translating these results to the clinical bedside needs to be confirmed in clinical trials aimed at determining which population of patients may benefit from this strategy.

Findings of the present study are subject to several limitations. The greatest threats to the validity of our findings are missing individual-patient cause-of-death data for 64 (38%) of 167 total deaths and the non-standardized approach to evaluating cause-of-death across all trials. However, as we included only RCTs, mortality data would have been collected uniformly across treatment arms. Another limitation to our study is that we do not have data on interventions following the cardiac catheterization, such as rates of PCI, re-stenosis of stented lesions, repeat cardiac catheterization or rates of cardiac surgery, all of which could have affected mortality. We were limited to the data provided by the randomized controlled trial manuscripts. Lastly, the patient population, dose and duration of the therapies and the definition of contrast-associated nephropathy varied across trials. Due to this variation, we only included randomized controlled trials published in the last ten years.

We recommend that current and future clinical trials, such as PRESERVE[27], should measure mortality and capture cause of death in order for other studies to be able to address the hypotheses related to sodium bicarbonate, sodium chloride, and mode of death. Additionally, bias in mortality ascertainment should be minimal in these trials, as all were subject to institutional review board approval and oversight.

To our knowledge, we are the first to conduct individual-patient data meta-analysis of RCTs comparing peri-procedural volume expansion with intravenous sodium bicarbonate to that with intravenous sodium chloride for either all-cause mortality or CAN. Our findings suggest that a simple change in a hospital's prophylactic strategy to employ sodium bicarbonate for volume expansion instead of sodium chloride could prevent 2 out of 5 deaths within the first year and reduce incidence of CAN. In order to prevent 1 death within 1 year,

only 32.5 patients would need to be treated with sodium bicarbonate rather than sodium chloride.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

References

1. Rudnick MR. Prevention of contrast-induced nephropathy UpToDate. Waltham, MA: UpToDate.

2. McCullough PA. Contrast-induced acute kidney injury. JACC 2008;51:1419–1428. [PubMed: 18402894]

3. James MT, Ghali WA, Knudtson ML, Ravani P, Tonelli M, Faris P, Pannu N, Manns BJ, Klarenbach SW, Hemmelgarn BR. Associations Between Acute Kidney Injury and Cardiovascular and Renal Outcomes After Coronary Angiography. Circulation 2011;123:409–416. [PubMed: 21242477]

4. Brown JR, Malenka DJ, DeVries JT, Robb JF, Jayne JE, Friedman BJ, Hettleman BD, Niles NW, Kaplan AV, Schoolwerth AC, Thompson CA, Dartmouth Dynamic Registry I. Transient and persistent renal dysfunction are predictors of survival after percutaneous coronary intervention: insights from the Dartmouth Dynamic Registry. Catheter Cardiovasc Interv 2008;72:347–354. [PubMed: 18729173]

5. Jang JS, Jin HY, Seo JS, Yang TH, Kim DK, Kim TH, Urm SH, Kim DS, Kim DK, Seol SH, Kim DI, Cho KI, Kim BH, Park YH, Je HG, Ahn JM, Kim WJ, Lee JY, Lee SW. Sodium bicarbonate therapy for the prevention of contrast-induced acute kidney injury – a systematic review and meta-analysis. Circulation J 2012;76:2255–2265.

6. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–481.

7. NSCLC Meta-analysis Collaborative Group. Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data. Lancet 2014;383:1561–1571. [PubMed: 24576776]

8. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. JNCI 1959;22:719–748. [PubMed: 13655060]

9. Solomon R Evaluation of Sodium Bicarbonate to Reduce the Incidence of Contrast Induced Chronic Kidney Injury in Patients With Kidney Disease (BOSS) 25th Annual Symposium of the Transcatheter Cardiovascular Therapeutics, TCT 2013. San Francisco, CA, 2013.

10. Brar SS, Shen AY, Jorgensen MB, Kotlewski A, Aharonian VJ, Desai N, Ree M, Shah AI, Burchette RJ. 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. [PubMed: 18768415]

11. Gomes VO, Lasevitch R, Lima VC, Brito FS Jr, Perez-Alva JC, Moulin B, Arruda A, Oliveira D, Caramori P. Hydration with sodium bicarbonate does not prevent contrast nephropathy: a multicenter clinical trial. Arquivos Brasil Cardiol 2012;99:1129–1134.

12. Klima T, Christ A, Marana I, Kalbermatter S, Uthoff H, Burri E, Hartwiger S, Schindler C, Breidthardt T, Marenzi G, Mueller C. Sodium chloride vs. sodium bicarbonate for the prevention of contrast medium-induced nephropathy: a randomized controlled trial. Eur Heart J 2012;33:2071–2079. [PubMed: 22267245]

13. Maioli M, Toso A, Leoncini M, Gallopin M, Tedeschi D, Micheletti C, Bellandi F. Sodium bicarbonate versus saline for the prevention of contrast-induced nephropathy in patients with renal
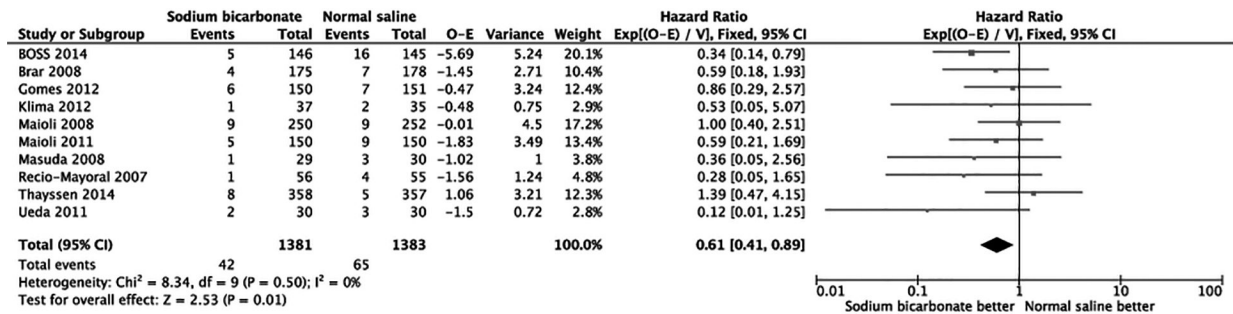
dysfunction undergoing coronary angiography or intervention. JACC 2008;52:599–604. [PubMed: 18702961]

14. Maioli M, Toso A, Leoncini M, Micheletti C, Bellandi F. Effects of hydration in contrast-induced acute kidney injury after primary angioplasty: a randomized, controlled trial. Circulation Cardiovasc Intv 2011;4:456–462.

15. Masuda M, Yamada T, Okuyama Y, Morita T, Sanada S, Furukawa Y, Tsukamoto Y, Okuda K, Iwasaki Y, Yasui T, Fukunami M. Sodium bicarbonate improves long-term clinical outcomes compared with sodium chloride in patients with chronic kidney disease undergoing an emergent coronary procedure. Circ J 2008;72:1610–1614. [PubMed: 18756037]

16. Recio-Mayoral A, Chaparro M, Prado B, Cozar R, Mendez I, Banerjee D, Kaski JC, Cubero J, Cruz JM. The reno-protective effect of hydration with sodium bicarbonate plus N-acetylcysteine in patients undergoing emergency percutaneous coronary intervention: the RENO Study. JACC 2007;49:1283–1288. [PubMed: 17394959]

17. Thayssen P, Lassen JF, Jensen SE, Hansen KN, Hansen HS, Christiansen EH, Junker A, Ravkilde J, Thuesen L, Veien KT, Jensen LO. Prevention of contrast-induced nephropathy with N-acetylcysteine or sodium bicarbonate in patients with ST-segment-myocardial infarction: a prospective, randomized, open-labeled trial. Circulation Cardiovasc Intv 2014;7:216–224.

18. Ueda H, Yamada T, Masuda M, Okuyama Y, Morita T, Furukawa Y, Koji T, Iwasaki Y, Okada T, Kawasaki M, Kuramoto Y, Naito T, Fujimoto T, Komuro I, Fukunami M. Prevention of contrast-induced nephropathy by bolus injection of sodium bicarbonate in patients with chronic kidney disease undergoing emergent coronary procedures. Am J Cardiol 2011;107:1163–1167. [PubMed: 21349483]

19. Kunadian V, Zaman A, Spyridopoulos I, Qiu W. Sodium bicarbonate for the prevention of contrast induced nephropathy: a meta-analysis of published clinical trials. EJR l 2011;79:48–55.

20. Theodoridis M, Tziakas D, Passadakis P, Kantartzi K, Roumeliotis A, Thodis E, Vargemezis V. The effect of bicarbonate peritoneal dialysis solutions on cardiac structural and functional alterations. Nephrol Dial Transplant 2011;26:4061–4067. [PubMed: 21543656]

21. Orogo AM, Gustafsson AB. Cell death in the myocardium: my heart won't go on. IUBMB life 2013;65:651–656. [PubMed: 23824949]

22. Halliwell B, Gutteridge JM. Role of free radicals and catalytic metal ions in human disease: an overview. Methods Enzymol 1990;186:1–85.

23. Jun Z, Duarte CG, Ellis S. Contrast Medium- and Mannitol-Induced Apoptosis in Heart and Kidney of SHR Rats. Toxicol Pathol 1999;27:427–435. [PubMed: 10485823]

24. Zhao Y, Tao Z, Xu Z, Tao Z, Chen B, Wang L, Li C, Chen L, Jia Q, Jia E, Zhu T, Yang Z. Toxic effects of a high dose of non-ionic iodinated contrast media on renal glomerular and aortic endothelial cells in aged rats in vivo. Toxicol Lett 2011;202:253–260. [PubMed: 21354280]

25. Aliev G, Obrenovich ME, Seyidova D, Rzayev NM, Aliyev AS, Raina AK, Lamanna JC, Smith MA, Perry G. X-ray contrast media induce aortic endothelial damage, which can be prevented with prior heparin treatment. J Submicrosc Cytol Pathol 2003;35:253–266. [PubMed: 14690173]

26. Chiang CH, Huang PH, Chiu CC, Hsu CY, Leu HB, Huang CC, Chen JW, Lin SJ. Reduction of circulating endothelial progenitor cell level is associated with contrast-induced nephropathy in patients undergoing percutaneous coronary and peripheral interventions. PLOS ONE 2014;9:e89942. [PubMed: 24646509]

27. Weisbord SD, Gallagher M, Kaufman J, Cass A, Parikh CR, Chertow GM, Shunk KA, McCullough PA, Fine MJ, Mor MK, Lew RA, Huang GD, Conner TA, Brophy MT, Lee J, Soliva S, Palevsky PM. Prevention of contrast-induced AKI: a review of published trials and the design of the prevention of serious adverse events following angiography (PRESERVE) trial. Clin J Am Soc Nephrol 2013;8:1618–1631. [PubMed: 23660180]
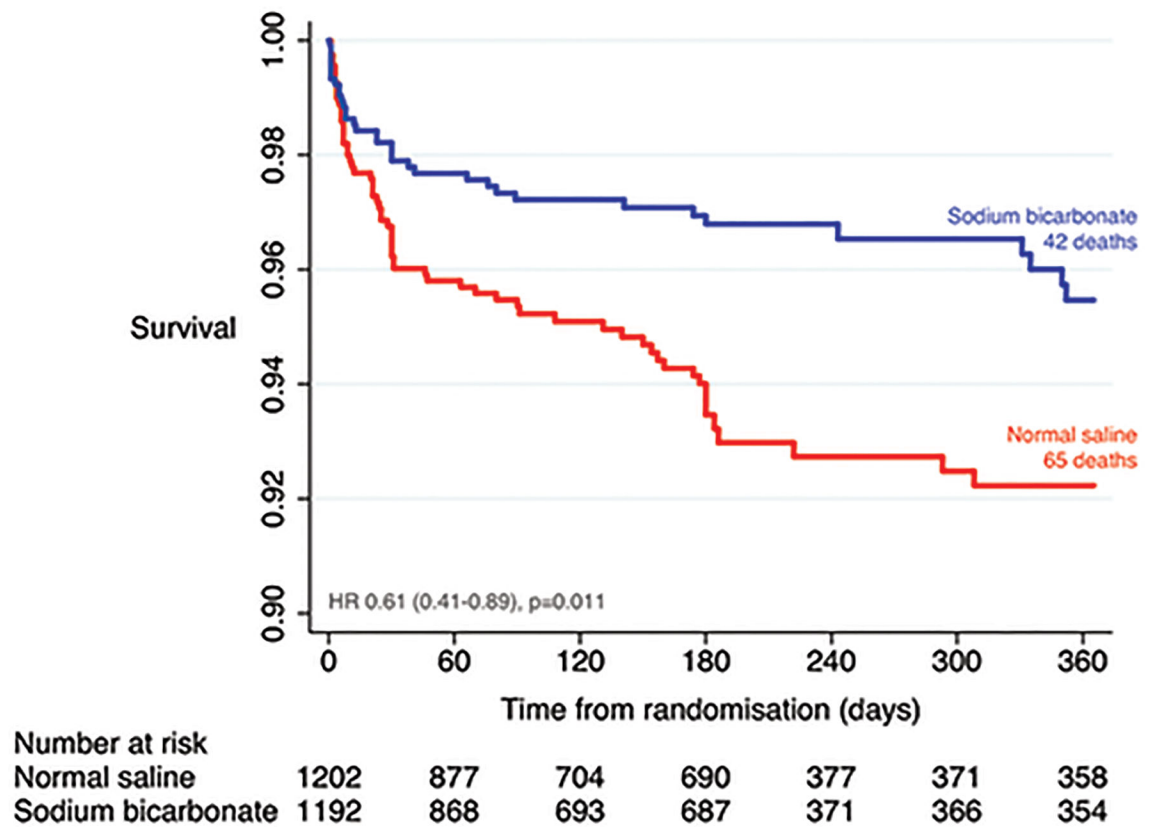
Figure 1: Kaplan-Meier survival function for all-cause mortality

Kaplan-Meier survival functions for all-cause mortality hazard up to 1 year after coronary angiography or intervention among participants randomized to intravenous fluid administration with sodium bicarbonate versus sodium chloride. HR=hazard ratio. CI=confidence interval. Please note that the Y-axis extends only from 0.9 to 1.0, which exaggerates the difference between the survival curves.

| Study or Subgroup | Sodium bicarbonate | | Normal saline | | | | | Hazard Ratio | Hazard Ratio |
	Events	Total	Events	Total	O−E	Variance	Weight	Exp[(O−E) / V], Fixed, 95% CI	Exp[(O−E) / V], Fixed, 95% CI
BOSS 2014	5	146	16	145	−5.69	5.24	20.1%	0.34 [0.14, 0.79]	
Brar 2008	4	175	7	178	−1.45	2.71	10.4%	0.59 [0.18, 1.93]	
Gomes 2012	6	150	7	151	−0.47	3.24	12.4%	0.86 [0.29, 2.57]	
Klima 2012	1	37	2	35	−0.48	0.75	2.9%	0.53 [0.05, 5.07]	
Maioli 2008	9	250	9	252	−0.01	4.5	17.2%	1.00 [0.40, 2.51]	
Maioli 2011	5	150	9	150	−1.83	3.49	13.4%	0.59 [0.21, 1.69]	
Masuda 2008	1	29	3	30	−1.02	1	3.8%	0.36 [0.05, 2.56]	
Recio-Mayoral 2007	1	56	4	55	−1.56	1.24	4.8%	0.28 [0.05, 1.65]	
Thayssen 2014	8	358	5	357	1.06	3.21	12.3%	1.39 [0.47, 4.15]	
Ueda 2011	2	30	3	30	−1.5	0.72	2.8%	0.12 [0.01, 1.25]	
Total (95% CI)		1381		1383			100.0%	0.61 [0.41, 0.89]	
Total events	42		65						

Heterogeneity: Chi² = 8.34, df = 9 (P = 0.50); I² = 0%
Test for overall effect: Z = 2.53 (P = 0.01)

0.01 0.1 1 10 100
Sodium bicarbonate better   Normal saline better

Figure 2: Forest plot comparing all-cause mortality

Forest plot comparing all-cause mortality hazard up to 1 year after coronary angiography or intervention among participants randomized to intravenous fluid administration with sodium bicarbonate versus sodium chloride. CI=confidence interval. HR=hazard ratio.

Table 1:

Study characteristics

	BOSS (2014)[9]	Brar (2008)[10]	Gomes (2012)[11]	Klima (2012)[12]	Maioli (2008)[13]	Maioli (2011)[14]	Masuda (2008)[15]	Recio-M. (2007)[16]	Thayssen (2014)[17]	Ueda (2011)[18]
Source										
PubMed identifier	Abstract	18768415	23184077	22267245	18702961	21972403	17719320	17394959	241714489	21349483
Individual patient data	●	○	●	●	●	●	○	●	●	○
Design										
Open-label	○	○	●	●	●	●	●	○	○	○
Single-blind	○	●	○	○	○	○	○	●	●	●
Double-blind	●	○	○	○	○	○	○	○	○	○
Parallel, 1:1	●	●	●	○	●	○	●	●	○	●
Factorial, 1:1:1:1 [*]	○	○	○	○	○	○	○	○	●	○
We excluded 1 trial arm	○	○	○	●	○	●	○	○	○	○
Confounded comparison	○	○	○	○	○	●	○	●	○	○
Setting										
Country	USA	USA	Brazil	Switzerland	Italy	Italy	Japan	Spain	Denmark	Japan
Accrual period	2010–12	2006–07	2004–08	2005–09	2005–06	2004–08	2005–06	2004–05	2010–12	2008–10
Single-centre	○	●	○	○	●	●	●	●	○	●
Index procedure [†]										
Coronary angiography	●	●	●	●	●	○	●	○	○	●
Other PCI	●	●	●	●	●	○	●	●	○	●
Primary PCI	○	○	○	○	○	●	○	○	●	○
Intention-to-treat (№)										
Sodium bicarbonate	146	175	150	37	250	150	29	56	358	30
Sodium chloride	145	178	151	35	252	150	30	55	357	30
Contrast medium										
Agent	Multiple [‡]	Ioxilan	Ioxaglate	Multiple [§]	Iodixanol	Iodixanol	Iopamidol	Iomeprol	Iodixanol	Multiple [¶]
Non-ionic	●	●	○	●	●	●	●	●	●	●
Ionic	○	○	●	○	○	○	○	○	○	○
High-osmolar	○	○	○	○	○	○	○	○	○	○
Low-osmolar	●	●	●	●	○	○	●	●	○	●
Iso-osmolar	●	○	○	●	●	●	○	○	●	○
Sodium bicarbonate protocol										
Concentration (mEq/L)	154	154	154	166	154	154	154	154	167	154
$Rate_1$ (mL/kg/h)	3	3	3	3	3	3	3	5	0	0.5
$Duration_1$ (h)	1	1	1	1	1	1	1	1	0	NR
$Rate_2$ (mL/kg/h)	1	1.5	1	1	1	1	1	1.5	1.4	1
$Duration_2$ (h)	6	4	6	6	6	12	6	12	5	6
Sodium chloride protocol										
Concentration (mEq/L)	154	154	154	154	154	154	154	154	NR	154

	BOSS (2014)[9]	Brar (2008)[10]	Gomes (2012)[11]	Klima (2012)[12]	Maioli (2008)[13]	Maioli (2011)[14]	Masuda (2008)[15]	Recio-M. (2007)[16]	Thayssen (2014)[17]	Ueda (2011)[18]
$Rate_1$ (mL/kg/h)	3	3	3	1	1	0	3	0	0	0.5
$Duration_1$ (h)	1	1	1	12	12	0	1	0	0	NR
$Rate_2$ (mL/kg/h)	1	1.5	1	1	1	1	1	1	NR	0 ∥
$Duration_2$ (h)	6	6	6	12	12	12	6	12	NR	0 ∥
Inclusion criteria										
Renal insufficiency	●	●	●	●	●	○	●	○	○	●
None	○	○	○	○	○	●	○	●	●	○
Contrast-associated nephropathy										
Endpoint assessment (h)	24–72	24–96	48–48	0–48	0–120	0–72	0–48	0–72	48–72	0–48
sCr >25% increase	●	○	○	●	○	●	●	○	●	●
sCr >0.5 mg/dL increase	●	○	●	●	●	●	●	●	○	●
eGFR >25% decrease	○	●	○	○	○	○	○	○	○	○

●=Yes. ○=No. =absolute difference between endpoint and baseline values. eGFR=estimated glomerular filtration rate. sCr=serum creatinine. PCI=percutaneous coronary intervention. Recio-M.=Recio-Mayoral.

*
4 trial arms: sodium bicarbonate; sodium bicarbonate plus N-acetylcysteine; sodium chloride; and sodium chloride plus N-acetylcysteine;

†
BOSS 2014 and Klima 2012 both involved a combination of patients having undergone eligible and ineligible procedures.

‡
Iopamidol, Iohexol, and Iodixanol;

§
Iopromide, Iomeprol, Iopentol, Iohexol, Iobitridol, and Iodixanol;

¶
Iopamidol and Iohexol;

∥
Per design, participants randomized to sodium chloride received sodium chloride before the procedure but then subsequently received sodium bicarbonate (154 mEq/L at 1 mL/kg/h over 6 h) after the procedure. $Rate_1$, $Duration_1$ refer to the rate and duration before the index procedure; $Rate_2$, $Duration_2$ refer to the rate and duration after the index procedure.

Table 2:

Participant characteristics

	Sodium bicarbonate (№=1381)		Sodium chloride (№=1383)	
	Events or Mean *	Total	Events or Mean *	Total
Follow-up (days)				
Mean (SD)	526(776)	1147	542(792)	1145
Median (IQR)	90(30–697)	1147	90(30–897)	1145
Age (years)				
Mean (SD)	67(12)	1147	68(11)	1145
Median (IQR)	68(59–76)	1147	69(60–76)	1145
75	341(30%)	1147	347(30%)	1145
Sex (№)				
Male	791(70%)	1147	797(70%)	1145
Female	356(31%)	1147	348(30%)	1145
Body-mass index (kg/m^2)				
Mean (SD)	27(4)	921	27(4)	910
Median (IQR)	26(24–29)	921	24(24–29)	910
40	8(1%)	921	6(1%)	910
35–39	28(3%)	921	21(2%)	910
30–34	128(14%)	921	111(12%)	910
Medical history (№)				
Diabetes mellitus	301(26%)	1147	278(24%)	1145
Hypertension	665(58%)	1139	639(56%)	1133
Congestive heart failure [†]	199(19%)	1042	232(22%)	1048
Left ventricular ejection fraction (%)				
Mean (SD)	47(11)	827	48(12)	832
Median (IQR)	50(40–55)	827	50(40–55)	832
40	682(82%)	827	666(80%)	832
30–39	112(14%)	827	131(16%)	832
20–29	31(4%)	827	30(4%)	832
<20	2(0%)	827	5(1%)	832
Mehran risk (score)				
Mean (SD)	10(4)	546	10(4)	547
Median (IQR)	9(7–12)	546	9(7–12)	547
20	11(2%)	546	11(2%)	547
15–19	56(10%)	546	55(10%)	547
10–14	172(32%)	546	197(36%)	547
5–9	280(52%)	546	260(48%)	547
Contrast volume (mL)				
Mean (SD)	177(103)	774	170(99)	777
Median (IQR)	160(100–220)	774	150(100–220)	777
300	97(13%)	774	85(11%)	777

	Sodium bicarbonate (№=1381)		Sodium chloride (№=1383)	
	Events or Mean *	Total	Events or Mean *	Total
250–299	72(9%)	774	70(9%)	777
200–249	103(13%)	774	119(15%)	777
150–199	168(22%)	774	142(18%)	777
Serum creatinine (mg/dL) ‡				
Mean (SD)	1.3(0.6)	1146	1.2(0.5)	1144
Median (IQR)	1.1(0.9–1.4)	1146	1.1(0.9–1.4)	1144
2.5	646(56%)	1147	631(55%)	1145
2.0–2.4	39(3%)	1147	39(3%)	1145
1.5–1.9	123(11%)	1147	142(12%)	1145
Estimated GFR (mg/min per 1.73 m^2)				
Mean (SD)	64(31)	1144	64(30)	1141
Median (IQR)	57(41–86)	1144	58(41–86)	1141
30–59	497(43%)	1144	501(44%)	1141
15–29	100(9%)	1144	69(6%)	1141
<15	5(0%)	1144	5(0%)	1141
Co-intervention (№)				
N-acetylcysteine	668(55%)	1206	668(55%)	1205
Procedure (№)				
Coronary angiography	362(32%)	1147	355(31%)	1145
Other PCI	283(36%)	785	277(35%)	790
Primary PCI	508(65%)	785	507(64%)	790

GFR=glomerular filtration rate. IQR=interquartile range. №=number of participants. PCI=percutaneous coronary intervention.

[†] For standardization, participants with an ejection fraction 35% were coded positive for congestive heart failure, irrespective of whether datasets included a variable for congestive heart failure, and if so, irrespective of its truth value

[‡] To convert units of serum creatinine from mg/dL to μmol/L, multiply by 88.4