

# Randomized Trial of Bicarbonate or Saline Study for the Prevention of Contrast-Induced Nephropathy in Patients with CKD

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## Abstract

**Background and objectives** Sodium bicarbonate has been proposed for protection of the kidney from contrast-induced AKI (CIAKI). However, the effects of bicarbonate on long-term important clinical outcomes are uncertain.

**Design, setting, participants, & measurements** In a prospective, double-blind, multicenter randomized clinical trial, 391 patients with an eGFR < 45 ml/min per 1.73 m<sup>2</sup> undergoing elective coronary or peripheral angiography were randomized to an infusion with a high dose of isotonic sodium bicarbonate (target 2.0 mEq/kg) or a similar molar amount of isotonic sodium chloride. The primary outcome was a composite of mortality, dialysis, or a sustained 20% reduction in eGFR at 6 months.

**Results** There were 391 patients enrolled between March 2010 and May 2012. The incidence of the primary outcome was 14.9% in the bicarbonate group and 16.3% in the control group in the intention-to-treat population ( $P=0.78$ ). There was also no difference in the incidence of CIAKI between the treatment groups (14.5% versus 12.1%, respectively;  $P=0.20$ ). CIAKI was associated with a higher incidence of sustained loss of kidney function at 6 months compared with those without CIAKI (21.2% versus 7.7%, respectively;  $P=0.06$ ).

**Conclusions** High-dose sodium bicarbonate infusion in patients with eGFR < 45 ml/min per 1.73 m<sup>2</sup> undergoing angiography did not demonstrate a difference in incidence of the composite of death, dialysis, or sustained 6-month reduction in eGFR or CIAKI compared with sodium chloride.

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## Introduction

Intravenous volume administration is a cornerstone of strategies for prevention of AKI resulting from iodinated contrast (contrast-induced AKI [CIAKI]) (1). The type of fluid, amount, and timing remain unclear. In 2004, the use of isotonic sodium bicarbonate was reported to be associated with a reduced incidence of CIAKI compared with an equimolar amount of sodium chloride. The proposed mechanism for this observed benefit was inhibition of the Haber–Weiss reaction, which generates toxic reactive oxygen species in an acidic environment similar to that present within the medulla of the kidney (2). By alkalinizing the renal parenchyma, administration of bicarbonate or acetazolamide (3) would hypothetically diminish the production of reactive oxygen species generated by the toxic and ischemic effects of contrast media (4). Subsequently, multiple prospective randomized trials have been conducted with diverse infusion protocols on a variety of patient cohorts and produced discordant results. Although some meta-analyses of these trials suggest a renoprotective benefit (5,6), there is sufficient heterogeneity and concern about the quality of the studies to leave the issue uncertain (7).

One possible explanation for the conflicting results of prior trials is variation in the dose of sodium bicarbonate administered. Following the protocol originally described by Merten *et al.*, a total dose of bicarbonate of 1.35–1.5 mEq/kg might be given (2). Sufficient bicarbonate must be administered to alkalinize the medulla of the kidney during the time of contrast excretion so as to potentially mitigate the generation of reactive oxygen species and nephrotoxicity of the contrast. Most bicarbonate trials do not report urine pH or changes in serum bicarbonate levels. It is possible that underdosing of bicarbonate results in some of the heterogeneity of results observed in these trials. Therefore, higher-dose bicarbonate infusions need further examination in trials of CIAKI prevention and might be expected to confirm the beneficial effects of bicarbonate.

The Bicarbonate Or Saline Study (BOSS) was designed to enroll patients at a high risk for CIAKI and assess the effect of a high dose of sodium bicarbonate (total dose of approximately 2.0 mEq/kg) on rates of adverse clinical outcomes. CIAKI is usually a transient phenomenon characterized by an increase in serum creatinine reflecting a decrease in clearance of

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creatinine. Injury to the kidney, however, may either be missed (injury not sufficient to increase serum creatinine) (8) or overdiagnosed (increase in creatinine for hemodynamic reasons without injury). Therefore, the primary end point in BOSS was to assess the effect of high-dose bicarbonate on the clinically significant composite of death, need for dialysis, or sustained reduction in eGFR of >20% from baseline to 6 months after the exposure to contrast media.

## Materials and Methods

### Study Population

Patients were considered eligible for the trial if they were  $\geq 18$  years in age, if they were scheduled for elective coronary or peripheral angiography, and if their calculated eGFR was  $< 45$  ml/min per  $1.73$  m<sup>2</sup> using the Modification of Diet in Renal Disease 4 equation (9). Exclusion criteria included hemodynamic instability per investigator judgment, RRT, or hypocalcemia (per local laboratory range of normal). Patients signed informed consent before entering the trial. The trial was registered with [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT 00930436) and approved by the institutional review boards at each participating site in accordance with the Declaration of Helsinki.

### Study Protocol

The study was a prospective, randomized, double-blind comparison between 1.3% sodium bicarbonate (154 mEq/L) and 0.9% sodium chloride (154 mEq/L) at 17 centers in the United States. Randomization was carried out using a central registry to which investigators had no knowledge of the randomization algorithm. Randomization was not stratified by either site or reason for angiography. Each bicarbonate solution was prepared by the local pharmacy using a kit that contained three 50 ml ampules of 1 m sodium bicarbonate and a partially filled 1 l bag with 830 ml of sterile water (Hospira). Standard 0.9% sodium chloride was used in the other group. The solution to be infused (sodium bicarbonate or sodium chloride) was then enclosed in a nontransparent bag to assure blinding of both patient and interventionalist. Patients received 5 ml/kg of either sodium bicarbonate or sodium chloride over 60 minutes before angiography and 1.5 ml/kg per h during and for 4 hours after angiography. In patients with a low ejection fraction ( $< 40\%$ ), history of congestive heart failure, or significant edema, the same total dose of study fluid (either bicarbonate or saline) could be infused over 5 hours post-angiography at the discretion of the investigator. It was recommended that diuretics and nonsteroidal anti-inflammatory drugs be held the day of the procedure. Continuation of angiotensin converting enzyme inhibitor/angiotensin receptor blocker/statins and choice of contrast agent were left to individual participating sites. Likewise, the use of N-acetylcysteine was site specific. At a site using N-acetylcysteine, the same dose was administered to all patients regardless of the treatment group.

The follow-up period was 6 months. Blood tests for electrolytes and serum creatinine were obtained within 12 hours before contrast administration (to establish baseline values) and days 1, 3, 7, 30, 90, and 180 after contrast administration.

### End Points

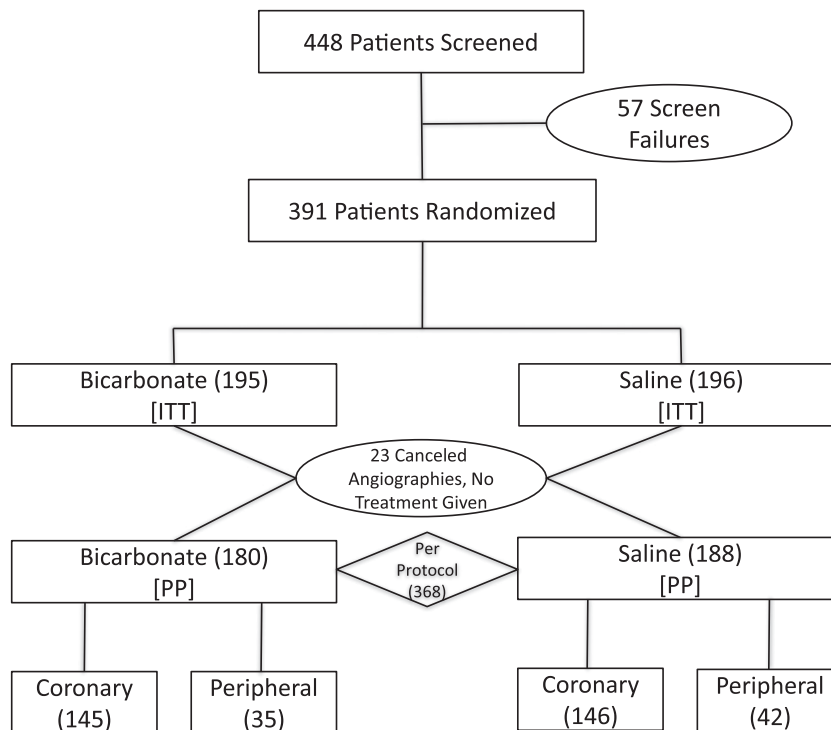
The primary end point was the first occurrence of death, RRT, or a reduction in eGFR of  $\geq 20\%$  confirmed by at least two separate measurements between day 30 and day 180 creatinine compared with the baseline value before contrast administration. All creatinine values used in the primary outcome (*i.e.*, precontrast and days 7, 30, 90, and 180) were measured in a central core laboratory using an isotope dilution mass spectrometry-traceable assay. Secondary end points included length of hospital stay and mortality and time to death or RRT. Acute changes in serum creatinine (baseline to days 1 and 3), measured in the local institution, were also analyzed as a secondary outcome. CIAKI was defined as a  $\geq 0.5$  mg/dl or 25% rise in creatinine from baseline during the first 3 days.

### Statistical Analyses

We based the calculation of sample size on published mortality rates. We assumed an 8% event rate in the saline group versus a 2.5% event rate in the bicarbonate group. These event rates were on the basis of prior clinical trial estimates indicating a 3- to 4-fold higher incidence of mortality in patients with CKD who developed CIAKI (10) and an absolute mortality rate for patients with this level of eGFR on the basis of the Mehran *et al.* risk score (11). There were 256 patients in each group who were required to observe an absolute difference of 5.5% in event rate with 80% power and  $\alpha = 0.05$ . Assuming 4% would be lost to follow-up, the trial planned to enroll 536 patients. An interim analysis was scheduled when approximately 60% of patients were enrolled (approximately 322 patients). The interim analysis was planned to adjust the size of the trial or stop the trial on the basis of safety. To maintain the 0.05 trial-wise error rate, the final analysis would be on the basis of a *P* value of 0.048 using the O'Brien-Fleming  $\alpha$ -spending function (12). A two-sided Fisher exact test was used to assess differences in outcomes between the two treatment groups and report relative risks. There were no predefined subgroups identified for the primary analysis. However, subgroups on the basis of age, type of procedure, history of diabetes, or history of congestive heart failure were evaluated in *post hoc* analyses as potential interaction variables. Logistic regression was used to assess for interactions using Stata 13. Because the sample size estimate was based primarily on mortality data, the incidence of mortality was a secondary outcome.

## Results

The BOSS randomized 391 patients between March 2010 and May 2012 at 22 United States centers up to the time of the interim analysis. There were 23 patients excluded in the per protocol analysis because they received either no investigational product or exposure to contrast (Figure 1). No data were collected on these patients, including what type of procedure was cancelled. The groups were similar for end point risk factors and procedural issues, including the use of different contrast agents, total dose of contrast administered, and total volume of sodium chloride or sodium bicarbonate (Table 1). However, the baseline level of kidney function was significantly worse in the subgroup undergoing coronary angiography that received sodium bicarbonate therapy.



**Figure 1. | Flow diagram of Bicarbonate Or Saline Study trial: 391 patients were randomized but only 368 actually underwent angiography and received one of the treatments.** Type of angiography is indicated by coronary or peripheral. ITT, intention-to-treat; PP, per protocol.

There was a significant difference in the pre- and postadministration serum bicarbonate levels between the groups. The group receiving sodium bicarbonate had an increase in serum bicarbonate from  $26.1 \pm 3.5$  to  $29.4 \pm 3.8$  mEq/L at 24 hours, whereas the group receiving sodium chloride experienced a decrease from  $26.0 \pm 3.8$  to  $25.4 \pm 3.5$  mEq/L ( $P < 0.001$ ). A significant difference in serum bicarbonate was maintained at 48 hours between the groups receiving bicarbonate and saline ( $27.5 \pm 3.6$  versus  $26.0 \pm 3.7$  mEq, respectively;  $P < 0.001$ ). These findings confirm that the high-dose bicarbonate resulted in significant changes in systemic acid-base balance that should be reflected in urinary alkalinization (2,13). Of note, there were no apparent safety issues related to high-dose bicarbonate: the rate of new onset congestive heart failure (determined by investigators' clinical assessment during mandated examinations at day 7, 30, 90, and 180) was 7.4% versus 7.5% ( $P = 0.99$ ) in the saline and bicarbonate groups, respectively.

There was no significant difference in the rate of the primary composite end point between the sodium bicarbonate and sodium chloride groups at the time of the interim analysis in either the intention-to-treat or per protocol analyses (Table 2). Death, dialysis, or a 20% sustained reduction in eGFR was found in 14.9% of the sodium bicarbonate group and 16.3% of the sodium chloride group (relative risk [RR]=0.91; 95% confidence interval [95% CI], 0.57 to 1.44;  $P = 0.78$ ). These composite rates were higher than predicted in the statistical analysis plan because we underestimated the effect of a 20% reduction in eGFR on the primary composite outcome. There were no differences in the composite outcome seen in the per protocol patients or in subgroups on the basis of age, history of diabetes or congestive heart failure, or type of procedure

(Figure 2). On the basis of the interim analysis, the number of patients required to reach statistical significance for a difference of the magnitude currently observed was  $>1500$ , and the sponsor decided to halt the trial.

CIAKI occurred in 44 of 368 patients in the per protocol analyses (12.0%) and was not statistically significant between the two groups (13.3% bicarbonate versus 9.2% saline) (unadjusted RR=1.45; 95% CI, 0.86 to 2.69;  $P = 0.20$ ). Furthermore, the occurrence of CIAKI was associated with sustained loss of kidney function at 6 months (unadjusted RR=2.85; 95% CI, 1.58 to 5.12;  $P = 0.002$ ).

An analysis of the individual components of the composite outcome in the per protocol patients found that patients treated with bicarbonate had statistically less mortality (Supplemental Table 1). No effect of treatment on dialysis or progression to CKD was observed.

## Discussion

The BOSS was designed to examine the effect of high-dose bicarbonate on clinically relevant outcomes of death, dialysis, and sustained reduction in eGFR after iodinated contrast exposure in high-risk patients. This study provides several meaningful insights into management of high-risk patients undergoing angiography.

First, the high-dose regimen of sodium bicarbonate administered in BOSS achieved its goal of producing significant systemic alkalosis for the period of time (48 hours) during which contrast was being eliminated from the body. Second, there were no adverse events attributed to bicarbonate compared with saline: new onset congestive heart failure was observed in 7.4% and 7.5% of patients, respectively.

Table 1. Patient and procedural characteristics

Characteristic	Intention-to-Treat			Per Protocol <sup>b</sup>					
	Bicarbonate (n=195)		Saline (n=196)	P Value	Coronary		Peripheral		P Value
	Bicarbonate (n=195)	Saline (n=196)			Bicarbonate (n=146)	Saline (n=145)	Bicarbonate (n=35)	Saline (n=42)	
Age (y)	72±10	72±9	0.73	71±11	72±9	75±10	74±9	0.33	0.41
Male sex (%)	57	58	1.00	70	58	54	57	0.51	0.82
Weight (kg)	89.1±19.7	88.3±22.3	0.71	91.7±19.8	90.1±23.0	80.3±18.0	82.1±19.9	0.09	0.70
CHF (%)	32	39	0.14	31	41	29	38	0.72	>0.99
Anemia (%)	45	45	>0.99	45	48	40	38	0.28	>0.99
Diabetes (%)	63	55	0.12	63	57	57	52	>0.99	0.82
Hypertension (%)	94	94	0.83	95	94	91	98	0.75	0.32
PAD (%)	30	31	>0.99	15	17	69	67	0.03	>0.99
Creatinine (mg/dl)	1.98±0.62	1.85±0.49	0.02	2.01±0.62	1.86±0.51	1.93±0.51	1.84±0.46	0.03	0.45
eGFR (ml/min per 1.73 m <sup>2</sup> )	31.7±7.7	33.8±7.3	0.01	31.7±8.0	33.7±7.5	31.2±7.2	33.2±6.7	0.37	0.23
CM volume (ml)	110±66	104±72	0.40	109±67	101±75	112±62	110±61	0.08	0.89
CM volume/eGFR	3.46±2.70	3.05±2.19	0.12	3.57±3.02	3.01±2.33	3.51±1.91	3.43±2.00	0.55	0.86
Mehran risk score <sup>a</sup>	11.0±3.9	10.9±3.8	0.80	11.0±3.9	11.3±3.7	10.2±3.8	9.9±3.8	>0.99	0.71
Use of NAC (%)	48	53	0.57	24	24	26	31	0.13	0.80
Volume of IV fluid (ml/kg)	12.54±3.74	13.11±2.99	0.10	13.00±2.49	13.41±2.07	3.51±2.67	3.43±2.31	0.50	0.86
Hospital LOS (h)	48	53	0.57	47	54	51	52		0.95

Values are mean±SD or as otherwise indicated. The group undergoing coronary angiography comprised 74% of the patients enrolled. Their characteristics are shown separately from those undergoing peripheral arteriography. CHF, congestive heart failure; PAD, peripheral arterial disease; CM, contrast media; NAC, N-acetylcysteine; IV, intravenous; LOS, length of stay in hospital (hours).

<sup>a</sup>Arbitrary units reflecting low (≤5), moderate (6–10), high (11–15), and very high (≥16) risk for contrast-induced AKI (11).

<sup>b</sup>Per protocol excludes 23 patients who did not undergo contrast exposure and receive either treatment.

**Table 2. Primary outcomes and incidence of contrast-induced AKI**

Endpoints	Total No. Events	All Angiograms (ITT/PP <sup>a</sup> )		
		Bicarbonate (n=195/181)	Saline (n=196/187)	P Value <sup>b</sup>
Primary composite end point	80	39	41	0.90
Sustained >20% loss of eGFR	37	21	16	0.39
Dialysis	14	8	6	0.60
Death	29	10	19	0.12
CIAKI	44	26	18	0.20

CIAKI, contrast-induced AKI; ITT, intention-to-treat; PP, per protocol.

<sup>a</sup>There are 391 patients in the ITT analysis and 368 patients in the PP analysis. Of the patients, 23 did not undergo the scheduled angiography and did not receive either saline or bicarbonate infusions. The number of events is the same for both ITT and PP, only the denominator changes. P values are similar for each event between the ITT and PP groups.

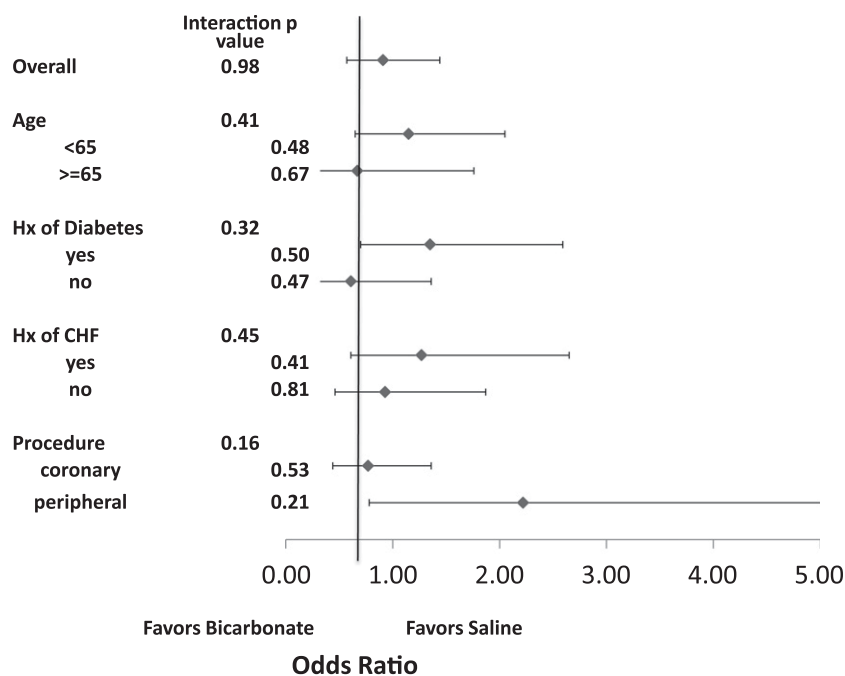
<sup>b</sup>P values by Fisher exact test for ITT and PP populations.

Third, BOSS revealed that despite systemic alkalosis, there was no observed benefit of high-dose bicarbonate on the incidence of acute AKI (CIAKI), a secondary end point. This may be because of a true lack of efficacy or inadequate power caused by early termination of the trial.

A number of issues are pertinent to interpretation of the BOSS results. Bicarbonate therapy did not reduce the incidence of CIAKI, a recognized risk factor for the composite outcomes. However, the two groups did differ in baseline eGFR, with a significantly lower mean value observed in the bicarbonate group (31.7 versus 33.8 ml/min per 1.73 m<sup>2</sup>, P=0.01) that might favor the saline group. Furthermore, the amount of sodium chloride administered was also greater than what has been reported in other trials with bicarbonate as a comparator. The benefit of higher-dose sodium chloride

is suggested by the results of the Prevention of Contrast Renal Injury with Different Hydration Strategies Trial. This trial used left ventricular end-diastolic pressure to guide intravenous sodium chloride administration and clearly showed that there was a reduction in CIAKI in those patients who received more saline (14). Whether the higher dose of sodium chloride administered to the control group or the small differences in baseline characteristics contribute to the lack of a difference between bicarbonate and sodium chloride on AKI is speculative.

Finally, there was a possible benefit on mortality with the use of bicarbonate in patients undergoing coronary angiography but not in those undergoing peripheral angiography. However, this was on the basis of a small number of events (n=21 in those undergoing coronary angiography)



**Figure 2. | Forest plot of the odds ratio for the composite end point in subgroups treated with either bicarbonate or saline in the per protocol cohort. Subgroups were chosen for biologically plausible effects on the composite end point. CHF, congestive heart failure; Hx, history.**



and may be the result of chance, particularly as the mechanism of the interaction is unclear. A recent observational trial (15) and two meta-analyses of bicarbonate versus saline trials for the prevention of CIAKI also found a similar point estimate for a benefit of bicarbonate on mortality (16,17). This issue will clearly require further confirmation in appropriately powered randomized trials and study of mechanism. The recently initiated Prevention of Serious Adverse Events following Angiography Trial will enroll approximately 8000 patients in a 2:2 design with bicarbonate and N-acetylcysteine [NCT 01467466]. This trial should have the power to confirm or refute the mortality benefit.

### Limitations

The BOSS enrolled patients with significant CKD (eGFR < 45 ml/min per 1.73 m<sup>2</sup>) and may not be generalizable to other populations with more preserved kidney function. The study was terminated prematurely when the power to detect a difference between groups was only 60%, potentially contributing to a risk of both false-positive and false-negative results. Although serum and urine pH were not directly measured, changes in serum bicarbonate strongly suggest that systemic alkalosis was achieved in the bicarbonate group. No additional measures of renal function, such as cystatin C, or renal injury were obtained.

High-dose sodium bicarbonate in patients with eGFR < 45 ml/min per 1.73 m<sup>2</sup> undergoing angiography was not associated with a statistically significant reduction in the composite of death, dialysis, or sustained reduction in eGFR compared with equimolar sodium chloride at 6 months. Furthermore, no statistically significant difference in the incidence of AKI (CIAKI) was observed between the bicarbonate and saline groups despite systemic alkalosis for at least 48 hours. We conclude that the use of high-dose bicarbonate should remain discretionary. Future studies should address the effect on mortality.

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### Disclosures

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### References

- Rojkowski I, Solomon R: Intravenous and oral hydration: Approaches, principles, and differing regimens. *Intervent Cardiol Clin* 2014
- Merten GJ, Burgess WP, Gray LV, Holliman JH, Roush TS, Kowalchuk GJ, Bersin RM, Van Moore A, Simonton CA 3rd, Rittase RA, Norton HJ, Kennedy TP: Prevention of contrast-induced nephropathy with sodium bicarbonate: A randomized controlled trial. *JAMA* 291: 2328–2334, 2004
- Assadi F: Acetazolamide for prevention of contrast-induced nephropathy: A new use for an old drug. *Pediatr Cardiol* 27: 238–242, 2006
- Heyman SN, Rosen S, Khamaisi M, Idée JM, Rosenberger C: Reactive oxygen species and the pathogenesis of radiocontrast-induced nephropathy. *Invest Radiol* 45: 188–195, 2010
- Hoste EA, De Waele JJ, Gevaert SA, Uchino S, Kellum JA: Sodium bicarbonate for prevention of contrast-induced acute kidney injury: A systematic review and meta-analysis. *Nephrol Dial Transplant* 25: 747–758, 2010
- Joannidis M, Schmid M, Wiedermann CJ: Prevention of contrast media-induced nephropathy by isotonic sodium bicarbonate: A meta-analysis. *Wien Klin Wochenschr* 120: 742–748, 2008
- Brar SS, Hiremath S, Dangas G, Mehran R, Brar SK, Leon MB: Sodium bicarbonate for the prevention of contrast-induced acute kidney injury: A systematic review and meta-analysis. *Clin J Am Soc Nephrol* 4: 1584–1592, 2009
- Murray P, Mehta RL, Shaw A, Ronco C, Endre Z, Kellum JA, Chawla LS, Cruz D, Ince C, Okusa MD; ADQI 10 workgroup: Potential use of biomarkers in acute kidney injury: report and summary of recommendations from the 10th Acute Dialysis Quality Initiative consensus conference. *Kidney Int* 85: 513–521, 2014
- 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* 130: 461–470, 1999
- Gruberg L, Mintz GS, Mehran R, Gangas G, Lansky AJ, Kent KM, Pichard AD, Satler LF, Leon MB: The prognostic implications of further renal function deterioration within 48 h of interventional coronary procedures in patients with pre-existent chronic renal insufficiency. *J Am Coll Cardiol* 36: 1542–1548, 2000
- Mehran R, Aymong ED, Nikolsky E, Lasic Z, Iakovou I, Fahy M, Mintz GS, Lansky AJ, Moses JW, Stone GW, Leon MB, Dangas G: A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: Development and initial validation. *J Am Coll Cardiol* 44: 1393–1399, 2004
- O'Brien PC, Fleming TR: A multiple testing procedure for clinical trials. *Biometrics* 35: 549–556, 1979
- Briguori C, Airolidi F, D'Andrea D, Bonizzoni E, Morici N, Focaccio A, Michev I, Montorfano M, Carlino M, Cosgrave J, Ricciardelli B, Colombo A: Renal insufficiency following contrast media administration trial (REMEDIAL). A randomized comparison of 3 preventive strategies. *Circulation* 115: 1211–1217, 2007
- Brar SS, Aharonian V, Mansukhani P, Moore N, Shen AY, Jorgensen M, Dua A, Short L, Kane K: Haemodynamic-guided fluid administration for the prevention of contrast-induced acute kidney injury: The POSEIDON randomised controlled trial. *Lancet* 383: 1814–1823, 2014
- Leone A, De Caterina AR, Sciahbasi A, Aurelio A, Baslile E, Porto I, Trani C, Burzotta F, Niccoli G, Mongiardo R, Mazzari MA, Buffon A, Panocchia N, Romagnoli E, Lioy E, Rebuzzi AG, Crea F: Sodium bicarbonate plus N-acetylcysteine to prevent contrast-induced nephropathy in primary and rescue percutaneous coronary interventions: The BINARIO (Bicarbonato e N-Acetil-cisteina nell'infarto miocardico acuto) study. *EuroIntervention* 8: 839–847, 2012
- Pearlman D, Solomon RJ, Bokyoung K, Brown JR: Sodium bicarbonate v. normal saline hydration for all-cause mortality risk following coronary angiography or angioplasty: systemic review and meta-analysis. Presented at the Transcatheter and Cardiovascular Therapeutics 29th Annual Meeting, San Francisco, CA, October 2013
- 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. *Circ J* 76: 2255–2265, 2012

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