

Sodium Bicarbonate for the Prevention of Contrast Induced-Acute Kidney Injury: A Systematic Review and Meta-analysis

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Background and objectives: Infusion of sodium bicarbonate has been suggested as a preventative strategy but reports are conflicting on its efficacy. The aim of this study was to assess the effectiveness of hydration with sodium bicarbonate for the prevention of contrast-induced acute kidney injury (CI-AKI).

Design, setting, participants, & measurements: Medline, EMBASE, Cochrane library, and the Internet were searched for randomized controlled trials comparing hydration between sodium bicarbonate and chloride for the prevention of CI-AKI between 1966 and November 2008. Fourteen trials that included 2290 patients were identified. There was significant heterogeneity between studies (P heterogeneity = 0.02; I^2 = 47.8%), which was largely accounted for by trial size (P = 0.016). Trials were therefore classified by size.

Results: Three trials were categorized as large (n = 1145) and 12 as small (n = 1145). Among the large trials, the incidence of CI-AKI for sodium bicarbonate and sodium chloride was 10.7 and 12.5%, respectively; the relative risk (RR) [95% confidence interval (CI)] was 0.85 (0.63 to 1.16) without evidence of heterogeneity (P = 0.89, I^2 = 0%). The pooled RR (95% CI) among the 12 small trials was 0.50 (0.27 to 0.93) with significant between-trial heterogeneity (P = 0.01; I^2 = 56%). The small trials were more likely to be of lower methodological quality.

Conclusions: A significant clinical and statistical heterogeneity was observed that was largely explained by trial size and published status. Among the large randomized trials there was no evidence of benefit for hydration with sodium bicarbonate compared with sodium chloride for the prevention of CI-AKI. The benefit of sodium bicarbonate was limited to small trials of lower methodological quality.

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Contrast-induced acute kidney injury (CI-AKI) is probably the most common iatrogenic cause of acute kidney injury and a common complication of iodinated contrast medium exposure, with a published incidence ranging from 2 to 50% (1–3). It results in increased morbidity, prolonged hospital stay, and increased healthcare expenditure and is associated with a higher mortality (4). The planned nature of the nephrotoxic insult in persons at risk of CI-AKI represents a unique opportunity to implement strategies for preventing renal injury (5). Hydration with saline has been an effective strategy and is postulated to act by diluting the hyperosmolar contrast load and improving renal perfusion (6). Infusion of sodium bicarbonate has been suggested as an alternative preventive treatment (7). It has been hypothesized that by alkalinizing tubular urine, sodium bicarbonate may prevent free radical formation and resultant injury (7). However, randomized trials and observational studies have been conflicting on the efficacy of sodium bicarbonate compared with chloride for the

prevention of CI-AKI (8,9). We performed a systematic review and meta-analysis to determine the true effectiveness of sodium bicarbonate compared with sodium chloride for the prevention of CI-AKI.

Subjects and Methods

Data Sources and Searches

We conducted a systematic literature search of MEDLINE (1966 to week 3 of November 2008), EMBASE (1980 to week 49 of 2008), and Cochrane CENTRAL (until third quarter 2008) for randomized controlled trials (RCTs) comparing periprocedural hydration with sodium bicarbonate and sodium chloride. The search was performed by combining various combinations of exploded versions of the Medical Subject Headings *sodium bicarbonate*, *contrast media*, *sodium chloride*, and *kidney failure (acute)* and the keywords *prevention* and *nephropathy*.

In addition, we searched the reference lists of all identified relevant publications and reviewed abstracts of selected scientific meetings (American College of Cardiology, American Heart Association, Transcatheter Cardiovascular Therapeutics, American Society of Nephrology, and the European Society of Cardiology). Websites, including cardiosource.com, TCTMD.com, theheart.org, escardio.org, and asn.org were also searched for relevant materials. Review articles and prior meta-analysis of the subject were also sought. The references for these were reviewed for additional possible studies. We considered articles published in any language.

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Study Selection

Three reviewers (S.S.B, S.H., and S.K.B.) identified articles for further review by performing an initial screen of identified abstracts or titles. Articles were considered for inclusion in the systematic review if they were randomized comparisons of hydration with sodium bicarbonate and sodium chloride for the prevention of CI-AKI in the adult population (age ≥ 18 yr). The observed agreement between reviewers for eligibility of articles was 88%. Articles identified by any reviewer were retained. The full text for the articles was then obtained to perform a second screening. In this second review the agreement between reviewers for eligibility of articles was 94%. Any disagreement was resolved by consensus.

Data Extraction and Quality Assessment

We extracted prespecified data elements from each trial, including study design, protocol, CI-AKI definition, sample characteristics, sample size, outcome measures, primary endpoint, contrast volume, *N*-acetylcysteine (NAC) use, and other study characteristics. The protocol definition of CI-AKI was used. For studies available only in abstract form, we also abstracted data from presentations given at the previously mentioned scientific meetings.

We categorized trials as either large or small by the sample size. For classification, we used the sample size calculation described by Merten *et al.*, and used by others, in which 290 patients would be required to show a significant reduction in CI-AKI from 15 to 5% with sodium bicarbonate, assuming 80% power and an α of 0.05. Studies meeting these criteria were defined as large RCTs whereas all others were classified as small. Study characteristics and measures of quality were also identified *a priori* for inclusion in stratified analysis and meta-regression. Quality measures included the Jadad score, publication status, allocation concealment, and blinding. Study characteristics included renal function, age, diabetes, contrast type, number of days serum creatinine was measured, and NAC use.

Statistical Analyses

From the abstracted data, we calculated the Mantel–Hansel risk ratio for development of CI-AKI. The average effects for the outcomes and 95% confidence intervals (CIs) were obtained using a random-effects model as described by DerSimonian and Laird (10). We chose the random-effects method because of its conservative summary estimate and incorporating between- and within-study variance. To assess heterogeneity of relative risks across trials, we used the Cochrane *Q* statistic test, with a *P* value < 0.1 considered significant, and the *I*² statistic. Sensitivity analyses were performed to assess the effects of selected measures of study quality and clinical factors. Stratified analyses and metaregression were applied to determine if these covariates might explain heterogeneity of results among the studies.

Random-effects metaregression using a linear mixed-effects model was applied to further explore between-trial heterogeneity. The restricted maximum likelihood method was used to estimate the variance components. Covariates considered were aggregate measures on the study level and were included if there was evidence of a univariate association, defined as *P* ≤ 0.10 . Study size and published status satisfied these criteria and were included in the model.

Using regression techniques, we also explored the relationship between baseline risk, defined as the CI-AKI rate in the sodium chloride group, and the treatment effects. A mixed model approach after a bivariate normal distribution was applied using Proc MIXED in SAS (11). The bivariate model had distinct random effects for the sodium bicarbonate and sodium chloride groups and yielded maximum likelihood estimates for between-trial variance in each treatment group. The model was also validated using Proc NLMIXED, which is better equipped for handling binomial data, and yielded similar results.

A funnel plot was used to assess for the presence of publication and other reporting biases by plotting the standard error against the log risk ratio. Using Egger's linear regression method, we examined the association between the study size and estimated treatment effects (12,13). *P* ≤ 0.1 was considered significant.

The *P*-value threshold for statistical significance was set at 0.05 for effect sizes. Analyses were conducted by S.S.B. in Stata 10.0 (Stata Corp., College Station, TX) and SAS 9.2 (SAS Institute Inc., Cary, NC). The study was performed in accordance to the recommendations set forth by the Quality of Reporting of Meta-Analysis (QUOROM) workgroup (14).

Results

Eligible Studies

Our electronic search strategy identified 469 citations, with 8 additional citations being selected from conference proceedings (Figure 1). Of these, 14 randomized trials, including 2290 patients, compared sodium bicarbonate with sodium chloride for the prevention of CI-AKI and satisfied our selection criteria. Eight trials have been published (7,8,15–20) and six remain unpublished (21–27). The unpublished studies were identified in abstract form. Three studies met the sample size criteria (≥ 290 patients) and were categorized as large (8,17,26). The study by Tamura *et al.* was not included in the analysis because the protocol used in this study markedly differed from all other identified trials (28). In this study, both groups were given sodium chloride at the same rate pre- and postcontrast exposure; however, the sodium bicarbonate group received a single 20-mEq bolus of sodium bicarbonate immediately before contrast exposure. All other trials identified in the systematic review administered sodium bicarbonate as an infusion of at least 5 h. The study by Recio-Mayoral was also excluded from the analysis (20). In this trial, the sodium bicarbonate group received more volume than the sodium chloride group (20). Moreover, the NAC dose and route also differed between

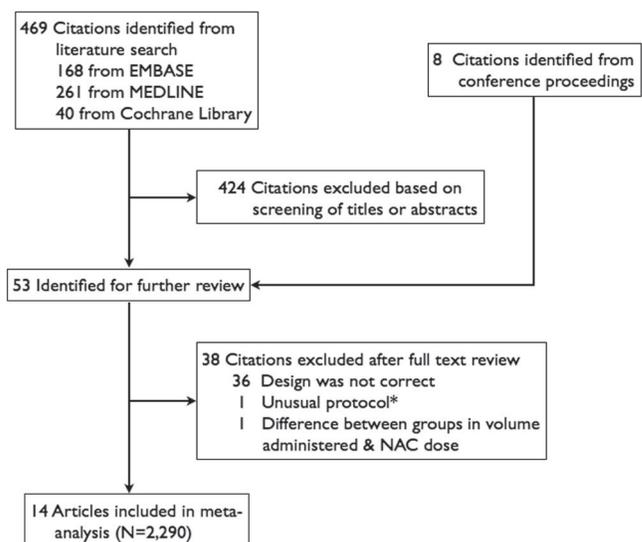


Figure 1. Flowchart of meta-analysis. *The study by Tamura *et al.* administered sodium bicarbonate as a single intravenous bolus before contrast exposure.

groups; the sodium bicarbonate group received intravenous NAC compared with oral in the sodium chloride group. These differences between treatment groups confound the results and complicate the interpretation of this trial.

Study characteristics are shown in Table 1 and population characteristics in Table 2. The most common infusion protocol was that described by Merten *et al.*, or slight variations of it (7). Briefly, Merten administered 154 mEq/L of sodium bicarbonate or chloride at 3 ml/kg per h for 1 h before contrast exposure and 1 ml/kg per h for 6 h after contrast exposure. Among the 14 trials, the pre- and postprocedure duration of hydration ranged from 1 to 12 h and 4 to 12 h, respectively.

Publication Bias and Metaregression

Visual inspection of the funnel plot (Figure 2) revealed asymmetry, suggesting the absence of small negative trials of sodium bicarbonate for the prevention of CI-AKI. Egger's regression test trended in support of this observation ($P = 0.067$). Among the 14 trials identified in the systematic review, there was a statistically significant benefit for hydration with sodium bicarbonate in 5, all of which have been published. In contrast, only three of the nine negative trials have been published.

Metaregression analyses provided evidence of small-study effects. Trials with larger standard errors (smaller studies) had greater estimated benefit with sodium bicarbonate hydration ($P = 0.046$). We then performed a multivariable random-effects metaregression with study size and published status as study level covariates. When the effects of each variable were controlled for the other in the linear mixed-effects model, there remained strong associations with study size ($P = 0.016$). The between-study estimate of the random effect was negligible relative to the residuals on the within-study level; therefore, the between-trial heterogeneity was largely explained by published status and trial size.

We also assessed the quality of trials using the Jadad score. The score assesses quality in randomization, description of withdrawals or dropouts, and whether the trial is double blinded; a trial can receive a maximum score of 5 (29). The Jadad score was not associated with treatment benefit ($P = 0.37$). However, the score may not be a reliable indicator of quality here because unpublished studies, which were more often negative, ranked lower because of lack of information in the abstracts.

CI-AKI

Figure 3 shows a Forest plot, including all identified trials with relative risk and 95% CI for developing CI-AKI. A summary statistic is not shown because of the significant heterogeneity (P heterogeneity = 0.02; $I^2 = 48\%$) that precluded the pooling of these results.

Because study size accounted for much of the statistical heterogeneity in the metaregression analysis, we choose to further stratify the analyses by this measure. As described previously, we used the sample size calculation described by Merten *et al.*, in which 290 patients would be required. This, or slight variations of it, remain the most commonly used power calculation.

On the basis of these criteria, three trials were identified as

large, of which two have been published (8,17,26). These three trials comprised 50% of the 2290 cumulative patients with sample sizes that ranged from 320 to 502 participants. The total number of CI-AKI events per trial ranged from 33 to 56. These trials all enrolled patients undergoing elective cardiac catheterization. The hydration protocols, volume administered, and NAC dose and route did not differ between treatment groups in these trials. Moreover, the studies by Brar and Maioli *et al.* had similar inclusion criteria, hydration protocols, and measured serum creatinine up to 4 to 5 d after contrast exposure. The relative risk (RR) for CI-AKI among these studies ranged from 0.75 to 0.91 and did not reach statistical significance in any trial. The cumulative incidence of CI-AKI among these trials was 12.5% (143 of 1145). The event rates in the sodium bicarbonate and sodium chloride groups were 10.7% (60 of 562) and 12.6% (72 of 572), respectively ($P = 0.32$). In the absence of clinical and statistical heterogeneity (P heterogeneity = 0.89; $I^2 = 0\%$), the large trials were felt suitable for pooling. The pooled RR was 0.85 (0.62 to 1.17, $P = 0.32$), suggesting no statistically significant difference between fluid types.

There were 11 studies categorized as small RCTs (7,16,18–25,27). The sample size of these trials ranged from 18 to 219 patients, with the total number of CI-AKI events per trial between 2 and 16. The RR for sodium bicarbonate *versus* sodium chloride in these studies ranged from 0.11 to 2.17 and was statistically significant in favor of sodium bicarbonate in 5. The incidence of CI-AKI among these 12 trials was 10.0% (126 of 1256). The event rates in the sodium bicarbonate and sodium chloride groups were 6.7% (43 of 643) and 13.5% (83 of 613), respectively; the pooled treatment effect was 0.50 (0.27 to 0.93, $P = 0.03$). However, there remained significant statistical heterogeneity between the small studies (P heterogeneity = 0.01; $I^2 = 55.6\%$). The incidence of CI-AKI in all identified trials is shown in Figure 4.

Sensitivity and Influence Analysis

The influence of each study was estimated by deleting each in turn from the analysis and noting the degree to which the pooled effect size changed. We considered a study influential if the exclusion of it changed our conclusion or the effect estimate by at least 20%. Among the large trials, the omission of any of the studies did not appreciably change the pooled estimate or our conclusions. Among the small trials, exclusion of any of the five trials in which sodium bicarbonate significantly reduced CI-AKI resulted in the pooled treatment effect no longer being statistically significant.

For our primary analysis, we used the protocol definition of CI-AKI in a random-effects analysis. The most commonly used definition of CI-AKI was a $\geq 25\%$ increase in serum creatinine. The large RCTs by Brar and Maioli used alternate definitions but also reported outcomes as a $\geq 25\%$ increase in serum creatinine (8,17). Using this alternate definition of CI-AKI for both of these studies did not appreciably change the point estimate of the treatment effect in the large trials. The RR (95% CI) using the protocol CI-AKI definition and the alternate definition of $\geq 25\%$ increase in serum creatinine was 0.85 (0.63 to 1.16) and 0.80 (0.61 to 1.05), respectively.

Table 1. Study characteristics^a

Study	CI-AKI Definition	Hydration Protocol	NAC	Clinical Setting	Contrast Type	Sample Size (<i>n</i>)	Published
Merten (7)	Creatinine increase of $\geq 25\%$ within 2 d.	3 ml/kg per h for 1 h preprocedure and 1 ml/kg per h for 6 h postprocedure.	Not permitted.	Mixed procedures. Creatinine ≥ 1.1 mg/dl.	Low osmolar (iopamidol)	119	Yes
Saidin (25)	Creatinine increase of $\geq 25\%$ within 72 h.	Infusion started 2 h preprocedure and for 6 h postprocedure. Rate not reported.	All received NAC. Dose not reported.	Elective coronary angiography or PCI. CKD stages 2 to 4.	–	57	No
Briguori (16)	Creatinine increase of $\geq 25\%$ within 48 h.	Saline: 1 ml/kg per h for 12 h pre- and postprocedure. Bicarbonate: 3 ml/kg per h for 1 h preprocedure, 1 ml/kg per h during procedure, and 6 h postprocedure.	NAC 1200 mg twice daily on the day before and day of the procedure.	Mixed procedures. Creatinine ≥ 2.0 mg/dl.	Iso-osmolar (iodixanol)	219	Yes
Chen (21)	Creatinine increase of ≥ 0.5 mg/dl within 72 h.	2 ml/kg per h for 6 h preprocedure and 80 ml/kg per h for 6 h postprocedure.	Not reported.	Elective coronary or renal angiography. Estimated GFR < 60 .	Low osmolar (iohexol)	105	No
Kim (23)	Creatinine increase $\geq 25\%$ within 48 h.	1 ml/kg per h pre- and postprocedure.	Half in each group received 600 mg \times 2 d.	Elective coronary angiography. Proteinuria, azotemia, or diabetes.	Iso-osmolar (iodixanol)	100	No
Ozcan (19)	Creatinine increase of $> 25\%$ or > 0.5 mg/dl within 48 h.	1 ml/kg per h for 6 h pre- and postprocedure.	Not permitted.	Elective coronary angiography or PCI. Creatinine > 1.2 mg/dl.	Low osmolar (ioxaglate)	176	Yes
Masuda (18)	Creatinine increase of > 0.5 mg/dl within 2 d.	3 ml/kg per h for 1 h (if possible) preprocedure, and 1 ml/kg per h during and 6 h postprocedure.	Not permitted.	Emergent PCI. Creatinine > 1.1 mg/dl.	Low osmolar (iopamidol)	59	Yes
Lin (24)	Creatinine increase of $\geq 25\%$ within 3 d.	3 ml/kg per h for 1 h preprocedure and 6 h postprocedure.	600 mg twice daily the day of and day after the procedure.	Mixed procedures. Creatinine ≤ 2.0 mg/dl.	Low osmolar (iopamidol)	60	No
Shavit (27)	Creatinine increase of $\geq 25\%$ within 2 d.	Saline: 1 ml/kg per h for 12 h preprocedure only. Bicarbonate: 3 ml/kg per h for 1 h preprocedure and 1 ml/kg per h for 6 h postprocedure.	600 mg twice daily the day before and day of the procedure in saline group only.	Elective coronary angiography or PCI. Estimated GFR 15 to 60.	Low osmolar (iopamidol)	87	No
Adolph (15)	Creatinine increase of > 0.5 mg/dl or $\geq 25\%$ within 2 d.	2 ml/kg per h for 2 h preprocedure. 1 ml/kg per h during and for 6 h postprocedure.	Not permitted.	Elective coronary angiography or PCI.	Iso-osmolar (iodixanol)	145	Yes
Heguilen (22)	Creatinine increase of $\geq 25\%$ within 3 d.	3 ml/kg per h for 1 h preprocedure, and 3 ml/kg per h for 6 h postprocedure.	Saline: 600 mg twice daily the day before and day of the procedure. Bicarbonate: same dose, but only half given NAC.	Mixed procedures. Creatinine ≥ 1.25 mg/dl or estimated GFR < 50 .	Low osmolar (ioversol)	18	No
Shaikh (26)	Creatinine increase of $\geq 25\%$ or ≥ 0.5 mg/dl within 48 h.	3 ml/kg per h for 1 h preprocedure and 1 ml/kg per h for 6 h postprocedure.	1200 mg 2 to 12 h pre- and 6 to 12 h postprocedure.	Elective coronary angiography or PCI.	–	320	No
Brar (8)	Estimated GFR decrease of $\geq 25\%$ within 4 d.	3 ml/kg per h for 1 h preprocedure, and 1.5 ml/kg per h during and 4 h postprocedure.	600 mg twice daily at the discretion of the referring physician.	Elective coronary angiography or PCI. Estimated GFR ≤ 60 .	Low osmolar (ioxilan)	353	Yes
Maioli (17)	Creatinine increase of ≥ 0.5 mg/dl within 5 d.	Saline: 1 ml/kg per h for 12 h pre- and postprocedure. Bicarbonate: 3 ml/kg per h for 1 h preprocedure and 1 ml/kg per h for 6 h postprocedure.	All given NAC 600 mg twice daily for 2 d.	Elective coronary angiography or PCI. Creatinine clearance < 60 mg/dl.	Iso-osmolar (iodixanol)	502	Yes

^aEstimated GFR values are reported as ml/min/1.73 m². PCI, percutaneous coronary intervention.

Table 2. Population characteristics

Study	Year	Age (yr)	Male (%)	Diabetes (%)	Baseline		Contrast Volume (ml)		Jadad Score
					Creatinine (mg/dl)	Estimated GFR ^a	Bicarbonate	Chloride	
Published									
Merten	2004	68	74	48	1.78	43	130	134	3
Briguori	2007	71	92	57	1.99	34	169	179	4
Ozcan	2007	69	75	45	1.39	–	110	100	2
Masuda	2007	75	61	31	1.31	39	112	120	3
Adolph	2008	72	77	32	1.56	–	141	138	5
Brar	2008	71	65	44	1.50	48	137	126	3
Maioli	2008	74	59	24	1.20	–	160	170	3
Unpublished									
Saidin	2006	62	79	–	–	–	–	–	2
Chen	2007	71	–	36	–	52	–	–	1
Kim	2007	–	–	–	1.10	–	–	–	1
Shaikh	2007	70	30	45	1.77	–	–	–	1
Heguilen	2007	67	94	–	–	–	–	–	2
Lin	2008	47	–	24	0.84	–	–	–	1
Shavit	2008	–	–	–	1.8	–	–	–	2

^aEstimated GFR values are reported as ml/min/1.73 m².

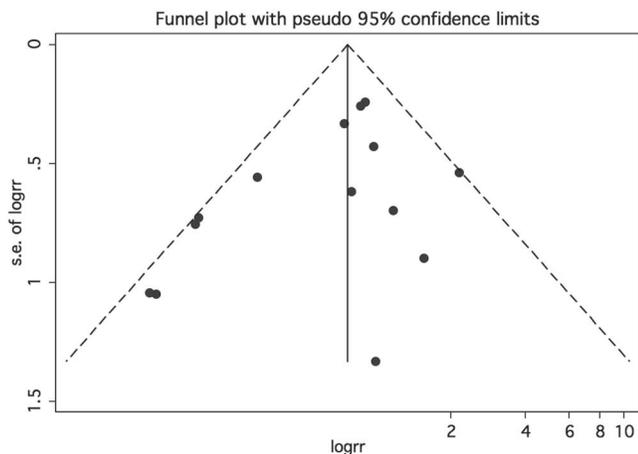


Figure 2. Funnel plot with pseudo-95% confidence limits for assessment of publication bias. Solid circles represent original studies. Open circles represent hypothetical or imputed studies. On visual inspection there is asymmetry in the funnel plot due to the presence of multiple small positive trials and the absence of small negative trials.

Measures of Quality

In addition to the observed statistical heterogeneity, there were also differences in measures of quality between trials. Whereas the large trials were fairly homogeneous and completed planned enrollment, there were marked differences between the small trials. The trials by Merten and Masuda were both prematurely terminated. The *P* value for the difference in event rates in both studies was higher than expected for early termination of a trial, *P* = 0.02 and *P* = 0.01, respectively. Moreover, one or two additional events in the five trials showing a favorable effect for hydration with sodium bicarbonate

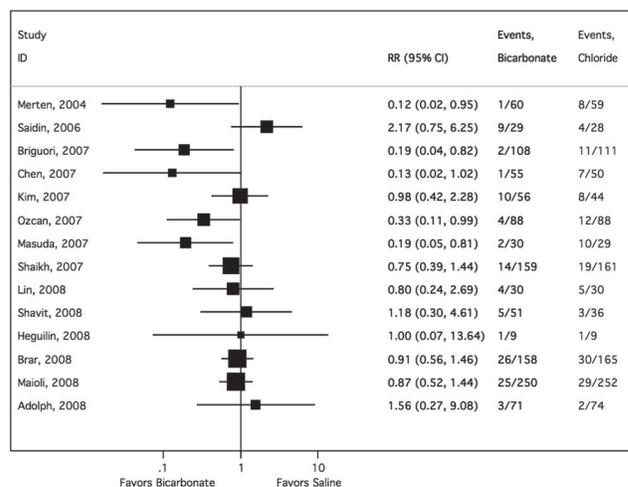


Figure 3. Forest plot of randomized trials meeting inclusion criteria. Size of data markers indicates the weight of the study. Studies are ordered by year.

would have yielded a statistically nonsignificant result. This lack of robustness in the results of these trials is driven largely by the relatively small sample sizes and is concerning for a type I error (false-positive result).

We also performed an analysis limited to studies meeting the following quality criteria: equal volume of fluid in each treatment group; no early termination; >100 patients enrolled; and, if NAC use was permitted, that the dose and route be similar between treatment groups. There were eight trials meeting these quality criteria. Among these 8 trials, the RR (95% CI) for sodium bicarbonate compared with sodium chloride was 0.71 (0.49 to 1.03) with a small amount of heterogeneity that was not

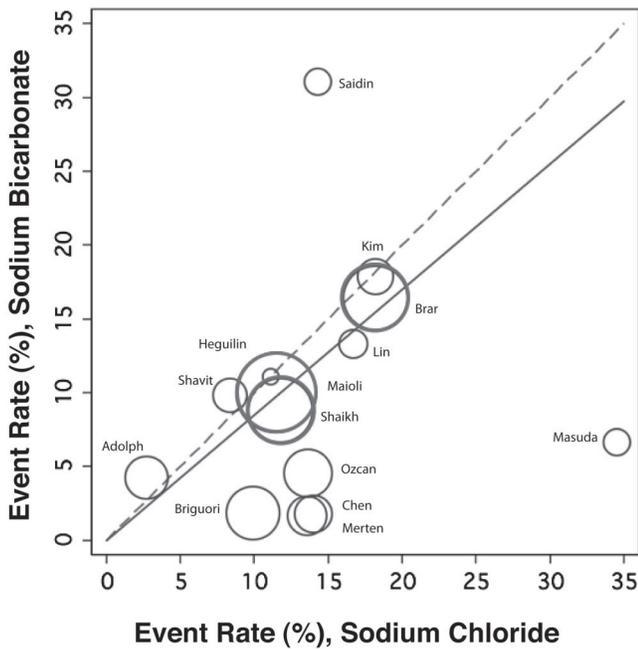


Figure 4. CI-AKI rates by trial. Modified L'Abbe plot of CI-AKI rates in the sodium bicarbonate and sodium chloride groups. The dotted line represents the no-effect line with identical CI-AKI rates in both groups. The thick circles represent the large trials, and the solid line corresponds to a pooled risk ratio of 0.85 as observed in these studies. The area of each circle is inversely proportional to the variance of the estimated treatment effect in the trial.

statistically significant (P heterogeneity = 0.16; $I^2 = 33\%$) (Figure 5). If we further limited the analysis to the five published trials from this group, the RR (95% CI) for sodium bicarbonate versus sodium chloride was largely unchanged (RR, 0.69; 95% CI, 0.42 to 1.14) (8,15–17,19).

Changes in Serum Creatinine

The absolute change in serum creatinine from baseline to study endpoint was available in all published trials. A modified

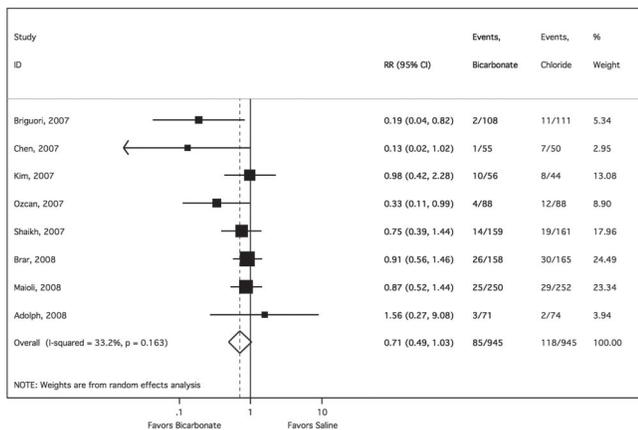


Figure 5. CI-AKI in studies meeting quality criteria. Size of data markers indicates the weight of the study. Studies are ordered by year.

L'Abbe plot of creatinine change in the sodium bicarbonate group versus the sodium chloride group for the published trials is shown in Figure 6. The negative trials, in which there was no difference between hydration strategies, grouped around the no-effect line. The four trials in favor of sodium bicarbonate hydration were all below the no-effect line. In each of these four trials, there was an increase in serum creatinine from baseline with sodium chloride hydration. However, in each of these trials there was a concomitant decrease (or improvement) in serum creatinine in the sodium bicarbonate group; moreover, in two of the trials the decrease in serum creatinine with sodium bicarbonate was of a greater magnitude than the increase in serum creatinine with sodium chloride.

Effect of Baseline Risk

We explored whether the baseline risk of the patients in each trial was related to the treatment effect with sodium bicarbonate for CI-AKI. A linear, quadratic, or cubic relationship using weighted ordinary least squares regression did not describe the association between treatment effect and the event rate in the control group, suggesting there was no relationship between baseline risk (measured as the control rate) and treatment effects. Because of the limitations of this approach, namely regression to the mean, we applied a bivariate multilevel random-effects model for the binomial outcomes (11,30,31). The bivariate model had distinct random effects for the sodium bicarbonate and sodium chloride groups. The estimated residual variance given the control rate was 0.3574 and was only slightly smaller than the variance of the treatment effect, 0.3682. In summary, only 2.9% of the variation or heterogeneity in the

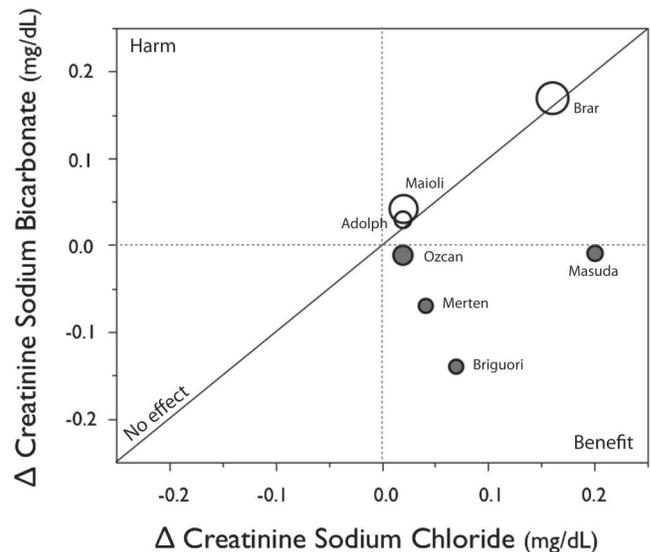


Figure 6. Changes in serum creatinine in published trials. Plot of change in serum creatinine from baseline to study endpoint in the sodium bicarbonate (y-axis) and sodium chloride (x-axis) groups. The open circles represent published negative trials for sodium bicarbonate hydration. Solid circles represent published positive trials for sodium bicarbonate hydration. The area of each circle is inversely proportional to the variance of the estimated treatment effect in the trial.

treatment effect was explained by the baseline risk, so the variation in the treatment effect was not able to explain variation in the baseline risk.

Power Analysis

A power analysis was performed using the point estimate of the treatment effect in the large randomized trials (RR = 0.85). This cohort was chosen because these trials were adequately powered, of higher quality, and lacked heterogeneity ($I^2 = 0\%$). A single randomized trial with a balanced design would require 7410 patients to have an 80% chance of showing a statistically significant benefit at an α of 0.05. A definitive study with 90% power would require 9918 persons.

Renal Replacement Therapy

The need for renal replacement therapy up to 30 d after contrast exposure was reported in 10 trials (7,8,15–20,27). The overall incidence was 1.0% and ranged from 0 to 6.8%; it was greatest in trials of emergent cardiac catheterization (18,20). The incidence within the small and large RCTs was 1.3% (12 of 934) and 0.6% (5 of 855), respectively. The RR (95% CI) for sodium bicarbonate *versus* sodium chloride in the small and large studies was 0.51 (0.15 to 1.72) and 0.68 (0.11 to 4.16), respectively, without any statistically significant difference. There was no evidence of statistical heterogeneity ($I^2 = 0\%$; $P = 0.96$).

Discussion

We identified 14 RCTs, including 2290 patients, comparing hydration with sodium bicarbonate with sodium chloride for the prevention of CI-AKI. In the presence of marked clinical and statistical heterogeneity between studies, evidence of publication bias, and small-study effects we do not report a pooled effect measure for all identified trials. In metaregression analysis, heterogeneity between studies was largely explained by trial size and published status. Therefore, we performed stratified analyses by trial size and published status. The three trials classified as large accounted for 50% of the study population. The large trials were homogeneous ($I^2 = 0\%$) and did not suggest benefit for hydration with sodium bicarbonate in the component studies or the pooled treatment estimate. In contrast, the pooled estimate from the smaller trials suggested benefit for sodium bicarbonate; however, this estimate was less reliable given the marked residual clinical and statistical heterogeneity between these studies. Moreover, smaller trials were more likely to be of lower quality, characterized by extreme treatment effects, wide CIs, and likely to be terminated prematurely. In influence analyses, omission of any of the large trials did not change our conclusion. However, among the small trials, omission of any one of the studies with a statistically significant benefit for sodium bicarbonate yielded a pooled estimate that was no longer statistically significant, suggesting the benefit in these studies was not very robust. In analysis limited to studies meeting certain quality criteria, there was no evidence of a statistically significant treatment benefit with sodium bicarbonate. We also investigated whether the treatment benefit of sodium bicarbonate may be greater in patients at higher risk of CI-AKI using control-rate regression. In these

bivariate random-effects models there was no evidence that the treatment benefit was related to the baseline risk, measured as the CI-AKI rate in the control group. Finally, the need for renal replacement therapy was an uncommon event and did not significantly differ by fluid type.

The funnel plot was in support of the presence of publication bias. All of the trials with a statistically significant positive effect for sodium bicarbonate identified in the systematic review have been published. In contrast, only three of nine negative or neutral trials are published. Furthermore, the small published trials report a large magnitude of benefit with sodium bicarbonate hydration, with RR ranging from 0.12 to 0.33. Given the small sample sizes, the CIs of each of these studies were extremely wide. This observation of treatment benefit limited to small studies with extreme treatment effects has been characterized as the “small-study effect” (12,32). In general, the smaller the study the larger the treatment effect needs to be to achieve statistical significance. Therefore, few studies with extreme treatment effects can have a disproportionate influence on the overall results of a meta-analysis. This is supported by the influence analysis in which removal of any one of these small positive trials yields a point estimate for treatment that is no longer statistically significant. The problem is compounded by the absence of small negative trials. Comparable small negative studies are less likely to be presented or published, making their identification and inclusion in systematic reviews more challenging. A common criticism of such studies is likely the lack of power and inadequate sample size, which are concerning for a type II error (false negative). In contrast, small trials with extreme reductions in CI-AKI with sodium bicarbonate are more readily published, raising the possibility of the more serious type I error (false positive).

The observed CI-AKI event rate with sodium bicarbonate of 1 to 2% in the small positive RCTs is not substantiated by larger trials. The cumulative incidence of CI-AKI with sodium bicarbonate in the large RCTs was 11.5%. This higher event rate is consistent with other studies. For example, in the Cardiac Angiography in Renally Impaired Patients (CARE) trial ($n = 414$), a randomized comparison of two contrast media, all patients received hydration with sodium bicarbonate and some also received NAC (33). The rate of CI-AKI was 10.6% in the group receiving sodium bicarbonate alone and 11.9% in the group receiving sodium bicarbonate and NAC. These observations raise further doubts about whether the large reductions in CI-AKI with sodium bicarbonate in some small RCTs are clinically plausible in light of the relatively homogeneous results of larger trials.

The conduct of future underpowered RCTs of hydration with sodium bicarbonate is likely to be of limited value. With too few patients to detect a positive effect, the CIs of such studies will be extremely wide. Furthermore, recruitment of patients in such trials may be unethical given the unrealistic probability of detecting a clinically plausible positive effect (34). Despite these concerns, this practice remains common as illustrated in our systematic review. The sample size calculation, described by Merten *et al.* and used in the large trials, still assumes a large treatment effect. In this calculation, 290 patients are required to

detect a reduction in CI-AKI from 15 to 5%, an absolute decrease of 10%. The results of this meta-analysis suggest that trials powered to detect an even larger difference in CI-AKI rates may be markedly underpowered and in search of a treatment benefit that is not likely to be clinically plausible. The present data suggest that if sodium bicarbonate is effective, the treatment benefit is likely considerably smaller than that suggested by published positive trials. Our sample size calculations suggest that to detect a RR of 0.85, as was observed in the large studies, a definitive trial with 90% power would require 9918 patients.

Compared with two prior smaller meta-analyses, our analyses, results, and conclusions differ (35,36). We present a more comprehensive assessment of published and unpublished studies. In addition to identifying a larger number of randomized trials, we identified study characteristics and measures of quality that largely explain the observed heterogeneity between studies. Our analysis highlights that the perceived benefit of sodium bicarbonate is largely driven by small, underpowered RCTs with extreme treatment effects and wide CIs. These observations, including the small-study effect, may help explain the discrepancies in the efficacy of sodium bicarbonate across studies and remain unaccounted for in prior analysis.

The analysis presented here does not directly address the efficacy of NAC for the prevention of CI-AKI in relation to hydration. The use of NAC varied across studies. In the large studies it did not appear to have a protective effect. Almost 50% of the patients in the study by Brar *et al.* received NAC at the discretion of the treating physician with similar rates of CI-AKI in each group. In the CARE trial, the rates of CI-AKI were comparable between sodium bicarbonate alone *versus* sodium bicarbonate plus NAC, 10.6 and 11.9%, respectively (37). Therefore, it is unlikely that NAC provides added benefit when used in conjunction with sodium bicarbonate. However, a large randomized trial will be required to confirm these observations.

The analysis presented here was based upon study-level data. An analysis incorporating individual patient-level data could, in general, allow for more flexible analysis. However, a patient-level analysis is unlikely to overcome the important sources of heterogeneity identified in this analysis and may be biased if only a subset of identified trials was included.

In the meta-analysis presented here, we detected significant clinical and statistical heterogeneity between trials that was largely explained by study size and published status. Although the small studies were more likely to show benefit for hydration with sodium bicarbonate, these studies were generally of lower methodology quality. Among the larger, randomized trials there was no statistically significant difference between hydration with sodium bicarbonate and sodium chloride and no evidence of heterogeneity. Results from these trials suggest that the true clinical benefit of sodium bicarbonate hydration, if any, is likely to be small for most patients.

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Disclosures

None.

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