Annals of Internal Medicine | Review

Systematic Review: Sodium Bicarbonate Treatment Regimens for the Prevention of Contrast-Induced Nephropathy

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Background: Intravenous sodium bicarbonate has been proposed to reduce the risk for contrast-induced nephropathy (CIN).

Purpose: To determine the effect of sodium bicarbonate on the risk for CIN.

Data Sources: MEDLINE, PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials from 1950 to December 2008; conference proceedings; and ClinicalTrials.gov, without language restriction.

Study Selection: Randomized, controlled trials of intravenous sodium bicarbonate that prespecified the outcome of CIN as a 25% increase in baseline serum creatinine level or an absolute increase of 44 μmol/L (0.5 mg/dL) after radiocontrast administration.

Data Extraction: Using standardized protocols, 2 reviewers serially abstracted data for each study.

Data Synthesis: 23 published and unpublished trials with information on 3563 patients and 396 CIN events were included. The pooled relative risk was 0.62 (95% CI, 0.45 to 0.86), with evidence of significant heterogeneity across studies ($I^2 = 49.1\%$; $P = 0.004$). Some heterogeneity was due to the difference in the estimates between published and unpublished studies: relative risk, 0.43 (CI, 0.25 to 0.75) versus 0.78 (CI, 0.52 to 1.17), respectively. Meta-regression showed that small, poor-quality studies that assessed outcomes soon after radiocontrast administration were more likely to suggest benefit ($P < 0.05$ for all). No clear effects of treatment on the risk for dialysis, heart failure, and total mortality were identified.

Limitation: Power to assess clinical end points was limited.

Conclusion: The effectiveness of sodium bicarbonate treatment to prevent CIN in high-risk patients remains uncertain. Earlier reports probably overestimated the magnitude of any benefit, whereas larger, more recent trials have had neutral results. Large multicenter trials are required to clarify whether sodium bicarbonate has value for prevention of CIN before routine use can be recommended.

Primary Funding Source: None.

Ann Intern Med. 2009;151:631-638. www.annals.org
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Contrast-induced nephropathy (CIN), which is the development of acute renal failure after administration of radiocontrast in the absence of other identifiable causes, is a leading cause of hospital-acquired acute kidney injury (1). It is defined as an increase in baseline serum creatinine level of 25% or an absolute increase of 44 μmol/L (0.5 mg/dL). In addition, CIN accounts for 10% of all cases of acute kidney injury requiring hospitalization (2). In its most severe form, CIN is associated with clinically significant morbidity and mortality, including prolonged hospitalization, requirement for dialysis, and an increased risk for death (3, 4). The implementation of strategies to prevent CIN is therefore an important area of research. However, no uniform approach has been advocated, with guidelines (2) generally recommending volume expansion but giving no firm recommendation on the role of pharmacologic agents.

Contrast-induced nephropathy is rare in patients with normal kidney function; however, its incidence increases by 25% in patients with preexisting renal impairment, such as those with diabetes and congestive heart failure, and with concurrent administration of nephrotoxic agents (5). Radiocontrast agents are believed to produce nephrotoxicity through acute sustained vasoconstriction and reduced renal perfusion resulting in regional hypoxia and tubular cytotoxicity (6). To date, strategies to prevent CIN have targeted renal vasoconstriction, hypoxia-induced oxidative stress, and tubular acidification. Preprocedural intravenous hydration is routinely administered; however, the evidence to support this practice is not compelling (6). Vasodilating agents, including dopamine, fenoldopam, and theophylline, and the antioxidant *N*-acetylcysteine also have been studied. The results of these individual studies (7–9) have been heterogeneous; however, 2 meta-analyses (7, 9) exploring the efficacy of *N*-acetylcysteine and theophylline compared with hydration alone have reported an overall beneficial effect.

Recent studies and meta-analyses suggest that intravenous sodium bicarbonate may protect against CIN (10–16). This protection is thought to be conferred by alkalinization of renal tubular fluid and increased urine flow (17–19). In addition, animal models suggest that sodium bicarbonate may protect against formation of reactive oxygen species in the kidney (20). However, the potential ben-

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Context

Previous reviews suggest that sodium bicarbonate prevents contrast-induced nephropathy.

Contribution

This review of 9 published and 14 unpublished trials of sodium bicarbonate suggests that the effect of this agent has been overestimated. Unpublished trials found smaller effects than published trials, and formal testing confirmed publication bias.

Caution

Too few patients were included in the trials to determine effects on clinically relevant outcomes, such as need for dialysis.

Implication

Sodium bicarbonate is probably less effective at preventing contrast-induced nephropathy than is currently thought. Routine use of sodium bicarbonate for prevention of contrast-induced nephropathy is therefore premature.

—The Editors

efits of intravenous sodium bicarbonate have been challenged by other studies suggesting no benefit (21–23) or harm, with an increased risk for CIN compared with *N*-acetylcysteine or no treatment (24). The inconsistency between these findings highlights the need for a comprehensive systematic overview of all trials using intravenous sodium bicarbonate.

We aimed to assess the effectiveness and safety of sodium bicarbonate–based treatment regimens for the prevention of CIN and clinical outcomes and to provide a reliable estimate of the nature and strength of any treatment effect.

METHODS

Data Sources and Searches

We performed a systematic review of the available literature according to the QUORUM (Quality of Reporting of Meta-analyses) guidelines for the conduct of meta-analyses of intervention studies. We identified relevant studies through electronic searches of MEDLINE via Ovid, PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials from 1950 through December 2008. We used relevant text words and Medical Subject Heading terms that included all spellings of *contrast media* combined with *nephropathy*, *renal insufficiency*, *nephritis*, and *nephrotoxicity* (**Appendix**, available at www.annals.org). We limited the search to clinical trials but did not restrict by language. To identify other relevant studies, we manually scanned reference lists from identified trials and review articles (11, 13–15), and we also searched ClinicalTrials.gov and conference proceedings. We requested original data by directly contacting authors or principal investigators.

Study Selection

Two authors independently conducted the literature search, data extraction, and quality assessment by using a standardized approach. All completed randomized, controlled trials assessing preventive strategies for CIN that included intravenous sodium bicarbonate in 1 of the treatment groups were eligible for inclusion. We defined CIN as a 25% increase in baseline serum creatinine level or an absolute increase of 44 μmol/L (0.5 mg/dL) 2 to 5 days after radiocontrast administration. We excluded studies with participants younger than 18 years. We did not restrict eligibility according to kidney function.

Data Extraction and Quality Assessment

Extracted data included patient characteristics (mean age, sex distribution, diabetes or hypertension status, and mean baseline creatinine level); type of imaging; inclusion and exclusion criteria; type and dose of contrast media; periprocedural hydration protocol; specific definition of CIN; treatment dose; serum creatinine level after radiocontrast injection; and the outcomes of requirement for dialysis, heart failure, and death. Quality assessment was judged on concealment of treatment allocation; similarity of both groups at baseline regarding prognostic factors; eligibility criteria; blinding of outcome assessors, care providers, and patients; completeness of follow-up; and intention-to-treat analysis (25). We quantified study quality by using the Jadad score (26). A third reviewer adjudicated any disagreement about abstracted data.

Data Synthesis and Analysis

We calculated relative risks and 95% CIs for individual studies before pooling data. We obtained summary estimates of overall and subgroup relative risk ratios by using a random-effects model. When either or both treatment groups of a study had no events, we added the reciprocal of the size of the opposite treatment group to each cell of the 2×2 table as a continuity correction factor (27). We also conducted sensitivity analyses by using continuity correction constants of various sizes (for example, 0.0001, 0.001, and 0.01) to ensure that the findings were robust. We estimated the percentage of variability across studies attributable to heterogeneity beyond chance by using the I^2 statistic (28). Publication bias was assessed by using the Egger test and represented graphically by using Begg funnel plots of the natural log of the relative risk versus its standard error (29). We explored potential heterogeneity in estimates of treatment effect attributable to each quality criterion for published studies only by using univariate meta-regression (28). We considered a P value less than 0.05 to be statistically significant for all analyses. We performed all statistical analyses with STATA, version 9.2 (Stata, College Station, Texas).

Role of the Funding Source

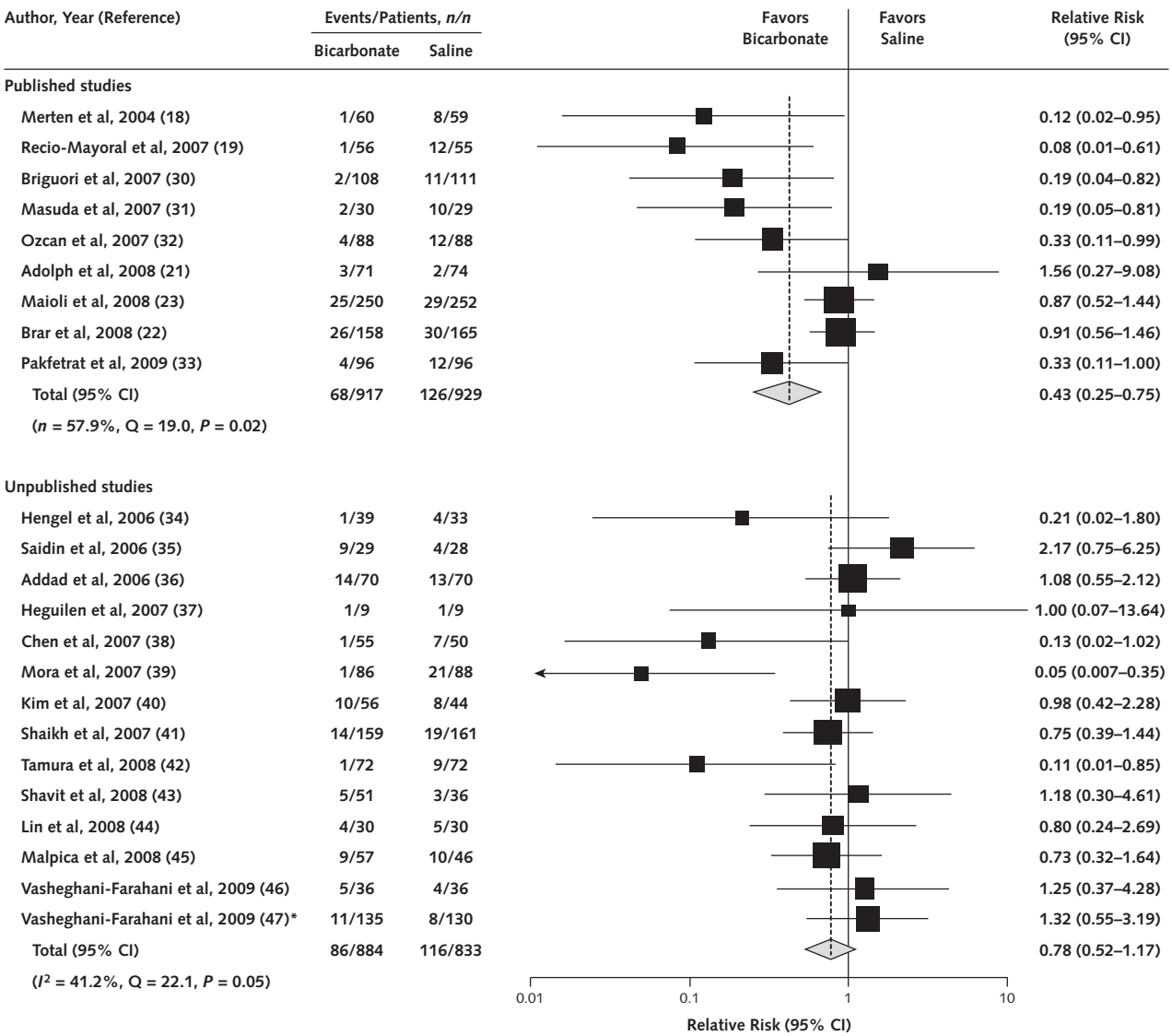
This study did not receive funding. The corresponding author, on behalf of all authors, had full access to all data in the study and had final responsibility for the decision to submit the manuscript for publication.

Results

Literature Search and Study Characteristics

The literature search yielded 1231 articles, of which 163 were reviewed in full text on the basis of our inclusion criteria (**Appendix Figure 1**, available at www.annals.org). Of these, 23 studies (including information on 3563 participants and 396 CIN events) were eligible for inclusion (**Figure 1**): 14 studies were not yet published in peer-reviewed journals but were presented at scientific sessions and reported in abstract form in conference proceedings or obtained directly from the investigators. **Appendix Table 1** (available at www.annals.org) summarizes the characteristics of the included studies, all of which were reported since 2004. Sample size ranged from 18 to 502 participants, and total events accrued ranged from 2 to 56. Eight studies were performed in the Americas; 5 in Asia; 4 in Europe; 3 in Iran; and 1 each in Israel, Turkey, and Tunisia. Only 2 studies included patients with normal renal function; therefore, separate evaluation of patients according to baseline renal function was not possible. Mean baseline serum creatinine level ranged from 71 to 177 μmol/L (0.8 to 2.0 mg/dL). Seventeen studies evaluated patients

Figure 1. **Forest plot of relative risks for contrast-induced nephropathy from 23 studies.**



* This study has been published since we did our review.

having cardiac catheterization, 5 studies evaluated patients having either cardiac catheterization or scheduled computed tomography or other arteriography, and 1 study evaluated patients having scheduled computed tomography or other arteriography. Ten studies compared sodium bicarbonate with sodium chloride; 8 studies compared sodium bicarbonate and *N*-acetylcysteine with sodium chloride and *N*-acetylcysteine; 2 studies compared sodium bicarbonate with and without *N*-acetylcysteine versus sodium chloride with and without *N*-acetylcysteine; and 1 study each compared sodium bicarbonate versus sodium chloride with *N*-acetylcysteine, sodium bicarbonate with and without *N*-acetylcysteine versus sodium chloride with *N*-acetylcysteine, and sodium bicarbonate with oral acetazolamide versus sodium chloride alone. The sodium bicarbonate and hydration protocols varied among the studies and treatment groups (**Appendix Table 1**). The average age of the participants in all studies was older than 48 years, and the proportion of men ranged from 59% to 84%. All studies included participants with diabetes (range, 24% to 58%), and 4 studies excluded persons with uncontrolled hypertension. The mean amount of radiocontrast media given (nonionic in 18 studies, ionic in 3 studies, and not specified in 2 studies) ranged from 65 to 285 mL. The outcome measure of CIN, reported in all studies, was determined according to change in serum creatinine level from baseline to 48 hours in 11 studies, to 72 hours in 7 studies, within 4 to 5 days in 4 studies, and was not specified in 1 study. The overall incidence of CIN varied from 3.4% to 20.3%. Few studies described concealment of allocation; blinding of outcome assessors, care providers, or patients; or intention-to-treat analysis (**Appendix Table 2**, available at www.annals.org).

Effect of Sodium Bicarbonate Treatment on CIN

The overall summary estimate from both published and unpublished data for the effect of sodium bicarbonate on the risk for CIN was 0.62 (95% CI, 0.45 to 0.86) compared with saline-based control regimens. We found evidence of significant heterogeneity ($I^2 = 49.1\%$; $P = 0.004$), which was due in part to differences in treatment effect reported by published studies (relative risk, 0.43 [CI, 0.25 to 0.75]) and unpublished studies (relative risk, 0.78 [CI, 0.52 to 1.17]). Formal statistical testing confirmed the presence of publication bias (Egger test $P = 0.009$) (**Appendix Figure 2**, available at www.annals.org). After pooling the studies according to their publication status (published versus unpublished), we found that significant heterogeneity remained across the studies (**Figure 1**). We examined possible sources of underlying heterogeneity in the published estimates by using meta-regression (**Appendix Table 3**, available at www.annals.org). Greater estimates of effect were typically reported in studies that were published before 2008; had fewer events and study participants; had measured CIN within 48 hours of an event; and were of low quality, as defined by lack of allocation concealment or Jadad score less than 3 (**Figure 2**).

Effect of Coadministration of *N*-Acetylcysteine on CIN

Among the 9 published trials, 4 studies, which included information on 983 patients, compared sodium bicarbonate–based treatment plus *N*-acetylcysteine versus standard therapy. No evidence suggested a difference in the effect achieved with sodium bicarbonate–based treatment that did or did not include *N*-acetylcysteine (P for heterogeneity = 0.73).

Effect of Sodium Bicarbonate Treatment on Requirement of Dialysis, Heart Failure, and Total Mortality

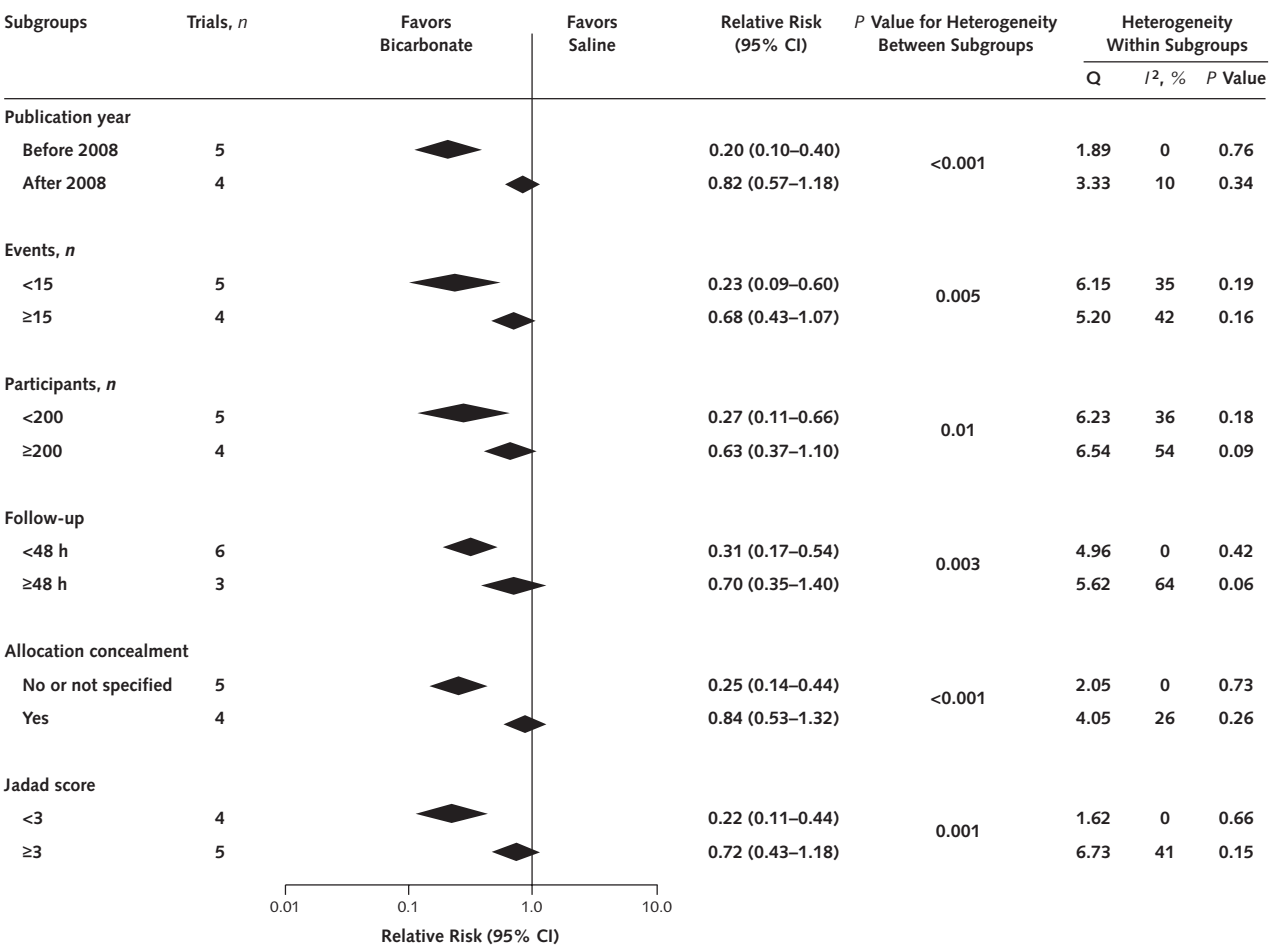
No beneficial or harmful effects of sodium bicarbonate treatment were detected on the risk for requirement of dialysis, heart failure, and total mortality (**Figure 3**), although few total events occurred (18 for requirement of dialysis, 25 for heart failure, and 20 for total mortality), resulting in limited statistical power for these end points. Findings from sensitivity analyses using continuity correction constants of various sizes to account for zero observed events were unchanged (data not shown).

DISCUSSION

In our comprehensive meta-analysis, which included data from all available published and unpublished studies involving 3563 patients total, we did not find clear evidence of overall benefit associated with the use of sodium bicarbonate to prevent CIN. We observed a substantial discrepancy between the summary estimates for published and unpublished studies, suggesting that the beneficial effects reported in earlier reviews may have been largely generated by reporting or publication bias. For this reason, as well as the poor methodological quality of many of the included studies, a large, well-designed, multicenter randomized, controlled trial to definitively address whether the use of sodium bicarbonate is effective at preventing CIN is warranted. Until such evidence is available, the routine use of sodium bicarbonate as prophylaxis for CIN is of uncertain value.

Although the summary estimate of all published trials indicated that sodium bicarbonate significantly reduced the risk for CIN by approximately half, this result was predominantly driven by findings from the smaller, poorer-quality (and therefore potentially less reliable) trials. Of the published trials, the most notable difference between the 6 positive studies and the 3 negative studies was their sample size: The positive studies were all relatively small, whereas 2 of the negative studies were much larger. For example, studies that typically had fewer than 15 events had a combined estimate that indicated a 75% lower risk compared with only a 20% lower risk in the 3 largest trials. The presence of publication bias, in which small studies are more likely to be published if they describe positive or more extreme results, was supported by formal testing (48).

Figure 2. **Subgroup analysis of possible sources of heterogeneity across the published studies.**

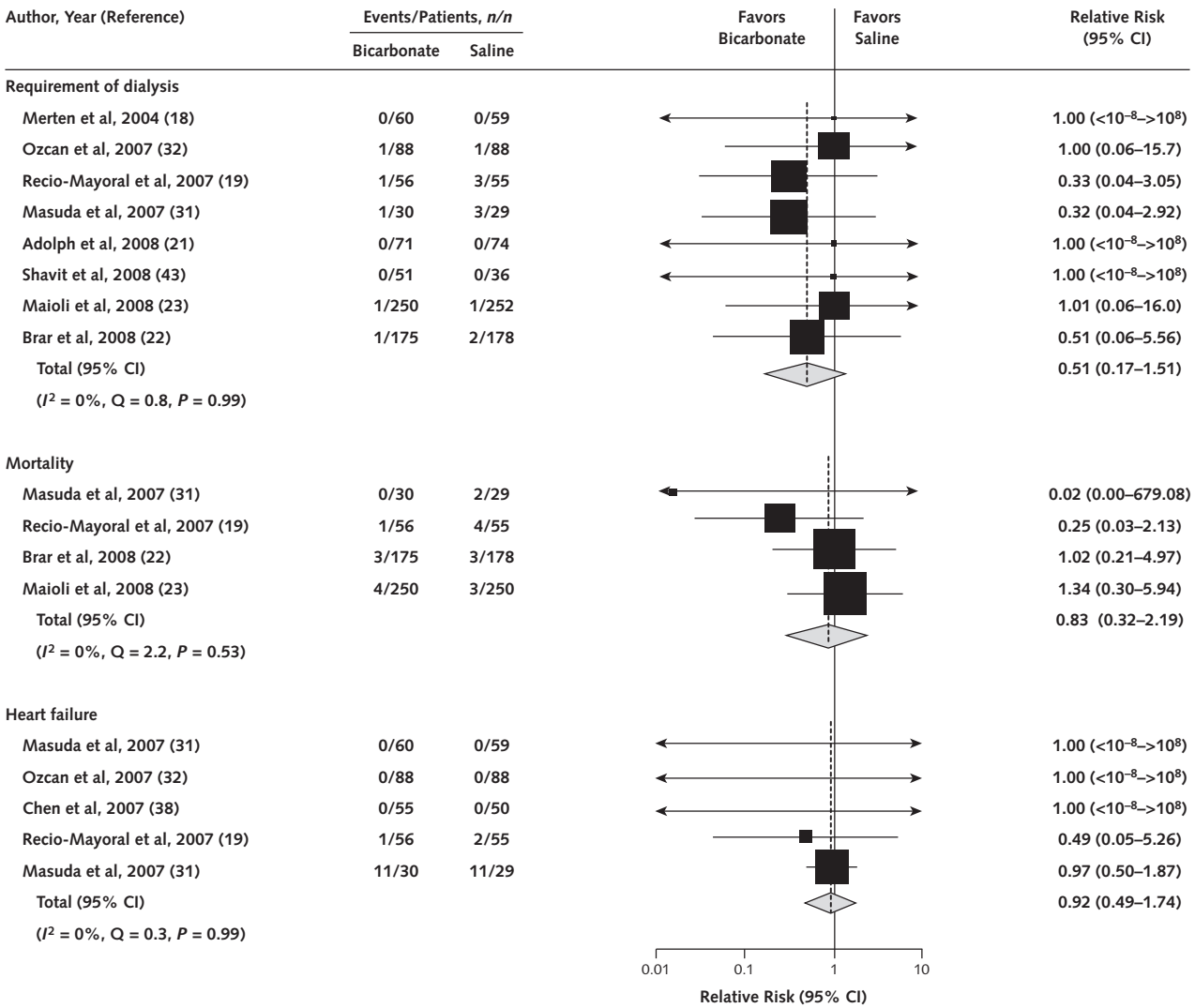


Further evidence of publication bias is provided by the identification of an additional 10 negative trials (35–37, 40, 41, 43–47) that were reported in conference proceedings or obtained by direct communication with the authors but have not yet been published.

A further consideration when determining whether evidence to support the use of this treatment is sufficiently robust was the presence of significant between-study heterogeneity in effect size. Much of the heterogeneity was due to differences in study sample size and event numbers; however, using meta-regression, 2 other factors explained the heterogeneity in the between-study effects of the published studies: study quality, quantified by the Jadad score or categorized by the presence or absence of allocation concealment, and timing of outcome measurement. The 6 positive studies all measured the primary outcome (change in serum creatinine level) earlier after radiocontrast administration (within 3 days) than the 3 negative studies (within 5 days). It is therefore possible that the routine administration of sodium bicarbonate delayed the onset of CIN, which suggests benefit in the trials that assessed outcomes earlier but not in those that assessed outcomes later. This is probable if sodium bicarbonate therapy is shown by mechanistic studies to suppress production or excretion of creatinine, as some suggest (11). In addition, our data support and extend concerns regarding the increasing reliance of clinical trials on powering studies on the basis of transitory, surrogate primary outcomes, such as change in serum creatinine levels, rather than patient-centered outcomes (9, 12). Increases in serum creatinine level have been demonstrated in hospitalized patients who were not exposed to radiocontrast media (49). In comparison, estimates from the unpublished studies (which, when combined, did not demonstrate a beneficial effect of treatment) were more homogeneous.

Our data do not support the recent notion that studies have not shown treatment effects because of inclusion of low-risk patients. Neither baseline renal function nor inclusion of more patients with diabetes was found to contribute to the between-study heterogeneity. In addition, when studies that used *N*-acetylcysteine were compared with those that did not, no treatment-modifying effects were evident.

Figure 3. **Forest plots of relative risks for adverse clinical events.**



We also assessed the effect of sodium bicarbonate treatment on the major clinical end points of requirement for dialysis, heart failure, and total mortality. In these analyses, no clear evidence for benefit or harm was demonstrated; however, few events occurred, resulting in low study power to detect a difference. It should be noted that none of the studies were specifically designed or powered to investigate these outcomes. The effect of treatment on hard clinical end points needs to be determined. Our findings indicate the need for further large, well-designed trials that examine all relevant clinical outcomes.

The strengths of our analysis include its rigorous methodology; systematic examination of potential sources of heterogeneity; and inclusion of all data, including those from unpublished studies. The limitations include persisting uncertainty that our search uncovered all unpublished studies, although we believe that our search was more comprehensive and therefore more complete than previous meta-analyses on this subject (10–16). Also, relatively few clinical events were reported in the trials, resulting in limited statistical power for detecting the effects on these more clinically significant key outcomes. Our attempts to understand the heterogeneity of the study findings were limited by reliance on published results, because we did not have access to the original study data sets from the unpublished studies. Most of the published trials in our analysis performed poorly on formal quality assessment based on their reports, providing an additional rationale for a circumspect approach to implementation of their findings. In this regard, the reliance of quality assessment on specific study components and unvalidated summary scores should be noted, because these approaches may not adequately represent the true quality of the studies included. Finally, more studies are re-

quired to be able to assess the contribution of different hydration protocols.

In summary, evidence from this review suggests that the reported benefits associated with the use of sodium bicarbonate for the prevention of CIN in high-risk patients may have been overestimated. The discrepancy between published and unpublished estimates is sufficiently large to merit caution in the use of this treatment in preventing CIN until sufficient large-scale randomized evidence supports its use. On the basis of current data, routine implementation of this treatment seems premature.

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Grant Support: Dr. Zoungas was supported by a National Health and Medical Research Council of Australia Health Professional Research Fellowship. Dr. Perkovic was supported by a National Heart Foundation of Australia AstraZeneca research fellowship. Dr. Cass was supported by a National Health and Medical Research Council of Australia Senior Research Fellowship. Drs. Huxley and Patel are supported by National Heart Foundation of Australia Career Development awards.

Potential Conflicts of Interest: None disclosed.

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Administrative, technical, or logistic support: V. Perkovic, T. Ninomiya.
Collection and assembly of data: S. Zoungas, T. Ninomiya.

Appendix: Search Strategy

MEDLINE (Ovid)

1. exp contrast media/
2. (contrast media or contrast medium or contrast dye or radiographic contrast).tw.
3. (radiocontrast media or radiocontrast medium).tw.
4. contrast agent$.tw.
5. or/#1-4
6. exp nephritis/
7. exp Renal Insufficiency/
8. exp diabetic nephropathies/
9. (nephritis or nephropath$ or nephrotoxic$).tw.
10. ((impair$ or damag$ or reduc$) adj2 (renal or kidney)).tw.
11. or/#6-10
12. #5 and #11
13. (contrast-induced nephr$ or contrast-associated nephr$).tw.
14. #12 or #13
15. exp Clinical Trial/
16. exp Random Allocation/
17. exp Single Blind Method/
18. exp Double Blind Method/
19. (random$ adj5 trial$).tw.
20. (random$ adj5 allocation$).tw.
21. (Blind$ adj5 method$).tw.
22. or/#15-21
23. #14 and #22

PubMed

1. "Contrast Media" [MeSH]
2. Contrast medium
3. Contrast media
4. contrast dye
5. radiographic contrast
6. radiocontrast media
7. radiocontrast medium
8. contrast agent
9. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
10. "Renal Insufficiency" [MeSH]
11. "Diabetic Nephropathies" [MeSH]
12. "Nephritis" [MeSH]
13. nephritis
14. nephropathy
15. nephrotoxic
16. (impair or damage or reduce) and (renal or kidney)
17. contrast-induced nephropathy
18. contrast-associated nephropathy
19. #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18
20. #9 and #19
21. "Clinical Trial" [Publication Type]
22. "Random Allocation" [MeSH]
23. "Single-Blind Method" [MeSH]
24. "Double-Blind Method" [MeSH]
25. #21 or #22 or #23 or #24
26. #20 and #25

EMBASE

i. 'contrast'/exp and media
ii. 'contrast'/exp and medium
iii. 'contrast'/exp and 'dye'/exp
iv. radiographic and 'contrast'/exp
v. radiocontrast and media
vi. radiocontrast and medium
vii. 'contrast'/exp and agent
viii. #1 or #2 or #3 or #4 or #5 or #6 or #7
ix. renal and insufficiency
x. 'diabetic'/exp and nephropathies
xi. 'nephritis'/exp
xii. 'nephropathy'/exp
xiii. 'nephrotoxic
xiv. (impair or damage or reduce) and (renal or 'kidney'/exp)
xv. 'contrast induced' and 'nephropathy'/exp
xvi. 'contrast associated' and 'nephropathy'/exp
xvii. #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16
xviii. #8 and #17
xix. clinical and trial
xx. randomized and controlled and trial
xxi. random and allocation
xxii. 'single blind' and ('method'/exp or 'method')
xxiii. 'double blind' ('method'/exp or 'method')
xxiv. #19 or #20 or #21 or #22 or #23
xxv. #18 and #24

Cochrane Central Register of Controlled Trials

Contrast Media explode all trees (MeSH)

(contrast media or contrast medium or contrast dye or radiographic contrast or radiocontrast media or radiocontrast medium or contrast agent)

Renal Insufficiency explode all trees (MeSH)

Diabetic Nephropathies explode all trees (MeSH)

Nephritis explode all trees (MeSH)

(nephritis or nephropathy or nephrotoxic or contrast-induced nephropathy or contrast-associated nephropathy)

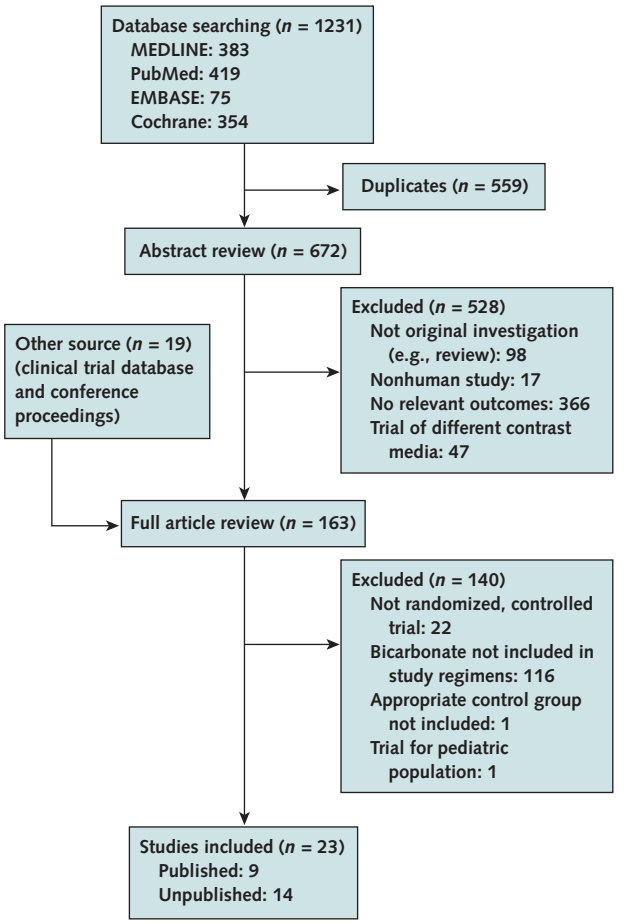
(impair or damage or reduce) and (renal or kidney)

(#1 or #2)

(#3 or #4 or #5 or #6 or #7)

(#8 and #9)

Appendix Figure 1. **Literature search and selection.**



Appendix Table 1. **Studies Reporting the Use of Sodium Bicarbonate to Prevent Contrast-Induced Nephropathy**

Author, Year (Reference)	Patients, *n*	Events, *n*	Inclusion Criteria	Sodium Bicarbonate Protocol	Control
Published trials					
Merten et al, 2004 (18)	119	9	Angiography or CT; stable sCr >97.2 μmol/L (>1.1 mg/dL)	$NaHCO_3$, 154 mEq/L in D_5W	NaCl, 154 mEq/L
Recio-Mayoral et al, 2007 (19)	111	13	Emergency CAG or PTCA	$NaHCO_3$, 154 mEq/L in D_5W + NAC, 2400 mg, before procedure; $NaHCO_3$, 154 mEq/L in D_5W + NAC, 600 mg, twice after procedure	NaCl, 154 mEq/L + NAC, 600 mg, twice after procedure
Briguori et al, 2007 (30)	219	13	Angiography or angioplasty; stable sCr >176.8 μmol/L (>2.0 mg/dL) or eGFR <40 mL/min per 1.73 m^2	$NaHCO_3$, 154 mEq/L in D_5W + NAC, 1200 mg, twice daily for 2 d	NaCl, 154 mEq/L + NAC, 1200 mg, twice daily for 2 d
Masuda et al, 2007 (31)	59	12	Emergency CAG or PTCA; stable sCr >97.2 μmol/L (>1.1 mg/dL) or eGFR <60 mL/min per 1.73 m^2	$NaHCO_3$, 154 mEq/L in D_5W	NaCl, 154 mEq/L
Ozcan et al, 2007 (32)	176	16	Scheduled CAG or PTCA; stable sCr >106.1 μmol/L (>1.2 mg/dL)	$NaHCO_3$, 154 mEq/L in D_5W	NaCl, 154 mEq/L
Adolph et al, 2008 (21)	145	5	CAG or PTCA; stable sCr >106.1 μmol/L (>1.2 mg/dL) or eGFR <63 mL/min per 1.73 m^2	$NaHCO_3$, 154 mEq/L in D_5W	NaCl, 154 mEq/L
Maioli et al, 2008 (23)	502	54	Scheduled CAG; eGFR <60 mL/min per 1.73 m^2	$NaHCO_3$, 154 mEq/L in D_5W + NAC, 600 mg, twice daily for 2 d	NaCl, 154 mEq/L + NAC, 600 mg, twice daily for 2 d
Brar et al, 2008 (22)	323	56	CAG; stable eGFR ≤60 mL/min per 1.73 m^2 and at least 1 of diabetes, congestive heart failure, hypertension, or age >75 y	$NaHCO_3$, 150 mEq/L in D_5W ± NAC, 600 mg, twice daily for 2 d	NaCl, 154 mEq/L ± NAC, 600 mg, twice daily for 2 d
Pakfetrat et al, 2009 (33)	192	16	Scheduled angiography or angioplasty	$NaHCO_3$, 154 mEq/L in D_5W	NaCl, 154 mEq/L
Unpublished trials					
Hengel et al, 2006 (34)	72	5	Emergency or scheduled CAG or PTCA; stable sCr >132.6 μmol/L (>1.5 mg/dL) or eGFR <60 mL/min per 1.73 m^2	$NaHCO_3$, 154 mEq/L in D_5W	NaCl, 154 mEq/L
Saidin et al, 2006 (35)	57	13	CAG or PTCA; CKD stage 2–4	$NaHCO_3$ + NAC	NaCl + NAC
Addad et al, 2006 (36)	140	27	CAG or PTCA	$NaHCO_3$ + NAC	NaCl + NAC
Heguilen et al, 2007 (37)	18	2	CAG or PTCA; stable sCr >110.5 μmol/L (>1.25 mg/dL) or eGFR <50 mL/min per 1.73 m^2	$NaHCO_3$, 154 mEq/L + NAC, 600 mg, twice daily for 2 d	NaCl, 154 mEq/L + NAC, 600 mg, twice daily for 2 d
Chen et al, 2007 (38)	105	8	CAG or renal angiography; eGFR <60 mL/min per 1.73 m^2	$NaHCO_3$, 150 mEq/L	NaCl, 154 mEq/L
Mora et al, 2007 (39)	174	22	CT or IVP; stable sCr of 132.6–221 μmol/L (1.5–2.5 mg/dL), or eGFR of 30–60 mL/min per 1.73 m^2	$NaHCO_3$, 154 mEq/L	NaCl, 154 mEq/L
Kim et al, 2007 (40)	100	18	CAG; sCr ≥132.6 μmol/L (≥1.5 mg/dL), proteinuria ≥0.5 g/d, or diabetes	$NaHCO_3$, 80 mEq/L ± NAC, 600 mg, twice daily for 2 d	NaCl, 154 mEq/L ± NAC, 600 mg, twice daily for 2 d
Shaikh et al, 2007 (41)	320	33	Scheduled angiography; renal insufficiency	$NaHCO_3$, 154 mEq/L ± NAC, 1200 mg, twice daily for 2 d	NaCl, 154 mEq/L ± NAC, 1200 mg, twice daily for 2 d
Tamura et al, 2008 (42)	144	10	Scheduled CAG or PTCA	$NaHCO_3$	NaCl, 154 mEq/L
Shavit et al, 2008 (43)	87	8	CAG; eGFR, 15–60 mL/min per 1.73 m^2	$NaHCO_3$, 154 mEq/L	NaCl, 154 mEq/L + NAC, 1200 mg, twice daily for 2 d
Lin et al, 2008 (44)	60	9	Scheduled radiocontrast; sCr ≤176.8 μmol/L (≤2.0 mg/dL)	$NaHCO_3$, 154 mEq/L + NAC, 600 mg, twice daily for 2 d	NaCl, 154 mEq/L + NAC, 600 mg, twice daily for 2 d
Malpica et al, 2008 (45)	103	19	CAG or PTCA	$NaHCO_3$	NaCl, 154 mEq/L
Vasheghani-Farahani et al, 2009 (46)	72	9	Scheduled CAG; stable sCr >132.6 μmol/L (>1.5 mg/dL) and at least 1 of uncontrolled hypertension, compensated severe heart failure, or history of pulmonary edema	$NaHCO_3$, 141.4 mEq/L in solution	NaCl, 77 mEq/L
Vasheghani-Farahani et al, 2009 (47)*	265	19	Scheduled CAG; stable sCr >132.6 μmol/L (>1.5 mg/dL)	$NaHCO_3$, 212.9 mEq/L in solution	NaCl, 154 mEq/L

CAG = coronary angiography; CKD = chronic kidney disease; CT = computed tomography; D_5W = 5% dextrose in water; eGFR = estimated glomerular filtration rate; IVP = intravenous pyelography; NAC = *N*-acetylcysteine; PTCA = percutaneous transluminal coronary angioplasty; sCr = serum creatinine.
*This study has been published since we did our review.

Appendix Table 1—**Continued**

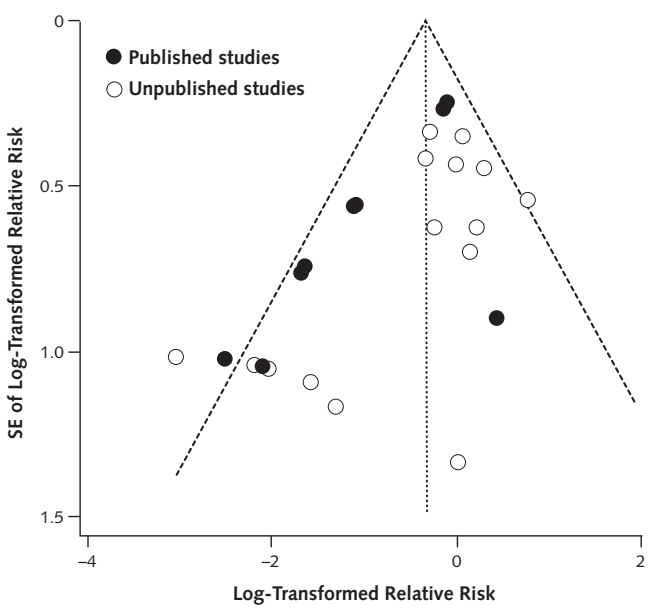
Hydration Procedure	Outcomes	Mean Age, *y*	Mean Contrast Volume, *mL*	Mean Baseline sCr Level, *μmol/L (mg/dL)*	Diabetic Patients, %
3 mL/kg per h for 1 h before procedure and 1 mL/kg per h for 6 h after	Increase of sCr >25% within 2 days	68	132	160 (1.8)	48
$NaHCO_3$, 5 mL/kg per h, for 1 h before procedure and 1.5 mL/kg per h for 12 h after; NaCl, 1 mL/kg per h, for 12 h after	Increase of sCr >44 μmol/L (0.5 mg/dL) within 3 d	65	285	88.4 (1.0)	30
$NaHCO_3$, 3 mL/kg per h, for 1 h before procedure and 1 mL/kg per h for 6 h after; NaCl, 1 mL/kg per h, for 12 h before and after procedure	Increase of sCr >25% within 2 d or need for dialysis	71	174	177 (2.0)	52
3 mL/kg per h for 1 h before procedure and 1 mL/kg per h for 6 h after	Increase of sCr >25% or 44 μmol/L (0.5 mg/dL) within 2 d	75	116	115 (1.3)	31
1 mL/kg per h for 6 h before and after procedure	Increase of sCr >25% or 44 μmol/L (0.5 mg/dL) within 2 d	69	110	124 (1.4)	45
2 mL/kg per h for 2 h before procedure and 1 mL/kg per h for 6 h after	Increase of sCr >25% or 44 μmol/L (0.5 mg/dL) within 2 d	71	139	141 (1.6)	24
$NaHCO_3$, 3 mL/kg per h, for 1 h before procedure and 1 mL/kg per h for 6 h after; NaCl, 1 mL/kg per h, for 12 h before and after procedure	Increase of sCr >25% within 5 d	74	165	106 (1.2)	24
3 mL/kg per h for 1 h before procedure and 1.5 mL/kg per h for 4 h after	Increase of sCr >25% within 4 d or decrease of eGFR >25%	71	132	133 (1.5)	44
3 mL/kg per h for 1 h before procedure and 1 mL/kg per h for 6 h after	Increase of sCr 132.6 μmol/L (1.5 mg/dL) within 2 d or decrease of eGFR >25%	58	63	97 (1.1)	30
3 mL/kg per h for 1 h before procedure and 1 mL/kg per h for 6 h after	Increase of sCr >25% or 44 μmol/L (0.5 mg/dL) within 3 d	–	152	–	–
–	Increase of sCr >25% within 3 d	62	–	–	–
–	Increase of sCr >25% within 2 d	62	–	–	–
3 mL/kg per h for 1 h before procedure and 1 mL/kg per h for 6 h after	Increase of sCr >25% within 3 d	67	–	–	–
2 mL/kg per h for 6 h before procedure and 80 mL/kg per h for 6 h after	Increase of sCr >25% or 44 μmol/L (0.5 mg/dL) within 3 d	71	–	–	36
3 mL/kg per h for 1 h before procedure and 1 mL/kg per h for 6 h after	Increase of sCr >25% or 44 μmol/L (0.5 mg/dL) within 2 d	62	–	160 (1.8)	–
1 mL/kg per h for 12 h before and after procedure	Increase of sCr >25% within 2 d	–	–	97 (1.1)	–
3 mL/kg per h for 1 h before procedure and 1 mL/kg per h for 6 h after	Increase of sCr >25% or 44 μmol/L (0.5 mg/dL) within 2 d	71	119	160 (1.8)	47
–	Increase of sCr >25% or 44 μmol/L (0.5 mg/dL) within 3 d	73	85	124 (1.4)	58
$NaHCO_3$, 3 mL/kg per h, for 1 h before procedure and 1 mL/kg per h for 6 h after; NaCl, 1 mL/kg per h, for 12 h before procedure	Increase of sCr >25% within 2 d	–	–	160 (1.8)	–
3 mL/kg per h for 1 h before procedure and 3 mL/kg per h for 6 h after	Increase of sCr >25% within 3 d	48	–	71 (0.8)	25
–	–	–	–	–	–
3 mL/kg per h for 1 h before procedure and 1 mL/kg per h for 6 h after	Increase of sCr >25% or 44 μmol/L (0.5 mg/dL) within 5 d	62	118	141 (1.6)	36
3 mL/kg per h for 1 h before procedure and 1 mL/kg per h for 6 h after	Increase of sCr >25% or 44 μmol/L (0.5 mg/dL) within 5 d	63	114	141 (1.6)	26

Appendix Table 2. **Quality of Published Studies Reporting Use of Sodium Bicarbonate to Prevent Contrast-Induced Nephropathy**

Author, Year (Reference)	Jadad Score	Allocation Concealment	Similarity of Baseline Characteristics	Eligibility Criteria	Blinding			Completeness of Follow-up	Intention-to-Treat Analysis
					Outcome Assessor	Care Provider	Patient		
Merten et al, 2004 (18)	3	Yes	Yes	Yes	Yes	No	Yes	Yes	No
Recio-Mayoral et al, 2007 (19)	1	NS	Yes	Yes	No	No	Yes	Yes	Yes
Briguori et al, 2007 (30)	1	NS	Yes	Yes	Yes	No	Yes	Yes	No
Masuda et al, 2007 (31)	1	NS	Yes	Yes	No	No	No	Yes	No
Ozcan et al, 2007 (32)	0	NS	Yes	Yes	NS	NS	NS	NS	NS
Adolph et al, 2008 (21)	5	Yes	Yes	Yes	NS	Yes	Yes	Yes	No
Maioli et al, 2008 (23)	3	Yes	Yes	Yes	No	No	No	Yes	Yes
Brar et al, 2008 (22)	3	Yes	Yes	Yes	Yes	No	Yes	Yes	No
Pakfetrat et al, 2009 (33)	4	NS	Yes	Yes	NS	Yes	Yes	Yes*	Yes*

NS = not specified or available.
* The data comparing sodium bicarbonate with saline were used for the analysis.

Appendix Figure 2. **Funnel plot with pseudo 95% CIs to assess for evidence of publication bias.**



Appendix Table 3. **Univariate Meta-regression Analysis of Possible Sources of Heterogeneity Across the Published Studies**

Possible Source of Heterogeneity	Scale	Studies, *n*	Proportional Change of Risk Ratio (95% CI)*	*P* Value
Published year	Per 1-y increment	9	1.58 (0.98 to 2.55)	0.06
Number of patients	Per 100-patient increment	9	1.42 (1.09 to 1.85)	0.009
Number of events	Per 10-event increment	9	1.31 (1.12 to 1.52)	<0.001
N-acetylcysteine†	Yes or no	9	1.38 (0.50 to 3.77)	0.53
Mean age	Per 1-y increment	9	1.06 (0.94 to 1.18)	0.34
Mean serum creatinine	Per 1-mg/dL increment	9	0.84 (0.09 to 7.67)	0.87
Proportion with diabetes	Per 1% increment	9	0.97 (0.92 to 1.03)	0.36
Days of follow-up for primary end point	Per 1-d increment	9	1.48 (1.15 to 1.90)	0.002
Dose of contrast media	Per 10-mL increment	9	0.96 (0.85 to 1.09)	0.51
Intention-to-treat analysis	Yes or no (or not specified)	9	1.02 (0.28 to 3.65)	0.98
Allocation concealment	Yes or no (or not specified)	9	3.50 (1.78 to 6.91)	<0.001
Jadad score	Per 1-score point increment	9	1.41 (1.00 to 1.99)	0.04

* Results were presented with exponentiated regression coefficients and their 95% CIs for every 1-scale increase between each factor as relative risk for treatment with sodium bicarbonate on contrast-induced nephropathy, with values >1.0 indicating less effectiveness of the sodium bicarbonate regimens.
† One study (Brar et al, 2008 [22]) reported risk estimates both for patients who were receiving *N*-acetylcysteine and those who were not.