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Sodium bicarbonate for prevention of contrast-induced acute kidney injury: a systematic review and meta-analysis

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Abstract

Background. There have been conflicting reports on the use of intravenous administration of sodium bicarbonate for prevention of contrast-induced acute kidney injury (CI-AKI). The aim of this study was to evaluate the use of sodium bicarbonate for prevention of CI-AKI.

Methods. This is a symptomatic review and meta-analysis of prospectively randomized studies, abstracts and manuscripts, published from 1950 to 20 February 2009.

Results. Of 192 identified publications, 18 studies (n = 3055) were included. Nine studies were only published as an abstract. CI-AKI occurred in 11.6%. Six prospective studies demonstrated that intervention with sodium bicarbonate resulted in a decreased risk of CI-AKI. The aggregate result of the prospective trials also demonstrated a benefit favouring sodium bicarbonate (RR = 0.66, 95% CI = 0.45–0.95). This effect was most prominent in coronary procedures and in patients with chronic kidney disease. There was no effect on need for renal replacement therapy (RRT) and mortality. Published manuscripts demonstrated a beneficial effect, while abstracts could not. Also, funnel plot analysis suggested a publication bias. In addition, we found significant clinical and statistical heterogeneity between studies. Finally, the quality of the individual studies was limited.

Conclusions. The incidence of CI-AKI was higher than recently reported, and varied among study cohorts. We found a preventive effect of the use of sodium bicarbonate on the risk for CI-AKI, however, with borderline statistical significance. There was no effect on need for RRT or mortality. The relative low quality of the individual studies, heterogeneity and possible publication bias means that only a limited recommendation can be made in favour of the use of sodium bicarbonate.

Keywords: acute coronary syndromes; acute kidney injury; contrast-induced nephropathy; meta-analysis; systematic review

Introduction

Contrast-induced acute kidney injury (CI-AKI) poses an important health issue, as it is common and associated with a major impact on outcome. The reported incidence may vary among studies as a consequence of the use of different definitions for CI-AKI and differences in case mix [1]. Nash *et al*. found that CI-AKI was the third most frequent aetiology of hospital-acquired AKI, accounting for 11% of all cases [2]. CI-AKI defined as a 25% or greater increase of serum creatinine may have an incidence in patients undergoing coronary angiography as high as 15% [3]. In addition, CI-AKI has been associated with an increased length of hospital stay and mortality, even after correction for various covariates [4]. Levy *et al*. found that patients with CI-AKI, again using the same definition of a 25% increase of serum creatinine, had a hospital mortality of 34% compared to 7% in patients without CI-AKI. After adjustment for comorbidity, CI-AKI still exhibited an odds ratio of 5.5 for hospital mortality [4]. A number of other studies have confirmed the association between CI-AKI, increased length of hospital stay, and in-hospital mortality and 1–5 year mortality [3,5–7]. Several strategies, including pharmacologic interventions, volume therapy and choice of contrast media, have been evaluated for prevention of CI-AKI. These strategies have been extensively evaluated in meta-analyses, reviews and consensus statements [8–13]. Intravenous administration of sodium bicarbonate prevented the development of CI-AKI in a relatively small prospective randomized controlled single-centre trial [14]. A large retrospective analysis on 11516 contrast exposures in 7977 patients in the Mayo Clinic Rochester could not confirm the initial findings of a protective effect of sodium bicarbonate, and found in fact an increased incidence of CI-AKI associated with the administration of sodium bicarbonate [15]. This led the authors of this study to the recommendation that the use of sodium bicarbonate for prevention of CI-AKI should be evaluated further before adoption into clinical practice [15].

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In the present manuscript, we present a systematic review and meta-analysis on the use of sodium bicarbonate for prevention of CI-AKI in patients undergoing intravascular iodinated contrast-enhanced radiography procedures. Sub-analyses include the effects of this therapy in patients who underwent elective and emergency coronary procedures and in high-risk patients such as those with diabetes mellitus or chronic kidney disease (CKD). Secondary endpoints are the need for renal replacement therapy (RRT) and in-hospital mortality.

Subjects and methods

Search strategy

A literature search was performed using PubMed (1950 to 20 February 2009) and the Web of Science, which includes abstracts of the major nephrological and cardiological societies (1955 to 20 February 2009). We included publications in all languages, reporting on the use of sodium bicarbonate for prevention of CI-AKI, with the following keywords 'contrast nephropathy' and 'sodium bicarbonate' or 'bicarbonate'. The abstracts of the retrieved publications were evaluated by three researchers (JDW, SG, EH) for inclusion. Articles that were included after the initial search were retrieved as full reports and re-evaluated for inclusion and exclusion. In addition, we hand-searched for relevant publications in the reference lists of retrieved articles and review articles and abstract books of the major nephrological and cardiological societies in 2006, 2007 and 2008. If additional information was needed, the authors were contacted.

Study selection and characteristics

Inclusion criteria included publication in a peer-reviewed journal and prospective controlled study design where one of the treatment groups received intravenous sodium bicarbonate for prevention of contrast nephropathy. Additionally, we required studies to have administered intravenous or intra-arterial iodinated contrast, to assure explicit reporting on contrast-induced nephropathy and to have collected sufficient data to calculate the primary effect, i.e. measure CI-AKI defined as an increase of serum creatinine of ≥25% or ≥0.5 mg/dL within 48 or 72 h after contrast administration.

Validity assessment and data extraction

Three reviewers (JDW, SG, EH) assessed the quality of trials for adequacy of sequence generation, allocation concealment, blinding, reporting of incomplete data, selective reporting, and other biases and scored these items as yes, no or unclear.

Data were extracted from the publications by one reviewer (EH) and controlled by another (SG).

Quantitative data analysis

The primary outcome measurement was the pooled estimate of the risk ratio (RR) for CI-AKI in patients who received sodium bicarbonate as prophylactic agent compared to those who did not. In addition, we analysed the effects of sodium bicarbonate in subgroups of studies including patients who underwent coronary procedures and those with diabetes mellitus and CKD, both risk factors for CI-AKI. CI-AKI, the primary endpoint of the study, was defined by an increase of serum creatinine of 25% or more or ≥0.5 mg/dL, within a 48- or 72-h period after administration of iodinated contrast, a commonly accepted definition for this condition [1]. Secondary outcome measures that were assessed were the change in serum creatinine, need for RRT and hospital mortality.

Data were analysed with the Mantel–Haenszel method. A random effect model was used in heterogeneous subsets. We used Forest plots to visualize the extent of heterogeneity among studies. Heterogeneity was also assessed with the I^2 statistic, a standard test that measures the degree of inconsistency across studies. This test results in a range from 0% to 100%, which describe the proportion of variation in treatment effect estimates due to inter-study variation. Higher values indicate more heterogeneity. Finally, a funnel plot was constructed for assessment of publication bias. Dichotomous data were compared with the Chi2 test, and correlation was assessed by the Spearman rank correlation coefficient.

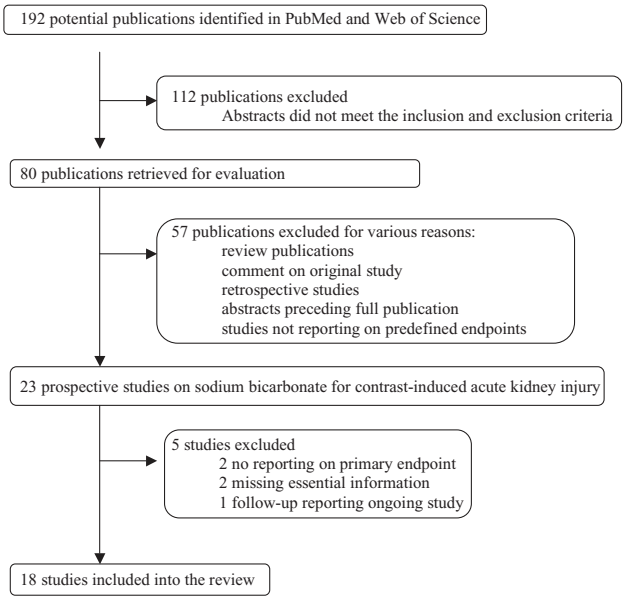

Fig. 1. Trial flow chart.

The meta-analyses were performed with the software package Review Manager version (RevMan) (Version 5.0 for Windows, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008). MedCalc (version 9.6.0.0, MedCalc Software, Mariakerke, Belgium) was used for calculation of the power of the study. The results are reported in accordance with the QUOROM and MOOSE guidelines on reporting of meta-analyses [16,17].

Results

A total of 192 publications were retrieved after the initial electronic search (Figure 1). Of these, 80 were selected for inclusion and further evaluated. Subsequently, 18 papers were included into the final analysis [14,18–31], of which 9 studies were only published in the abstract form [18,21,25,28,30–34]. Additional information was requested and was provided by two research groups [19,27].

A detailed description of the baseline characteristics of the included trials is given in Table 1. The type of contrast agent used was not reported in four studies [25,28,31,34]. Only one study reported using contrast agents other than low osmolar or iso-osmolar [18]. There was considerable heterogeneity on the total volume of the contrast agent administered, and the route contrast was administered. Most studies were of patients who underwent coronary procedures; therefore, contrast was administered via the intra-arterial route. Eight studies also included patients who received contrast for non-coronary angiography procedures [14,18–21,26,28,32]. The sodium bicarbonate intervention protocol as originally described by Merten *et al.* [14] was used in all but seven studies [18,21,23,24,31,33,34]. The 'Merten protocol' consists of the administration of 3 mL/kg/h of a sodium bicarbonate in a glucose solution containing 154 mmol/L of sodium bicarbonate during the first 1 h preceding the contrast procedure, followed by administration of this solution at a rate of 1 mL/kg/h for 6 h.

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Table 1. Characteristics of the studies

Study	Single centre (S)/multicentre (M)	Cohort	CKD inclusion criteria	Intervention	Control	Contrast type	Median contrast volume (mL)		
Addad [18]	S	Coronary procedure, peripheral angiography	No	500 mL BIC 1.4%, 12 h before and 12 h after contrast ± NAC 1200 mg oral bid day before and day of contrast	Saline 1000 mL, 12 h before and after contrast + NAC 1200 mg oral bid day before and day of contrast	Ionic, high osmolar (1500 mOsm/kg H_2O)	BIC	BIC+NAC	Saline+ NAC
							147.7	132.4	127.1
Adolph [26]	S	All contrast procedures	Creatinine >1.2 mg/dL, or eGFR<63 mL/ min/1.73 m^2	'Merten protocol'	Saline	Nonionic, low osmolar (796 mOsm/kg H_2O)	BIC	Saline	
							141	138	
Assadi [19]	S	All contrast procedures	CrCl <65 mL/ min/1.73 m^2	'Merten protocol'	Saline + acetazolamide 5 mg/kg oral 2 h prior and 12 h postprocedure	Nonionic, low osmolar (796 mOsm/kg H_2O)	BIC	Saline+ acetazolamide	
							76	69	
Brar [27]	S	Coronary procedures	eGFR<60 mL/ min/1.73 m^2	150 mmol BIC, 3 mL/kg for 1 h before, 1.5 mL/kg/h during and after the procedure ± NAC, 600 mg oral bid day before and day of contrast	Saline, 3 mL/kg for 1 h before, 1.5 mL/kg/h during and after the procedure ± NAC, 600 mg oral bid day before and day of contrast	Nonionic, low-osmolar (695 mOsm/kg H_2O)	BIC	Saline	
							126	137	
Briguori [20]	M (two centres)	Coronary procedure, peripheral angiography	Creatinine ≥2 mg/dL, eGFR <40 mL/min/ 1.73 m^2	'Merten protocol' + NAC,1200 mg oral bid day before and day of procedure	Saline ± NAC, 1200 mg oral bid day before and day of procedure + AA, 3 g IV 2 h before procedure and 2 × 2 g oral after procedure	Nonionic, iso-osmolar (290 mOsm/kg H_2O)	BIC	Saline	Saline+ NAC+ AA
							169	179	169
Chen [21]	S	Coronary and renal angiography	eGFR<60 mL/kg/ 1.73 m^2	1.25% BIC, 2 mL/kg/h for 6 h before procedure, and 80 mL/h for 6 h after procedure	Saline 2 mL/kg/h for 6 h before procedure, and 80 mL/h for 6 h after procedure	Nonionic, low-osmolar (844 mOsm/kg H_2O)	BIC	Saline	
							Not reported	Not reported	

Continued

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Table 1. *Continued*

Study	Single centre (S)/multicentre (M)	Cohort	CKD inclusion criteria	Intervention	Control	Contrast type	Median contrast volume (mL)	
Heguilen [32]	S	All contrast procedures	Creatinine >1.25 mg/dL or eGFR<50 mL/min/1.73 m^2	Merten protocol' ± NAC 600 mg oral bid day before and day of contrast	Saline+ NAC 600 mg oral bid day before and day of contrast	Nonionic, iso-osmolar	BIC± NAC	Saline+ NAC
							Not reported	Not reported
Kim [33]	S	Coronary procedure	Creatinine >1.5 mg/dL, DM, or proteinuria (>500 mg/day)	80 mEq/L BIC, 1 mL/kg/h for 12 h before and after procedure ± NAC, 600 mg oral bid day before and day of contrast	80 mEq/L NaCl, 1 mL/kg/h for 12 h before and after procedure ± NAC, 600 mg oral bid day before and day of contrast	Nonionic, iso-osmolar	BIC± NAC	NaCl± NAC
							Not reported	Not reported
Lin [28]	S	All	No	'Merten protocol' + NAC 600 mg oral bid day 0 and day after contrast	Saline+ NAC 600 mg oral bid day 0 and day after contrast	Not reported	BIC+ NAC	Saline+ NAC
							Not reported	Not reported
Maioli [29]	S	Coronary procedures	eCrCl <60 mL/min	'Merten protocol' + NAC 600 mg oral bid per day from day before to day after procedure	Isotonic saline, 1 mL/kg/h for 12 h before and after the procedure + NAC 600 mg oral bid per day from day before to day after procedure	Nonionic, iso-osmolar (290 mOsm/kg H_2O)	BIC+ NAC	Saline+ NAC
							160	170
Masuda [22]	S	Emergency coronary procedures	Creatinine >1.1 mg/dL, eGFR <60 mL/min	'Merten protocol'	Saline 'Merten protocol'	Nonionic, low-osmolar (796 mOsm/kg H_2O)	BIC	Saline
							112	120
Merten [14]	S	Coronary procedures, CT, arteriography, TIPS	Creatinine >1.1 mg/dL	154 mmol/L BIC, 3 mL/kg/h for 1 h before procedure, and 1 mL/kg/h during and 6 h after procedure	Saline, 3 mL/kg/h for 1 h before procedure, and 1 mL/kg/h during and 6 h after	Nonionic, low osmolar (796 mOsm/kg H_2O)	BIC	Saline
							130	134

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Study	Single centre (S)/multicentre (M)	Cohort	CKD inclusion criteria	Intervention	Control	Contrast type	Median contrast volume (mL)			
Ozcan [23]	S	Coronary procedures	Creatinine >1.2 mg/dL	154 mmol/L BIC, 1 mL /kg/h, 6 h before and 6 h after + NAC, 600 mg oral, bid, day before and day of procedure	Saline, 1 mL /kg/h, 6 h before and 6 h after ± NAC, 600 mg oral, bid, day before and day of procedure	Ionic, low osmolar (600 mOsm/kg H_2O)	BIC	Saline + NAC	Saline	
							100	100	110	
Recio-Mayoral [24]	S	Emergency coronary procedure	No	154 mmol/L BIC, 5 mL/kg/h + 2400 mg NAC IV over 1 h before procedure. After procedure, 1.5 mL/kg/h for 12 h + NAC 600 mg bid oral day after procedure	After procedure, saline 1 mL/kg/h for 12 h + NAC oral bid 600 mg day after	Nonionic, low osmolar (726 mOsm/kg H_2O)	BIC	Saline		
							290	279		
Saidin [34]	S	Coronary procedures	CKD stages 2–4	BIC 2 h before and 6 h after procedure + NAC oral	Saline 2 h before and 6 h after procedure + NAC oral	Not reported	BIC+ NAC	Saline+ NAC		
							Not reported	Not reported		
Shaikh [25]	S	Coronary procedures	Yes, not defined	'Merten protocol' ± NAC 1200 mg oral 2–12 h before and 6–12h after procedure	Saline, 'Merten protocol' ± NAC 1200 mg oral 2–12 h before and 6–12h after procedure	Not reported	BIC	BIC+ NAC	Saline	Saline+ NAC
							131.5	117.3	109.5	119.5
Shavit [30]	S	Coronary procedures	GFR 15–60 mL/min/1.73 m^2	'Merten protocol'	Saline 1 mL/kg/h 12 h before, and NAC 1200 mg oral day before and day of procedure	Nonionic, low osmolar, (796 mOsm/kg H_2O)	BIC	Saline+ NAC		
							Not reported	Not reported		
Tamura [31]	M	Coronary procedures	Creatinine >1.1 and <2.0 mg/dL	Saline + BIC bolus (20 mEq), 5 min before contrast	Saline	Not reported	Not reported			

AA, ascorbic acid; BIC, sodium bicarbonate; CKD, chronic kidney disease; CrCl, creatinine clearance; CT, computed tomography; DM, diabetes mellitus; eCrCl, estimated creatinine clearance; eGFR, estimated glomerular filtration rate; Merten protocol, 154 mmol/L bicarbonate, 3 mL/kg/h for 1 h before procedure, and 1 mL/kg/h during and 6 h following procedure; NAC, *N*-acetylcysteine; saline, isotonic saline; TIPS, transjugular portosystemic shunt.

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The control intervention consisted of administration of isotonic saline in all studies, except the study by Kim *et al.*, where 80 mEq/L of NaCl was used [33]. Assadi *et al*. used isotonic saline + acetazolamide as a control arm [19]. Administration of acetazolamide, like sodium bicarbonate, results in alkalinization of the urine; however, this effect was more pronounced in the acetazolamide arm. Six trials evaluated sodium bicarbonate intervention with two or more different controls [18,20,23,25,32,33]. In the case of multiple study arms, we pooled data on outcome into one sodium bicarbonate intervention arm and one control arm [18,20,23,25,32,33]. A sensitivity analysis, in which the meta-analysis was repeated with the individual study arms, demonstrated that this did not have an important impact on the aggregate results.

The patient characteristics from all included studies are summarized in Table 2. There was considerable clinical heterogeneity considering baseline kidney function, and proportion of patients with diabetes, both risk factors for the development of CI-AKI. Only three studies also included patients without a form of CKD (Table 1) [18,24,28].

In the four studies that reported on the evolution of serum creatinine, sodium bicarbonate exposed patients had a trend for a decrease of serum creatinine (mean difference = −0.08 mg/dL; 95% CI = −0.19, 0.04; P = 0.19) [14,22,26,29].

Occurrence of CI-AKI

CI-AKI defined by a ≥25% increase of serum creatinine or an increase of ≥ 0.5 mg/dL. The incidence of CI-AKI showed considerable variation in the control groups, with the highest incidence reported in the studies on patients who underwent emergency coronary procedures (21.8–34.5% in the control arm) (Figure 2) [22,24]. CI-AKI occurred in 355 of 3055 patients studied (11.6%). The incidence was lower in patients who were exposed to sodium bicarbonate (9.6%), compared to those in the control group (13.5%) (P = 0.001). Six out of 18 studies, including 1023 patients, demonstrated that administration of sodium bicarbonate resulted in a statistically significant decreased incidence of CI-AKI [14,20,22–24,31]. The aggregate effect of the included prospective trials demonstrated a preventive effect of sodium bicarbonate administration on the development of CI-AKI (Figure 3a). There was statistical heterogeneity among studies as evaluated by the I^2 statistic of 52%.

Effect of sodium bicarbonate in coronary and mixed procedures. Sub-analysis demonstrated that the preventive effect of sodium bicarbonate was only present with borderline statistical significance in studies that included coronary procedures (Figure 3a), especially urgent coronary procedures [22,24] (Figure 3b). There was no preventive effect of sodium bicarbonate in studies that included a mixed cohort of both coronary and non-coronary procedures (Figure 3a).

Aggregate effect of sodium bicarbonate in abstracts and published full reports. Exactly half of the included studies were published as a full manuscript. Two of the abstracts were already reported in 2006, four in 2007 and three in 2008. The aggregate effect of sodium bicarbonate on the occurrence of CI-AKI as reported in the abstracts (n = 1110 patients) was not significant, while the full papers reported a marked significant effect (n = 1945 patients) (Figure 3c).

CI-AKI in patients with diabetes or CKD. The proportion of diabetics varied among the studies. The one study that had diabetes as an inclusion criterion could not demonstrate a significant effect of sodium bicarbonate on prevention of CI-AKI [18]. The correlation between the proportion of diabetics included in a study and the RR for the development of CI-AKI after intervention with sodium bicarbonate was very low (r = −0.168, 95% CI = −0.658, 0.422; P = 0.561).

CKD, defined as an estimated GFR of <60 mL/min/1.73 m^2, was an inclusion criterion in most studies. The aggregate effect of sodium bicarbonate in studies that only included patients with CKD (n = 2674 patients) only showed a borderline significant trend for benefit for intervention with sodium bicarbonate (RR = 0.66, 95% CI = 0.44, 1.01; P = 0.05) [14,19–23,25–27,29–34]. However, in the three studies where CKD was not an inclusion criterion (n = 381 patients) [18,24,28], the preventive effect of sodium bicarbonate for CI-AKI was not present anymore (RR = 0.53, 95% CI = 0.17, 1.72; P = 0.29).

CI-AKI and the need for RRT

Need for RRT was reported in 11 of the trials [14,18,20,22–24,26,27,29,30,32]. Four trials reported that none of the patients were treated with RRT [14,26,30,32]. The overall incidence for RRT was low: 26 patients out of 2203 (1.0%). Patients treated with sodium bicarbonate had a trend for less need for RRT (0.9% versus 1.5%; P = 0.259) (Figure 4).

Mortality

In-hospital mortality was reported in five trials [18,22,23,27,29]. Bicarbonate therapy for CI-AKI did not result in a lower in-hospital mortality (1.7% versus 2.1%; P = 0.793) (Figure 5).

Assessment of methodological quality allocation concealment reported

The quality of the individual trials was relatively low (Figure 6). In only 33% of the trials was allocation concealment reported. Blinding was reported in only 11 trials (61%) and was not done in 8 of these (73%). Finally, incomplete outcome data were addressed in only six trials (33%).

In addition to an assessment of the quality of the individual studies, we also evaluated the possibility of publication bias by means of a funnel plot analysis. The funnel plot of all included studies was symmetrical, but the funnel plot of the manuscripts had an asymmetrical distribution, suggesting that there may have been publication bias in favour of studies with a RR <1 (Figure 7).

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Table 2. Baseline characteristics of the patients in the individual studies

Study	*N*	Age (years)/diabetic (%)			Baseline serum creatinine (mg/dL)				
Addad [18]	210	Bicarbonate 60.7/98.6%	Bicarbonate + NAC 64.5/98.6%	Saline + NAC 60.8/95.7%	Bicarbonate 1.08	Bicarbonate + NAC 1.11	Saline + NAC 1.16		
Adolph [26]	145	Bicarbonate 70.1/36.6%		Saline 72.7/28.3%	Bicarbonate 1.54		Saline 1.57		
Assadi [19]	96	Bicarbonate 10.3/4.3%		Saline + acetazolamide 10.9/2%	Bicarbonate 1.43		Saline + acetazolamide 1.43		
Brar [27]	353	Bicarbonate 71/43.4%		Saline 71/45.5%	Bicarbonate 1.49		Saline 1.49		
Briguori [20]	326	Bicarbonate+NAC 70/49%	Saline+NAC 71/55%	Saline+AA+NAC 69/59%	Bicarbonate+NAC 2.04	Saline+NAC 1.95	Saline+AA+NAC 1.93		
Chen [21]	105	Bicarbonate NR/38.2%		Saline NR/34%	Bicarbonate eGFR: 52 ± 11 mL/kg/1.73m^2		Saline eGFR: 52 ± 8 mL/kg/1.73m^2		
Heguilen [32]	27	NR			NR				
Kim [33]	100	NR	NR	BIC 0.96	BIC+NAC 1.28	Saline 1.00	Saline+NAC 1.18		
Lin [28]	60	Bicarbonate+NAC 45/26.7%	Saline+NAC 50/23.3%	Bicarbonate+NAC 0.89		Saline+NAC 0.78			
Maioli [29]	502	Bicarbonate+NAC 74/25%	Saline+NAC 74/23%	Bicarbonate+NAC 1.21		Saline+NAC 1.20			
Masuda [22]	59	Bicarbonate 75/27%	Saline 76/35%	Bicarbonate 1.31		Saline 1.32			
Merten [14]	119	Bicarbonate 66.7/50%	Saline 69.2/46%	Bicarbonate 1.89		Saline 1.71			
Ozcan [23]	264	Bicarbonate 68/42.0%	Saline 70/47.7%	Saline+NAC 67/45.5%	Bicarbonate 1.36	Saline 1.40	Saline+NAC 1.40		
Recio-Mayoral [24]	111	Bicarbonate+NAC 65/32%		Saline+NAC 64/27%	Bicarbonate+NAC 1.0		Saline+NAC 1.0		
Saidin [34]	57	NR	NR	NR	NR				
Shaikh [25]	320	Bicarbonate 72.1/43%	Bicarbonate + NAC 70.4/55%	Saline 69.9/45%	Saline + NAC 71.4/45.7%	Bicarbonate 1.85	Bicarbonate + NAC 1.96	Saline 1.72	Saline + NAC 1.82
Shavit [30]	92	Bicarbonate NR		Saline+NAC NR		Bicarbonate 1.9		Saline+NAC 1.76	
Tamura [31]	144	NR				NR			

AA, ascorbic acid; NAC, *N*-acetylcysteine; NR, not reported; saline, isotonic saline.

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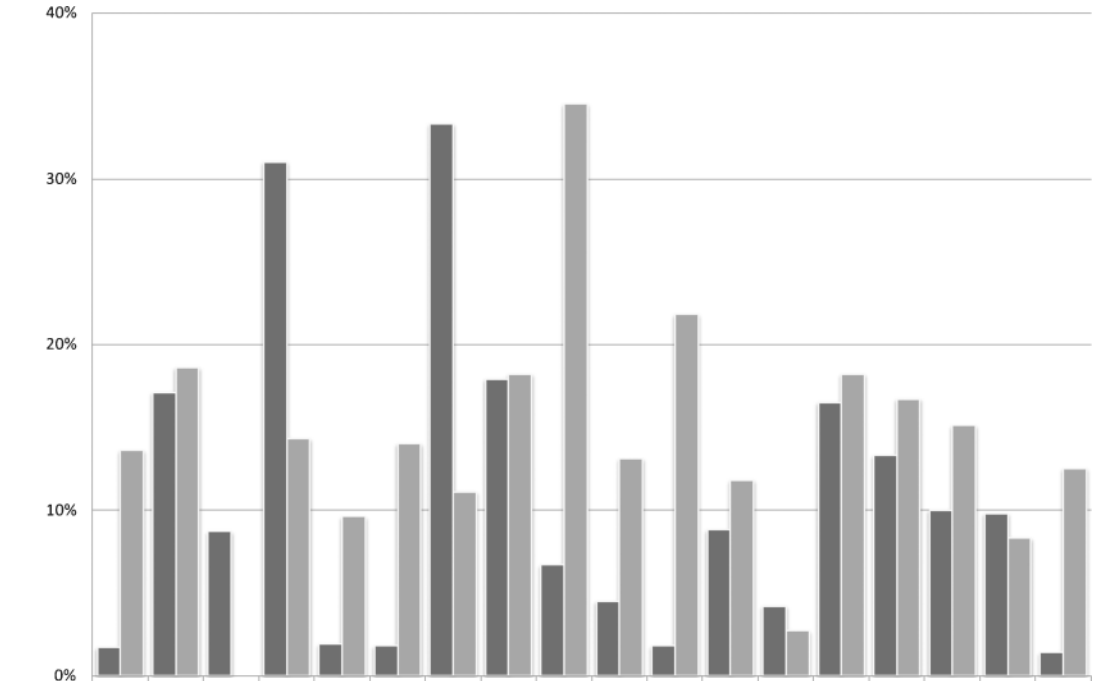

	Merten (14)	Addad (18)	Assadi (19)	Saidin (34)	Briguori (20)	Chen (21)	Heguilen (32)	Kim (33)	Masuda (22)	Ozcan (23)	Recio-Mayoral (24)	Shaikh (25)	Adolph (26)	Brar (27)	Lin (28)	Maioli (29)	Shavit (30)	Tamura (31)
Bicarbonate	1,7%	17,1%	8,7%	31,0%	1,9%	1,8%	33,3%	17,9%	6,7%	4,5%	1,8%	8,8%	4,2%	16,5%	13,30%	10,0%	9,8%	1,4%
Control	13,6%	18,6%	0,0%	14,3%	9,6%	14,0%	11,1%	18,2%	34,5%	13,1%	21,8%	11,8%	2,7%	18,2%	16,70%	15,1%	8,3%	12,5%

Fig. 2. Incidence of contrast-induced acute kidney injury in bicarbonate exposed and control groups.

Discussion

In the present meta-analysis, we found that CI-AKI occurred in 11.6% of study patients, which is higher than recently reported [35,36]. There was a varying incidence among the different study cohorts with greatest risk for CI-AKI in patients who underwent emergency coronary procedures. Use of sodium bicarbonate provided a benefit for prevention of CI-AKI with borderline statistical significance. Bicarbonate therapy was most effective in coronary procedures, especially when emergent, and in patients with CKD. There was no effect on need for RRT or mortality. However, there was marked clinical and statistical heterogeneity between studies. In addition, our analysis demonstrates publication bias in favour of positive trials.

After the publication of the study by Merten *et al*. [14] on the protective effect of a sodium bicarbonate protocol on the incidence of CI-AKI, several similar studies were performed. Not all studies found beneficial effects of sodium bicarbonate on the occurrence of CI-AKI; however, all prospective studies to date are underpowered. In order to detect a decrease in the incidence of CI-AKI from 13.3% to 8.8% (aggregate incidence of CI-AKI in the intervention and control arms of the prospective studies), studies need to include at least 759 patients in each arm (α-error 0.05; β-error 0.20). Therefore, in the absence of a definitive trial, a pooled estimate of effect, if homogenous, would provide the best estimate of effectiveness of this intervention.

We found that in prospective trials (n = 3055 patients), sodium bicarbonate administration cut the risk of CI-AKI by one-third (RR = 0.66), although there was only borderline statistical significance. On sub-analysis, we found that sodium bicarbonate was effective in studies on coronary procedures, especially in emergency procedures, and not effective in studies that included a mix of patients who underwent coronary and non-coronary procedures. The effect of sodium bicarbonate on prevention of RRT or on in-hospital mortality was also inconclusive although these events were rare, necessitating even larger studies, but the trends were in the direction of benefit in both cases. Subanalysis in risk groups for CI-AKI, patients with diabetes and/or CKD, could strengthen or weaken our findings. The data for this were, however, scarce. The one study that included only diabetics (n = 210) was inconclusive. We also could not demonstrate a correlation between the proportion of patients with diabetes included in a study and the effect of sodium bicarbonate on prevention of CI-AKI. The three studies that included patients without CKD found no preventive effect of sodium bicarbonate. However, the number of patients included was insufficient to draw meaningful conclusions.

In 12 studies, sodium bicarbonate did not result in a decreased incidence of CI-AKI [18,19,21,25–30,32–34]. This may have occurred because sodium bicarbonate is not effective in reducing the risk of CI-AKI. However, the negative result could also be explained by the lower risk profile of CI-AKI in the patients included in these trials—lower serum creatinine levels [18,28,29], younger age [19,28], iso-osmolar contrast [29,32,33] or less contrast were used [18,19,25–27]. In the trial by Assadi *et al*. [19], the control arm consisted of administration of acetazolamide, a drug that caused a much more profound alkalinization of the

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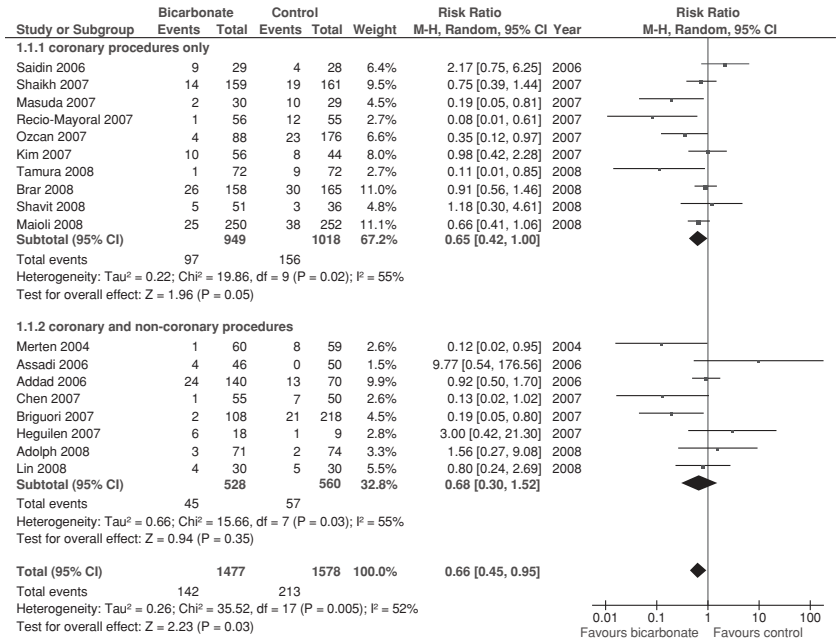
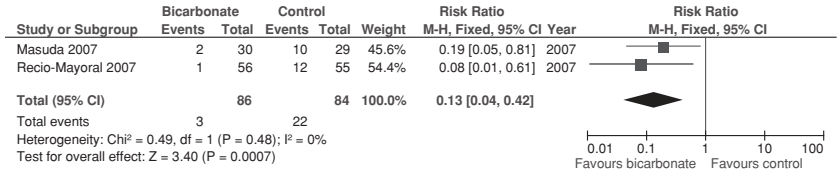
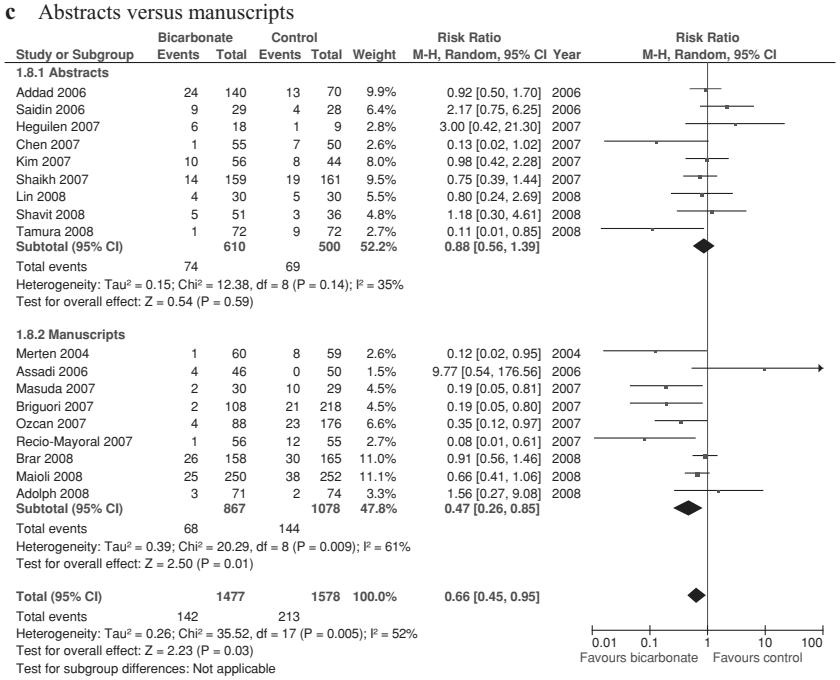
a Prospective studies on the use of sodium bicarbonate for prevention of CI-AKI.



b Prospective studies, including only studies on acute coronary procedures



c Abstracts versus manuscripts



*Contrast nephropathy defined by a ≥25% or an >0.5 mg/dL increase of serum creatinine.

Fig. 3. Effect of sodium bicarbonate on the occurrence of contrast-induced acute kidney injury. (**a**) Prospective studies on the use of sodium bicarbonate for prevention of CI-AKI. (**b**) Prospective studies, including only studies on acute coronary procedures. (**c**) Abstracts versus manuscripts.

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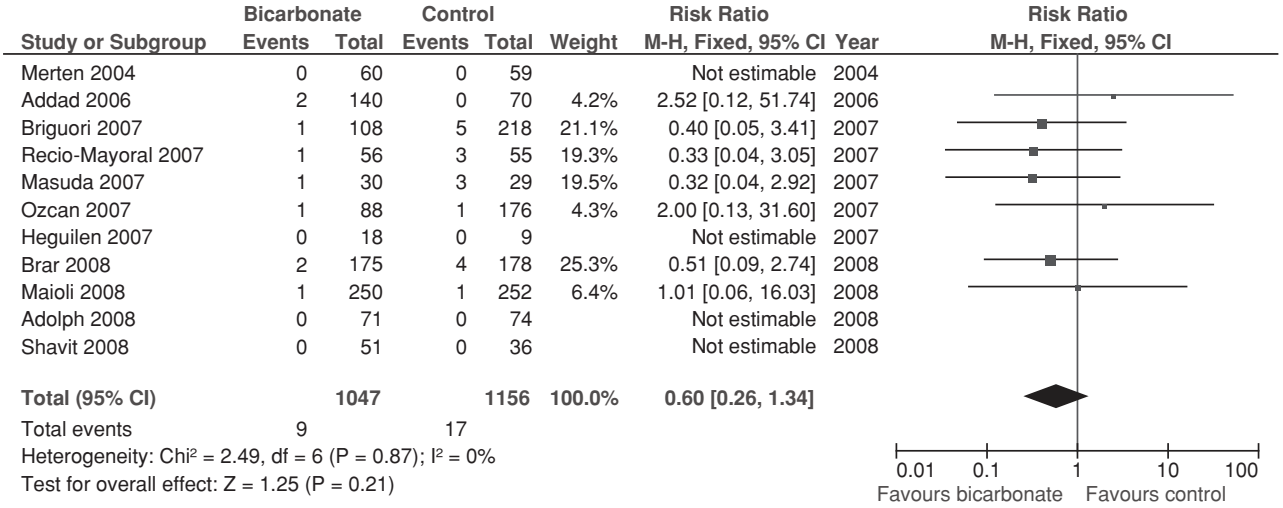

Fig. 4. Effect of sodium bicarbonate on need for renal replacement therapy after contrast exposure.

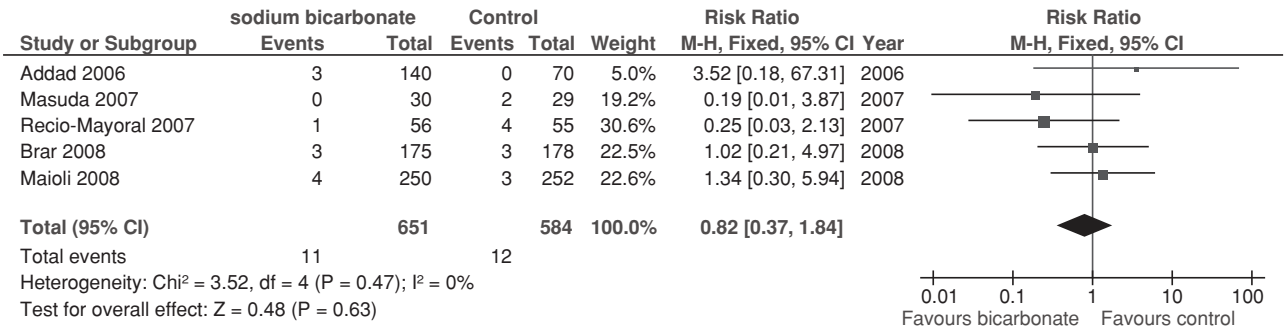

Fig. 5. Effect of sodium bicarbonate administration on in-hospital mortality.

urine compared to that established in the sodium bicarbonate arm. As alkalinization of the urine may in fact be the mechanism by which sodium bicarbonate prevents the development of CI-AKI, this study may in a sense provide an additional support for the use of sodium bicarbonate prevention regimens over standard hydration regimens with isotonic saline. Indeed, Pakfetrat *et al*. found that the effect of acetazolamide was comparable to that of sodium bicarbonate for prevention of CI-AKI defined by the RIFLE classification [37]. Finally, in the trial by Addad *et al*. [18], patients were administered an ionic high-osmolar contrast agent. Administration of these agents is associated with an increased risk for CI-AKI [36].

Two recent studies hypothesized that CI-AKI actually is an overestimated problem, because control patients without exposure to iodinated contrast media had a comparable incidence of AKI [38,39]. A major limitation to these retrospective studies is that patients with high risk for CI-AKI will less likely receive iodinated contrast. On the other hand, AKI typically has a multifactorial origin and may also develop as a consequence of acute disease and comorbidity. Therefore, it is likely that some patients were classified as having suffered from CI-AKI, while in fact AKI was unrelated to contrast administration. Especially, in the critically ill patient, multiple factors may contribute to the pathogenesis of AKI. We propose the term contrast-associated AKI as more appropriate in this setting. This is to highlight that although the episode of AKI occurs after contrast administration, other factors may also have contributed to the occurrence of AKI.

The quality of a meta-analysis is dependent on the quality of the individual studies [40], which in this study was low. Another limitation is the observation that there was considerable heterogeneity between studies, and in treatment effect. Also, publication bias may pose a limitation. Neutral or negative studies may not reach the final point of publication in a peer-reviewed journal, while positive studies will get published more easily. The sub-analysis on abstracts and manuscript suggests that this may be the case here also. On the other hand, it is notable that recently published larger studies report neutral results [27,29]. The funnel plot of this meta-analysis suggests that there may indeed have been publication bias for this topic.

This meta-analysis included the largest number of patients and studies. Unlike prior meta-analyses [41–43], we included all published abstracts that may have minimized the risk of an over-estimate risk reduction with this treatment. Also, the different risk factors for the development of CI-AKI such as intra-arterial contrast administration, CKD and diabetes have been explored in

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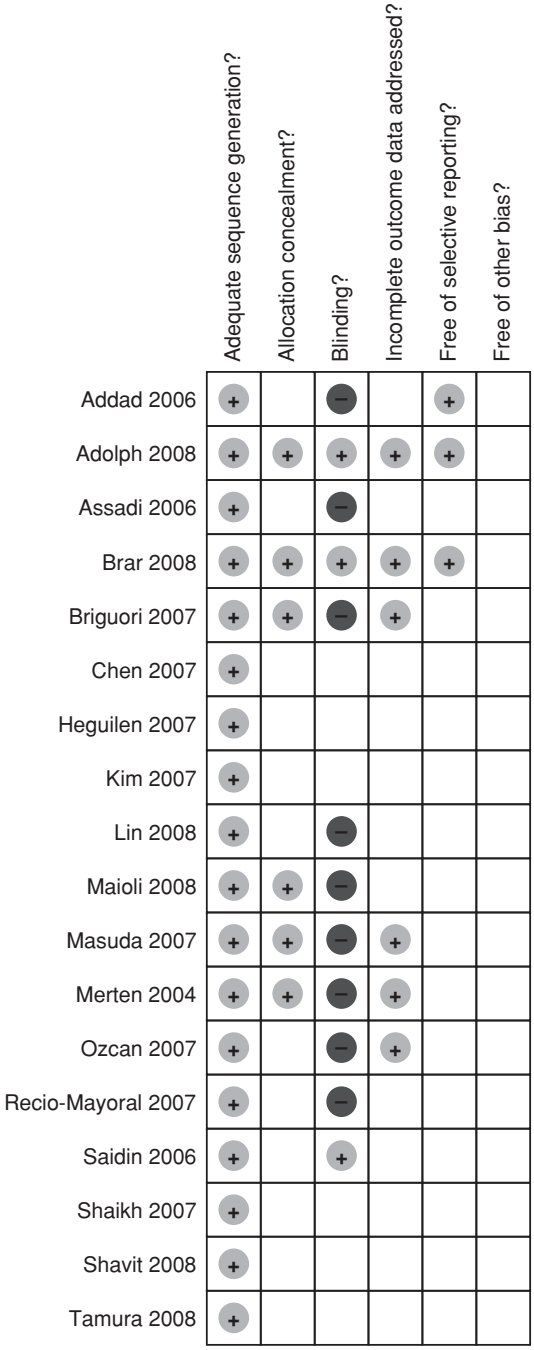

Fig. 6. Risk of bias in individual studies.

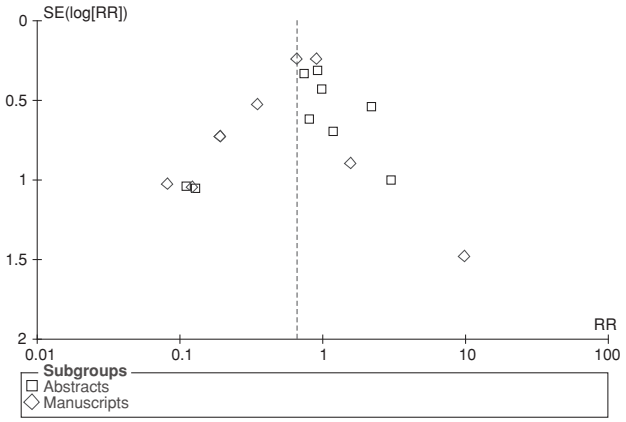

Fig. 7. Funnel plot analysis of included studies.

sub-analyses. Here, we showed that sodium bicarbonate is probably most effective in patients who underwent (emergency) coronary procedures and in patients with CKD. We also demonstrated that insufficient data are available on patients with diabetes and those without CKD. Finally, we provided a systematic and standardized overview of possible biases of the included studies—an often overlooked, but very important aspect for the correct interpretation of meta-analyses.

Future studies will need large prospective trials of well-defined, less heterogeneous subsets. Apart from studies on patients who undergo coronary angiography with different risk profiles, we need studies on relevant cohorts of patients at risk for CI-AKI, e.g. ICU patients who undergo contrast-enhanced CT scans or interventional angiography procedures.

In conclusion, the prospective studies in this meta-analysis have demonstrated a higher incidence of CI-AKI than recently reported, with important variation among different cohorts. It is uncertain whether all episodes of AKI were caused by the nephrotoxic effects of iodinated contrast media. Severity of illness and comorbidity may have also contributed to the pathogenesis of AKI. Therefore, we propose contrast-associated AKI as a more appropriate term to describe AKI occurring after contrast administration in critically ill patients. There was a protective effect of sodium bicarbonate on the risk of CI-AKI, especially in patients who underwent coronary procedures and those with CKD, without effect on need for RRT or mortality. Due to the borderline statistical significance, the relative low quality of the individual studies, heterogeneity and publication bias, only a limited recommendation can be made in favour of the use of sodium bicarbonate.

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Conflict of interest statement. None declared.

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