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Systematic review of the impact of N-acetylcysteine on contrast nephropathy

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Background. The efficacy of N-acetylcysteine (NAC) for preventing contrast nephropathy is uncertain. We performed a systematic review and meta-analysis to assess the efficacy of NAC for preventing contrast nephropathy after administration of intravenous contrast media.

Methods. Data were obtained from searching MEDLINE (1969–2003) and EMBASE (1988–2003), Cochrane Controlled Clinical Trial Registry (2002, Volume 3), and conference proceedings. We considered all randomized studies that compared changes in renal function between groups that received and did not receive NAC. Studies in which the control group also received active therapy were excluded, although cointervention directed at both groups was permitted. Two reviewers independently extracted quantitative and qualitative data. Disagreements were resolved by consensus with the aid of a third party.

Results. Fifteen studies with a total of 1776 patients satisfied inclusion and exclusion criteria. Contrast nephropathy was typically defined by an increase in serum creatinine of 0.5 mg/dL within 24 to 48 hours of contrast administration. The pooled random effect relative risk was 0.65 (0.43–1.00, $P = 0.049$), indicating that NAC significantly reduced the incidence of contrast nephropathy. However, the effect of NAC was not statistically significant in several prespecified subgroup analyses, and the results were not robust to the addition of hypothetical new or unidentified randomized trials. There was evidence of significant heterogeneity in NAC effect across studies ($Q = 26.3$, $P = 0.02$). Random effects meta-regression did not implicate identified differences in participant or study characteristics as responsible for the observed heterogeneity.

Conclusion. NAC may reduce the incidence of acutely increased serum creatinine after administration of intravenous contrast, but this finding was of borderline statistical significance, and there was significant heterogeneity between trials. Before NAC becomes the standard of care for all patients receiving intravenous contrast, new randomized trials evaluating its effect on clinically relevant outcomes are required.

Key words: acute renal failure, meta-analysis, contrast media, acetylcysteine.

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Contrast nephropathy is a common cause of acute renal failure among hospitalized patients, and is a recognized complication of diagnostic and therapeutic procedures in which intravenous contrast agent is required [1]. Although its incidence varies widely depending on the population studied, acutely elevated serum creatinine after the administration of intravenous contrast is associated with increased morbidity and mortality [2].

Use of nonionic low osmolarity contrast media and preprocedural hydration with intravenous fluids both appear to decrease the risk of contrast nephropathy [3–5]. Recent work suggests that administration of N-acetylcysteine (NAC) further reduces the likelihood of contrast nephropathy [6, 7], but other trials have failed to confirm this finding [8, 9].

We performed a systematic review and meta-analysis of published and unpublished randomized trials to quantify the effect of NAC on contrast nephropathy. Our goal was to synthesize the available information on this topic, with extensive use of sensitivity analysis to test the robustness of our conclusions.

METHODS

Search strategy

Two reviewers searched MEDLINE (1969 to May 2003) and EMBASE (1988 to May 2003) in duplicate using the free text/textword terms [(acetylcysteine or n-acetylcysteine) and (renal OR kidney OR contrast)]. Two reviewers examined reference lists from review articles identified in the search, and searched abstracts from the American Society of Nephrology (1999–2002), American Heart Association (2000–2003), American College of Cardiology (1999–2003), and Society of Interventional Radiology (2002–2003) meetings. Two reviewers

examined the reference lists of investigations meeting our inclusion criteria for other potentially relevant studies. Finally, one reviewer searched the Cochrane Controlled Clinical Trials Registry, the Science Citation Index, and the Database of Abstracts and Reviews using only the term (acetylcysteine or n-acetylcysteine). Any trial that was deemed worthy of manual review was recorded, as well as the reasons for subsequent exclusion (if applicable). We did not restrict the search to the English language.

Study selection

The search strategy and data abstraction were defined by a prospective protocol. To minimize the effects of publication bias, all randomized studies that compared the incidence of changes in renal function between groups that received and did not receive NAC were eligible for inclusion, whether published or unpublished. We excluded data comparing NAC to another active therapy. However, trials that specified cointervention (i.e., intravenous saline) were included, providing that it was given to both groups.

Validity assessment and data extraction

We assessed qualitative details of study methodology that were likely to influence internal validity [10, 11]. We did not attempt to assess allocation concealment in blinded studies, although certain NAC preparations may be more amenable to concealment than others because of differences in taste. If multiple publications from the same group were found, the studies were carefully reviewed to ensure that no data was analyzed in duplicate. All data was extracted separately by two authors and results compared; disagreements were resolved by consensus with the aid of a third party. Extracted data was recorded on a standardized form. At least two attempts were made to contact the corresponding and/or first author on every included study. Additional data was provided and the original data was confirmed by 14 of the 15 original authors.

Outcome measures

The primary outcome was the pooled estimate of the relative risk (RR) for contrast nephropathy in patients randomized to receive NAC, compared with those who did not (CN). The definition of "contrast nephropathy" was similar in the included studies (Table 1). Although pooling results from trials that used slightly different definitions may affect the estimated incidence of contrast nephropathy, it would not affect the difference in outcomes between treatments. Secondary outcomes included the relative risk of requiring acute dialysis treatment and the differential change in serum creatinine between groups.

Quantitative data synthesis

We first performed a funnel plot for the primary outcome, considering only studies that have successfully undergone peer review (published or in press as full manuscripts) [12]. We formally tested for the presence of publication bias using Begg's test [13]. Next, data from the 15 eligible studies were combined using random effect models calculated by the method of Der Simonian and Laird [14]. Heterogeneity was calculated using the inverse variance method, and the Q statistic was employed to provide a numerical measure of heterogeneity for each analysis [15]. This statistic tests the null hypothesis that the underlying effect measured by each of the pooled studies is equivalent. When $P < 0.1$ for Q, this assumption is invalid and heterogeneity exists. All measures of effect refer to the risk of outcomes in patients who received NAC, compared with those who did not. Differences in categorical outcomes were expressed as relative risks; differences in continuous outcomes were expressed as weighted mean differences.

We used random effects meta-regression [16] to examine whether certain study characteristics modified the effect of NAC on the incidence of contrast nephropathy. In each meta-regression analysis, the incidence of contrast nephropathy was the dependent variable, and NAC use plus one study characteristic (based on participants in both groups: overall proportion of diabetic participants, mean baseline serum creatinine, mean volume of contrast administered) were independent variables. Finally, we estimated the effect size and number of participants in hypothetical (new or unidentified) trials that would significantly change our results.

All analyses were performed using Intercooled Stata 8.0 (Stata Corporation, College Station, TX, USA). The level of statistical significance was set at $P < 0.05$.

RESULTS

Trial flow and study characteristics

The abstracts of 2476 studies were reviewed. Of these, 71 were deemed worthy of further exploration and were retrieved for review. Sixteen potentially eligible randomized studies were found. Of these, one was excluded because the control group received theophylline [abstract; Bader et al, *J Am Soc Nephrol* 13:447A, 2002). Fifteen studies satisfied inclusion and exclusion criteria and appear in Table 1. Several studies that were initially published as abstracts were subsequently published as full papers. To avoid including data in duplicate, we therefore excluded the abstracts, and included only the full

Table 1. Study characteristics

First author	Publication year	Country of origin	Number of patients	Blinding	Diagnostic study	NAC regimen	Cointervention
Oldemeyer [24]	2003	U.S.A.	96	Double	Coronary angiography	1500 mg po bid × 48 hours	0.45% saline 1 mL/kg/hr 12 hours pre and 12 hours post
Loutrianakis[a]	2003	U.S.A.	47	No	Coronary or peripheral angiography	600 mg bid × 48 hours	0.45% saline 1 mL/kg/hr (outpatients 4 h, inpatients 12 h)
Baker [21]	2003	U.K.	80	No	Coronary angiography/angioplasty	IV NAC 150 mg/kg over 30 minutes pre followed by 50 mg/kg over 4 hours	0.9% saline 1 mL/kg/hr for 12 hours pre and 12 hours post (placebo)[a]
Le Feuvre	2003	France	120	No	Coronary angiography	600 mg bid × 4 doses	0.9% saline 1 mL/kg/hr for 12 hours pre and 12 hours post
Kay [7]	2003	China	200	Double	Coronary angiography/angioplasty	600 mg po bid × 48 hours	0.9% saline 1 mL/kg/hr 12 hours pre and 6 hours post
Durham [8]	2002	U.S.A.	79	NS	Coronary angiography/angioplasty	1200 mg po 1 hr pre, 3 hrs post	0.45% saline 1 mL/kg/hr 12 hours pre and 12 hours post
Briguori [17]	2002	Italy	183	No	Coronary or peripheral angiography/angioplasty	600 mg po bid, × 48 hours	0.45% saline 1 mL/kg/hr 12 hours pre and 12 hours post
Diaz-Sandoval [18]	2002	U.S.A.	54	Double	Coronary angiography/angioplasty	600 mg po bid, × 48 hours	0.45% saline 1 mL/kg/hr 2–12 hours pre and 12 hours post
Shyu [19]	2002	Taiwan	121	Single	Coronary angiography/angioplasty	400 mg po bid, × 48 hours	0.45% saline 1 mL/kg/hr 12 hours pre and 12 hours post
Vallero [20]	2002	Italy	100	No	Coronary angiography	600 mg po bid, × 48 hours	0.45% saline 1 mL/kg/hr 2 hours pre for total of 24 hours
Allaqaband [9][a]	2002	U.S.A.	85	No	Coronary or peripheral angiography	600 mg po bid, × 48 hours	0.45% saline 12 hours pre and 12 hours post
Kahlon	2002	U.S.A.	51	Double	Coronary angiography	600 mg po bid × 48 hours	0.9% saline 1 mL/kg/hr 12 hours pre and 12 hours post‡
Ochoa [23]	2002	U.S.A.	80	Double	Coronary angiography/angioplasty	1000 mg po 1 hour pre and 4 hours post	0.45% saline, minimum volume 1000 mL
Azmus [22]	2002	Brazil	397	Double	Coronary angiography	600 mg po bid × 2 doses pre and × 3 doses post cath	2L 0.9% saline (1 L pre-, 1 L post-)
Tepel [6]	2000	Germany	83	No	Computed tomography	600 mg po bid, × 48 hours	0.45% saline 12 hours pre and 12 hours post

Continued

Table 1. continued

Definition of CIN	Volume of contrast *mL*	Age	Female %	Diabetic %	Baseline serum creatinine *mg/dL*	Non-ionic, low-molecular-weight contrast
≥25% increase in SCr or ≥0.5 mg/dL increase in serum SCr at 48 hours	130.6	76	45	45	1.65	Yes
≥25% increase in SCr	147	67	31.9	36	1.94	Yes
≥25% increase in SCr at 48 hours	230.2	69	12.5	42.5	1.81	Yes
≥25% increase in SCr at 48 hours	176.5	67	19	30	1.91	Yes
>25% increase in SCr within 48 hours after cath	125.1 (median)	69	38.5	37.5	1.25	Yes
≥0.5 mg/dL increase in SCr at 48 hours post cath	82.9	71	34	48	2.25	Yes
≥25% increase in SCr at 48 hours or need for dialysis	197	64	13.4	36	1.53	Yes
>25% increase in SCr or ≥0.5 mg/dL increase in SCr at 48 hours post cath	184	73	20.2	50	1.61	Yes
≥0.5 mg/dL increase in serum SCr at 48 hours post cath	117	70	32	63.5	2.8	Yes
≥0.5 mg/dL or ≥33% increase in SCr at 48 hours post contrast	203.9	62	24	23	0.91	Yes
≥0.5 mg/dL increase in SCr at 48 hours	121.5	71	39	48	2.12	Yes
≥0.5 mg/dL increase in SCr at 96 hours post cath	124	69	36	63	2.06	Yes
>25% increase in SCr or >0.5mg/dL at 48 hours post cath	141.9	71	56	55	1.93	Yes
≥25% increase in SCr or absolute increase in SCr ≥0.5 mg/dL at 24 to 48 hours post cath	125.5	66	41	50	1.29	No
≥0.5 mg/dL increase in SCr at 48 hours post cath	75	66	43	33	2.4	Yes

NAC recipients received 500 mL of intravenous saline during the procedure, and 500 mL over 4-hour post-procedure. Some participants received only a 70 mL/kg bolus of intravenous saline.
[a]These trials had three experimental arms: NAC, fenoldopam, and control. Table considers only the NAC and control arms.

papers. The remaining studies did not examine the effect of NAC on contrast nephropathy.

Of the 15 studies for which the relative risk of the primary outcome could be calculated, nine had already been published [6–9, 17–21], three were in press [22–24], and three were published only in abstract form [abstract; Loutrianakis et al, *J Am Coll Cardiol*, 41:327A, 2003; Le Feuvre et al, *J Am Coll Cardiol* 41:192A, 2003; Kahlon et al, *Circulation* 106:11–691, 2002). Information on the individual studies appears in Tables 1–4. All studies were randomized, although allocation sequence was not always specified, and only six studies were double blind. A power calculation and the characteristics of ineligible patients were not provided in most studies.

Quantitative data synthesis

Meta-analysis (contrast nephropathy). The plot of effect size against its precision showed a relative absence of small published studies that found the relative risk of contrast nephropathy with NAC to be >1, suggesting at least some degree of publication bias (Fig. 1). Begg's test confirmed the visual impression of publication bias ($P = 0.02$). Inspection of the data using a Galbraith plot showed no obvious correlation between effect of NAC and year of publication, country of origin, protocol for administration of intravenous fluid, or definition of contrast nephropathy (data not shown).

We first analyzed all 15 trials to evaluate the primary end point. The Q statistic suggested significant heterogeneity across studies ($Q = 26.3$, $P = 0.02$). The random effect relative risk was of borderline statistical significance: 0.65 (0.43–1.0, $P = 0.049$), suggesting that NAC significantly reduced the incidence of contrast nephropathy (Fig. 2).

Restricting the analysis to those studies which had successfully completed peer review ($N = 12$) did not change our results—RR (CN): 0.55 (0.35–0.85, $P < 0.01$), and substantial heterogeneity remained. The relative risk of contrast nephropathy associated with NAC treatment was statistically nonsignificant when analysis was limited to trials which studied only coronary angiography/angioplasty ($N = 11$)—RR (CN): 0.62 (0.41–1.01, $P = 0.06$). Finally, limiting analyses to trials which used a more stringent definition of CN (a single criterion rather than a composite of two or more criteria, $N = 7$) also rendered the effect of NAC statistically nonsignificant—RR (CN): 0.64 (0.30–1.35, $P = 0.24$).

Sensitivity analysis—Risk of contrast nephropathy

We estimated how large a sample size would be required for a hypothetical new or undetected trial to change our conclusions (i.e., render the pooled RR of contrast nephropathy associated with NAC therapy statistically nonsignificant). We assumed that such a study

Table 2. Study quality

First author	Allocation sequence adequate[a]	Number lost to follow-up reported	Loss to follow-up <10% of *N*	Reasons for loss to follow-up provided[b]	Power calculation	Inclusion and exclusion criteria specified	Cointervention potentially unequal between groups[c]	Characteristics of rejected or ineligible patients listed
Oldemeyer [24]	yes	yes	yes	yes	yes	yes/yes	no	no
Loutrianakis	yes	no	–	–	no	yes/yes	yes	no
Baker [21]	yes	yes	yes	yes	yes	yes/yes	yes	no
Le Feuvre	yes	yes	yes	–	no	yes/no	no	no
Kay [7]	yes	yes	yes	yes	yes	yes/yes	no	yes
Durham [8]	yes	yes	yes	yes	no	yes/yes	yes	no
Briguori [17]	yes	yes	yes	–	no	yes/no	no	no
Diaz-Sandoval [18]	yes	yes	yes	–	no	yes/yes	yes	no
Shyu [19]	NS	yes	yes	–	yes	yes/yes	no	no
Vallero [20]	NS	yes	yes	–	no	yes/yes	no	no
Allaqaband [9]	yes	yes	yes	–	no	yes/no	no	no
Kahlon	NS	yes	yes	–	no	yes/yes	yes	no
Ochoa [23]	NS	yes	no	no	no	yes/no	yes	no
Azmus [22]	NS	no	–	–	yes	yes/yes	yes	no
Tepel [6]	yes	yes	yes	–	no	yes/yes	no	no

NS, not specified. All studies were randomized controlled trials comparing NAC to a control group with no specific intervention. In all studies, both groups received intravenous fluids according to protocols that were identical for NAC and control groups.

[a]We did not assess the success of allocation concealment.

[b]This characteristic was not tabulated for studies with no loss to follow-up.

[c]For example, trials in which one group was deliberately given less intravenous saline, or trials in which the volume of intravenous saline used could be varied at the discretion of clinicians/the investigators. In general, variable cointervention is a greater potential source of bias in trials without adequate blinding and concealment.

would show that NAC substantially increased the risk of contrast nephropathy (RR of 1.25) and find the incidence of CN to be 12% in the control group [7]. Using a random effects model, the required *N* was 50, indicating that the pooled result was not robust to the addition of new trials.

Requirement for dialysis

Complete data on the need for dialysis were available from 12 trials. However, in seven of these, no participants in either group required dialysis, making it impossible to calculate a relative risk. The pooled relative risk of dialysis associated with NAC in the remaining five trials was 0.90 (95% CI: 0.24–3.37, $P = 0.77$).

Sensitivity analyses—Requirement for dialysis

We found that a new trial would need to be very large (or to enroll participants with a high likelihood of requiring dialysis) to render the pooled risk of dialysis statistically lower in NAC recipients. For example, a single trial that found that NAC reduced the absolute risk of dialysis by 1.6% [19] would require 1200 subjects to establish a significantly lower pooled risk of dialysis among NAC recipients. Alternatively, assuming that NAC reduced the risk of dialysis by 50%, a new trial with 200 participants would require that 26% of control participants received dialysis to render the pooled risk reduction for dialysis among NAC recipients statistically significant.

Evaluation of heterogeneity

There was evidence of significant heterogeneity between studies in the relative risk of contrast nephropathy with NAC therapy. Although all studies administered intravenous saline to both groups, the exact volume/duration of infusion was not specified (or could be modified at the discretion of the investigator) in six studies [8, 18, 22, 23] [abstract; Loutrianakis et al, *J Am Coll Cardiol* 41:327A, 2003; Kahlon et al, *Circulation* 106:11–691, 2002 (of which two were unblinded) [8], raising the possibility that saline was differentially administered between groups, either randomly or deliberately. In one trial, the NAC group was purposely given less intravenous saline [21]. Although NAC did not significantly prevent CN in six of these seven trials, the effect of NAC remained nonsignificant when results from the remaining eight trials were combined (RR 0.58, CI 0.31–1.09, $P = 0.09$), and significant heterogeneity remained ($P = 0.08$).

To evaluate the possibility that identifiable differences between trials accounted for the heterogeneity, we performed random effects meta-regression examining one covariate at a time. These analyses demonstrated no significant relationships between the effect of NAC on contrast nephropathy and the proportion of participants with diabetes mellitus ($P = 0.68$), the average volume of contrast agent required ($P = 0.85$), average baseline serum creatinine ($P = 0.53$), or total number of study participants ($P = 0.96$), suggesting that these variables were not responsible for the heterogeneity. However, the effect of NAC was less likely to be protective in trials that had not completed peer review ($P = 0.03$).

Fourteen of 15 trials used non-ionic, low-molecular-weight intravenous contrast, and in 12 trials NAC was given over a 48-hour period. In three studies, participants received NAC only on the day that intravenous

Table 3. Results for categorical outcomes

First author	Control *N*	NAC *N*	% CN in controls	% CN in NAC recipients	RR of CN (95% CI)	Need for dialysis in controls	Need for dialysis in NAC recipients
Oldemeyer [24]	47	49	6.4%	8.2%	1.28 (0.30–5.41)	0%	0%
Loutrianakis	23	24	13.0%	25.0%	3.83 (0.46–31.8)	4.3%	4.2%
Baker [21]	39	41	20.5%	4.9%	0.24 (0.05–1.05)	0%	0%
LeFeuvre	60	60	3.4%	5%	1.5 (0.26–8.66)	0%	0%
Kay [7]	98	102	12.2%	3.9%	0.32 (0.11–0.96)	0%	0%
Durham [8]	41	38	22.0%	26.3%	1.20 (0.55–2.63)	NS	NS
Briguori [17]	91	92	11.0%	6.5%	0.59 (0.23–1.57)	1.1%	0%
Diaz-Sandoval [18]	29	25	44.8%	8.0%	0.18 (0.04–0.72)	0%	0%
Shyu [19]	61	60	24.6%	3.3%	0.14 (0.03–0.57)	1.6%	0%
Vallero [20]	53	47	7.5%	8.5%	1.13 (0.30–4.26)	0%	0%
Allaqaband [9]	40	45	15.3%	17.7%	1.19 (0.45–3.12)	0%	4.4%
Kahlon	24	27	17.1%	29%	1.71(0.50–5.89)	0%	0%
Ochoa [23]	44	36	25.0%	11.1%	0.44 (0.15–1.28)	0%	0%
Azmus [22]	201	196	8.4%	7.1%	0.84 (0.43–1.67)	0.5%	0.5%
Tepel [6]	42	41	21.4%	2.4%	0.11 (0.02–0.86)	0%	0%

Abbreviations are: NAC, n-acetylcysteine; CN, contrast nephropathy; RRR, relative risk reduction; NS, not specified; 95% CI, 95% confidence interval.

Table 4. Results for continuous outcomes

First author	Control *N*	NAC *N*	Change in SCr in controls	Change in SCr in NAC recipients
Oldemeyer [24]	47	49	−0.05	−0.01
Loutrianakis	23	24	−0.055 ± 0.26	0.15 ± 0.64
Baker [21]	39	41	0.05 ± 0.31	−0.08 ± 0.34
Le Feuvre	60	60	0.07 ± 0.43	−0.02 ± 0.29
Kay [7]	98	102	0.02	−0.13
Durham [8]	41	39	NS	NS
Briguori [17]	91	92	−0.01 ± 0.41	−0.04 ± 0.40
Diaz-Sandoval [18]	29	25	0.3 ± 0.06	−0.1 ± 0.06
Shyu [19]	61	60	0.24 ± 0.56	−0.29 ± 0.41
Vallero [20]	53	47	0.04 ± 0.16	0.04 ± 0.19
Allaqaband [9]	40	45	0.09 ± 0.3	0.01 ± 0.6
Kahlon	24	27	NS	NS
Ochoa [23]	44	36	0.23 ± 0.64	0.06 ± 0.72
Azmus [22]	201	196	0.10 ± 0.28	0.08 ± 0.21
Tepel [6]	42	41	0.2 ± 0.6	−0.4 ± 0.4

Abbreviations are: NAC, n-acetylcysteine; CN, contrast nephropathy; SCr, serum creatinine (mg/dL); NS, not specified.

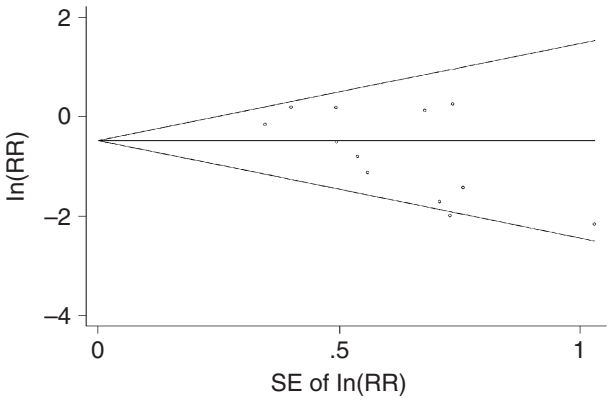

Fig. 1. Funnel plot of effect size versus precision of effect size. The figure plots an index of effect size (ln relative risk) against its precision [standard error (SE) of ln relative risk]. There is an absence of small trials that found an increased incidence of contrast nephropathy associated with N-acetylcysteine (NAC).

contrast was administered. However, exclusion of these three trials did not significantly reduce the heterogeneity of NAC effect or change results. When only the six double-blinded trials were combined, heterogeneity was reduced (P for heterogeneity >0.1), and the overall effect of NAC on contrast nephropathy was rendered statistically nonsignificant (RR 0.61, 95% CI: 0.33–1.13).

Other clinical effects

We performed a pooled analysis of the differential change in serum creatinine between groups for trials that reported the standard deviation of this change. The weighted mean increase in serum creatinine was significantly lower in NAC recipients compared with control (0.20 mg/dL lower, 95% CI 0.05–0.35, $P = 0.01$). Two trials provided information on mean length of stay by group, which was significantly lower among NAC recipients in one (3.4 vs. 3.9, $P = 0.02$) [7], but not the other (5.4 vs. 5.4, $P = 0.80$) [23]. No trial reported a significantly increased risk of adverse events among NAC recipients.

DISCUSSION

This systematic review combined results from 15 randomized studies evaluating the effect of NAC on the incidence of acutely elevated serum creatinine in people receiving intravenous contrast. In our primary analysis, the use of NAC was associated with a reduction in the incidence of contrast nephropathy, but this difference was of borderline statistical significance ($P = 0.049$), and

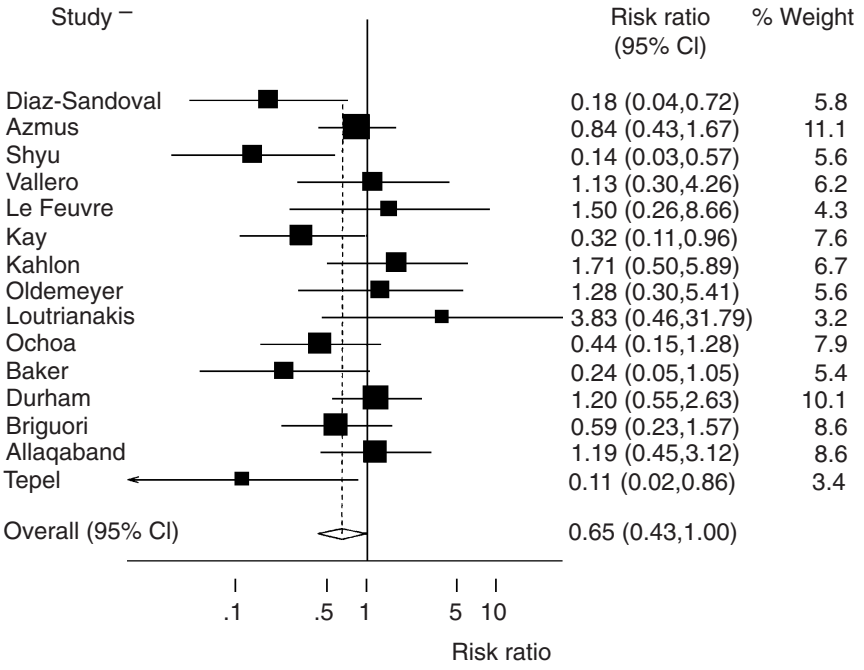

Fig. 2. Relative risk of contrast nephropathy associated with NAC: All identified trials. Relative risk refers to the risk of contrast nephropathy in the N-acetylcysteine (NAC) group, compared with control. The squares represent the point estimate of relative risk for each study, and their size is proportional to their weight in the pooled estimate of relative risk (represented by the diamond). Bars indicate 95% CI. $Q = 26.3$, $P = 0.02$.

the pooled mean difference in serum creatinine between groups was small (0.2 mg/dL).

Sensitivity analyses showed that the pooled estimate of NAC effect was not robust to the inclusion of hypothetical new or unidentified studies, and the protective effect of NAC was observed in one prespecified subgroup of trials (randomized trials which have completed peer review), but not others (trials considering cardiac interventions only, or those in which a more stringent definition of CN was used). The effect of NAC was also statistically nonsignificant in post-hoc analyses, which excluded trials with potentially unequal intensity of cointervention, and those that were not double-blinded, suggesting that differences in study design may have influenced the effect of NAC. Finally, there was no reduction in the risk of dialysis between treatment groups. Together, these findings may cast doubt on whether NAC truly improves clinical outcomes in people receiving intravenous contrast.

Although there was evidence of significant heterogeneity in the effect of NAC, meta-regression did not implicate measured differences in participant characteristics or study interventions as responsible for this. In particular, mean contrast dose, mean baseline serum creatinine, and the proportion of diabetic patients enrolled did not appear to influence the efficacy of NAC. While the limitations of meta-regression are well known [16, 25], this technique may be more susceptible to type I than type II error, suggesting that the covariates we considered do not explain the observed heterogeneity. However, because the effect of NAC appeared more homogeneous when only double-blinded studies, or those that ensured equal cointervention were included, it is possible that differences in study quality were responsible for some of the heterogeneity. Finally, although we were unable to show a relation between the effect of NAC and the dose or timing of its administration, it is possible that the different NAC protocols used resulted in heterogeneity.

The pathophysiology of contrast nephropathy is well described, and is caused by a combination of toxic and ischemic effects on renal tubular and medullary cells [26]. However, the basis for the nephroprotective action of NAC is unknown. It has been suggested that this effect is mediated by scavenging oxygen free radicals [27, 28], or by enhancing the vasodilatory effects of nitric oxide [29]. Alternatively, NAC may exert a direct protective effect on renal cells that have sustained ischemic injury [30, 31].

The mechanism by which NAC acts is potentially relevant, because acute elevations in serum creatinine after administration of contrast media are not always caused by contrast nephropathy. For example, acute tubular necrosis or prerenal azotemia might occur in patients with acute coronary syndromes, and atheroemboli might be triggered by coronary angiography. Although in theory such episodes would be evenly balanced between treatment arms in randomized trials, this is not always the case, especially in smaller studies. Even for large studies, acute increases in serum creatinine that are not caused by contrast nephropathy would be expected to bias the estimate of NAC effect toward the null. Thus, unmeasured differences in the acuity of illness of participants, or the incidence of atheroemboli between studies may have been responsible for some of the observed heterogeneity. Because atheroemboli does not occur after contrast-enhanced computed tomography, a protective effect of

NAC might be most apparent in this population. We speculate that this is why NAC appeared most beneficial in the only trial which studied patients undergoing computed tomography [6]. However, even in this trial, there was no reduction in the incidence of clinically relevant outcomes such as the need for dialysis.

We found evidence of publication bias, reflected by an absence of smaller published trials, which show no protective effect of NAC. Our primary analysis considered all identified trials, whether or not they had completed peer review. In a secondary analysis, we included only those trials which were published or in press, and found that NAC appeared to be more effective in this group. Besides publication bias, an alternate explanation for this finding might be that the unpublished trials are of poorer quality than the others. In our opinion, review of Table 2 suggests that this is unlikely. Our decision to include all identified studies probably reduced the effect of publication bias. However, if such bias remains, the true effect of NAC is likely smaller than our primary analysis suggests.

Data from observational studies suggest that serum creatinine will return to baseline in most individuals with contrast nephropathy [2, 32]. Therefore, prevention of contrast nephropathy would be expected to improve health outcomes by reducing the frequency with which acute dialysis is required, or by further increasing the likelihood of complete recovery. Unfortunately, data on the ability of NAC to achieve these clinical objectives are sparse. No study reported long-term outcomes of participants with contrast nephropathy, and acute dialysis occurred too infrequently to determine whether it was less common among NAC recipients. To conclusively demonstrate clinically relevant benefit, future trials would need to enroll participants at higher risk for adverse renal outcomes, collect data on longer-term outcomes, or both.

If NAC therapy simply reduces the risk of transient increases in serum creatinine without improving other clinical outcomes, it might still decrease healthcare costs by reducing the duration of hospitalization in patients receiving intravenous contrast. Unfortunately, only one study compared this outcome between groups. Although these authors found a significant reduction in length of stay in the NAC arm, the absolute difference was small (0.5 days), and it is unclear how this would translate to centers which perform most procedures requiring intravenous contrast on outpatients [7]. Thus, in our opinion, the evidence that routine use of NAC would reduce length of hospital stay in patients receiving intravenous contrast is inconclusive.

A recent editorial suggested that NAC should be given to all patients at risk for contrast nephropathy [33]. Given the lack of evidence that NAC prevents clinically relevant outcomes, we believe that this recommendation is premature, and that further studies are required before periprocedural administration of NAC becomes the standard of care. In addition, the costs associated with the prescription and administration of NAC are unknown. Therefore, a formal economic evaluation might assist in determining whether NAC should be routinely prescribed before administration of intravenous contrast—and if so, to which patients. Finally, even if NAC truly reduces the incidence of contrast nephropathy, physicians must remember the importance of other strategies, such as avoiding unnecessary contrast studies and ensuring adequate intravenous hydration.

Strengths of our study include the comprehensive search strategy and the careful statistical methodology used. We identified 15 trials with a total of 1776 subjects, considerably more than a recently published meta-analysis, which included only 805 participants [34]. These authors found that NAC reduced the risk of contrast nephropathy in their primary analysis and several sensitivity analyses. Unfortunately, they were unable to include several recently completed studies in which the effect of NAC was nonsignificant, including the largest trial to date [22]. Unlike the findings of Birck et al, our results indicate some uncertainty as to whether NAC actually reduces the risk of contrast nephropathy. This discrepancy appears to be due to our inclusion of the more recent data. However, both meta-analyses are limited by differences in the definitions of contrast nephropathy and NAC protocols in the various studies, and probably other poorly quantified factors. Because of the multiple analyses performed, conclusions drawn from any particular subset of studies (those considering only cardiac interventions, for example) should be interpreted with caution. Nonetheless, our systematic review summarizes what is known about the effect of NAC on contrast nephropathy, and suggests that further work is needed to determine which patients, if any, derive clinical benefit from its use.

CONCLUSION

NAC may reduce the incidence of acutely increased serum creatinine after administration of intravenous contrast, but this finding was of borderline statistical significance and was not observed in several prespecified subgroups. In addition, there is currently no direct evidence that its use decreases healthcare costs, the risk of permanent renal damage, or the need for acute dialysis. Before NAC becomes the standard of care for all patients receiving intravenous contrast, new randomized trials evaluating its effect on clinically relevant outcomes are required.

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