N-Acetylcysteine for the Prevention of Radiocontrast Induced Nephropathy: A Meta-Analysis of Prospective Controlled Trials

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Abstract. N-acetylcysteine has been recommended for patients with renal insufficiency who are to receive radiocontrast media. However, trials of oral N-acetylcysteine for the prevention of radiocontrast-induced nephropathy have yielded inconsistent results. A systematic review of patient and study characteristics was undertaken to discover possible explanations of the inconsistencies. The databases MEDLINE, EMBASE, and CENTRAL (1966 to March 2003) were searched in all languages, and conference proceedings from several professional societies from the years 1999 to 2003 were also searched. Only prospective controlled trials of oral N-acetylcysteine were included. Risk difference estimates and 95% confidence intervals were calculated. The estimates were examined for evidence of publication bias and heterogeneity. Stratified and meta-regression analyses were used to compare estimates by study and patient characteristics. Identified were 16 studies, 15 published and 1 unpublished. There was no evidence of publication bias, but there was substantial evidence of heterogeneity, thus precluding reliance on a meaningful summary effect estimate. Meta-regression identified several patient and study characteristics, with some evidence of association with study-specific estimates. None of these characteristics, however, formed subsets of studies with results that were homogeneous enough to aggregate. Research on N-acetylcysteine and the incidence of radiocontrast nephropathy is too inconsistent at present to warrant a conclusion on efficacy or a recommendation for its routine use. Identified patient and study characteristics may be responsible for some, but not all, of this inconsistency. A large, randomized, placebo-controlled trial, a pooled analysis of patient-level data, or both may resolve this issue.

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Over the last 3 yr, enthusiasm for the use of oral N-acetylcysteine to prevent radiocontrast-induced nephropathy has been growing (1). A breakthrough study (2) first reported a large and significant reduction in the risk of radiocontrast-induced nephropathy compared with placebo among patients with moderate renal dysfunction. Subsequent studies produced mixed results (3–6). Recently, a large study (7), arguably with a relatively high degree of power and sound methods, seemed to confirm the beneficial effect of this agent. N-acetylcysteine is now being routinely recommended as preventative therapy, as an additive to low-osmolar contrast media and intravenous hydration, for patients with reduced renal function who are to undergo a planned exposure to radiocontrast media (8,9). Yet the reasons for discrepant findings among the trials need investigation before the widespread use of N-acetylcysteine can be recommended.

We therefore performed a systematic review and meta-analysis of available prospective controlled trials to quantify and compare reported associations of oral N-acetylcysteine with the incidence of nephropathy after exposure to radiocontrast media. For this review, we examined several key questions. Is there evidence of publication bias? Are there differences among the study results compatible with chance variation? Are there characteristics of studies or participating patients associated with meaningful changes in the association of administration of N-acetylcysteine and the incidence of radiocontrast-induced nephropathy? And most importantly, does the existing literature currently support a conclusion regarding the effectiveness of administration of oral N-acetylcysteine to reduce the occurrence of radiocontrast-induced nephropathy?
Materials and Methods

Inclusion Criteria

The inclusion criteria were determined by the three study authors (AVK, AM, NF) involved in planning the meta-analysis. Trials were included in the systematic review only if they were prospective and controlled. Trials had to include individuals with renal insufficiency, defined as an average trial serum creatinine (SCr) concentration 1.2 mg/dl or more, or average creatinine clearance less than 70 ml/min per 1.73 m². These individuals had to be assigned to oral N-acetylcysteine or to placebo/no intervention before the administration of intravenous radiocontrast. The comparison groups could not be assigned to other interventions, such as fenoldopam or theophylline.

Identification of Relevant Trials

Identification of relevant trials was performed by three study authors (AVK, AM, NF). We performed a MEDLINE search of the literature from 1966 to March 2003 using the terms N-acetylcysteine and radiocontrast. Searches of EMBASE and the Cochrane Collaboration’s register, CENTRAL, were also performed between 1974 and March 2003 using the terms N-acetylcysteine, contrast, and clinical trial. In addition, we reviewed abstracts from the annual meetings of the American Society of Nephrology, National Kidney Foundation, American Heart Association, and Radiologic Society of North America from 1999 to 2002, and from the American College of Cardiology from 1999 to 2003, to identify studies not yet published at the time of our literature search. We also reviewed the bibliographies of original and review articles that investigated N-acetylcysteine. We were also aware of an ongoing trial at the University of North Carolina examining the effect of N-acetylcysteine on the prevention of radiocontrast nephropathy directed by three of the contributing authors (MA, CDC, EMO). The study was initially designed to enroll 100 patients but was terminated after recruitment of 25 patients for reasons of study personnel. The study authors (MA, CDC, EMO) offered to share results of their unpublished study after learning of our intention to perform this systematic review.

Data Analyses

Specific data to be incorporated into the analysis were abstracted independently from the articles by three researchers (AVK, AM, NF) without masking. The three researchers extracted the information and recorded it on preprinted forms. The three researchers then met to confirm findings and to resolve any differences. We did not test formally for agreement among the three researchers with a kappa statistic. The extracted information included the following: definition of radiocontrast-induced nephropathy, number of patients at initiation of study, average patient age, prevalence of diabetes and congestive heart failure, average baseline SCr concentration, hydration protocol, total hydration volume, weight before and after administration to assess hydration status, type of radiocontrast medium, average volume of radiocontrast medium, dose of N-acetylcysteine, timing of N-acetylcysteine administration, change in SCr concentration after 48 h, incidence of radiocontrast-induced nephropathy (as defined below), and the proportion of individuals needing dialysis. Information that was not clearly presented within the body of the article or abstract was clarified by contacting the primary investigators (5,6,10,11).

The clinical end point investigated was the risk of radiocontrast-induced nephropathy measure at or after 48 h. Radiocontrast-induced nephropathy was defined as (1) a 0.5 mg/dl or more increase in SCr from baseline after 48 h, or (2) a 25% or more increase in SCr from baseline after 48 h. Our definition was based on the current literature and was used by all studies incorporated in the meta-analysis. Physiologically, the peak elevation of the SCr concentration after administration of radiocontrast media is known to occur after 48 h and generally begins to drop after 96 h. Furthermore, studies have shown that a creatinine change of 25% or more has the same mortality as larger changes and is a sensitive predictor of the future need for dialysis (12,13).

Statistical Analyses

Evidence of publication bias was investigated by means of funnel plot, Beggs and Mazumdar’s test (14), and the test of Egger et al. (15) If there is no publication bias, the expected shape of this plot is a symmetrical, funnel-shaped distribution of effect estimates above and below the summary estimate, with the more precise estimates more tightly clustered and the less precise estimates more widely dispersed around the summary value. Beggs and Mazumdar’s test is a rank correlation test of the null hypothesis that the studies’ estimates are not associated with their estimated standard errors. The test of Egger et al. regresses the z-score on the standard error. The expected intercept of this regression equation is zero when the estimates and their standard errors are unassociated. Thus, both tests are tests of funnel plot symmetry.

Heterogeneity of the trials was assessed by means of Cochran’s Q statistic, which has a χ² distribution with degrees of freedom equal to one minus the number of estimates. When all trials produce unbiased estimates of the same true population value and their results therefore differ only by chance, the expected value of this statistic equals the degrees of freedom (16). The test of homogeneity was conducted for all studies and also for various subsets of studies, including the trials that used a randomization scheme and trials that used both randomization and placebo. We also conducted tests of homogeneity for all studies using relative risk or odds ratio as a means of sensitivity analysis.

We performed meta-regression analyses to assess the association between risk difference estimates from the trials and characteristics of those trials and their participating patients. All study characteristics were selected a priori as potentially influential. The small number of trials precluded the use of multivariable meta-regression. Selected characteristics were: (1) randomized trial (versus nonrandomized); (2) N-acetylcysteine given the day before (versus day of); (3) placebo used (versus no placebo); (4) abstract (versus peer-reviewed journal article); (5) iso-osmotic contrast used (versus low-osmolality contrast used); (6) average baseline SCr of all study subjects within each trial; (7) difference in average baseline SCr between treatment and control groups within each trial; (8) average contrast volume within each trial; (9) difference in average volume between treatment and control groups within each trial; (10) average age of subjects within each trial; (11) difference in average age between treatment and control groups; (12) average prevalence of diabetes within each trial; (13) difference in diabetes prevalence between treatment and control groups within each trial; and (14) the type of saline used, 0.9% or 0.45%. The meta-regression was conducted both for all studies and, as a sensitivity analysis, for the studies in which randomization to treatment group was a feature of the study design. We estimated the association between treatment and outcome by using the risk difference with 95% confidence intervals calculated for each study, and a summary or aggregate risk difference by using the Metan program in Stata.

Results

Our search strategy yielded a total of 18 clinical trials of N-acetylcysteine used to prevent radiocontrast-induced nephropathy (Figure 1). Sixteen studies met the inclusion criteria.
Eighteen clinical trials were identified

16 prospective controlled trials used in the analysis

Two sets of univariate linear meta-regressions were performed; the first set used all 16 trials, and is summarized in Table 2. Most of the study characteristics were associated with risk difference estimates from the individual studies to an extent that, although imprecisely estimated, would be clinically meaningful. For example, how the primary study authors defined radiocontrast nephropathy—absolute versus percentage change in Scr—changed the risk difference by 0.05. The prevalence of diabetic patients was associated with a change in the risk difference by 0.06; other notable examples include the timing measurement of Scr and the use of iso-osmolar radiocontrast media. The level of baseline renal function, as assessed by Scr concentration, did not meaningfully affect the summary estimate. None of these characteristics of the studies and patients completely resolved the inconsistencies, however.

There was no clinically significant change in the identified patient and study characteristics when meta-regression was limited to only the 11 randomized clinical trials. There was no difference in the incident need for hemodialysis between the two groups.

Discussion

This systematic review suggests that currently, there is not a wholly positive answer to the question: does the use of oral N-acetylcysteine before radiocontrast media reduce the incidence of acute radiocontrast-induced nephropathy? The analysis of 16 prospective controlled clinical trials (with a total of 1538 subjects) suggests, first and foremost, that there is sub-
stantial interstudy variability of estimated effects outcomes, despite an outwardly similar design (prospective, controlled, patients with baseline renal insufficiency). This interstudy variability was strongly confirmed by formal statistical testing for heterogeneity and held even when only randomized trials were analyzed.

We regarded the presence of such pronounced heterogeneity to contraindicate reliance on any single summary estimate of treatment effect. An aggregated summary estimate in such a circumstance would be an oversimplification, as the presence of heterogeneity clearly suggests the existence of study characteristics, patient characteristics, or both, that appreciably influence the magnitude, and perhaps also the direction, of the effect estimates that different trials produce. We did not subscribe to the view that incorporation of the among-study variance (random-effects model) into the computation of a summary estimate accommodates or accounts for inconsistent results among the studies. Rather, we concurred with the observation of DerSimonian and Laird that “in drawing inferences from heterogeneous but logically related studies...the use of regression analysis to characterize differences in study outcomes may be more appropriate” (21) and have followed that advice.

As such, univariate meta-regression analysis has suggested that patient characteristics and study design may account for discrepant results of the effect of N-acetylcysteine. On closer examination, these characteristics are plausible explanations of the observed heterogeneity and may serve to direct future investigations of the use of N-acetylcysteine. Speculatively, the identified characteristics may also guide clinicians to carefully choose certain groups of patients for the intervention.

Take for example, the characteristic, the time of dosing of...
<table>
<thead>
<tr>
<th>Primary Author of Study</th>
<th>Year</th>
<th>Design&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Publication Type</th>
<th>Indication for Contrast Media&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Dosing of NAC</th>
<th>IV Hydration Regimen (ml/kg/h)</th>
<th>Treatment Arms&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Average Age (yr)</th>
<th>Prevalence of Diabetes (%)</th>
<th>Average Baseline Serum Creatinine, μmol/L (SD)</th>
<th>Average Contrast Volume, ml (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tepel (2)</td>
<td>2000</td>
<td>RPCT</td>
<td>Peer reviewed</td>
<td>CT scan</td>
<td>600 mg bd 1 d before day of study</td>
<td>0.45% NS 12 h before &amp; 12 h after</td>
<td>Iopromide</td>
<td>NAC</td>
<td>66 (11)</td>
<td>32 (220 (114) NA)</td>
<td>75 (NA)</td>
</tr>
<tr>
<td>Adamian (47)</td>
<td>2002</td>
<td>CT</td>
<td>Abstract</td>
<td>LHC + intervention</td>
<td>600 mg bd 1 d before &amp; 1 d after</td>
<td>NA</td>
<td>Iodixanol</td>
<td>Placebo</td>
<td>65 (15)</td>
<td>33 (211 (114) NA)</td>
<td>75 (NA)</td>
</tr>
<tr>
<td>Allaqaband (10)</td>
<td>2002</td>
<td>RCT</td>
<td>Peer reviewed</td>
<td>Peripheral or LHC ± intervention</td>
<td>600 mg bd 1 d before &amp; 1 d after</td>
<td>0.45% NS 12 h before &amp; 12 h after</td>
<td>Iodixanol</td>
<td>Control</td>
<td>72 (10)</td>
<td>53 (215 (115) NA)</td>
<td>115 (59)</td>
</tr>
<tr>
<td>Briguori (4)</td>
<td>2002</td>
<td>RCT</td>
<td>Peer reviewed</td>
<td>Peripheral or LHC ± intervention</td>
<td>600 mg bd 1 d before &amp; 1 d after</td>
<td>0.45% NS 12 h before &amp; 12 h after</td>
<td>Iopromide</td>
<td>Control</td>
<td>71 (10)</td>
<td>43 (179 (42) 68)</td>
<td>133 (68)</td>
</tr>
<tr>
<td>Dua-Sandoval (30)</td>
<td>2002</td>
<td>BRPCT</td>
<td>Peer reviewed</td>
<td>LHC</td>
<td>600 mg bd 1 dose before and 3 d after</td>
<td>0.45% NS 2–12 h before and 12 h after</td>
<td>Ioxilan</td>
<td>Placebo</td>
<td>74 (2)</td>
<td>40 (146 (5) 32)</td>
<td>179 (8)</td>
</tr>
<tr>
<td>Durham (3)</td>
<td>2002</td>
<td>RPCT</td>
<td>Peer reviewed</td>
<td>LHC ± intervention</td>
<td>1200 mg 1 h before and 3 h after</td>
<td>0.45% NS up to 12 h before and 12 h after</td>
<td>Iodixanol</td>
<td>Placebo</td>
<td>72 (2)</td>
<td>45 (137 (4) 38)</td>
<td>180 (12)</td>
</tr>
<tr>
<td>Goldenberg (48)</td>
<td>2003</td>
<td>BRPCT</td>
<td>Abstract</td>
<td>LHC ± intervention</td>
<td>600 mg tid 1 d before and 1 d after</td>
<td>0.45% NS 12 h before and 12 h after</td>
<td>Iopamidol</td>
<td>Placebo</td>
<td>70 (10)</td>
<td>46 (202 (44) 38)</td>
<td>85 (42)</td>
</tr>
<tr>
<td>Kahlon (5)</td>
<td>2002</td>
<td>RPCT</td>
<td>Abstract</td>
<td>LHC ± intervention</td>
<td>600 mg bd 1 d before and 1 d after</td>
<td>0.9% NS 70 ml/kg bolus for 12 h before and 12 h after</td>
<td>Iodixanol</td>
<td>Placebo</td>
<td>66 (12)</td>
<td>57 (185 (60) 53)</td>
<td>105 (65)</td>
</tr>
<tr>
<td>Oldemeyer (6)</td>
<td>2003</td>
<td>BRPCT</td>
<td>Abstract</td>
<td>LHC</td>
<td>1500 mg bd × 4 doses</td>
<td>0.45% NS 12 h before and 12 h after</td>
<td>Iopamidol</td>
<td>Placebo</td>
<td>71 (9)</td>
<td>59 (172 (41) 72)</td>
<td>108 (68)</td>
</tr>
<tr>
<td>Shyu (19)</td>
<td>2002</td>
<td>RPCT</td>
<td>Peer reviewed</td>
<td>LHC ± intervention</td>
<td>400 mg bd 1 d before and 3 d after</td>
<td>0.45% NS 12 h before and 12 h after</td>
<td>Iopamidol</td>
<td>Placebo</td>
<td>75 (8)</td>
<td>49 (146 (57) 32)</td>
<td>127 (73)</td>
</tr>
<tr>
<td>Vallero (45)</td>
<td>2002</td>
<td>CT</td>
<td>Peer reviewed</td>
<td>LHC ± intervention</td>
<td>600 mg bd 1 d before and 1 d after</td>
<td>0.45% NS 1–2 h before and 24 h after</td>
<td>Iodixanol</td>
<td>Placebo</td>
<td>70 (7)</td>
<td>64 (246 (70) 46)</td>
<td>115 (48)</td>
</tr>
<tr>
<td>Boccalandro (46)</td>
<td>2003</td>
<td>CT</td>
<td>Peer reviewed</td>
<td>LHC ± intervention</td>
<td>600 mg bd 1 d before and 1 d after</td>
<td>0.45% NS 12 h before and 12 h after</td>
<td>Iodixanol</td>
<td>Placebo</td>
<td>65 (11)</td>
<td>67 (135 (39) 58)</td>
<td>192 (142)</td>
</tr>
<tr>
<td>Kay (7)</td>
<td>2003</td>
<td>BRPCT</td>
<td>Peer reviewed</td>
<td>LHC ± intervention</td>
<td>600 mg bd 1 d before and 1 d after</td>
<td>0.45% NS 12 h before and 12 h after</td>
<td>Iopamidol</td>
<td>Placebo</td>
<td>66 (11)</td>
<td>58 (167 (53) 109 (68 to 263))</td>
<td>191 (120)</td>
</tr>
<tr>
<td>Loutrianakis (49)</td>
<td>2003</td>
<td>RPCT</td>
<td>Abstract</td>
<td>LHC</td>
<td>600 mg bd 1 d before and 1 d after</td>
<td>NA</td>
<td>NA</td>
<td>Placebo</td>
<td>69 (50–81)</td>
<td>36 (111 (66 to 320) 36)</td>
<td>120 (70 to 300)</td>
</tr>
<tr>
<td>Nogareda&lt;sup&gt;d&lt;/sup&gt; (11)</td>
<td>2003</td>
<td>CT</td>
<td>Abstract</td>
<td>LHC + RA ± intervention</td>
<td>600 mg immediately before then bd × 2 d</td>
<td>NA</td>
<td>Ioversol</td>
<td>Placebo</td>
<td>73 (68–79)</td>
<td>42 (147 (115 to 159) 109)</td>
<td>164 (128 to 200)</td>
</tr>
<tr>
<td>Agrawal Unpublished</td>
<td></td>
<td>RCT</td>
<td>Unpublished</td>
<td>LHC ± intervention</td>
<td>800 mg 24 h before then 600 mg bd × 1 d</td>
<td>0.45% NS 12 h before &amp; 12 h after</td>
<td>Iodixanol</td>
<td>Placebo</td>
<td>75 (70–80)</td>
<td>34 (122 (99 to 139) 162)</td>
<td>162 (125 to 389)</td>
</tr>
</tbody>
</table>

<sup>a</sup> BRPCT, Double blinded randomized placebo-controlled trial; RPCT, randomized placebo-controlled trial; RCT, randomized controlled trial; CT, controlled trial.

<sup>b</sup> LHC, Left heart catheterization; RA, renal arteriogram.

<sup>c</sup> N, NAC; P, placebo.

<sup>d</sup> Median and interquartile range specified.

<sup>e</sup> NA, not available.
Studies whose participants were dosed with N-acetylcysteine on the day before the procedure were more likely to demonstrate a reduction of radiocontrast-induced nephropathy than those studies dosing participants on the day of the procedure. Individuals receiving their first dose of N-acetylcysteine on the day before, rather than on the day of, the radiocontrast media may have greater systemic levels of the antioxidant agent. However, peak serum levels of N-acetylcysteine occur 1 h after oral administration, and the half-life of reduced N-acetylcysteine is approximately 2 h (22). Reduction in renal function, furthermore, should not alter the elimination pathway for the agent.

Other important characteristics identified by the univariate meta-regression include the age of subjects, prevalence of diabetes mellitus, and the type and volume of radiocontrast media used by the individual studies. Studies with a higher proportion of elderly individuals or diabetic patients, or studies that used a high volume of radiocontrast media or that used a relatively high osmolality agent, were associated with a change in the estimated risk difference in a direction favoring N-acetylcysteine. Most of these identified characteristics are known to be risk factors for the development of radiocontrast-induced nephropathy (23). Thus, it is conceivable that the effectiveness of N-acetylcysteine may be greatest among a population of individuals with a high baseline risk of developing radiocontrast-induced nephropathy.

Yet there were some inconsistent findings with respect to the risk factors for contrast nephropathy. Notably, the level of renal function at baseline was not associated with a change in the estimated effect of N-acetylcysteine. It may be that SCr concentration is too imprecise and insensitive as an estimate of GFR (24). Furthermore, the estimated effect N-acetylcysteine was greater among the group of individuals with intravenous hydration greater than 12 h compared to the group receiving less than 12 h of saline hydration. We have no pathophysiological explanation for the finding, and speculatively, this may reflect an intrinsic anomaly of the data set.

The findings of our systematic review should be interpreted in the context of both intrinsic limitations of meta-analysis, and in the context of our own study-specific (subject matter) limitations. In systematic reviews, the traditional unit of analysis is each study, rather than patients. Thus, the power to detect a difference in aggregate or to identify explanatory variables by meta-regression is greatly diminished compared with large primary trials with individual-level data (or to meta-analyses with individual-level data). Furthermore, interpretation of any results for study or patient characteristics that must be represented by study population average values or percentages are prone to the ecologic fallacy (25).

Second, although we have strongly demonstrated heterogeneity, we were not able to identify any single characteristic of studies or patients within levels or categories of which the results are consistent. Nor, among the randomized trials, did the results of the placebo-controlled trials differ materially from those that did not use placebo controls. The small number of studies made it difficult to determine whether multiple study and patient characteristics in combination might render the results more consistent.

Third, we predominately identified and used published studies. Our search strategy identified only one unpublished trial, and thus our results are heavily weighted on the findings of these published trials. We identified an unpublished study of quality at our local institution. It is quite likely that other unpublished studies exist at other institutions, and we hope that the publication of this study will allow for the eventual analysis of these other studies. The exclusion of unpublished data are generally associated with an overestimate of the true effect in

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**Figure 2.** Funnel plot with pseudo 95% confidence limits for all 16 trials. rd, risk difference; s.e., standard error.

**Figure 3.** Forest plot of weighted risk difference of all 16 controlled clinical trials. Relative weight is reported in parentheses after year of publication.

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meta-analysis (26). By far the single most common reason for the inability to publish a trial is the lack of statistical significance, although some have suggested that the quality of unpublished trials may not be comparable to those accepted in peer-reviewed journals (27). The unpublished study included in this analysis was of high quality, randomized, placebo controlled, and masked. In addition, we did not use a masked assessment of study quality, nor did we formally test agreement among the independent observers.

Acute renal failure remains a common clinical occurrence
among hospitalized patients (28–30). The development of acute renal failure increases morbidity (31,32), cost (33), and mortality (34–37). Exposure to radiocontrast media is a common iatrogenic cause of acute renal failure among hospitalized patients with chronic kidney disease (38). The use of nonionic, low-osmolality radiocontrast media (39,40) and the administration of intravenous fluids (41,42) have attenuated the risk of developing acute renal failure. Initial studies suggested a highly beneficial effect of N-acetylcysteine, and clinicians rapidly adopted the agent into their armamentarium.

This systematic review suggests that the role of oral N-acetylcysteine in the prevention of radiocontrast-induced nephropathy has yet to be defined. The literature as it currently exists is profoundly heterogeneous, making any single summary estimate invalid. Thus, the analysis could not demonstrate an added benefit of oral N-acetylcysteine among all individuals with preexistent renal insufficiency. Meta-regression analysis identified some important study and patient characteristics that may partially explain the heterogeneity: the time of N-acetylcysteine administration, advanced age, presence of diabetes mellitus, and the volume and type of radiocontrast media. It is biologically plausible that these characteristics would affect the relationship of N-acetylcysteine and therefore may serve to guide future research in this field.

Our results may have some important immediate and long-term implications. First, rather than the indiscriminate use of N-acetylcysteine, clinicians may better direct their efforts at proven interventions (intravenous saline, low-osmolality/isosmolality contrast media). Second, clinicians should be judicious in their decision to order radiographic tests. Third, given the low side-effect profile and cost of N-acetylcysteine, a large, randomized, placebo-controlled trial should be conducted. Large randomized-controlled trials have been known to differ with findings of meta-analyses (43,44). Alternatively, a pooled analysis of individual patient data may be a more economical way of answering the question and likely should be done as a prelude to a mega-trial. In conclusion, the findings of this systematic review do not support the routine use of N-acetylcysteine for the prevention of radiocontrast-induced nephropathy.

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References
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