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In the Literature

Prevention of Contrast-Associated Acute Kidney Injury: What Should We Do?

Commentary on Eng J, Wilson RF, Subramaniam RM, et al. Comparative effect of contrast media type on the incidence of contrast-induced nephropathy: a systematic review and meta-analysis. Ann Intern Med. *2016;164(6):417-424, and Subramaniam RM, Suarez-Cuervo C, Wilson RF, et al. Effectiveness of prevention strategies for contrast-induced nephropathy: a systematic review and meta-analysis.* Ann Intern Med. *2016;164(6):406-416.*

Contrast-associated acute kidney injury (AKI) is a common iatrogenic complication associated with increased health resource utilization and adverse outcomes, including short- and long-term mortality and accelerated progression of underlying chronic kidney disease (CKD). Although the causal nature of these associations is not established, these findings underlie past and ongoing efforts to identify interventions to reduce patients' risks for this condition. Contrast-associated AKI is potentially preventable because high-risk patients often are identifiable by the presence of underlying comorbid conditions such as CKD, the precise timing of the kidney insult is known in advance, and most contrast-enhanced procedures are performed nonemergently with ample time to implement prophylactic measures. Early studies confirmed that use of low-osmolal contrast media (osmolality 2-3 times that of plasma) compared with high-osmolal contrast media (osmolality > 4 times that of plasma) and the administration of periprocedural intravenous (IV) isotonic crystalloid both reduce the risk for contrast-associated AKI in at-risk patients.[1-3] More recent clinical trials that compared newer generation contrast agents; evaluated pharmacological interventions, including antioxidants and statins; and investigated IV crystalloid solutions containing bicarbonate have yielded conflicting findings. This led to efforts to systematically examine trial results using meta-analyses.

WHAT DO THESE STUDIES SHOW?

Two recently published meta-analyses[4,5] based on comparative effectiveness reviews prepared for the Agency for Healthcare Research and Quality (AHRQ)[6,7] evaluated interventions for the prevention of contrast-associated AKI. Key findings of the studies are summarized in Box 1. In the first study, Eng et al[4] examine clinical trials that compared different low-osmolal contrast media and that compared iso-osmolal iodixanol with low-osmolal contrast media. Each trial was assessed for risk of bias and all pooled comparisons were graded on their strength of evidence, ranging from insufficient to high. The investigators assessed each comparison for clinical importance, defined a priori as a point estimate of the reduction in risk for contrast-associated AKI of no less than 25% (ie, risk ratio [RR] ≤ 0.75) and statistical significance, assessed based on whether the 95% confidence interval (CI) excluded a pooled RR of 1.0.

Twenty-nine trials were included in this meta-analysis, of which 5 (826 patients) compared different low-osmolal contrast media and 25 (5,053 patients) compared iodixanol with low-osmolal contrast media. The investigators found that none of the trials comparing low-osmolal contrast media demonstrated statistically significant or clinically important differences in effect, while reporting low strength of evidence for these comparisons. Of 25 trials comparing iodixanol with low-osmolal contrast media, 2 were omitted due to the absence of a clear definition of contrast-associated AKI. The other 23 trials collectively demonstrated a statistically significant, yet clinically unimportant, reduction in risk for contrast-associated AKI with iodixanol (RR = 0.80; 95% CI, 0.65-0.99). Subgroup analyses based on route of contrast administration, dose of contrast, and underlying patient characteristics found no benefit to iodixanol. The investigators concluded that there was no difference in risk for contrast-associated AKI among low-osmolal contrast media and that despite finding a statistically significant reduction in risk for contrast-associated AKI with iodixanol, the observed point estimate of the reduction in relative risk (20%) did not exceed the 25% minimal threshold for clinical importance.

The second study by Subramaniam et al[5] examines the efficacy of *N*-acetylcysteine (NAC), statins, sodium bicarbonate, and ascorbic acid in mitigating contrast-associated AKI risk. Overall, 86 clinical trials were included, 54 of which compared NAC along with IV saline to IV saline with or without placebo. The investigators reported that low-dose NAC (RR = 0.75; 95% CI, 0.63-0.89) and NAC in the setting of low-osmolal contrast media use (RR = 0.69; 95% CI, 0.58-0.84) were associated with

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Box 1. Key Findings of Meta-analyses of Prevention Strategies for Contrast-Associated AKI

Type of contrast media

- There were no differences in risk for contrast-associated AKI associated with different types of low-osmolal contrast media
- Iodixanol was associated with a non–clinically significant reduction in risk for contrast-associated AKI as compared, in aggregate, with low-osmolal contrast media

NAC

- In patients receiving intravenous saline, NAC was associated with a reduction in risk for contrast-associated AKI when low-osmolal contrast media were used, but not when iodixanol was the contrast medium used
- In patients receiving intravenous saline, low-dose NAC was associated with a borderline clinically significant reduction in risk for contrast-associated AKI, regardless of type of contrast media used
- In patients receiving intravenous saline, high-dose NAC was not associated with reduction in risk for contrast-associated AKI, regardless of type of contrast media used

Intravenous sodium bicarbonate

- Intravenous sodium bicarbonate as compared to intravenous saline was not associated with a reduction in risk for contrast-associated AKI

Statins

- In patients receiving both intravenous crystalloid and NAC, statins were associated with a clinically significant reduction in risk for contrast-associated AKI
- In patients receiving intravenous saline without NAC, statins were not associated with a reduction in risk for contrast-associated AKI

Ascorbic Acid

- In patients receiving intravenous saline, ascorbic acid was not associated with reduction in risk for contrast-associated AKI

Abbreviations: AKI, acute kidney injury; NAC, *N*-acetylcysteine.
Source: Eng et al[4] and Subramaniam et al.[5]

reductions in risk for contrast-associated AKI, whereas low-dose NAC with intra-arterial contrast administration (RR = 0.77; 95% CI, 0.66-0.91) and oral NAC (RR = 0.77; 95% CI, 0.65-0.92) were associated with "clinically unimportant" but statistically significant reductions in risk. No benefit was found for high-dose NAC, low-dose NAC with IV contrast administration, IV NAC, or NAC in the setting of iodixanol use. The strength of evidence for most comparisons was low.

Pooling 19 trials, the investigators found that IV sodium bicarbonate was not associated with reduction in risk for contrast-associated AKI (RR = 0.93; 95% CI, 0.68-1.27), with low strength of evidence. The use of statins (with IV crystalloid) was associated with a clinically important but non–statistically significant reduction in risk (RR = 0.68; 95% CI, 0.39-1.20) in 8 studies with low strength of evidence. In 5 studies that evaluated statins in addition to NAC and IV crystalloid, statins were associated with a reduction in risk for contrast-associated AKI (RR = 0.52; 95% CI, 0.29-0.93). Finally, in the setting of IV crystalloid administration, ascorbic acid was associated with a clinically important but non–statistically significant reduction in risk (RR = 0.72; 95% CI, 0.48-1.01). The investigators concluded that the largest reduction in risk for contrast-associated AKI was with NAC among patients receiving low-osmolal contrast media and with statins administered with NAC.

These meta-analyses have important limitations. While acknowledged by the authors, Eng et al considered all low-osmolal contrast media collectively despite prior studies suggesting that iohexol may be associated with increased nephrotoxicity compared with other low-osmolal agents.[8,9] Furthermore, nearly half the 29 trials overall and 4 of the 5 trials comparing low-osmolal contrast media enrolled patients without underlying CKD and thus with relatively low risk for contrast-associated AKI, biasing analyses toward the null. In addition, differences across trials in use, dose, and timing of administration of other potentially preventive interventions such as NAC and IV fluids could not be fully accounted for in this meta-analysis. A notable proportion of trials included in the analysis by Subramaniam et al also enrolled patients without CKD, which predisposed the pooled analyses to finding no benefit. Moreover, Subramaniam et al reported a benefit with low-dose NAC that was not seen with high-dose NAC, a finding that lacks biological plausibility and likely reflects the larger size and greater methodological rigor of trials that used high-dose NAC.[10]

Other caveats common to both meta-analyses also warrant consideration. First, most comparisons had low strength of evidence related to the low quality of the included clinical trials, almost all of which enrolled small numbers of patients. These trials were designed based on implausibly large postulated effect sizes and therefore had very limited statistical power.[11] Second, none of the interventions reduced clinically important outcomes such as need for dialysis therapy, mortality, or cardiac events. Although small increments in serum creatinine levels used to define contrast-associated AKI have been associated with subsequent mortality and persistent decline in kidney function, the causal nature of these associations is not established. Finally, the arbitrary definition of clinical importance based exclusively on the point estimate of risk reduction (≥25%) without considering the CI is potentially misleading. For example, an intervention with a point estimate for the RR of contrast-associated AKI of 0.76 with a narrow CI (eg, 0.72-0.80) would be labeled clinically unimportant, whereas an intervention with a slightly lower

point estimate of 0.74 but a much wider CI (eg, 0.49-0.99) would be deemed clinically important.

Importantly, several of the interventions analyzed in the study by Subramaniam et al are imprecisely described in both the AHRQ Comparative Effectiveness Review[7] and the *Annals of Internal Medicine* article.[5] Although IV crystalloid was administered in both the treatment and control arms in all included clinical trials, the comparisons are variably characterized as NAC, statin, or ascorbic acid versus IV saline, suggesting that these agents can be administered in lieu of IV crystalloid, which is not the case.

HOW DO THESE STUDIES COMPARE WITH PRIOR STUDIES?

During the past decade, several meta-analyses have compared iodixanol with low-osmolal contrast media for the prevention of contrast-associated AKI.[8,9,12-14] Two studies reported finding no statistically significant differences; one found a statistically significant benefit to iodixanol, particularly in patients with CKD, and one found no difference overall but noted significant heterogeneity among trials that included patients with kidney disease who received intra-arterial contrast. Specifically, the effect differed when trials using iohexol were segregated from trials comparing other low-osmolal contrast media to iodixanol.[8] In this analysis, although there was no difference in risk for contrast-associated AKI observed when iodixanol was compared with low-osmolal contrast media other than iohexol (RR = 0.97; 95% CI, 0.72-1.32), the RR was notably lower (RR = 0.45; 95% CI, 0.26-0.76) in the pooled analysis of 5 trials comparing iodixanol to iohexol. Additionally, a network meta-analysis that included 42 trials with more than 10,000 patients found that iohexol and ioxaglate were associated with increased risk for contrast-associated AKI compared with iodixanol and 4 other low-osmolal contrast media.[9] These findings contrast with the interpretation by Eng et al, which described the evidence of greater risk with iohexol as "indirect" and consequently analyzed all low-osmolal contrast media collectively.

Remarkably, there have been more than 20 meta-analyses examining the effect of NAC on contrast-associated AKI, a similar number examining the effect of statins on contrast-associated AKI, and more than 15 evaluating sodium bicarbonate for the prevention of contrast-associated AKI.[15,16] The findings of these meta-analyses are as conflicting as results of the clinical trials upon which they are based. Although the current meta-analysis by Subramaniam et al used slightly different methodological approaches and analytic techniques from the prior analyses, the considerable overlap of included trials and low quality of the primary data explain the inability for these analyses to determine the true benefit, if any, of these interventions.

WHAT SHOULD CLINICIANS AND RESEARCHERS DO?

The literature is replete with methodologically flawed and inadequately powered trials that have largely failed to inform the use of evidence-based care for the prevention of contrast-associated AKI. Although systematic reviews and meta-analyses represent the pinnacle of the evidence-based medicine hierarchy, their value is dependent on the quality of the primary trials upon which they are based. Consequently, despite numerous meta-analyses, equipoise persists with regard to the role of most interventions for the prevention of contrast-associated AKI because the primary trials are largely of low quality with significant methodological limitations. At the same time, a growing number of observational analyses have documented the underutilization of coronary angiography in patients with CKD, at least in part out of concern for the development of contrast-associated AKI, a phenomenon aptly labeled renalism.[17,18] This observation is particularly notable given that cardiovascular disease is the leading cause of death in patients with CKD, whereas the associations of contrast-associated AKI, defined by small increments in blood creatinine levels, with serious patient-centered outcomes have yet to be proved causal. It is therefore imperative that clinicians appreciate the limitations in research to date related to various interventions for the prevention of contrast-associated AKI; understand that the administration of periprocedural IV isotonic crystalloid, the use of either iodixanol or low-osmolal contrast media, and avoidance of concomitant nephrotoxins such as nonsteroidal anti-inflammatory drugs are effective evidence-based interventions; and ensure that patients with CKD who have clear indications for contrast-enhanced procedures undergo these procedures, albeit with appropriate use of evidence-based preventive care.

It is similarly important for researchers to appreciate why the multiple trials and meta-analyses of interventions to prevent contrast-associated AKI have yielded limited meaningful data. The conduct of small inadequately powered trials focused on small short-term changes in serum creatinine levels rather than more important clinical outcomes has fueled the proliferation of meta-analyses that are unable to generate consistent convincing results. Large adequately powered clinical trials that enroll high-risk patients and evaluate more meaningful outcomes, such as persistent decline in kidney function, need for

dialysis, and death, are essential to move this field forward.

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Effectiveness of Prevention Strategies for Contrast-Induced Nephropathy

A Systematic Review and Meta-analysis

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Background: *N*-acetylcysteine, sodium bicarbonate, statins, and ascorbic acid have been studied for reducing contrast-induced nephropathy (CIN).

Purpose: To evaluate the comparative effectiveness of interventions to reduce CIN in adults receiving contrast media.

Data Sources: MEDLINE, EMBASE, Cochrane Library, ClinicalTrials.gov, and Scopus databases through June 2015. Risk of bias and overall strength of evidence (SOE) of studies were assessed.

Study Selection: Randomized, controlled trials of *N*-acetylcysteine, sodium bicarbonate, statins, or ascorbic acid that used intravenous (IV) or intra-arterial contrast media and defined CIN with enough data for meta-analysis.

Data Extraction: Two reviewers independently extracted data and assessed study quality.

Data Synthesis: Low-dose *N*-acetylcysteine plus IV saline compared with IV saline (risk ratio [RR], 0.75 [95% CI, 0.63 to 0.89]; low SOE), *N*-acetylcysteine plus IV saline compared with IV saline in patients receiving low-osmolar contrast media (RR, 0.69 [CI, 0.58 to 0.84]; moderate SOE), and statins plus *N*-acetylcysteine plus IV saline versus *N*-acetylcysteine plus IV saline (RR, 0.52 [CI, 0.29 to 0.93]; low SOE) had clinically important and statistically significant benefits. The following 3 comparisons suggested a clinically important difference that was not statistically significant: sodium bicarbonate versus IV saline in patients receiving low-osmolar contrast media (RR, 0.65 [CI, 0.33 to 1.25]; low SOE), statins plus IV saline versus IV saline (RR, 0.68 [CI, 0.39 to 1.20]; low SOE), and ascorbic acid versus IV saline (RR, 0.72 [CI, 0.48 to 1.01]; low SOE). Strength of evidence was generally insufficient for comparisons of the need for renal replacement, cardiac events, and mortality.

Limitation: Too few studies were done in patients receiving IV contrast media.

Conclusion: The greatest reduction in CIN was seen with *N*-acetylcysteine plus IV saline in patients receiving LOCM and with statins plus *N*-acetylcysteine plus IV saline.

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Iodine contrast medium is an essential component of many diagnostic and therapeutic procedures that involve medical imaging. One important side effect of iodine contrast is contrast-induced nephropathy (CIN), defined as an increase in serum creatinine levels of more than 25% or 44.2 μmol/L (0.5 mg/dL) within 3 days of intravascular administration in the absence of an alternative cause (1). Because of increasing use of contrast media in radiologic and cardiologic procedures and the increasing prevalence of persons who are vulnerable to CIN (those with chronic kidney disease, diabetes mellitus, or hypertension, as well as elderly persons), kidney failure due to CIN is a substantial concern (2, 3). The reported incidence varies between 7% and 11% depending on the definition of CIN, study population, and setting (2–4). Some studies suggest that this incidence may be overestimated (4), especially when intravenous (IV) contrast media are used. An average additional cost of $10 345 is associated with a CIN-related hospital stay (5).

Many strategies have been used to prevent CIN. They include oral hydration; volume expansion with sodium chloride or bicarbonate or both; administration of *N*-acetylcysteine; withdrawal of metformin, angiotensin-converting enzyme inhibitors, angiotensin II–receptor blockers, or nonsteroidal anti-inflammatory drugs; hemofiltration or hemodialysis; statins; use of low-osmolar contrast media (LOCM), iso-osmolar contrast media (IOCM), or nonionic contrast media; and reducing the volume of contrast media administered. Despite these varied strategies, no clear consensus exists in clinical practice about the most effective intervention to prevent or reduce CIN.

Many meta-analyses have been published, but almost all of them have focused on specific therapies or included subspecialty–specific populations, which reduced the general applicability in clinical practice (6–11). The route of administration of contrast media may be a confounder because the baseline risk profile of patients having intra-arterial (IA) versus IV procedures may differ. Whether effectiveness of preventive interventions depends on the route of administration or the type of contrast media (IOCM or LOCM, the 2 types

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now in regular clinical use in the United States) is also unclear. We did a systematic review and meta-analysis to compare the preventive effect of strategies to reduce CIN, including subgroup analyses based on route of administration of contrast media or preventive strategies and the type of contrast media used.

METHODS

We developed a protocol for this systematic review, which we posted online and registered in PROSPERO (CRD42013006217). The complete protocol is in the full report on which this article is based (12).

Data Sources and Searches

We searched MEDLINE, EMBASE, and the Cochrane Library through 30 June 2015 (**Appendix Table**, available at www.annals.org). In addition, we searched the Scopus database for conference proceedings and other reports. We reviewed the reference lists of relevant articles and related systematic reviews to identify original articles that we might have missed. We also searched ClinicalTrials.gov and the U.S. Food and Drug Administration Web site.

Study Selection

We included studies of patients of all ages. We identified observational and randomized, controlled trials (RCTs) that included administration of *N*-acetylcysteine, sodium bicarbonate, sodium chloride, statins, or ascorbic acid to prevent CIN. The study groups received IOCM or LOCM via IV or IA injection, CIN outcome was explicitly defined, and sufficient data were reported to calculate the primary effect measure (relative risk reduction of CIN). Secondary outcomes included the need for renal replacement therapy, cardiac events, and mortality. We included only RCTs for the meta-analyses. All data from other studies and other strategies to reduce CIN incidence (such as adenosine antagonists, renal replacement therapy, diuretics, antioxidants, and vasoactive agents) were analyzed and included in the full report (12). We excluded studies of high-osmolar contrast medium because it is no longer used in clinical practice in the United States. We did not contact the authors for original data.

Data Extraction and Quality Assessment

Two reviewers independently screened the titles and abstracts for eligibility and independently assessed each study's risk of bias by using 5 items from the Cochrane Risk of Bias Tool for RCTs (3). We solved disagreements by consensus or a third reviewer when consensus was not possible. At random intervals during screening, we did quality checks to ensure that eligibility criteria were applied consistently. The second reviewer checked the accuracy of the data extracted by the first reviewer.

We graded the strength of evidence (SOE) on comparisons of interest for the key outcomes by using the grading scheme recommended in the Methods Guide of the Evidence-based Practice Center and considered the domains of study limitations, directness, consistency, precision, reporting bias, and magnitude of effect (13). Following the guidance of the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) Working Group (14), we rated evidence as precise if the total number of patients exceeded an optimum information size and the 95% CI excluded a risk ratio (RR) of 1.0. If the number of patients exceeded the optimum information size and the CI did not exclude the possibility of no difference (that is, RR of 1.0), we only rated the evidence as precise if the CI excluded the possibility of a clinically important benefit or harm (that is, RR <0.75 or >1.25). We classified the SOE pertaining to each comparison into 4 category grades (high, moderate, low, and insufficient) and assigned SOE grades by group consensus. The body of evidence was considered high-grade if study limitations were low and there were no problems in any other domain, and it was subsequently downgraded for each domain in which a problem was identified. If the magnitude of effect was very large, the SOE could be upgraded.

Data Synthesis and Analysis

The primary outcome was CIN, defined as an increase in serum creatinine levels of more than 25% or 44.2 μmol/L (0.5 mg/dL) within 3 days of intravascular administration of contrast media. We calculated individual study RRs and CIs and then obtained overall and subgroup summary RRs by using a random-effects model. For large comparisons with 18 or more studies, we used the DerSimonian–Laird random-effects estimator, with the estimate of heterogeneity taken from the inverse-variance, fixed-effect model (15). Although this method is often the standard estimator used by many meta-analysis software programs, it tends to underestimate CIs when fewer than 18 studies are compared (15). To compensate, we used the Knapp–Hartung small-sample estimator approach for comparisons with fewer than 18 studies. This method allows for small sample adjustments to the variance estimates and calculates CIs on the basis of the t distribution with $k - 1$ degrees of freedom (15). We used the Harbord modified test for small study effects to determine whether there was asymmetry in effect estimates.

To assess the clinical importance of differences in CIN incidence, a binary outcome, we followed guidance for selecting a minimally important difference on the basis of the overall event rate in the studies (14). Our clinical experts decided that a relative risk reduction of 25% would be clinically important, which is consistent with the guidance that suggests a reduction of 20% to 30% in determining optimal information size.

To account for factors that could be associated with a difference in CIN risk, we did a subgroup analysis on the basis of the route of administration (IA vs. IV) and type of contrast media (IOCM vs. LOCM), baseline serum creatinine level, sex, age, and prevalence of diabetes mellitus. A priori, we assumed that there would be considerable heterogeneity and therefore used a random-effects model. We also examined the I^2, which measures the degree of heterogeneity across studies (I^2 varies from 0% to 100%, with 0% indicating no het-

Table 1. Pooled RRs for CIN With NAC Compared With IV Saline

Pooled Group	Studies, *n*	Pooled RR for CIN (95% CI)
High-dose NAC	18	0.78 (0.59–1.03)
IA administration	16	0.78 (0.55–1.12)
IV administration	2	0.55 (0.12–2.62)
Low-dose NAC	35	0.75 (0.63–0.89)
IA administration	30	0.77 (0.66–0.91)
IV administration	5	0.62 (0.18–2.10)
Oral NAC	40	0.77 (0.65–0.92)
IV NAC	14	0.90 (0.72–1.12)
NAC when LOCM are used	40	0.69 (0.58–0.84)
NAC when IOCM are used	7	1.12 (0.74–1.69)

CIN = contrast-induced nephropathy; IA = intra-arterial; IOCM = iso-osmolar contrast media; IV = intravenous; LOCM = low-osmolar contrast media; NAC = *N*-acetylcysteine; RR = risk ratio.

erogeneity). All statistical analyses were done in Stata, version 13 (StataCorp).

Role of the Funding Source

The Agency for Healthcare Research and Quality selected the topic and assigned it to the Johns Hopkins University Evidence-based Practice Center. The Agency assigned a task order officer who provided comments on the protocol and draft versions of the full evidence report. The Agency did not directly participate in the literature search, determination of study eligibility, data analysis or interpretation, or preparation of the manuscript for publication.

RESULTS

The literature search revealed 86 RCTs on interventions for preventing CIN (**Appendix Figure**, available at www.annals.org). These study results were published between 1998 and 2015. Six studies were funded by industry sources (16–21), 16 were funded by academia or government agencies, 33 had no funding statement, and the remainder reported no conflicts of interest. All findings from these studies were analyzed and described in the full report (12).

N-acetylcysteine Plus IV Saline Versus IV Saline

N-acetylcysteine is a direct scavenger of free radicals and improves blood flow through nitric oxide–mediated pathways, which results in vasodilatation. As a result, both the antioxidant and vasodilatory properties of *N*-acetylcysteine are believed to protect against CIN.

We included 54 RCTs on *N*-acetylcysteine plus IV saline versus IV saline with or without a placebo published since 2002 in the meta-analysis (16–69).

The studies varied widely in patient and intervention characteristics. Study patients had renal dysfunction at baseline (defined as serum creatinine levels >106.08 μmol/L [>1.2 mg/dL]) in 35 studies. **Table 1** summarizes the pooled RRs and CIs for subgroups by high- or low-dose *N*-acetylcysteine administration, route of administration (oral or IV), and type of contrast media (LOCM or ICOM). Pooled RRs for CIN and CIs were derived by using a random-effects model to pool studies comparing *N*-acetylcysteine with IV saline versus IV saline with or without a placebo.

High-dose *N*-acetylcysteine plus IV saline had a small effect on reducing CIN risk that was clinically unimportant and not statistically significant, and low-dose *N*-acetylcysteine plus IV saline had a borderline clinically important effect on preventing CIN. Both comparisons had low SOE. Sensitivity analyses revealed imprecise estimates of the pooled RR for CIN, when stratified by route of administration (**Table 1**). When given orally, *N*-acetylcysteine plus IV saline had a small effect on reducing CIN risk that was clinically unimportant but statistically significant, with low SOE. *N*-acetylcysteine plus IV saline had a clinically important benefit in reducing CIN risk when LOCM were used, with moderate SOE, but had a clinically unimportant effect when IOCM were used, with low SOE (**Figure 1**). We examined how the RRs varied according to baseline characteristics of the study population and did not see any significant difference by age, sex, baseline renal function, or the presence or absence of diabetes mellitus. We did not see a pattern indicative of a trend by study quality.

The overall analysis did not suggest that any intervention was superior when we evaluated secondary outcomes, and the SOE was low or insufficient. The Harbord test for small study effects was done for all comparisons, and no asymmetry was detected (**Table 2**).

IV Sodium Bicarbonate Versus IV Saline

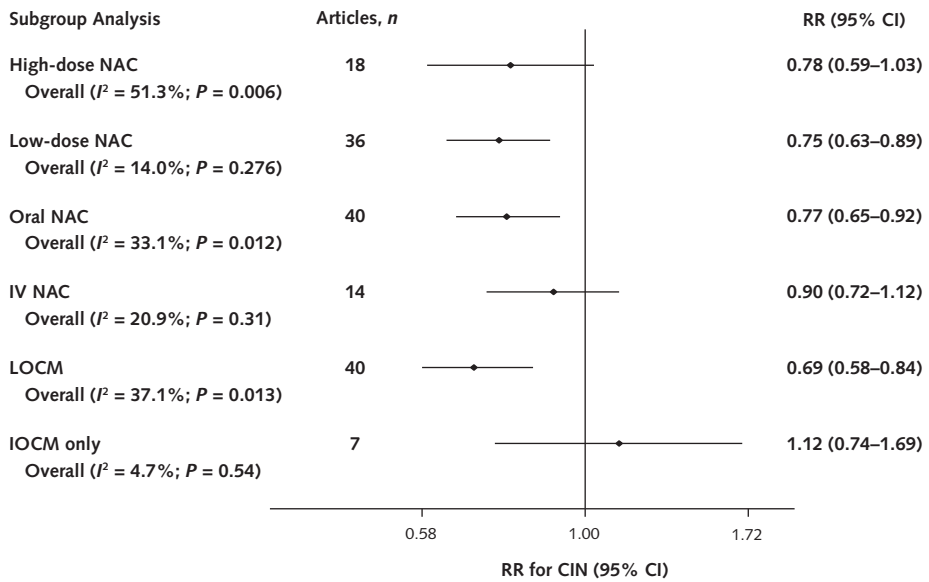
A major hypothesis for using IV sodium bicarbonate to prevent CIN is that the alkalinization of tubular fluid diminishes the production of free oxygen radicals, which may cause CIN.

We included 19 RCTs on IV sodium bicarbonate versus IV saline (21, 35, 48, 59, 62, 69–82). The studies varied widely in patient and intervention characteristics. Study patients had renal dysfunction at baseline in 10 studies. Contrast medium was administered via IV in 2 studies, IA in 14 studies, and IA or IV in 1 study, and 1 study did not report the route of administration. Six studies used IOCM, 12 used LOCM, and 1 did not report the type of contrast media (**Supplement**, available at www.annals.org).

Intravenous sodium bicarbonate did not have a clinically important effect on CIN risk when compared with IV saline in all studies (pooled RR, 0.93 [95% CI, 0.68 to 1.27]). Intravenous sodium bicarbonate led to a clinically important reduction in CIN that was not statistically significant when compared with IV saline in patients receiving LOCM (RR, 0.65 [CI, 0.33 to 1.25]) and did not lead to reduction in CIN in patients receiving IOCM (RR, 1.02 [CI, 0.70 to 1.48]) (**Figure 2**). The SOE was low for all comparisons of IV sodium bicarbonate (**Table 2**).

The overall analysis did not suggest that IV sodium bicarbonate was superior to IV saline when we evaluated secondary outcomes, and the SOE was low or insufficient. The Harbord test for small study effects was done for all comparisons, and no asymmetry was detected (**Table 2**).

Figure 1. Pooled RRs for development of CIN in comparisons of *N*-acetylcysteine plus IV saline versus IV saline in patients receiving contrast media.



CIN = contrast-induced nephropathy; IOCM = iso-osmolar contrast media; IV = intravenous; LOCM = low-osmolar contrast media; NAC = *N*-acetylcysteine; RR = risk ratio.

N-acetylcysteine Plus IV Saline Versus Sodium Bicarbonate

We included 7 RCTs (*n* = 1619) (21, 35, 48, 59, 62, 69, 83) that compared *N*-acetylcysteine with sodium bicarbonate (6 studies used IA administration, 1 did not report route of administration; 4 used LOCM, 3 used IOCM) (Supplement). This comparison showed no clinically important benefit in reducing CIN risk in 1 intervention over the other (RR, 1.11 [CI, 0.51 to 2.41]). The CI was so wide that we could not rule out the possibility of an important decrease or important increase in CIN risk (Figure 2). The SOE was graded as insufficient to draw conclusions about potential differences between the interventions in any outcome evaluated. The Harbord test for small study effects was done, and no asymmetry was detected (Table 2).

Statins

Statins have cholesterol-independent functionalities that play a role in various clinical contexts. The proposed mechanism related to CIN prevention is that they acted as stabilizers of the endothelium and free-radical scavengers in a model of ischemic nephropathy (84).

We did 2 separate meta-analyses on the studies of statins to reduce CIN incidence in patients receiving IA contrast. One analysis included 8 studies (*n* = 5024) on statin-naive patients that compared a statin plus IV saline with IV saline alone (85–92). Two of the studies included only patients with chronic kidney disease, 3 included only those with cardiac issues, and 2 included patients with diabetes mellitus and chronic kidney disease. The analysis showed that statins had a clinically important but not statistically significant effect on reducing CIN risk (RR, 0.68 [CI, 0.39 to 1.20]) and low SOE (Table 2 and Figure 2). When we evaluated secondary outcomes, the SOE was insufficient to determine whether any intervention was superior.

Five studies (*n* = 1477) compared statins added to *N*-acetylcysteine and IV saline with *N*-acetylcysteine plus IV saline (93–96) or sodium bicarbonate (97) (Supplement). Two of these studies included only patients with chronic kidney disease, 1 included those with cardiac disorders, 1 had a general population, and 1 had patients with diabetes mellitus and chronic kidney disease. Seven studies were not included in the meta-analyses because they included comparisons that were not similar enough to analyze (98–104) or did not include a CIN outcome (105). The analysis showed a clinically important and statistically significant reduction in CIN (RR, 0.52 [CI, 0.29 to 0.93]) (Figure 2) and low SOE. When we evaluated secondary outcomes, the SOE was graded as insufficient. The Harbord test for small study effects was done for all comparisons, and no asymmetry was detected (Table 2).

Ascorbic Acid

As an antioxidant, ascorbic acid acts as a scavenger of reactive oxygen species, reducing oxidative stress and possibly preventing CIN.

We identified 8 RCTs (*n* = 2026) that compared ascorbic acid with IV saline or *N*-acetylcysteine and included 6 in the meta-analysis (32, 106–110). We did not include 2 of the studies because they included *N*-acetylcysteine in both groups (111, 112). These studies included patients receiving cardiovascular interventions with IA administration of LOCM (3

Table 2. Summary of the Main Findings and SOE*

Outcome	Studies, *n*	Participants, *n*	Study Limitations	Consistency	Precision	Summary of Outcomes
NAC plus IV saline vs. IV saline with or without placebo						
CIN						
In patients receiving high-dose NAC	18	4336	Medium	Inconsistent	Precise	Low SOE of a clinically unimportant effect
In patients receiving low-dose NAC	36	4874	Medium	Inconsistent	Precise	Low SOE of a borderline clinically important benefit
In patients receiving oral NAC	40	6465	Medium	Inconsistent	Precise	Low SOE of a clinically unimportant benefit
In patients receiving IV NAC	14	2864	Medium	Inconsistent	Precise	Low SOE of no effect
In patients receiving LOCM	40	6665	Medium	Consistent	Precise	Moderate SOE of a clinically important benefit
In patients receiving IOCM	7	1339	Medium	Consistent	Precise	Moderate SOE of no benefit
Need for RRT	20	4881	Medium	Consistent	Imprecise	Low SOE of no difference
Cardiac events	7	1207	Medium	Consistent	Imprecise	Low SOE of no difference
Mortality	14	4592	Medium	Inconsistent	Imprecise	Insufficient SOE to determine effect
IV sodium bicarbonate vs. IV saline						
CIN						
All	19	3498	Medium	Inconsistent	Precise	Low SOE of no benefit
In patients receiving LOCM	11	1555	Medium	Inconsistent	Precise	Low SOE of clinically important benefit that was not statistically significant
In patients receiving IOCM	7	1748	Medium	Inconsistent	Precise	Low SOE of no benefit
Need for RRT	10	2238	Medium	Consistent	Imprecise	Low SOE of no difference
Cardiac events	4	1451	High	Consistent	Imprecise	Insufficient SOE to determine effect
Mortality	6	1237	Medium	Consistent	Imprecise	Low SOE of no difference
NAC plus IV saline vs. sodium bicarbonate						
CIN	7	930	Medium	Inconsistent	Imprecise	Insufficient SOE to determine effect
Need for RRT	4	710	Medium	Consistent	Imprecise	Insufficient SOE to determine effect
Cardiac events	3	613	Medium	Consistent	Imprecise	Insufficient SOE to determine effect
Mortality	2	442	Medium	Consistent	Imprecise	Insufficient SOE to determine effect
Statins						
CIN						
Statin vs. IV saline	8	5024	Medium	Consistent	Imprecise	Low SOE of a clinically important benefit that was not statistically significant
Statin plus NAC vs. NAC	5	1477	Medium	Consistent	Imprecise	Low SOE of a clinically important benefit
Need for RRT						
Versus saline	2	3245	High	Consistent	Imprecise	Insufficient SOE to determine effect
Plus NAC vs. NAC	3	1017	Medium	Consistent	Imprecise	Insufficient SOE to determine effect
Cardiac outcomes						
Versus saline	1	2998	High	Only 1 study	Imprecise	Insufficient SOE to determine effect
Plus NAC vs. NAC	1	304	Medium	Only 1 study	Imprecise	Insufficient SOE to determine effect
Mortality						
Versus saline	1	2998	High	Only 1 study	Imprecise	Insufficient SOE to determine effect
Plus NAC vs. NAC	3	1017	Medium	Consistent	Imprecise	Insufficient SOE to determine effect
Ascorbic acid						
CIN						
Versus saline	6	1025	Low	Inconsistent	Imprecise	Low SOE of a clinically important benefit that was not statistically significant
Versus NAC	3	583	Low	Inconsistent	Imprecise	Low SOE of no difference
Need for RRT						
Versus saline	2	397	Medium	Consistent	Imprecise	Insufficient SOE to determine effect
Versus NAC	1	212	Medium	Only 1 study	Imprecise	Insufficient SOE to determine effect
Cardiac events						
Versus saline	2	237	Medium	Consistent	Imprecise	Insufficient SOE to determine effect
Versus NAC	1	212	Medium	Only 1 study	Imprecise	Insufficient SOE to determine effect
Mortality Versus NAC	1	212	Medium	Only 1 study	Imprecise	Insufficient SOE to determine effect

CIN = contrast-induced nephropathy; IOCM = iso-osmolar contrast media; IV = intravenous; LOCM = low-osmolar contrast media; NAC = *N*-acetylcysteine; RRT = renal replacement therapy; SOE = strength of evidence.
* All studies were randomized, controlled trials and were direct.

studies), IOCM (1 study), or either LOCM or IOCM (2 studies) (Supplement).

Studies comparing ascorbic acid with IV saline showed a clinically important and statistically insignificant reduced risk for CIN (RR, 0.72 [CI, 0.48 to 1.01]). Three RCTs were included in a meta-analysis that compared ascorbic acid with *N*-acetylcysteine. The difference was clinically unimportant and statistically insignif-

icant (RR, 0.89 [CI, 0.34 to 2.30]) (Figure 2). The SOE was low for both comparisons and insufficient for all secondary outcomes. The Harbord test for small study effects was done for all comparisons, and no asymmetry was detected (Table 2).

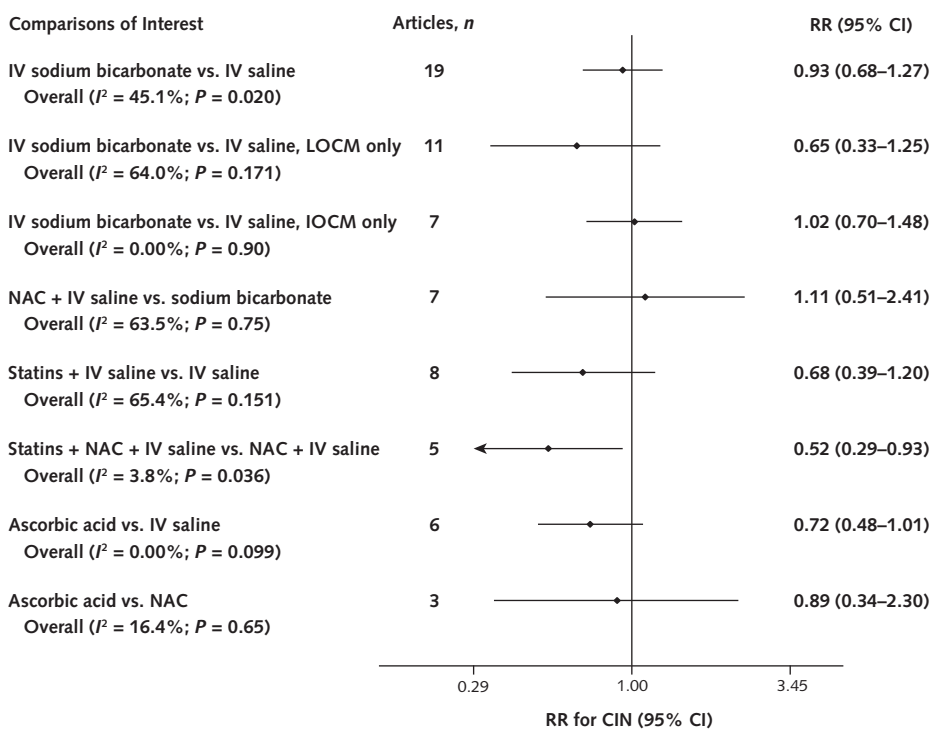
DISCUSSION

Many interventions to reduce CIN risk have been studied, but to date, the evidence has been inconclusive. In our analysis, evidence of a clinically important and statistically significant benefit was seen in studies of the following 3 comparisons: low-dose *N*-acetylcysteine plus IV saline versus IV saline (low SOE), *N*-acetylcysteine plus IV saline versus IV saline in patients receiving LOCM (moderate SOE), and statins plus *N*-acetylcysteine versus *N*-acetylcysteine (low SOE). A clinically important but statistically insignificant benefit was seen in studies of the following 3 comparisons: sodium bicarbonate versus IV saline in patients receiving LOCM (low SOE), statins plus IV saline versus IV saline alone (low SOE), and ascorbic acid plus IV saline versus IV saline (low SOE).

Our results are similar to the most recent meta-analysis on the effect of statins, published with a search end date of March 2014 (6), although that meta-analysis did not do a sensitivity analysis on the basis of IV saline or *N*-acetylcysteine administration along with statins. Despite previous reviews highlighting evidence on the effectiveness of statins to prevent CIN, they are not routinely used in clinical practice and we are not aware of any guidelines that recommend them for this indication. The findings reported in these studies could be partly explained by their direct effect on glomerular filtration rates that is independent of a protective effect on kidney function, as has been reported in 1 study (113). With increasing recognition of the cholesterol-independent vascular effects of statins, we need to reassess the role of statins in preventing CIN, especially because they are readily available, easy to administer, and relatively inexpensive.

Compared with IV saline alone, low-dose *N*-acetylcysteine plus IV saline had a clinically important decrease in CIN in patients receiving either IA or IV contrast media or when either low or high doses were used in patients receiving LOCM. The SOE was low for the first comparison (low-dose *N*-acetylcysteine) and moderate for the second comparison (in patients receiving LOCM), primarily because of limitations in the quality of studies and inconsistency in results. Our results are consistent with a recent meta-analysis that ended its search in September 2013 (7) and did not include sensitivity analysis by type of contrast media or high versus low doses. The low SOE may explain why low-dose *N*-acetylcysteine is not used more often and helps to explain differing recommendations on its use to prevent CIN. The joint American College of Cardiol-

Figure 2. Pooled RRs for development of CIN in studies of sodium bicarbonate, statins, and ascorbic acid in patients receiving contrast media.



CIN = contrast-induced nephropathy; IOCM = iso-osmolar contrast media; IV = intravenous; LOCM = low-osmolar contrast media; NAC = *N*-acetylcysteine; RR = risk ratio.

ogy/American Heart Association 2012 guideline recommends against the use of *N*-acetylcysteine for patients receiving IA contrast media in cardiac procedures (114), whereas the 2012 Kidney Disease: Improving Global Outcomes Clinical Practice Guideline for Acute Kidney Injury suggests using oral *N*-acetylcysteine with IV fluids in patients with increased CIN risk, acknowledging low SOE (115). Although *N*-acetylcysteine is inexpensive and seems to be safe, the evidence may not be strong enough to support routine use, especially without more robust evidence of clinical outcomes other than CIN incidence.

Our analysis is less positive about the effectiveness of IV sodium bicarbonate compared with IV saline relative to recent meta-analyses by Jang (8) and Zhang (9) and their colleagues with search end dates of January 2012 and August 2014, respectively. Another meta-analysis reported that sodium bicarbonate was superior to IV saline (8) but included studies using a combination of IV sodium bicarbonate and *N*-acetylcysteine that we did not want to include in the comparison of sodium bicarbonate and IV saline. The meta-analysis by Zhang and colleagues (9) reported that sodium bicarbonate plus *N*-acetylcysteine was better than sodium bicarbonate alone, but that conclusion was based on a single study that used the combination of sodium bicarbonate plus *N*-acetylcysteine. All 3 meta-analyses suggested that sodium bicarbonate could benefit patients receiving LOCM, but we did not find a statistically significant benefit.

Although our meta-analysis suggested a possible clinical benefit for ascorbic acid plus IV saline compared with IV saline alone, the difference was not statistically significant. The SOE was low because the studies had important limitations, the comparators varied too much, and the effects were inconsistent and imprecise.

Future studies of the comparative effectiveness of interventions for preventing CIN should stratify patients according to baseline risk for CIN, especially because detecting a treatment effect in patients with low risk may be difficult. More research could strengthen the evidence about whether *N*-acetylcysteine or IV sodium bicarbonate is beneficial in a particular clinical context, such as patients with increased CIN risk who receive LOCM. The clinically important benefit of statins plus *N*-acetylcysteine demonstrated in this analysis provides a rationale for studies investigating whether the effect differs by dose, timing of administration, type of contrast media, or baseline risk of the patient population. Future studies could be done in persons without cardiovascular risk factors to determine whether the effectiveness of statin therapy for reducing CIN occurs in the absence of physiologic effects of statins on coexisting cardiovascular disease.

Applying existing evidence to patients receiving IV contrast media is difficult because most studies involved patients receiving IA contrast media for cardiovascular procedures. More research is needed to determine the effectiveness of interventions for preventing CIN in patients receiving IV contrast media because little evidence exists on the effectiveness of different regimens for hydration when administering contrast media.

Our search was broad but our meta-analysis may overestimate the effect of prevention strategies to reduce CIN if studies with negative results were not reported in our sources. The studies span over 2 decades, and there may have been changes in the practice of CIN prevention, such as increased screening, variation in definition of acute kidney injury, and variation in hydration, over time. Such changes could contribute to differences in outcomes.

This comprehensive review highlights the generally low SOE on interventions for preventing CIN while indicating that the greatest reduction in CIN risk has been achieved with low-dose *N*-acetylcysteine plus IV saline in patients receiving LOCM or with statins plus *N*-acetylcysteine plus IV saline.

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Reproducible Research Statement: *Study protocol, statistical code, and data set:* Available from Ms. Wilson (e-mail, rwilsob@jhmi.edu).

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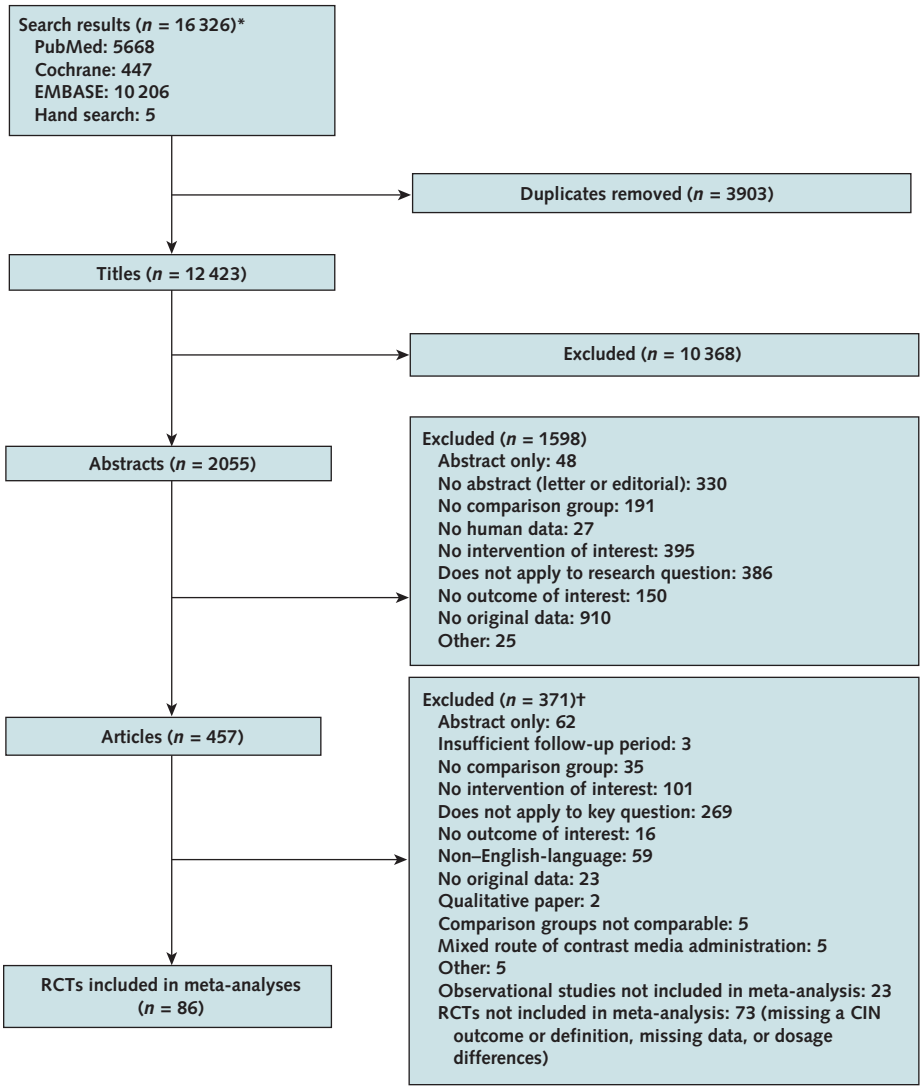
Appendix Figure. Summary of evidence search and selection.



CIN = contrast-induced nephropathy; RCT = randomized, controlled trial.
* 24 647 gray literature results were also found.
† Total does not sum to 371 because the 2 reviewers were not required to agree on reasons for exclusion.

Appendix Table. Detailed Search Strategy

Database	Search	Included Returns	Notes
PubMed	(("Kidney diseases"[mh] OR "Kidney disease"[tiab] OR "kidney diseases"[tiab] OR Nephropathy[tiab] OR "acute kidney injury"[mh] OR "acute kidney injury"[tiab] OR "acute renal injury"[tiab] OR "renal disease"[tiab] OR "renal diseases"[tiab]) AND ("contrast media"[mh] OR "contrast media"[tiab] OR "contrast medium"[tiab] OR "contrast material"[tiab])) NOT (animal[mh] NOT human[mh])	5668	–
EMBASE	('contrast medium'/exp OR 'contrast medium':ab,ti OR 'contrast media':ab,ti OR 'contrast material':ab,ti) AND ('kidney disease'/exp OR 'kidney disease':ab,ti OR 'kidney diseases':ab,ti OR nephropathy:ab,ti OR 'acute kidney injury':ab,ti OR 'renal disease':ab,ti OR 'acute renal failure':ab,ti OR 'acute renal injury':ab,ti)	10 206	12 151 Limit to humans (study type): 9972 Limit to Article, Review, Conference Abstract, Conference Paper, Short Survey, Article in Press, Conference review (Publication type): 8952
Cochrane	ID #1: MeSH descriptor: [Kidney Diseases] explode all trees ID #2: "kidney disease":ti,ab,kw (Word variations have been searched) ID #3: nephropathy:ti,ab,kw (Word variations have been searched) ID #4: "acute kidney injury":ti,ab,kw (Word variations have been searched) ID #5: "renal disease":ti,ab,kw (Word variations have been searched) ID #6: "acute renal injury":ti,ab,kw ID #7: "renal diseases":ti,ab,kw ID #8: #1 or #2 or #3 or #4 or #5 or #6 or #7 ID #9: MeSH descriptor: [Contrast Media] explode all trees ID #10: "contrast media":ti,ab,kw (Word variations have been searched) ID #11 "contrast material":ti,ab,kw (Word variations have been searched) ID #12: "contrast medium":ti,ab,kw ID #13: #9 or #10 or #11 or #12 ID #14: #8 and #13	447	Other reviews: 52 Trials: 368 Technology assessments: 4 Economic evaluations: 5
Total	–	16 326	–

MeSH = Medical Subject Heading.

Annals of Internal Medicine

REVIEW

Comparative Effect of Contrast Media Type on the Incidence of Contrast-Induced Nephropathy

A Systematic Review and Meta-analysis

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Background: Iodine contrast media are essential components of many imaging procedures. An important potential side effect is contrast-induced nephropathy (CIN).

Purpose: To compare CIN risk for contrast media within and between osmolality classes in patients receiving diagnostic or therapeutic imaging procedures.

Data Sources: PubMed, EMBASE, Cochrane Library, Clinical Trials.gov, and Scopus through June 2015.

Study Selection: Randomized, controlled trials that reported CIN-related outcomes in patients receiving low-osmolar contrast media (LOCM) or iso-osmolar contrast media for imaging.

Data Extraction: Independent study selection and quality assessment by 2 reviewers and dual extraction of study characteristics and results.

Data Synthesis: None of the 5 studies that compared types of LOCM reported a statistically significant or clinically important difference among study groups, but the strength of evidence was low. Twenty-five randomized, controlled trials found a slight reduction in CIN risk with the iso-osmolar contrast media agent iodixanol compared with a diverse group of LOCM that just reached statistical significance in a meta-analysis (pooled relative risk, 0.80 [95% CI, 0.65 to 0.99]; $P = 0.045$). This comparison's strength of evidence was moderate. In a meta regression of randomized, controlled trials of iodixanol, no relationship was found between route of administration and comparative CIN risk.

Limitations: Few studies compared LOCM. Procedural details about contrast administration were not uniformly reported. Few studies specified clinical indications or severity of baseline renal impairment.

Conclusion: No differences were found in CIN risk among types of LOCM. Iodixanol had a slightly lower risk for CIN than LOCM, but the lower risk did not exceed a criterion for clinical importance.

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For author affiliations, see end of text.
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Iodine contrast media are essential to many diagnostic and therapeutic procedures that involve imaging. An important potential side effect is contrast-induced nephropathy (CIN), most commonly defined in past studies as an increase in serum creatinine levels of more than 25% or 44.2 μmol/L (0.5 mg/dL) within 3 days of intravascular contrast administration in the absence of an alternative cause (1).

The precise mechanism of CIN is not entirely understood. The leading theories are that it results from hypoxic injury to the renal tubules induced by renal vasoconstriction or by direct cytotoxic effects of contrast media (2, 3); alternatively, some experts have argued—and recent evidence suggests—that acute kidney injury occurring after intravascular contrast administration is caused by coexisting risk factors and is only coincidentally related to the contrast media, especially when administered intravenously (4, 5). Regardless of the cause, acute kidney injury after intravascular contrast administration remains a major concern for referring clinicians.

Osmolality of contrast media is a key factor determining its tolerability (6). Since the 1990s, low-osmolar contrast media (LOCM) (2 to 3 times plasma osmolality) have been the standard of care for intravascular injection. A newer class of intravascular contrast, iso-osmolar contrast media (IOCM), is isotonic to plasma. Iodixanol is the only IOCM available for intravascular injection. The literature contains conflicting reports about whether iodixanol is associated with less risk for CIN than LOCM (7, 8). International guidelines from the Kidney Disease: Improving Global Outcomes Acute Kidney Injury Work Group mention IOCM and LOCM, but they do not make recommendations about selection between them (9).

We did a systematic review of randomized, controlled trials (RCTs) to determine the comparative effects of different types of intravascular contrast media on CIN risk in patients having diagnostic imaging studies or image-guided procedures. We hypothesized that updating past reviews with more recent RCTs may help us understand conflicting reports about CIN risk. Some reports suggest that intra-arterial administration may be associated with greater risk than intravenous administration (4, 10, 11), so we also investigated whether the comparative effects vary according to the route of administration.

See also:

Related article 406

METHODS

We developed and followed a review protocol, which is included in the full technical report on which this article is based (12).

Data Sources and Searches

We searched (without date or language restrictions) PubMed, EMBASE, and the Cochrane Library for RCTs published through 30 June 2015, as well as the Scopus database for conference proceedings and other reports (**Appendix Table 1**, available at www.annals.org). We also reviewed the reference lists of relevant articles and related systematic reviews, searched ClinicalTrials.gov to identify ongoing studies, and asked an external expert panel to identify trials missing from our final list of eligible articles.

Study Selection

We selected all RCTs that compared 1 or more contrast media types (LOCM or IOCM) with CIN incidence as the main outcome in patients having diagnostic imaging or image-based therapeutic procedures. Studies had to report the incidence of CIN based on serum creatinine levels or glomerular filtration rates at baseline and within 72 hours of contrast injection. Studies could involve patients of any age and preprocedure risk for CIN. There were no restrictions on how the contrast classes were compared, so studies comparing different types of LOCM and those comparing LOCM with IOCM were included.

Two reviewers independently screened titles and abstracts to identify articles for inclusion. If necessary, the full text of articles was reviewed. Articles in a language other than English were excluded at the full-text level. Discrepancies between the 2 reviewers that remained after full-text review were resolved by consensus. At random intervals during screening, quality checks were done to ensure that eligibility criteria were applied consistently.

Data Extraction and Quality Assessment

For each eligible study, 1 investigator extracted pertinent data about study characteristics, patient population, imaging procedure type, comparisons, results, and statistical analysis. A second investigator reviewed the extracted data for accuracy. Discrepancies between the 2 investigators were resolved by consensus. Article and data management were done within the DistillerSR Web service (Evidence Partners).

Two reviewers independently assessed each study's risk of bias using the following 5 items from the Cochrane Risk of Bias Tool for randomized studies: allocation sequence generation, allocation concealment, investigator blinding, incomplete outcomes, and selective outcome reporting (13). Discrepancies were resolved by consensus.

Data Synthesis and Analysis

When evaluating changes in CIN risk, we followed published guidelines for selecting a minimally important clinical difference based on the overall observed event rate in the studies (14). Taking into consideration the potential effect of CIN on a patient's overall health and well-being, the clinical experts on our team decided that a 25% reduction in the relative risk for CIN would be clinically important, which is consistent with the published guidance suggesting a range of reduction in relative risk of 20% to 30% in determining optimal information size (14).

For each comparison in our review, the study team assigned a grade (high, moderate, low, or insufficient) for the strength of evidence (SOE) associated with the entire group of studies that represented the particular comparison. Grades for SOE were assigned by consensus of the senior study team members (J.E., R.W., R.S., and E.B.). This grading scheme considered all of the following domains in the Agency for Healthcare Research and Quality guidelines for comparative effectiveness reviews: study limitations, precision, directness, consistency, reporting bias, and magnitude of effect (15).

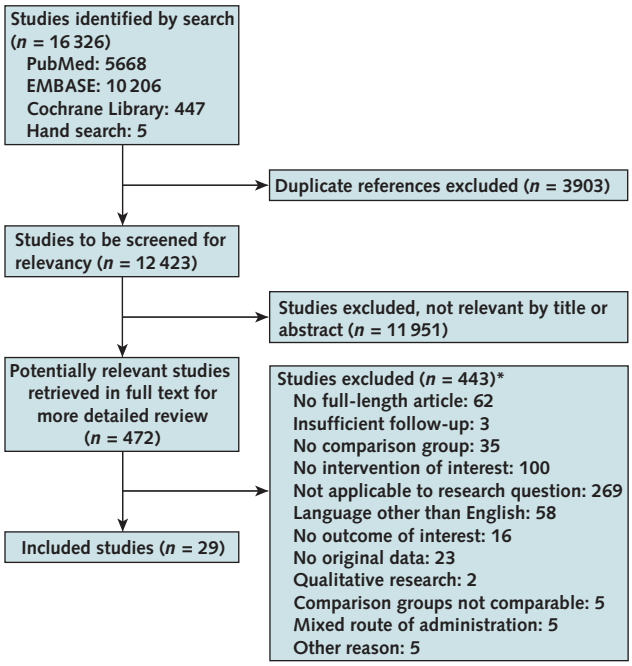
The study limitations domain was assessed by examining the risk-of-bias items for each study involved in the comparison. Study limitations were considered high if more than half of the studies in a group scored negatively in at least 1 of the risk-of-bias items, low if more than half of the studies in the group scored positively in all 5 risk-of-bias items, or medium if neither the high nor the low criteria were met.

The precision domain was assessed by following guidance from the GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group (14). We rated a group of studies as precise if the total number of patients exceeded the optimum information size (14) and the 95% CI excluded a pooled relative risk of 1.0. If the total number of patients exceeded the optimum information size but the CI did not exclude a relative risk of 1.0, we only rated the evidence as precise if the CI excluded the possibility of a 25% minimally important clinical difference as defined previously (relative risk <0.75 or >1.25). For the main outcome of interest, CIN, we calculated an optimum information size of 2000 patients based on an expected 0.1 probability of CIN and a minimally important relative risk of less than 0.75 or greater than 1.25.

The SOE of a group of studies was graded high if the study limitations domain was considered low and all other SOE domains were scored positively. The SOE was downgraded for each domain that was scored negatively. If the magnitude of effect was very large, the SOE was upgraded.

We did de novo meta-analyses of all studies on a given comparison if study heterogeneity was not important by clinical, qualitative, and statistical criteria (16). We calculated pooled risks by using a random-effects model and the DerSimonian–Laird method (17). We used a funnel plot and the Harbord modified test for small study effects (18) to look for asymmetry in the reporting of results, which can be seen when publication bias exists. Analyses were done in Stata, version 13 (StataCorp).

Figure 1. Summary of evidence search and selection.



* Sum of reasons for exclusion exceeds 443 because reviewers were not required to agree on the reason.

Role of the Funding Source

The Agency for Healthcare Research and Quality selected the review topic and funded this research under a contract. A representative from the Agency provided technical assistance during creation of the full evidence report on which this article is based and provided comments on draft versions of that report (12). The Agency did not directly participate in the literature search; determination of study eligibility criteria; data collection, analysis, or interpretation; or preparation, review, or approval of the manuscript for publication.

RESULTS

The literature search revealed 29 RCTs for summary and analysis (**Figure 1**). Five RCTs compared 2 or more types of LOCM in 826 patients (**Appendix Table 2**, available at www.annals.org) (19–23). Twenty-five RCTs compared the IOCM iodixanol with 1 or more types of LOCM in 5053 patients (**Appendix Table 2**) (19, 24–47). One RCT reported data on both types of comparisons (19). In the 5 RCTs that compared LOCM, 4 studies scored negatively in 1 or more of the 5 risk-of-bias items (**Appendix Table 3**, available at www.annals.org). In the 25 RCTs comparing iodixanol and LOCM, all studies scored negatively in 1 or more of the 5 risk-of-bias items (**Appendix Table 4**, available at www.annals.org). Of the 29 RCTs included in our review, 14 (48%) studies (19, 20, 29, 33–38, 40–43, 45) received funding support from industry sources, all of which were contrast media manufacturers.

No study comparing 2 LOCM reported a statistically significant or clinically important difference between study groups in the incidence of CIN or a related measure of renal function change (**Table 1**). The overall analysis did not suggest that any 1 LOCM was superior to another, although the number of studies and total sample sizes were small. The SOE of this comparison was graded as low (**Table 2**). Randomized, controlled trials comparing LOCM did not report CIN outcomes similarly enough to be combined numerically in a meta-analysis.

In the meta-analysis, we found a slight reduction in CIN risk with iodixanol compared with a diverse group of LOCM that just reached statistical significance (pooled relative risk, 0.80 [95% CI, 0.65 to 0.99]; $P = 0.045$) (**Figure 2** and **Appendix Table 5**, available at www.annals.org). Two studies (19, 24) were omitted from the meta-analysis because they did not explicitly classify renal outcomes as CIN. The SOE associated with this comparison was graded as moderate (**Table 2**). The point estimate of the reduced risk did not exceed the minimally important relative risk of 0.75. When the analysis was stratified by route of administration, the pooled relative risk for the intra-arterial route was 0.80 (CI, 0.64 to 1.01; $P = 0.059$) and for the intravenous route it was 0.84 (CI, 0.42 to 1.71; $P = 0.64$), suggesting no difference in comparative CIN risk by route of administration. No statistically significant or clinically important differences were reported between iodixanol and types of LOCM with regard to the need

Table 1. Results of Studies Comparing LOCM

Study, Year (Reference)	LOCM	Primary Outcome	Mean Creatinine Change, μmol/L (mg/dL)	Study Conclusion	Risk of Bias
Becker et al, 2013 (19)	Iohexol, iopamidol, iopromide	GFR change	NR	NS	Medium
Dillman et al, 2012 (20)	Iohexol, iopamidol	Peak SCr change	Iohexol: 6.2 (0.07); iopamidol: 4.4 (0.05)	NS	Low
Koutsikos et al, 1992 (21)	Iohexol, ioxaglate	SCr change	Iohexol: 9.7 (0.11); ioxaglate: 10.6 (0.12)	NS	High
Koutsikos et al, 1992 (21)	Iohexol, ioxaglate	SCr change	Iohexol: 0.18 (0.002); ioxaglate:, 8.13 (0.092)	NS	High
Campbell et al, 1990 (22)	Iohexol, ioxaglate, iopamidol	SCr change in those with detectable increase	Iohexol: 30.1 (0.34); ioxaglate: 12.4 (0.14); iopamidol: 22.1 (0.25)	NS	High
Jevnikar et al, 1988 (23)	Iohexol, ioxaglate	SCr change	NR	NS	High

GFR = glomerular filtration rate; LOCM = low-osmolar contrast media; NR = not reported; NS = no significant difference; SCr = serum creatinine.

Table 2. Grading Strength of Evidence

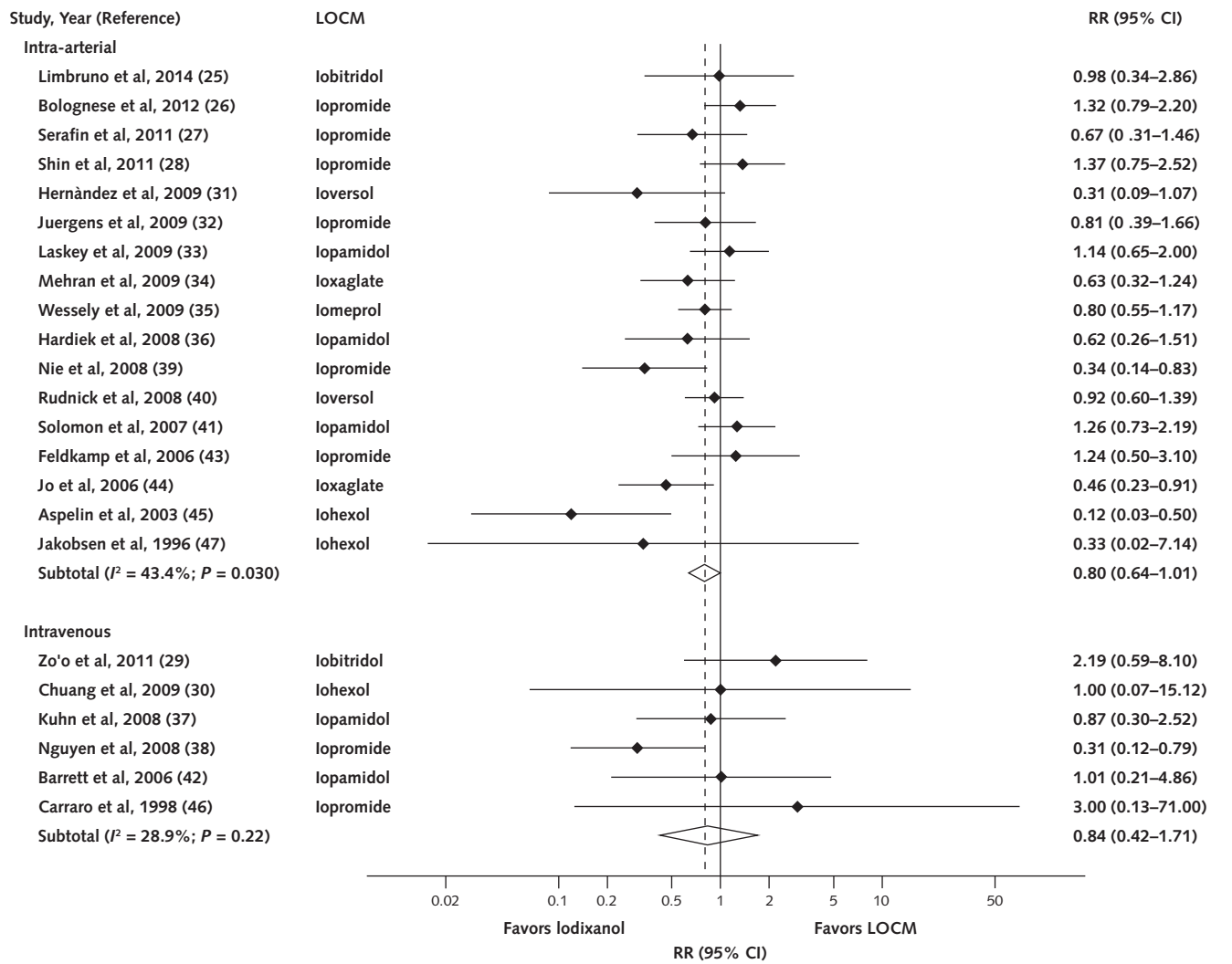
Comparison	RCTs (Sample Size), *n*	Study Limitations	Directness	Consistency	Precision	Strength of Evidence
LOCM vs. LOCM	5 (429)	Medium	Direct	Consistent	Imprecise	Low
Iodixanol vs. LOCM	25 (5097)	Medium	Direct	Consistent	Precise	Moderate

LOCM = low-osmolar contrast media; RCT = randomized, controlled trial.

for renal replacement therapy (24, 26, 33, 35, 37, 44), cardiovascular outcomes (26, 28, 32, 34, 35, 39, 41), death (26, 27, 33–35, 37–39), adverse events (24, 26, 28–30, 32–36, 39, 41, 44), or image and diagnostic quality (29, 39). We did not see any definitive evidence of a difference in CIN incidence between iodixanol and LOCM that varied according to patient characteristics or contrast dose.

We did meta regression analyses between CIN incidence and each of the following covariates: age, baseline creatinine, diabetes, sex, route of administration, and funding support from industry sources. No significant associations were found, although the statistical power was limited by the relatively small number of studies that involved each covariate. We found no suggestion of publication bias by funnel plot or

Figure 2. Graphical summary of meta-analysis of randomized, controlled trials comparing iodixanol and LOCM with contrast-induced nephropathy as the primary outcome.



The solid vertical line represents the null hypothesis (relative risk equal to 1), and the dashed vertical line represents the pooled estimate from the meta-analysis. Studies are shown in reverse chronologic order, grouped by route of administration. LOCM = low-osmolar contrast media, RR = relative risk.

the Harbord modified test for small study effects ($P = 0.47$).

DISCUSSION

In this systematic review, the small number of trials comparing 2 LOCM reported no statistically significant or clinically important differences in the risk for CIN. For the trials comparing iodixanol with LOCM, we found a slight reduction in CIN risk for iodixanol that just reached statistical significance. However, the point estimate of this reduction did not exceed a minimally important relative risk difference of 0.25. Most trials in our review involved patients receiving intra-arterial contrast media. In the few trials involving intravenous contrast, we saw no evidence that the relationship between contrast type and CIN risk differed from that seen in the intra-arterial trials.

We found no difference among types of contrast media in the potential sequelae of CIN, such as cardiovascular events, death, need for renal replacement therapy, or other adverse events. Because we excluded studies that did not report data on CIN, studies that reported only nonrenal outcomes were excluded from our analysis. A recent meta-analysis of RCTs comparing iodixanol and LOCM that included studies of nonrenal outcomes found no conclusive evidence that iodixanol is superior to LOCM with respect to cardiovascular events (48). This is congruent with the findings from our data set, which focused on renal outcomes.

Considering systematic reviews that have been published during the period of our literature search, our estimate of relative risk was very similar to that of 3 meta-analyses comparing iodixanol with LOCM (7, 49, 50), even though our review included 6 RCTs that have been published since those studies, which reported no significant reduction of CIN with iodixanol compared with LOCM. Five other systematic reviews reported a lower incidence of CIN with iodixanol than with LOCM, but all had important limitations and included different sets of studies than our review (8, 51–54). In one of these meta-analyses (51), the 2 studies that most favored iodixanol (55, 56) were excluded from our analysis because CIN-related outcomes were inadequately defined. Two other systematic reviews made indirect comparisons of contrast agents (52, 53) and reported differences between iodixanol and the LOCM iohexol but not with other types of LOCM. One of the indirect comparison studies was a network analysis that pooled all outcomes (not just CIN) (52), and the other indirect comparison study included observational data (not just RCTs) (53). The fourth review included only trials of iodixanol that were sponsored by its manufacturer (54), and the fifth meta-analysis (8) included a large unpublished positive trial comparing iodixanol with iopromide. Data for this trial are only available in a 2010 meeting abstract; to date, the study has not been published.

Our review addressed a clinical comparison involving contrast media and did not seek to review evidence about the pathophysiology, causal pathway, or epidemiology of CIN. The precise mechanism of CIN is not entirely understood. Some evidence exists from propensity score–matched, retrospective studies that questions the strength of the relationship between contrast administration and CIN (5). This relationship is important for designing future research (11, 57), but it does not affect the conclusions of this review about the comparative effect of contrast media type on observed CIN.

This review's definition of CIN is the one most commonly found in past studies examining the risk, prevention, and treatment of CIN. More recent consensus definitions of acute kidney injury have been developed (58, 59), but these classification systems have not yet been used extensively in the CIN literature. Although some guidelines have used the term "contrast-induced acute kidney injury" instead of CIN (9), we chose the older term, CIN, because of its dominance in published studies.

Our review has limitations. We generally considered LOCM together as a group even though 7 different LOCM chemical compounds were used in the studies we reviewed. Although direct comparisons of types of LOCM are sparse, indirect evidence suggests that iohexol may differ from other types of LOCM. The greatest CIN reduction with iodixanol was reported in a study comparing it with iohexol (45). Two indirect comparisons also suggested that differences exist between iohexol and other types of LOCM (52, 53), but these comparisons are not compelling. As mentioned previously, 1 study was a network meta-analysis that pooled all outcomes without focusing on a homogeneous body of studies using a similar definition of the main outcome of interest. The other study was designed to assess other comparisons, such as *N*-acetylcysteine versus intravenous saline, and the iodixanol versus LOCM comparison was a secondary, nonrandomized analysis.

We found that studies examining the risk for CIN with different types of contrast media generally provided little detail about clinical indications for the diagnostic or therapeutic procedures or other clinical details, such as the severity of renal impairment. As a result, we could not assess whether the comparisons among types of contrast media depended on the indications for use of contrast media or baseline renal function. The studies frequently omitted details about total contrast volume, length of procedure, and contrast injection rates. These clinical and technical factors are potential sources of heterogeneity among the studies. Our inclusion criteria did not select studies based on these characteristics, so the results probably apply to a diverse population of patients and procedures. Future research should focus on identifying clinical factors that may be associated with a benefit of iodixanol compared with LOCM.

In conclusion, CIN risk did not differ among types of LOCM, but the body of evidence was small and associated with low SOE. We found moderate SOE that iodixanol had a slightly lower risk for CIN than a diverse group of LOCM that just reached statistical significance, but the lower risk did not exceed a minimally important clinical difference. No relationship was found

between route of administration and comparative CIN risk. For clinicians, these findings suggest that the choice between the IOCM iodixanol and types of LOCM will not have a clinically important effect on CIN risk.

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Reproducible Research Statement: *Study protocol, statistical code, and data set:* Available from Dr. Eng (e-mail, jeng@jhmi.edu).

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Appendix Table 1. Search Strategy

Database	Search Specification	Articles Returned, *n*
PubMed	(("Kidney diseases"[mh] OR "Kidney disease"[tiab] OR "kidney diseases"[tiab] OR Nephropathy[tiab] OR "acute kidney injury"[mh] OR "acute kidney injury"[tiab] OR "acute renal injury"[tiab] OR "renal disease"[tiab] OR "renal diseases"[tiab]) AND ("contrast media"[mh] OR "contrast media"[tiab] OR "contrast medium"[tiab] OR "contrast material"[tiab])) NOT (animal[mh] NOT human[mh])	5308
EMBASE	('contrast medium'/exp OR 'contrast medium':ab,ti OR 'contrast media':ab,ti OR 'contrast material':ab,ti) AND ('kidney disease'/exp OR 'kidney disease':ab,ti OR 'kidney diseases':ab,ti OR nephropathy:ab,ti OR 'acute kidney injury':ab,ti OR 'renal disease':ab,ti OR 'acute renal failure':ab,ti OR 'acute renal injury':ab,ti) Limit to humans (study type); limit to article, review, conference abstract, conference paper, short survey, article in press, conference review (publication type)	8952
Cochrane Library	#1 MeSH descriptor: [Kidney Diseases] explode all trees #2 "kidney disease":ti,ab,kw (Word variations have been searched) #3 nephropathy:ti,ab,kw (Word variations have been searched) #4 "acute kidney injury":ti,ab,kw (Word variations have been searched) #5 "renal disease":ti,ab,kw (Word variations have been searched) #6 "acute renal injury":ti,ab,kw #7 "renal diseases":ti,ab,kw #8 #1 or #2 or #3 or #4 or #5 or #6 or #7 #9 MeSH descriptor: [Contrast Media] explode all trees #10 "contrast media":ti,ab,kw (Word variations have been searched) #11 "contrast material":ti,ab,kw (Word variations have been searched) #12 "contrast medium":ti,ab,kw #13 #9 or #10 or #11 or #12 #14 #8 and #13	429*

MeSH = Medical Subject Heading.
* Comprised of 52 other reviews, 368 trials, 4 technology assessments, and 5 economic evaluations.

Appendix Table 2. Study Characteristics

Comparison	Study, Year (Reference)	Sample Size	Route	Procedure Type	Patient Population	CKD	Mean Age, *y*	Female, %
L vs. L	Becker et al, 2013 (19)	113	IV	CT	No renal impairment	No	52	54
L vs. L	Dillman et al, 2012 (20)	389	IV	CT	No renal impairment	No	56	52
L vs. L	Koutsikos et al, 1992 (21)	16	IA	Renal	No renal impairment	No	43	33
L vs. L	Koutsikos et al, 1992 (21)	40	IV	Renal	No renal impairment	No	56	20
L vs. L	Campbell et al, 1990 (22)	252	IA	Peripheral arteriography	General	No	58	45
L vs. L	Jevnikar et al, 1988 (23)	16	IA	Coronary	No renal impairment	No	56	17
I vs. L	Semerci et al, 2014 (24)	44	IA	Coronary	No renal impairment	No	56	32
I vs. L	Becker et al, 2013 (19)	113	IV	CT	No renal impairment	No	52	54
I vs. L	Limbruno et al, 2014 (25)	113	IA	Coronary	Renal impairment	Yes	76	43
I vs. L	Bolognese et al, 2012 (26)	475	IA	Coronary	Myocardial infarction	No	66	23
I vs. L	Serafin et al, 2011 (27)	92	IA	Cerebral	Neurosurgical	No	50	71
I vs. L	Shin et al, 2011 (28)	420	IA	Coronary	Renal impairment	Yes	72	46
I vs. L	Zo'o et al, 2011 (29)	145	IV	CT	Children	No	8	41
I vs. L	Chuang et al, 2009 (30)	50	IV	IVU	Renal impairment or diabetes	Yes	58	32
I vs. L	Hernández et al, 2009 (31)	250	IA	Coronary	Diabetes	No	70	37
I vs. L	Juergens et al, 2009 (32)	382	IA	Coronary	Renal impairment	Yes	70	24
I vs. L	Laskey et al, 2009 (33)	418	IA	Coronary	Renal impairment and diabetes	Yes	70	35
I vs. L	Mehran et al, 2009 (34)	146	IA	Coronary	Renal impairment	Yes	71	12
I vs. L	Wessely et al, 2009 (35)	324	IA	Coronary	Renal impairment	Yes	74	31
I vs. L	Hardiek et al, 2008 (36)	106	IA	Coronary	Diabetes	No	66	83
I vs. L	Kuhn et al, 2008 (37)	248	IV	CT	Renal impairment and diabetes	Yes	69	53
I vs. L	Nguyen et al, 2008 (38)	117	IV	CT	Renal impairment	Yes	64	29
I vs. L	Nie et al, 2008 (39)	208	IA	Coronary	Renal impairment	Yes	61	32
I vs. L	Rudnick et al, 2008 (40)	299	IA	Coronary	Renal impairment	Yes	72	41
I vs. L	Solomon et al, 2007 (41)	414	IA	Coronary	Renal impairment	Yes	71	36
I vs. L	Barrett et al, 2006 (42)	166	IV	CT	Renal impairment	Yes	67	31
I vs. L	Feldkamp et al, 2006 (43)	83	IA	Coronary	No renal impairment	No	62	24
I vs. L	Jo et al, 2006 (44)	275	IA	Coronary	Renal impairment	Yes	67	44
I vs. L	Aspelin et al, 2003 (45)	129	IA	Coronary, aortofemoral	Renal impairment and diabetes	Yes	71	41
I vs. L	Carraro et al, 1998 (46)	64	IV	IVU	Renal impairment	Yes	68	14
I vs. L	Jakobsen et al, 1996 (47)	16	IA	Aorta, pelvic	Renal impairment	Yes	55	25

CKD = chronic kidney disease; CT = computed tomography; I vs. L = iso- vs. low-osmolar contrast media; IA = intra-arterial; IV = intravenous; IVU = intravenous urography; L vs. L = low- versus low-osmolar contrast media.

Appendix Table 3. Risk of Bias for RCTs Comparing LOCMs*

Study, Year (Reference)	Allocation Sequence Generation	Allocation Sequence Concealment	Blinding	Incomplete Outcomes Addressed	Free of Selective Outcomes	Free of Other Problems	Risk of Bias
Becker et al, 2013 (19)	1	0	0	1	1	0	Medium
Dillman et al, 2012 (20)	1	1	1	1	1	1	Low
Koutsikos et al, 1992 (21)	0	0	0	1	1	1	High
Koutsikos et al, 1992 (21)	0	0	0	1	1	1	High
Campbell et al, 1990 (22)	0	0	1	0	0	0	High
Jevnikar et al, 1988 (23)	0	0	1	0	1	1	High

LOCM = low-osmolar contrast media; RCT = randomized, controlled trial.
* 1 = criterion satisfied; 0 = criterion not satisfied.

Appendix Table 4. Risk of Bias for RCTs Comparing Iodixanol and LOCMs*

Study, Year (Reference)	Allocation Sequence Generation	Allocation Sequence Concealment	Blinding	Incomplete Outcomes Addressed	Free of Selective Outcomes	Free of Other Problems	Risk of Bias
Semerci et al, 2014 (24)	0	0	0	1	1	1	High
Becker et al, 2013 (19)	1	0	0	1	1	0	Medium
Limbruno et al, 2014 (25)	0	0	0	0	1	1	High
Bolognese et al, 2012 (26)	1	1	1	1	1	1	Low
Serafin et al, 2011 (27)	1	0	1	1	1	1	Medium
Shin et al, 2011 (28)	1	1	1	1	1	1	Low
Zo'o et al, 2011 (29)	1	1	1	1	1	1	Low
Chuang et al, 2009 (30)	0	0	0	1	1	1	High
Hernández et al, 2009 (31)	0	0	0	1	1	0	High
Juergens et al, 2009 (32)	1	1	1	1	1	1	Low
Laskey et al, 2009 (33)	0	1	1	1	1	1	Medium
Mehran et al, 2009 (34)	1	1	1	1	0	1	Medium
Wessely et al, 2009 (35)	0	0	1	1	1	1	Medium
Hardiek et al, 2008 (36)	1	1	1	1	1	1	Low
Kuhn et al, 2008 (37)	0	0	0	1	1	1	High
Nguyen et al, 2008 (38)	1	0	1	1	0	1	Medium
Nie et al, 2008 (39)	1	0	1	1	1	1	Medium
Rudnick et al, 2008 (40)	1	1	1	1	1	1	Low
Solomon et al, 2007 (41)	1	0	1	1	1	1	Medium
Barrett et al, 2006 (42)	1	1	1	1	1	1	Low
Feldkamp et al, 2006 (43)	0	0	0	1	1	1	High
Jo et al, 2006 (44)	0	0	1	1	1	1	Medium
Aspelin et al, 2003 (45)	0	0	1	1	1	1	Medium
Carraro et al, 1998 (46)	0	0	1	0	0	1	High
Jakobsen et al, 1996 (47)	0	0	1	1	1	1	Medium

LOCM = low-osmolar contrast media; RCT = randomized, controlled trial.
* 1 = criterion satisfied; 0 = criterion not satisfied.

Appendix Table 5. Results of Studies Comparing Iodixanol With LOCM

Study, Year (Reference)	LOCM	CIN Definition*	CIN Incidence, *n/N*		*P* Value	Study Conclusion	Risk of Bias
			Iodixanol	LOCM			
Semerci et al, 2014 (24)	Iopamidol	ND	0/19	0/19	NR	NS	High
Becker et al, 2013 (19)	Iohexol, iopamidol, iopromide	ND	NR	NR	NR	NS	Medium
Limbruno et al, 2014 (25)	Iobitridol	>25%	6/57	6/56	1.0	NS	High
Bolognese et al, 2012 (26)	Iopromide	>25%	30/231	23/234	0.31	NS	Low
Serafin et al, 2011 (27)	Iopromide	>25% or >44.2 μmol/L (0.5 mg/dL)	8/44	13/48	0.33	NS	Medium
Shin et al, 2011 (28)	Iopromide	>25% or >44.2 μmol/L (0.5 mg/dL)	23/215	16/205	0.32	NS	Low
Zo'o et al, 2011 (29)	Iobitridol	>25% decrease in CrCl	7/66	3/62	0.33	NS	Low
Chuang et al, 2009 (30)	Iohexol	>25%	1/25	1/25	1.0	NS	High
Hernández et al, 2009 (31)	Ioversol	>25% or >44.2 μmol/L (0.5 mg/dL)	3/118	11/132	0.056	NS	High
Juergens et al, 2009 (32)	Iopromide	>25% or >44.2 μmol/L (0.5 mg/dL)	11/91	15/100	0.67	NS	Low
Laskey et al, 2009 (33)	Iopamidol	>44.2 μmol/L (0.5 mg/dL)	24/214	20/203	0.75	NS	Medium
Mehran et al, 2009 (34)	Ioxaglate	>25% or >44.2 μmol/L (0.5 mg/dL)	11/72	18/74	0.21	NS	Medium
Wessely et al, 2009 (35)	Iomeprol	>25% or >44.2 μmol/L (0.5 mg/dL)	36/162	45/162	0.30	NS	Medium
Hardiek et al, 2008 (36)	Iopamidol	>25%	7/54	10/48	0.30	NS	Low
Kuhn et al, 2008 (37)	Iopamidol	>25%	6/123	7/125	1.0	NS	High
Nguyen et al, 2008 (38)	Iopromide	>25%	5/61	15/56	0.013	Favor iodixanol	Medium
Nie et al, 2008 (39)	Iopromide	>25% or >44.2 μmol/L (0.5 mg/dL)	6/106	17/102	0.014	Favor iodixanol	Medium
Rudnick et al, 2008 (40)	Ioversol	>44.2 μmol/L (0.5 mg/dL)	34/156	34/143	0.78	NS	Low
Solomon et al, 2007 (41)	Iopamidol	>25%	26/210	20/204	0.44	NS	Medium
Barrett et al, 2006 (42)	Iopamidol	>25%	3/76	3/77	1.0	NS	Low
Feldkamp et al, 2006 (43)	Iopromide	>25%	9/105	8/116	0.80	NS	High
Jo et al, 2006 (44)	Ioxaglate	>25% or >44.2 μmol/L (0.5 mg/dL)	11/140	23/135	0.027	Favor iodixanol	Medium
Aspelin et al, 2003 (45)	Iohexol	>44.2 μmol/L (0.5 mg/dL)	2/64	17/65	0.0003	Favor iodixanol	Medium
Carraro et al, 1998 (46)	Iopromide	>50%	1/32	0/32	1.0	NS	High
Jakobsen et al, 1996 (47)	Iohexol	>25%	0/8	1/8	1.0	NS	Medium

CIN = contrast-induced nephropathy; CrCl = creatinine clearance; LOCM = low-osmolar contrast media; ND = not defined; NR = not reported; NS = no significant difference.
* Values are percentages or absolute increase in serum creatinine, unless otherwise stated.