Comparative Effectiveness Review Disposition of Comments Report

Research Review Titles:
Contrast-induced Nephropathy: Comparative Effectiveness of Preventive Measures
and
Contrast-induced Nephropathy: Comparative Effects of Different Contrast Media

Draft review available for public comment from October 14, 2014 to November 13, 2014.

Research Review Citations:
Subramaniam RM, Wilson RF, Turban S, Suarez-Cuervo C, Zhang A, Sherrod C, Aboagye J, Eng J, Choi MJ, Hutfless S, Bass EB. Contrast-Induced Nephropathy: Comparative Effectiveness of Preventive Measures. Comparative Effectiveness Review No. 156. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. 290-2012-00007-I.) AHRQ Publication No. 15(16)-EHC023-EF. Rockville, MD: Agency for Healthcare Research and Quality; January 2016. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

And

Eng J, Subramaniam RM, Wilson RF, Turban S, Choi MJ, Zhang A, Suarez-Cuervo C, Sherrod C, Hutfless S, Iyoha EE, Bass EB. Contrast-Induced Nephropathy: Comparative Effects of Different Contrast Media. Comparative Effectiveness Review No. 155. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. 290-2012-00007-I.) AHRQ Publication No. 15(16)-EHC022-EF. Rockville, MD: Agency for Healthcare Research and Quality; December 2015. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Reviews

The Effective Health Care (EHC) Program encourages the public to participate in the development of its research projects. Each research review is posted to the EHC Program Web site in draft form for public comment for a 4-week period. Comments can be submitted via the EHC Program Web site, mail or E-mail. At the conclusion of the public comment period, authors use the commentators' submissions and comments to revise the draft research review.

Comments on draft reviews and the authors' responses to the comments are posted for public viewing on the EHC Program Web site approximately 3 months after the final research review is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator, if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

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Published Online: January 7, 2016

#	Commentator and Affiliation	Section	Comment	Response
1	Peer Reviewer #1	General	General Comments: The populations should be divided into urgent, elective, and mixed. In general, those studies that included urgent cases had much higher event rates. This is partially due to lack of prophylaxis but also that in the setting of acute coronary syndromes, there is cardiorenal signaling that contributes to kidney injury	It was not possible to classify all of the study populations according to whether imaging was done on an urgent or elective basis. To acknowledge this limitation, we added the following text to the Discussion section of the executive summary of the contrast media report and the "limitations of the evidence/overall limitations" of the Discussion chapter in both reports: "We found that studies examining the risk of CIN with different types of contrast media generally provided little detail about clinical indications for the diagnostic or therapeutic procedures whether imaging was done on an urgent or elective basis, or other details such as the severity of renal impairment. "
2	Peer Reviewer #1	Introduction	Introduction: Please change "CIN" to "CI-AKI" throughout for contrast-induced acute kidney injury. CIN is now out of favor after the KDIGO guidelines were published.	We prefer to keep the CIN term because that is what has been used in most of the studies included in the review. We acknowledge the new term CI-AKI in the introduction.
3	Peer Reviewer #1	Methods	Methods: Yes	NA
4	Peer Reviewer #1	Results	Results: Too much detail. Can reduce the text and show the tables	We reduced the text throughout the results sections and increased the focus on analysis in the results sections. We will not add summary tables to the main reports: The addition of summary tables would make the report on prevention methods extremely long.
5	Peer Reviewer #1	Discussion/ Conclusion	Discussion/ Conclusion: The abstract should be balanced and include treatments that did have a significant protective effect including statins. For NAC, the authors should specify in the abstract and the text what high dose is and if it was given IV or po. Please keep in mind the ACT trial with NAC was by far the largest and completely neutral, so NAC at that dose is very unlikely to be effective. Hence much larger doses, longer durations, and IV route are the only real chances this therapy can have an effect.	We reexamined the ACT trial and have extracted the data that are relevant to our targeted population of patients receiving LOCM or IOCM, while excluding the data on patients receiving HOCM. The ACT trial is now included in the results for high-dose NAC. We revised the abstract, executive summary, and main report to be consistent with the final results for each of the main interventions of interest, including each intervention that had evidence of a beneficial effect.
6	Peer Reviewer #1	Clarity and Usability	Clarity and Usability: Yes	NA

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7	Technical Expert #1	General	General Comments: The report is scientifically robust. However, the clinician who is reading it to find new cutting edge, practice-changing recommendations will be disappointed, as the quality of the evidence in the reviewed studies is generally low and there are no new recommendations. It is like watching a very competitive soccer game and it ends up in a 0 - 0 tie.	We created a 1-page summary of key points to be located at the beginning of the report for both the report on contrast media and the report on prevention methods.
8	Technical Expert #1	Introduction	Introduction: This is well done and covers the landscape in terms of previous meta-analyses, the needs, and recommendations by professional societies.	Thank you for your comment
9	Technical Expert #1	Methods	Methods: I am not a statistician, so I cannot comment whether the methodology is correct.	Thank you for your comment.
10	Technical Expert #1	Results	a. Results: The amount of detail is appropriate. Tables comparing various studies with each other are helpful.	Thank you for your comment
11	Technical Expert #1	Results	b. Were studies done prior to 1998 excluded, or were there simply no studies conducted prior to 1998 that met the review criteria? The time frame for potential studies in the search process should be explicitly stated.	As stated in the Methods, we searched databases through 1 October 2014 (this was added as the new search limit), and "We did not add any date limits to the search." We did not set a date for excluding older studies because we thought it was sufficient to include studies based on whether they included patients receiving LOCM or IOCM rather than the older HOCM.
12	Technical Expert #1	Discussion/ Conclusion	a. Discussion/ Conclusion: It seems that there were many studies related to CIN after interventional cardiology procedures. if that population constitutes a significant number of the overall number of patients, perhaps a separate analysis should be conducted related to patients undergoing cardiac interventional procedures.	The IA vs. IV results are clearly stated in the results. The vast majority of IA studies were cardiac procedures, so IA is essentially a surrogate for cardiac procedures. Where there was a sufficient number of studies, we reported results separately for IV and IA administration.
13	Technical Expert #1	Discussion/ Conclusion	b. It was mentioned that CIN might be under-reported, as patients are often discharged immediately after their procedures. Perhaps there should be a recommendation for clinicians to be more proactive and vigilant in screening patients for CIN in those patients with appropriate risk factors.	It is beyond the scope of this report to make a recommendation about screening for CIN. However, we acknowledge that CIN might be under-reported because patients often are discharged immediately after the imaging procedures are done. See last paragraph of the Overall Limitations in the Discussion section
14	Technical Expert #1	Discussion/ Conclusion	c. It appears that one potential area for future research was omitted. Because there are so many proposed interventions to prevent CIN, it seems to me that the disease mechanism has not been fully uncovered. A better understanding of the underlying pathology might point investigators to more appropriate preventive measures.	We added to the discussion/conclusions: To develop more effective interventions for preventing CIN, it may be necessary to conduct additional research on the pathophysiologic mechanisms by which contrast media may contribute to acute kidney injury, while trying to differentiate the direct effects of contrast media from other factors that can contribute to acute kidney injury in patients receiving IV or IA contrast media.

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15	Technical Expert #1	Clarity and Usability	Clarity and Usability: Is there enough data to recommend statin therapy, and specifically atorvastatin? It seems that recommending that statins be only further studied is conservative. Would it be safe in stating that, given the lack of other proven alternatives, it would be reasonable to consider using statins on a regular basis for CIN prevention?	We point out as an AHRQ supported comparative effectiveness review, we cannot make recommendations of one intervention over another. We pointed out that the evidence supports the use of statins in certain populations.
16	Technical Expert #2	General	General Comments: In general, the manuscript is well-written, clear, and informative. Readers will find it useful. I have some specific comments that I have tried to segment into their various sections below.	Thank you for your comment
17	Technical Expert #2	Introduction	a. Introduction: The question of whether the diagnosis of "CIN" is really AKI secondary to contrast or AKI coincident to contrast is not well addressed despite recent studies (Davenport et al, Newhouse et al, Bruce et al, McDonald et al, etc.) indicating that this is an open question. The manuscript begins by citing Nash et al and claiming that CIN is a leading cause of hospital-acquired AKI, despite the lack of control groups used to establish the true incidence of CIN and discriminate it from post-contrast AKI (coincident AKI).	We agree with your comments and revised the introduction sections in both the contrast media comparison paper and the preventive measures paper to make it more clear that CIN may not really be due to the contrast media: The following wording has been added to the prevention report and the contrast media report (Introduction): "It is unclear to what extent acute kidney injury that develops after iodinated contrast exposure is causally or coincidentally related."
18	Technical Expert #2	Introduction	b. Page 22 line 30 and following: The reported incidence of CIN has not been stratified by route of administration, baseline renal function, or risk factors. This incidence no doubt varies greatly by these parameters and therefore is highly dependent on the population under study.	We report results separately for IV and IA administration when there are enough studies to merit doing so. We stratified analyses according to selected characteristics of the study populations, such as age, sex, baseline renal function, and presence of diabetes mellitus, when it was possible to do so. Details of these stratified analyses were not included in the report but are discussed where applicable.
19	Technical Expert #2	Introduction	c. Page 22 line 36: There is discussion about the large number of CT studies performed each year, attempting to justify the potential significance of CIN, but this review and most of the studies it was able to investigate are focused on IA administration. In some parts of the review, this issue is acknowledged, and in other parts of the review it is stated that no data was found to consider IV and IA different. There seems to be somewhat of a conflicting message here. It is relevant because in clinical practice patients getting CT are handled much differently with respect to CIN prophylaxis compared to patients getting cardiac angiography.	As indicated above (reply to comment #18), we report results separately for IV and IA administration when it is possible to do so, and we have acknowledged the limitation that more studies are needed in patients receiving IV contrast media.

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20	Technical Expert #2	Introduction	d. page 106 line 21, page 115 line 23, and page 119 line 15 claims that iodixanol is the only iso-osmolar agent; this is true now, but there was another iso-osmolar agent that was taken off the market several years ago. Minor point.	We revised the introduction to clarify that there is more than 1 IOCM, but only 1 is in use. We have added information to indicate that there was another IOCM called iotrolan. It was available in Europe and Japan but was temporarily taken off the market in 1996 after an unexpected number of delayed reactions were reported. It eventually was discontinued for intravascular use. It was approved for intrathecal use in the US, but has been discontinued. Reference: Niendorf HP. Delayed allergy-like reactions to X-ray contrast media: problem statement exemplified with iotrolan (Isovist) 280. Eur Radiol 1996, vol 6, pp S8-S10.
21	Technical Expert #2	Methods	a. Methods: The methods are sound and well-explained. I have some comments:	Thank you for your comment
22	Technical Expert #2	Methods	b. Although IV administration is partially distinguished from IA administration when the included studies are listed in the executive summaries and study descriptions, the results, discussion, and conclusions fail to do so. Most references to "CIN" throughout the text collapse IA and IV administration, and collapse post-contrast AKI (AKI coincident to contrast) and CIN (AKI caused by contrast). "CIN" is used in many instances as a blanket term for "IA administration, IV administration, suprarenal catheter-directed administration, infrarenal peripheral IA administration, peripheral IV cannula administration, AKI caused by contrast, and AKI coincident to contrast, regardless of baseline renal function or relevant risk factors". This is a very broad definition obviously and assumes that whoever was conducting the study(-ies) is to be believed that contrast was causative when there were no control groups to establish that.	The following text was added to the Introduction sections of both reports: “It is unclear to what extent acute kidney injury that develops after iodinated contrast exposure is causally or coincidentally related.”

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23	Technical Expert #2	Methods	c. As an example of the relevance of this point, the data are presented to the casual reader as if statins may be helpful for preventing "CIN" when there is zero evidence to support that this works for patients undergoing CT. On page 20 lines 5-13, this topic is finally broached at the end of the "Future Research" section. I think this needs a lot more attention in the beginning of the discussions (or better yet, the introductions) so that the reader is aware of these issues and not misled. To expand on this point, I think the review would benefit from an explicit statement made about the term "CIN" and how it may be spurious in many cases. What this review (and essentially all of the studies it includes) does is assume that coincident changes in laboratory function tests (creatinine, eGFR) after contrast administration implies causal AKI from contrast material despite the absolute absence of any control group to prove that (e.g., 'sham procedure', CO2, etc.). Until this is disentangled, we aren't sure what it is we are trying to prevent. Are we preventing AKI caused by contrast? Or are preventing AKI coincident to contrast? This is not a minor issue.	The following text was added to the Discussion sections of both reports: "It should be noted that our review addressed a clinical comparison involving contrast media and did not seek to review evidence concerning the pathophysiology, causal pathway, or epidemiology of CIN. The precise mechanism of CIN is not entirely understood, and there is some evidence from propensity-score matched, retrospective studies that questions the strength of the relationship between contrast administration and CIN. Thus, uncertainty persists about whether there is a direct causal relationship between administration of contrast media and the development of acute kidney injury. This area of research was beyond the scope of our review." When we describe the characteristics of the studies in the results section on statin studies, we point out that all of the studies involved IA use of contrast media. We reinforce this important point by adding reference to "patients receiving IA contrast" when we present the results of the meta-analyses. – "We conducted two separate meta-analyses on studies of statins to reduce the incidence of CIN in patients receiving IA contrast." Study characteristics under statins includes: "Contrast media were administered intra-arterially in all studies"
24	Technical Expert #2	Methods	d. The definition of CIN (0.5 mg/dL or 25% change) is historical and although should be used for this review (based on the definitions used in the available literature), there is a movement toward defining CIN in the same way as all other causes of AKI (RIFLE / AKIN). It may be worth mentioning this context when the definition of "CIN" is described.	We use the definitions of CIN presented by each study author. We acknowledge the RIFLE criteria for defining CIN : "More recent consensus definitions of acute kidney injury, such as RIFLE[2] and AKIN[3], have not yet been used extensively in the CIN literature."
25	Technical Expert #2	Results	a. Results: Page 41 Table 3; I think there is a typo. Should the heading above Poletti 2007 say "IV", not "in"?	Thank you, we corrected this
26	Technical Expert #2	Results	b. Page 127 table 3, "development of CIN" in the column "Summary of key outcomes" has a typo. Delete the word 'that'.	Thank you, we corrected this

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27	Technical Expert #2	Discussion/ Conclusion	a. Discussion/ Conclusion: A major limitation of the analysis of all key questions is that no stratification was done based on risk factors, most notably of which is baseline renal function. We know that CIN incidence varies dramatically based on baseline renal function, and the absence of stratification information (although not feasible by this review) limits the conclusions for all key questions.	We have added text that points to the CIN outcome by characteristics of the study populations, including age, gender, baseline kidney function (serum creatinine), and percent of the population with diabetes mellitus where applicable. In general, there were not enough studies to support meta-regression on these study population characteristics. Specifically in the contrast media report, we add this text to the results section: "We performed simple meta-regression analyses between CIN incidence and each of the following covariates: age, baseline creatinine, diabetes, gender, and route of administration. No statistically significant associations were found."
28	Technical Expert #2	Discussion/ Conclusion	b. Page 19 line 29-33. It is hypothesized that patients with normal or near-normal renal function "may have" a lower risk of CIN. Multiple studies have shown this conclusively to be the case. I don't think this is a hypothetical at this point. I agree that studies evaluating CIN interventions need to restrict their populations to those who are actually at risk for this condition. This is also mentioned on pages 81 and 82.	We revised the statement in the executive summary and Discussion to read: "Also, patients with risk factors for CKD have a higher risk of developing CIN than patients without such risk factors."
29	Technical Expert #2	Discussion/ Conclusion	c. The future research sections are clear.	Thank you for your comment
30	Technical Expert #2	Clarity and Usability	Clarity and Usability: The report is well structured and organized. The main points are clearly presented. The conclusions can be used to inform policy and/or practice decisions.	Thank you for your comment

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31	Peer Reviewer #2	General Comments	General Comments: Although the authors have defined the target populations and key questions quite clearly, the overall value of this report is questionable, driven in large part by the nature of the clinical trials and issues related to the definition of CIN. Do we know that the small changes in serum creatinine that are used to defin CIN are actually clinically meaningful? The argument is made that CIN is associated with development of/progression of CKD, but how strong is the data supporting a causal relationship, especially in patients with mild, transient increases in serum creatinine? Do small changes in serum creaitnine necessarily represent changes in kidney function (e.g. AKI) or might they represent epiphenomenon resulting from changes in creatinine production, tubular secretion, volue of distribution or extra-renal disposition?	Contrast media report: This text was added to the Introduction sections: ""It is unclear to what extent acute kidney injury that develops after iodinated contrast exposure is causally or coincidentally related. The following text was added to the Discussion sections of both reports: "It should be noted that our review addressed a clinical comparison involving contrast media and did not seek to review evidence concerning the pathophysiology, causal pathway, or epidemiology of CIN. The precise mechanism of CIN is not entirely understood, and there is some evidence from propensity-score matched, retrospective studies that questions the strength of the relationship between contrast administration and CIN. This area of research was beyond the scope of our review."
32	Peer Reviewer #2	Introduction	a. Introduction: See comments above	Thank you for your comments
33	Peer Reviewer #2	Introduction	b. The discussion of existing guidelines is highly selective and incomplete. For example, there is no mention of the KDIGO Clinical Practice Guideline for AKI that was based on a rigorous data review and which devotes an entire section to Contrast-induced AKI.	We have revised the introduction to address your concern and cite the KDIGO guidelines: "The reported incidence of contrast- induced nephropathy (CIN), also called contrast-induced acute kidney injury in recent studies varies, but it is cited as a leading cause of hospital-acquired kidney failure."
34	Peer Reviewer #2	Introduction	c. Minor point: it is stated that withdrawal of metformin is a potential preventative strategy - I am unaware of any data supporting this; rather discontinuation has been recommended based on concern that if a patient develops severe AKI while still on this agent, they are at risk for lactic acidosis.	We revised the introduction to reflect that the discontinuation of metformin is recommended because if a patient develops CIN they are at higher risk for lactic acidosis.
35	Peer Reviewer #2	Methods	a. Methods: Reasons for exclusion/non-inclusion of some studies is not entirely clear and may be of questionable justification. For example, the ACT study (reference 63) is excluded because 20-25% of patients received HOCM. Interestingly, although this study is excluded from the analysis of CIN, it is included in the analysis of other endpoints. It is likely that including this study (even if only the data from the 1742 patients treated with IOCM/LOCM) were included would alter the results of the analysis of benefit of high-dose NAC.	Thank you for this very important comment. We have re-evaluated the ACT study and are including the ACT data on LOCM administration and IOCM administration in the NAC versus IV saline section of the prevention report. We also added this data to the meta-analyses.
36	Peer Reviewer #2	Methods	b. Similarly, it is not clear why the study of rosuvastatin for the prevention of CIN by Leoncini et al (PMICD: 24076283) was not included even though the study by Han et al, published on-line in the same journal on the same day was included.	This study was added to the updated version of the report.

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37	Peer Reviewer #2	Methods	c. In the methods, there appear to have been minimal consideration of multiple aspects of the design of the primary studies which may invalidate either their primary results or the ability to pool results in a meta-analysis. For example, there are data that statins (specifically rosuvastatin) have an independent effect on eGFR (increasing), and hence on serum creatinine - separate from any protective effect on kidney function (see, for example Vidt EG, et al. Am J Cardiol 2006; PMID: 16728222). Similarly, for studies of RRT, can a change in serum creatinine be used to define CIN when the interventions directly change the serum creatinine concentration. These issues need to be considered and discussed in the methodologic approach.	We added the following statement to the Discussion: "It is possible that the findings reported in the studies of statins could be partly explained by a direct effect of statins on glomerular filtration rate that is independent of a protective effect on kidney function, as has been reported in one study (Vidt 2006)."
38	Peer Reviewer #2	Methods	d. In the analysis of IOCM vs LOCM, it is not clear why an analysis by type of LOCM was not performed	Discussion, in the section on Limitations of the Evidence, we added: "We considered whether a network meta-analysis could be performed to combine this indirect information with the data from direct comparisons. However, the sparse number of direct LOCM comparisons compared to indirect comparisons via iodixanol severely limits the reliability of such an analysis. For this reason, a network meta-analysis was not performed in our review of the evidence."
39	Peer Reviewer #2	Results	a. Results: The opening statement describing the NAC studies fundamentally mischaracterizes the studies, since they are described as comparing NAC to intravenous saline. This is not correct - the studies compare saline +NAC to saline w/o NAC.	We revised this report to ensure that the correct comparisons are in the text
40	Peer Reviewer #2	Results	b. In the presentation of the study characteristics for the NAC studies, it is stated that "...and one study used IOCM, LOCM or HOCM" with the cited study being Ochoa et al Ref 45). This is incorrect; this study did not use HOCM; this is probably referring to the ACT study(Reference 63).	The correct reference has been called out here.
41	Peer Reviewer #2	Results	c. Differences in study design are not adequately detailed. For example, in the studies comparing IV bicarbonate to IV saline, there is insufficient detail regarding the overall concentration of the solutions and the rates of administration. Was the rate of fluid administration the same in both treatment arms of the study? If not, does this matter? Was the concentration of sodium the same in both the NaCl and the NaHCO3 treatment solutions?	This data is detailed in the appendix and the text of the report points to the appropriate appendix for the reader to reference
42	Peer Reviewer #2	Results	d. In the presentation of data, the term "Hydration"should not be used to describe the administration of intravenous salt solutions	We are more consistent throughout the report about IV hydration versus administration of IV saline fluids.
43	Peer Reviewer #2	Results	e. In the comparison of saline versus bicarobnate and NAC+saline versus bicarbonate, it is not clear whey some studies are characterized as NaCl and others as saline.	NaCl has been revised to read either saline or NS (normal saline) as appropriate in this section
44	Peer Reviewer #2	Discussion/ Conclusion	Discussion/ Conclusion: The statements describing the results of the analysis of the NAC studies is worded inappropriate. For example, it is stated that "The strength of evidence was low that high-dose N-acetylcysteine was effective for the prevention of CIN when compared with intravenous saline..." As stated above, the actual comparison was between saline+NAC versus saline w/o NAC.	We revised this report to ensure that the correct comparisons are in the text

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45	Peer Reviewer #2	Clarity and Usability	Clarity and Usability: The report is adequately structured. Unfortunately, the strength of data are weak and the conclusions reached are may not be supported over time. The conclusions are unlikely to meaningfully inform policy or clinical practice decisions. What this analysis does make clear is that the level of clinical research in this area - while voluminous in numbers of studies - is characterized by a multitude of poor quality studies. There needs to be a concerted effort to have high quality studies addressing the key research questions related to prevention of CINB - particularly whether interventions that prevent small, short-term changes in serum creatinine provide meaningful longer-term benefits with regard to preventing development of or progression of CKD.	In the discussion section of the contrast media report, we added information on other outcomes that are detailed in the paragraph starting with: "In our systematic review, we sought evidence on the relationship between contrast type and renal function. Therefore, our inclusion criteria focused on CIN as the primary outcome under consideration. We collected data on other outcomes of interest, however. Since the majority of studies involved coronary artery procedures, cardiovascular event outcomes were of particular interest…."
46	Technical Expert #3	General Comments	General Comments: I think the report is clinically meaningful. I think the key question is clear but the abstract and exec summary focus on the prevention of CIN (as opposed to the other listed outcomes in the key question). Based on how the abstract is written, it's not obvious that the key question included outcomes other than CIN. Consider adding additional text to the abstract and exec summary (including discussion and conclusions) on the findings (or lack of data) for other outcomes.	We revised the Abstract objectives with" …to reduce the risk of contrast-induced nephropathy (CIN), need for renal replacement therapy, mortality, cardiac complications, prolonged length of stay, and other adverse events, after receiving low osmolar contrast media (LOCM) or iso-osmolar contrast media (IOCM)."
47	Technical Expert #3	Introduction	Introduction: Seems reasonable. See also comments below pertaining to exec summary.	Thank you for your comment
48	Technical Expert #3	Methods	Methods: Yes. See also comments below pertaining to methodology described in exec summary.	Thank you for your comment
49	Technical Expert #3	Results	Results: Statin section: Although the text refers to particular studies via a footnote, the accompanying table showing the meta-analysis shows by author and year so it is hard to link the text to what is shown in the table.	We revised the text to refer to the author and year of each study to make it easier to link the text to the information in the corresponding figures. Additionally, we added the reference numbers to all of the meta-analysis figures.
50	Technical Expert #3	Results	I think it's important to report the size of trials when describing results. You don't consistently do this.	We have added information to the Executive Summary and added population sizes of studies analyzed throughout the report
51	Technical Expert #3	Results	In the statin section you report the statin doses used in trials but don't tell me the drug. A dose of 20 mg of one drug is not the same as a dose of 20 mg of another.	Dose information for each study is provided in detail in evidence tables (Evidence Table 3)
52	Technical Expert #3	Results	Statin section: Table shows "control" (as opposed to placebo) for trial by Li, 2012. Do you indicate what the control was?	This figure was revised. "Control" has been changed to "Placebo" as this is the more appropriate description.
53	Technical Expert #3	Results	You indicate that statins didn't add anything when administered on top of NAC but doesn't that seem inconsisent with the reported magnitude of benefit associated with statin (large) vs NAC (small) in preventing CIN? How do you explain (assuming these findings are real)?	A new analysis has been added to the statin section comparing statin plus NAC v NAC alone. Through this analysis (conducted because new studies were identified that addressed this comparison) we did find a benefit in adding statins to NAC.

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54	Technical Expert #3	Discussion/ Conclusion	Discussion/ Conclusion: I found the presentation a little confusion. Consider presenting the findings/conclusions in a similar manner/order for each intervention: (1) what the finding was (point estimate, 95% CI); (2) whether finding meets your criteria for a clinically meaningful treatment effect (I assume you can only assess if finding is clinically significant? how do you usually handle?) (3) what you think the strength of evidence is (with an explanation of why you gave the evidence that particular grade).	The Results section better explains the clinical importance and statistical significance of the results of the meta-analyses. This is reflected throughout the Results section
55	Technical Expert #3	Clarity and Usability	Clarity and Usability: As a whole, I think the structure is reasonable. I found some of the text in the exec summary and abstract confusing. See below and prior comments.	Thank you for your comment. During the revision and update of the report we made the Executive Summary clearer and more consistent with the main report.
56	Technical Expert #3	Exec summary Background	Exec summary Comments on Background text: 1. What do you mean by kidney failure? You open by saying kidney failure is the most serious adverse event that can occur after admin of contrast media and then move to the incidence of CIN. These terms are not synonymous, and as you later note, relative to CIN, kidney failure is a rare/uncommon event.	We revised the opening sentence of the Executive Summary: "The reported incidence of contrast-induced nephropathy (CIN) varies, but it is a leading cause of hospital-acquired kidney failure.[1] CIN is usually defined as an impairment of renal function with an increase in serum creatinine of more than 25 percent or 0.5 mg/dL within 3 days of intravascular administration of contrast media in the absence of an alternative etiology."
57	Technical Expert #3	Exec summary Background	Exec summary Comments on Background text: 2. What do you mean by "…it can progress to acute kidney injury and chronic kidney failure in a small proportion of patients who develop CIN." CIN is acute kidney injury, no? What do you mean it progresses to AKI? (comment also pertains to Figure on page 4, 25 of 555) 3. The intro includes a short discussion on LOCM vs IOCM- I might indicate that a separate report was issued on this topic.	We revised this statement in the Executive Summary to: "it can progress to acute kidney injury, which may require renal replacement therapy, and chronic kidney disease in those who may not recover fully from acute kidney injury in a small proportion of patients who develop CIN."
58	Technical Expert #3	Exec summary Data Sources	Exec summary Comments on Data Sources: 1. You state "We did not search for data held by the U.S. Food and Drug Administration." Consider deleting. I assume you mean that you didn't have access to proprietary/non-public information held by the FDA. I would think that this is always the case with these reviews (and hence a given).	The search of the FDA site was completed and we were unable to identify any new information.
59	Technical Expert #3	Exec summary Study Appraisal and Synthesis Methods	Exec summary Comments on Study Appraisal and Synthesis Methods: 1. You state: "We performed de novo meta-analyses of all studies on a given comparison if the studies were not too heterogeneous by qualitative or statistical criteria". Term "not too heterogeneous" is vague.	We revised the wording in the Executive Summary: "We performed de novo meta-analyses of all studies on a given comparison if the studies were similar by qualitative or statistical criteria."

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60	Technical Expert #3	Exec summary Study Appraisal and Synthesis Methods	Exec summary Comments on Study Appraisal and Synthesis 2. You discuss factors that were considered in calculating the overall rating for potential bias but don't clearly tie this back to the SOE issue. How did you incorporate this rating into your SOE determination? Also you refer to CIN as the "main outcome of interest"- was this the main outcome of interest or just the outcome for which you had the most data?	We revised this section to not imply that we only looked at CIN since we had the most evidence there: "The team graded the strength of evidence (strength of evidence) on comparisons of interest for the key outcomes, focusing mainly on the primary outcome of incidence of CIN. We used the grading scheme recommended in the Methods Guide[6] and considered all domains: study limitations, directness, consistency, precision, reporting bias, and magnitude of effect.[6] " We better describe how risk of bias is used to assess study limitations when using the GRADE criteria: "Study limitations were determined for each comparison group for CIN and other reported outcomes. Study limitations were determined using the following algorithm for a body of evidence: A body of evidence was assessed as having high study limitations if greater than 50 percent of the studies scored negative (-) in one or more of the criteria. A body of evidence was assessed as having low study limitations if most (51 percent or greater) of the studies scored positive (+) in all 5 domains. Bodies of evidence not meeting one of the above criteria were assessed as having medium study limitations."
61	Technical Expert #3	Exec summary Study Appraisal and Synthesis Methods	Exec summary Comments on Study Appraisal and Synthesis 3. You state: We rated the evidence as imprecise if the 95% CI did not exclude the possibility of a clinically important benefit or harm (i.e., RR less than 0.75 or greater than 1.25) despite having an optimum information size". I don't understand this sentence. Unless there is a third category, it seems to conflict with your prior sentence where you state "we rated evidence as precise if the total number of patients exceeded an optimum information size, and the 95% CI excluded a risk ratio of 1.0."	We revised the statement to: "If the total number of patients exceeded the optimum information size, and the 95% CI did not exclude the possibility of no difference (i.e., risk ratio of 1.0), we rated the evidence as imprecise if the 95% CI did not exclude the possibility of a clinically important benefit or harm (i.e., RR less than 0.75 or greater than 1.25)."
62	Technical Expert #3	Exec summary Results	Exec summary Comments on Results: 1. You tell me they number of trials but not the total number of subjects studied in these trials. I think total n (and possibly other info on average size of trial) provides important context.	We added the number of subjects to this section of the report

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63	Technical Expert #3	Exec summary Results	Exec summary Comments on Results: 2. You tell me the total n for NAC trials but when you provide the results you show by dose. Basis for doing so? How do you address oral vs IV administration (I may have missed this).	We revised this section to summarize the differences in IA vs IV administration: "In sensitivity analyses, the pooled RR for CIN was: 0.80 (CI: 0.6 to 1.1) for high-dose N-acetylcysteine when intra-arterial contrast media was used; 0.60 (CI: 0.1 to 2.4) for high-dose N-acetylcysteine when intravenous contrast media was used; 0.80 (CI: 0.7 to 0.9) for low-dose N-acetylcysteine when intra-arterial contrast media was used; 0.70 (CI: 0.3 to 1.4) for low-dose N-acetylcysteine when intravenous contrast media was used; 0.70 (CI: 0.6 to 0.9) for N-acetylcysteine when LOCM was used; and 1.10 (CI: 0.8 to 1.4) for N-acetylcysteine when IOCM was used based on a small set of five studies on patients with varying comorbidities."
64	Technical Expert #3	Exec summary Results	Exec summary Comments on Results: 3. Upper bound of 95% CI appears to include 1 for high dose NAC. Was the finding statistically significant or not?	We revised the wording in the Executive Summary to read: "indicating a small effect that is clinically unimportant and statistically insignificant benefit."
65	Technical Expert #3	Exec summary Results	Exec summary Comments on Results: 4. Found presentation of results confusing (see my prior comment about presenting in a consistent manner).	Have revised this section to be more consistent.
66	Technical Expert #3	Exec summary Results	Exec summary Comments on Results: 5. As I understand, statin trials were conducted in a specific population. Can you say more about the population in which the benefit was shown?	We added the following information in the Executive Summary to further describe the specific populations in the statin studies: "one study included only patients with CKD, two included only patients with cardiac issues, and one included only patients with diabetes."
67	Technical Expert #3	Exec summary Discussion	Exec summary Comments on Discussion: 1. You say KDIOG guideline recommends using NAC but it looks like the report "suggests" use and gives it a grade of 2D. In describing the effects of NAC, I would also provide your conclusions about efficacy of NAC as relates to other outcomes.	We revised this to read: "(KDIGO) Clinical Practice Guideline for Acute Kidney Injury suggests using oral N-acetylcysteine with intravenous fluids in patients at increased risk for CIN.

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68	Technical Expert #3	Exec summary Discussion	Exec summary Comments on Discussion: 2. In discussing statins, I would discuss population in which trials showed benefit/were conducted.	We identified the specific study populations in the results sections. All studies included in the meta-analyses are on disease specific populations with the exception of one. The disease populations differ and the number of studies on each disease population is too small to determine how results might differ by characteristics of the study population.
69	Peer Reviewer #3	General Comments	The authors of this evidence-based review are to be congratulated for the huge amount of work that they have obviously put into their document. For the topics they have covered, their evidence-based review has been comprehensive. When their work is published by AHRQ, it should be an important source document for cardiology and nephrology practitioners.	Thank you for your comment
70	Peer Reviewer #3	General Comments	As a reviewer, I read through the entire manuscript (including all of the evidence tables and bibliography) several times. I think one general area that could be improved in this very large document is the quality of editing. For example, on page 1 of 555 it says "The following report on Contrast-induced Nephropathy has been organized by the Key Questions (KQ). The sections that address KQ 1 and 2 appear first, on pages 2 to 97. The sections addressing KQ 3 and 4 appear on pages 98 to 140." I would conclude that there are four key questions addressed in the document.	We revised the text to be clear about the questions that are addressed in each report.
71	Peer Reviewer #3	General Comments	On page 8 (or 29 of 555) The Key Question relates to patients undergoing imaging studies requiring contrast and there are three sub-categories: a. How does the comparative effectiveness of prevention measures vary by patient characteristics; b. How does the comparative effectiveness of prevention measures vary according to the type of contrast media used; and c. How does the comparative effectiveness of prevention measures vary by characteristics of the interventions?	We revised the text to be clear about the questions that are addressed in each report.

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72	Peer Reviewer #3	General Comments	On page 116 of 555, the Key Question is what are the comparative benefits and harms of different contrast media, categorized as either subcategory a. related to patient characteristics, or b. differing according to the use of co-interventions. How many Key Questions are posed in the document? Did I miss any? By subcategories, this would be five, but by main categories, only two.	In the report on the risks of different contrast media the Key question is **Key Question:** What are the comparative benefits and harms of different contrast media in patients receiving imaging studies requiring intravenous or intra-arterial administration? a. How do benefits or harms of contrast media differ by patient characteristics (known risk factors such as age, comorbidity, glomerular filtration rate, or creatinine clearance)? How do benefits or harms differ by the dose of contrast medium (i.e., by volume of dose and number of doses)? How do benefits or harms of contrast media differ according to the type of preventive strategy used? In the report on interventions to prevent CIN the Key question is: **Key Question:** In patients undergoing imaging studies requiring intravenous or intra-arterial contrast media, what is the comparative effectiveness of interventions to prevent contrast-induced nephropathy (CIN), for the outcomes of incidence of CIN, chronic kidney disease (CKD), end stage renal disease (ESRD), mortality, and other adverse events? a. How does the comparative effectiveness of prevention measures vary by patient characteristics (known risk factors such as age, comorbidity, glomerular filtration rate (GFR), or creatinine level)? b. How does the comparative effectiveness of prevention measures vary according to the type of contrast media used (i.e., LOCM versus IOCM)? How does the comparative effectiveness of prevention measures vary by characteristics of the interventions (e.g., dose, duration, and timing)?

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73	Peer Reviewer #3	Executive Summary	The Executive Summary is a good high-level view of the document, and highlights overall major areas of focus: N-acetylcysteine, intravascular volume expansion, types of contrast agents, and the potential role of statins. The strongest evidence according to the authors was the potential use of statins for prevention of contrast-induced nephropathy (CIN). It is not clear to me how many potential interventions were assessed and rejected because of lack of evidence. I would suggest that the authors include a table that is prominently figured somewhere early in the report on all of the interventions that they actually did consider, i.e., which are summarized on ES-1 on the background section. For example, avoidance of nephrotoxic agents has been suggested in some practice guidelines, but from a non-evidence-based point of view as more of an ungraded recommendation. In one line, the authors do allude to nonsteroidal and inflammatory drugs in their background section. Similarly, withholding ACE inhibitors has been recommended by some groups before administration of contrast. Did the authors attempt to address these issues and found them wanting for evidence and thus they are not included in the results section? It would be helpful for them to tabulate interventions of potential interest that could not be studied because of inadequate data.	Table A was added to the Executive Summary and lists all of the miscellaneous comparisons in addition to the main comparisons discussed in the report.

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74	Peer Reviewer #3	Executive Summary	In the Executive Summary, and later in the document, the authors summarize the body of evidence for use of N-acetylcysteine and include reference to differing recommendations by various professional societies. For example, the ACC/AHA 2012 Guidelines recommend against the use of NAC for patients receiving intra-arterial contrast in cardiac procedures. In contrast the 2012 KDIGO Clinical Practice Guidelines for Acute Kidney Injury (AKI) recommended the use of oral NAC with intravenous fluids in patients at increased risk for CIN and the current review provides modest support for the conclusion of the KDIGO AKI Task Force. As a member of the KDIGO AKI Task Force (who specifically worked on CIN), I think it should be pointed out that the strength of recommendation for the use of NAC was the weakest possible (i.e., barely a positive recommendation). Specifically, Guideline 4.4.3 "We suggest using oral NAC together with i.v. isotonic crystalloids, in patients at increased risk of CI-AKI" was a class 2D recommendation. Class 2 ("we suggest") would have a policy recommendation of "likely to require substantial debate and involvement of stakeholders before policy can be determined" and the level of evidence grade D is "very low" which means "The estimate of effect is very uncertain, and often will be far from the truth." In other words, the KDIGO recommendation for NAC was about as unenthusiastic as it could possibly be and still be a "positive recommendation". I think that this needs to be included in the discussion of societal recommendations regarding the use of NAC. I do find it interesting, however, that when all is said and done, the authors have made a very similar conclusion from the evidence regarding the evidence-base for the use of NAC that we did for KDIGO a number of years ago. Although the agent is safe, in some institutions it is not as inexpensive as one might think. One disconcerting experience of this reviewer was that one of his patients received a pharmacy charge of $100.00 for two outpatient doses of 600 mg of oral NAC to be administered before elective coronary angiography. I think that the calculation of potential benefit does need to be considered in the context of not only wholesale cost of the drug, but what patients might actually be expected to pay (which may not be as low as the authors think).	We revised the introduction to address your concern and cite the KDIGO guidelines: "The reported incidence of contrast- induced nephropathy (CIN), also called contrast-induced acute kidney injury in more recent studies, varies but it is cited as a leading cause of hospital-acquired kidney failure."
75	Peer Reviewer #3	Methods	It is never stated if the assumptions made by the authors are only intended to apply to the United States or to all countries. For example, the statement is made on the use of contrast that high osmolar contrast is no longer used in clinical practice. This is certainly true in the United States, but as was pointed out to me in my work with KDIGO, there are parts of the world that still may use high osmolar contrast due to cost issues. If the authors actually have data to indicate that high osmolar contrast is no longer used anywhere; that would be useful to cite in their discussion.	We revised the text in the Executive Summary, Introduction and Discussion sections to clarify that we were mainly interested in interventions applicable to the use of contrast media in the U.S.

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76	Peer Reviewer #3	Executive Summary	One obvious point to raise in the Executive Summary is that the task of the authors is not to make recommendations for clinical practice, but rather (as they have done in great detail) to attempt to extract and summarize available data to answer their Key Questions regarding comparative effectiveness. I'm sure this point is painfully obvious, but as a reader of this document and of the KDIGO Clinical Practice Guidelines for AKI, there are some interesting parallel divergences that occur when the documents are read in tandem. A good example of this issue is the discussion regarding oral vs. intravenous reprocedure volume expansion. I believe the authors have accurately abstracted the literature on this issue and appropriately concluded from the evidence that there is no strong evidence-based difference (based on review of very incomplete data) favoring oral or intravenous volume expansion before administration of radiocontrast media. In contrast, the KDIGO recommendation pertaining to this issue was Guideline 4.4.2: "We recommend not using oral fluids alone in patients at increased risk of CI-AKI", strength of recommendation (1C). Due to the small numbers, this is really a question of noninferiority margins, and the authors did not approach this issue in this way because the confidence intervals are so large with such small sample sizes. The problem here is that very small inconclusive trials may have a null result leading to the perception that either is acceptable in clinical practice, and patient outcomes may actually be compromised. This issue is of some clinical concern: based on nationwide surveys of interventional cardiologists, adherence to practice guidelines relating to any type of pre-procedural volume expansion has shown a large disconnect between recommendations from professional societies and actual behavior of practitioners. Specifically, in the current practice environment it is extremely difficult to start intravenous volume expansion twelve hours before an elective procedure and the number of hours that practitioners would be able to stomach is a lot shorter than twelve hours (or even six hours) at the present time. I think this issue of actual non inferiority vs. "we cannot tell" needs to be strongly emphasized given the potential downside of practitioners concluding that it is okay to give someone a couple of glasses of water before a procedure, rather than several hours of intravenous volume expansion (or the even more aggressive tactic of catheter-directed volume expansion as described by the REMEDIAL investigators).	We found little evidence to support the use of oral hydration over IV hydration. We have addressed this in the FRN section of the ES and Discussion: "Surprisingly little evidence exists on the comparative effectiveness of different regimens for giving fluids to patients receiving contrast media, despite the fact that current clinical practice often involves use of oral hydration alone for studies with intravenous contrast media. Oral hydration is a simple and potentially cost-effective strategy for preventing CIN, if shown to be as effective as intravenous saline. Unfortunately, very few studies investigated oral hydration versus intravenous saline. Hence, more studies are needed to investigate the effectiveness of oral hydration versus intravenous saline, especially for intra-arterial contrast procedures such as coronary angiography. "
77	Peer Reviewer #3	Results	As a reader, I think the easiest way to appreciate the results of a meta-analysis is by using forest plots. This is done to good effect in the Figures in this document. One thing I don't understand, however, is why certain studies that were cited were not included in the forest plots? For example, the Acetylcysteine for Contrast-induced nephropathy Trial (ACT) (*Circulation* 2011; 124: 1250-1259) does appear in the appendix tables. As far as I can tell, though, even though it is by far the largest randomized clinical trial (RCT) ever undertaken using NAC, it does not appear in any of the forest plots. Were the results of this trial included in the overall calculation of the estimated effects of NAC summarized in the forest plots? If it was not included, why not?	We added the ACT data that are relevant to our focus on interventions for preventing CIN after use of LOCM or IOCM. We also added text to explain why some studies were included in the review, but were not included in the meta-analyses (e.g., lack of usable data, or no CIN outcomes despite related serum creatinine or estimate glomerular filtration rate data).

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78	Peer Reviewer #3	Results	I think the ACT trial brings up another general issue that the authors could address in different parts of the document. Specifically, if there are large well done trials which are either not included in the analysis, or appear to have results that are counter to the overall conclusions, it would be worth having a discussion of these pivotal trials in the context of the overall conclusions of the authors. Going back to the ACT trial, I quote my colleague Peer Reviewer #1's editorial in *Circulation* that accompanied the ACT trial, which says, "The implications of this adequately powered, well-conducted clinical trial are clear: the short-term use of N-acetylcysteine for the prevention of CI/AKI in clinical practice should be abandoned." This is a very strong editorial recommendation accompanying the largest RCT ever published on the use of NAC for prevention of CIN or other adverse outcomes. The authors should definitely address this specific trial, and any other trials that are of sufficient size or importance that are not included in the analysis, or that offer results that seem counter to the authors' conclusions. I think this would serve to enhance the level of credibility of the document.	We added the ACT data that are relevant to our focus on interventions for preventing CIN after use of LOCM or IOCM. We also added text to explain why some studies were included in the review, but were not included in the meta-analyses (e.g., lack of usable data, or no CIN outcomes despite related serum creatinine or estimated glomerular filtration rate data).
79	Peer Reviewer #3	Results	On page 23 of 555, the authors summarize nine areas of uncertainty, and number 9 is the "Effect of the volume of contrast media administered, and the possibility of preventing CIN by keeping the volume of contrast media below a threshold." I may have missed it in my review of the document, but I could not find the summary of what actually was determined from an evidence-based review on this topic. Specifically, did the authors find there was a paucity of evidence and they could make no evidence-based assessment, or something else? Going back to my earlier comments about the difference between the authors' present manuscript and attempts at practice guidelines in the past, the KDIGO AKI workgroup's approach to this issue was the following: Guideline 4.3.1., "Use the lowest possible dose of contrast medium in patients at risk for CI-AKI" ; This guideline was not graded, although there have been publications that do link risk to overall volume. More importantly, the workgroup recommended that the dose of contrast medium should better be expressed in relation to both volume and concentration, e.g., grams of iodine, because that is really the issue. It is not just volume; it is the actual amount of iodine received by the patient.	We added information on contrast volume where it is available.
80	Peer Reviewer #3	Results	I think that the part of the document that will have potentially the most clinical impact relates to the discussion of the potential role of statins in preventing CIN. This may be a hard area to study, given that the population of patients who would be receiving intraarterial contrast is also likely to be receiving statin therapy (given their widespread using in primary and secondary prevention of cardiovascular disease. Nevertheless, for those few patients undergoing intra-arterial contrast procedures who are not currently receiving statins, generic simvastatin (or atorvastatin) is an inexpensive drug. The authors are to be commended for focusing on this relatively still unappreciated area in the clinical practice world.	Thank you for your comment. The included studies are on subjects who are statin naive. We clarified this in the report.

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81	Peer Reviewer #3	General Comments	In summary, I would like to thank the authors for their hard work on this comprehensive document. I look forward to seeing it in its final form.	Thank you for your comment.
82	Peer Reviewer #4	General Comments	General Comments: The report is clinically meaningful. The key questions are both appropriate and explicitly stated. There are neither significant changes nor omissions that should be made. However the challenge with the review is the underlying assumption of a causal relationship between exposure to IV doses of iodinated contrast and the development of nephropathy. The authors also explicitly call out this fact (page 23/555, line 15-23). A more recent study, not included in this review provides additional compelling data arguing against the causal relationship between IV contrast exposure and adverse events: "The results of our large, single-center, propensity score–adjusted retrospective study failed to demonstrate an excess risk of short-term mortality or excess incidence of emergent dialysis among patients who were exposed to intravenous contrast material compared with a similar matched group of patients who were not exposed to intravenous contrast material. These results were observed even among patients with compromised renal function and comorbidities associated with greater purported risk for contrast material–mediated nephrotoxicity. Further, these findings were validated against other propensity score methods by using a sensitivity analysis. These results challenge the long-held assumption that intravenous contrast material exposure is associated with excess morbidity and mortality and the purported causal association between contrast material exposure and nephrotoxicity. Although higher rates of dialysis and death were observed among individuals who experienced AKI following CT scanning, our findings suggest that these outcomes are unrelated to intravenous iodinated contrast material exposure." (PMID: 25203000)	A statement appears in the discussion sections of both reports: "It should be noted that our review addressed a clinical comparison involving contrast media and did not seek to review evidence concerning the pathophysiology, causal pathway, or epidemiology of CIN. The precise mechanism of CIN is not entirely understood, and there is some evidence from propensity-score matched, retrospective studies that questions the strength of the relationship between contrast administration and CIN. This area of research was beyond the scope of our review"
83	Peer Reviewer #4	Introduction	Introduction: The introduction is clear. The clinical question is one that is common and important. The goals and intent of the review is well stated. However, the risk of nephropathy is different between intravenous (IV) and intraarterial (IA) iodinated contrast administration. The authors explicitly make this statement (page 22/555 line 34). Table 1 description of the Populations explicitly states that the all routes of vascular contrast exposure are of interest. However, this makes conclusions and interpretation of the analysis more difficult, because of the underlying causal inference.	Both reports are more clear about the route of administration in each study, and we stratified results by route of administration whenever possible.
84	Peer Reviewer #4	Methods	Methods: Mixing of results for studies that looked at the comparative effectiveness of CIN reduction between IA and IV routes of contrast administration is understandable. Overall, the review might have been improved by analyzing the routes of administration and risk reduction of different strategies separately, rather than all together. I would not be surprised if it was too difficult to extract that information from the studies. However if that is the case, it would be helpful the reader to make that statement more clearly in both the introduction and the methods.	Both reports are more clear about the route of administration in each study, and we stratified results by route of administration whenever possible.
85	Peer Reviewer #4	Results	Results: The table that I kept looking for was one that separated the studies that referenced IV vs IA routes of administration. Otherwise the information that is presented is clearly explained and illustrated. The figures are appropriate.	We include discussion of meta-analyses stratified by route of administration when sufficient studies were available. Otherwise, we revised the text to clarify when additional information about route of administration is available in the appendix.

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86	Peer Reviewer #4	Discussion/ Conclusion	Discussion/ Conclusion: The implication and uncertainty in the results are clearly stated. The limitations of the baseline assumption are well explained in the overall limitations section (page 81/555 line 20-26). While I agree that the future research suggested is reasonable, it may be mis-directed as a suggestion. That is, if a causal link between IV doses of iodinated contrast material, whether low-osmolar or iso-osmolar, and nephrotoxicity/other renal related poor outcomes does not exist, then the results of any study that showed an apparent impact on outcomes might be suspect.	The following wording has been added to the prevention report and the contrast media report (Introduction): "It is unclear to what extent acute kidney injury that develops after iodinated contrast exposure is causally or coincident related."
87	Peer Reviewer #4	Clarity and Usability	Clarity and Usability: Overall, the review and the coverage of the two areas of Key Questions related to Contrast Induced Nepropathy (CIN) is comprehensive and believable as to what is available in the literature. The major limitation is highlighted in the paragraph above from a recent article looking at the incidence of adverse events after exposure to intravenous contrast. If there is no a causal association between contrast material exposure and nephrotoxicity, then there would not be a "winner" in a comparative effectiveness analysis of interventions that are intended to mitigate CIN risk, nor would the current forms of contrast media, low-osmolar or iso-osmolar be associated with differing risk. Thus, the lack of evidence or limited consensus is more likely a result of the independent relationship between contrast exposure and nephrotoxicity. However, this discussion was not the goal of the report. The report presents the known literature well, and appears to make the only possible conclusions.	The following wording has been added to the prevention report and the contrast media report (Introduction): "It is unclear to what extent acute kidney injury (AKI) that develops after iodinated contrast exposure is causally or coincident related."
88	Peer Reviewer #5	Results	The methodology used to compare NAC included both open label and double blinded studies. The meta-analysis included 63 randomized controlled trials which were mostly small and open label. The study by ACT investigators, Berwanger et al. Circulation 2011, which was a well powered (n= 2308), multicenter, randomized, placebo controlled trial of NAC 1200mg 12 hours before, and 12 hours after the procedure, showed absolutely no benefit of NAC + IV fluids compared to IV hydration alone. This study seems to not have been included in the analysis (figure 3, or 4). This seems odd, as this is the only trial with enough events (147 CIN events in each arm) without showing any benefit. This needs to be explained to the clinical community at large, as the rationale for exclusion is not at all explained.	Thank you for pointing this out. We have revised this section and have added the ACT trial data on IOCM v LOCM.
89	Peer Reviewer #5		Inclusion of ACT would completely change this analysis and conclusions. I am therefore still not clear how such a study should be ignored, when the guidelines committee used this study as the important evidence for lack of benefit of NAC in prevention of CIN.	We revised this section and added the ACT trial data on IOCM v LOCM.
90	Peer Reviewer #5		However, while the CIN outcome was not included, the investigators chose to use the ACT study for secondary outcomes. This needs to be explained.	We revised this section and added the ACT trial data on IOCM v LOCM.
91	Peer Reviewer #5		The NAC studies are all negative for any benefit, however the statin studies continue to show controversial results. I would therefore recommend that the AHRQ group reconsider the analysis for NAC, or at the very least discuss the exclusion of the important, well run study of ACT in detail and re-structure the conclusions regarding the clinical significance of high dose NAC in prevention of CIN.	We revised this section and added the ACT trial data on IOCM v LOCM.

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#	Commentator and Affiliation	Section	Comment	Response
92	Glenn Levine	Introduction, Discussion, References (Prevention and contrast media reports)	There is very little mention of the recent work from Michigan and mayo with propensity matching showing minimal additional risk for renal injury with contrast in pts with eGFR 45 or even 30. Would like to see some discussion of this by the authors in the intro and conclusion section. Davenport MS Khalatbari S Dillman RJ et al. Contrast material induced nephrotoxicity and intravenous low osmolality iodinated contrast material. Radiology 2013 26794105 McDonald RJ McDonald JS Bida JP et al. Intravenous contrast material induced nephropathy causal or coincident phenomenon Radiology 2013 267106118 McDonald JS McDonald RJ Carter RE et al. Risk of Intravenous Contrast Material mediated Acute Kidney Injury A Propensity Score matched Study Stratified by Baseline estimated Glomerular Filtration Rate. Radiology 2014 Jan 16130775	Thanks you for your comment we have considered your recommendations and added references as described below: The Davenport, 2013, and the McDonald, 2013 papers are both cited in the two reports. In the prevention report: Davenport, 2013 is cited in the discussion; McDonald 2013 is cited in the introduction and discussion. In the contrast media report, both articles are cited introduction and the discussion. We did not include the McDonald, 2014 paper in the introduction or discussion sections. This paper contained information similar to that available in the Davenport, 2013 and McDonald, 2013 papers.
93	ACC/AHA/SCAI writing group	General	It has been suggested that the alleged beneficial effect of NAC in CIN is related to its serum creatinine (SCr)-lowering ability rather than to improved GFR. It is believed that NAC directly reduces SCr by increasing SCr's excretion (tubular secretion), decreasing its production (augmenting activity of creatine kinase), or possibly interfering with its laboratory measurement, enzymatic or nonenzymatic (Jaffe method). This was supported by a study that demonstrated a significant decrease in SCr after 4 doses of 600 mg of oral NAC in healthy volunteers with normal kidney function and no exposure to radiocontrast media[4]. This brings into question the results of at least 13 randomized, controlled trials that reported NAC to be protective in CIN, with SCr used as the endpoint.	Thank you for your insightful comments regarding NAC and the lowering of serum creatinine to a significant degree (absolute change of -3.35%) at 4 hours reported in the manuscript by Hoffman et al. The change at 48 hours was not significant in this paper (absolute change-2.36%) which would be the time frame that is used to define CIN. However, it is possible the effect on patient with chronic kidney disease may be greater than those with normal renal function. Unfortunately we do not know to what degree this would influence the increase in serum creatinine of >25% that we use to define CIN. We have added the following wording to the discussion sections of both the executive summary and the full report.: “One study has questioned whether N-acetylcysteinen is effective at preventing CIN or if it simply reduces serum creatinine. This is an important finding, however the reduction in serum creatinine reported that was significant was measured at four hours, and was insignificant at 48 hours, which was the time frame for the measure of CIN in this report.”

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#	Commentator and Affiliation	Section	Comment	Response
94	ACC/AHA/SCAI writing group	Results	The analyses do not address more clinically relevant hard endpoints, such as need for dialysis.	Need for renal replacement therapy is addressed in all comparisons. We did not meta-analyze this data due to differences in reporting, or lack of data on the specific outcome
95	ACC/AHA/SCAI writing group		As best we can determine, the Acetylcysteine for Contrast-Induced Nephropathy Trial (ACT)[3], the best study assessing NAC and CIN, was not included in the primary analyses of NAC and CIN (though it seems to be included in a secondary analyses). It is unclear why this study is not included in the primary analysis; its inclusion would likely significantly change the findings of the AHRQ analyses.	The ACT study appears in the analyses of the revised version of the CIN prevention report. We include only data on comparisons where IOCM and LOCM were administered in this report, comparisons of NAC vs saline in groups receiving HOCM were not included.
96	ACC/AHA/SCAI writing group		The AHRQ analyses reports that high-dose (>1200 mg/day) NAC was more effective than *IV saline in* preventing CIN (RR: 0.70 CI: 0.50-1.0), consistent with a "clinically important benefit" and number needed to treat of 21 (CI:13-172), with low strength of evidence (SOE). This means that there is l*ow confidence* that the evidence reflects the true effect. This finding, even if accepted, should not be the basis of recommending NAC to prevent CIN	The updated literature search included a number of new studies (including the ACT report) which changed the RR to 0.81 (95% CI: 0.63 to 1.04).
97	ACC/AHA/SCAI writing group		The methodology used to assess the potential benefit of NAC included both open label and double blinded studies.	We included RCTs in the analyses. If the study was not blinded the risk of bias score would be lowered.
98	ACC/AHA/SCAI writing group		Since October 2013, the cut point of study inclusion in the AHRQ analyses, three more studies [5-7]have been published finding no benefit of NAC administration for the prevention of CIN.	These articles are included in the revised version of the report.

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